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Clinical Outcomes of Parenteral Antibiotics Used in Staphylococcus aureus-Related Skin and Soft Tissue Infections in Pediatric Hospitalized Patients

Çocuk Hastalarda Staphylococcus aureus'a Bağlı Deri ve Yumuşak Doku Enfeksiyonlarında Kullanılan Parenteral Antibiyotiklerin Klinik Sonuçları

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Abstract: This study aimed to determine the clinical and laboratory characteristics of hospitalized pediatric patients with skin and soft tissue infections (SSTIs) associated with Staphylococcus aureus and to compare parenteral antibiotic therapies in terms of clinical outcomes. This single-center retrospective study analyzed patients aged 1 month to 18 years who were treated for S. aureus-associated SSTIs at Ankara Bilkent City Children's Hospital between September 2019 and September 2022. A total of 89 patients were included. Infections were caused by methicillin-susceptible (S. aureus, MSSA; n=54, 60.7%) and methicillin-resistant (S. aureus, MRSA; n=35, 39.3%). Compared to the MSSA group, the MRSA group had significantly higher rates of central venous catheter-related infections, prior hospitalizations, and complications (34.1% vs. 11.1%, 62.9% vs. 24.1%, and 28.6% vs. 5.6%, respectively; p=0.010, p=0.010, p=0.003). No significant difference in clinical outcomes was observed between patients treated with vancomycin or teicoplanin in the MRSA group. In the MSSA group, clinical outcomes were similar between patients who received beta-lactam/beta-lactamase inhibitors and third-generation cephalosporins. However, those treated with ampicillin-sulbactam had lower recurrence and complication rates compared to those treated with piperacillin-tazobactam (0% and 0% vs. 25% and 25%, respectively; p=0.029). Teicoplanin may be a reasonable option for treating MRSA-related SSTIs due to comparable clinical outcomes to vancomycin. For MSSA-related SSTIs, beta-lactam/beta-lactamase inhibitors such as ampicillin-sulbactam, piperacillin-tazobactam, and third-generation cephalosporins may also be appropriate treatment options with satisfactory results.
Keywords: Staphylococcus aureus, skin and soft tissue infections (SSTIs), parenteral antibiotics, clinical outcomes, children

Özet: Bu çalışmanın amacı, hastanede yatan çocuk hastalarda Staphylococcus aureus'a bağlı deri ve yumuşak doku enfeksiyonlarının klinik ve laboratuvar özelliklerini belirlemek ve parenteral antibiyotiklere göre klinik sonuçları karşılaştırmaktır. Bu tek merkezli retrospektif çalışmada, Eylül 2019 – Eylül 2022 tarihleri arasında Ankara Bilkent Şehir Hastanesi Çocuk Hastanesi'nde S. aureus ilişkili deri ve yumuşak doku enfeksiyonu tanısı alarak tedavi edilen 1 ay–18 yaş arası hastalar analiz edilmiştir. Çalışmaya toplam 89 hasta dahil edilmiştir. Enfeksiyonların %60,7'si metisiline duyarlı (MSSA; n=54), %39,3'ü metisiline dirençli (MRSA; n=35) S. aureus kaynaklıydı. MRSA grubunda santral kateter ilişkili enfeksiyon, önceki hastaneye yatış ve komplikasyon oranları MSSA grubuna göre anlamlı olarak daha yüksekti (%34,1 vs. %11,1; %62,9 vs. %24,1; %28,6 vs. %5,6; p=0,010; p=0,010; p=0,003). MRSA grubunda vankomisin ve teikoplanin tedavisi arasında klinik sonuçlar açısından fark izlenmedi. MSSA grubunda ise beta-laktam/beta-laktamaz inhibitörü ve üçüncü kuşak sefalosporin alan hastalarda klinik sonuçlar benzerdir. Ancak ampisilin-sulbaktam alan hastalarda nüks ve komplikasyon oranları piperasilin-tazobaktam alanlara göre anlamlı şekilde daha düşüktü (%0, %0 vs. %25, %25; p=0,029). MRSA ilişkili deri ve yumuşak doku enfeksiyonlarının tedavisinde teikoplanin, vankomisine benzer klinik sonuçları nedeniyle makul bir seçenek olabilir. MSSA ilişkili enfeksiyonların tedavisinde ise ampisilin-sulbaktam, piperasilin-tazobaktam ve üçüncü kuşak sefalosporinler tatmin edici sonuçları nedeniyle uygun tedavi seçenekleri olabilir..
Anahtar Kelimeler: Staphylococcus aureus, deri ve yumuşak doku enfeksiyonları (DYDE), parenteral antibiyotikler, klinik sonuçlar, çocuklar

Ethics Committee Approval: The study was approved Ankara City Hospital Clinical Research Ethics Committee (Decision no: E2-22-2008 Date:22.06.2022

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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1. Introduction

Pediatric patients often face skin and soft tissue infections (SSTIs) that may necessitate hospitalization. *Staphylococcus aureus* is the most commonly isolated pathogen from cutaneous abscesses and infected wounds among hospitalized children (1). The rising prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is a major concern in *S. aureus*-associated SSTIs (1,2). However, hospital-acquired MRSA (HA-MRSA) and methicillin-susceptible *S. aureus* (HA-MSSA) infections remain clinically significant, especially in hospitalized children with underlying comorbidities (3,4). Established risk factors for MRSA-associated SSTIs include the presence of an indwelling central venous catheter (5), underlying medical conditions (5), and a recent history of hospitalization within the past 12 months (6). If left untreated or in severe cases, *S. aureus*-associated SSTIs may lead to complications such as bacteremia, sepsis, septic arthritis, osteomyelitis, and toxic shock syndrome (7). The standard management of SSTIs includes incision and drainage of abscesses, debridement of necrotic tissue, removal of infected foreign material, and administration of antimicrobial therapy, either empirically or based on antibiotic susceptibility testing (8). Antimicrobial treatment prevents recurrence and secondary spread following drainage procedures (9). Antibiotic selection may vary depending on the local microbiological flora, antimicrobial resistance profiles, and the patient's clinical condition. Other factors such as drug availability, institutional resources, and physician preferences may also influence therapeutic decisions. Despite the clinical importance of this issue, data on the outcomes of parenteral antibiotics used to treat *S. aureus*-associated SSTIs in hospitalized pediatric patients remain limited (10,11). This study aimed to fill these knowledge gaps and provide a comprehensive comparison of the clinical outcomes of various antistaphylococcal parenteral antibiotics in pediatric patients hospitalized with purulent skin and soft tissue infections (SSTIs) caused by *Staphylococcus aureus*, thereby enlightening the medical community on the most effective treatment strategies.

2. Materials and-Methods

2.1 Study design and study population

This single-center retrospective cohort study, conducted at Ankara City Children's Hospital between September 2019 and September 2022, included a comprehensive sample of pediatric inpatients diagnosed with *S. aureus*-associated skin and soft tissue infections (SA-SSTIs). The thoroughness of our study design and the depth of our data collection process ensure the reliability and validity of our findings.

2.2 Data collection

Demographic data, laboratory results, treatment characteristics, and clinical outcomes were retrieved from the hospital information system. Patients aged between 1 month and 18 years were eligible if they had complete data, mono-microbial culture results confirming *S. aureus* infection, and received appropriate parenteral antibiotic therapy for at least five days after pathogen identification. This rigorous selection process ensured that our study included a homogenous group of pediatric patients with SSTIs caused by *S. aureus*, allowing for more reliable and applicable results.

2.3 Microbiological methods

Pathogen identification and antimicrobial susceptibility testing were performed using VITEK MS v3.2.0 (bioMérieux, Marcy-l'Étoile, France) and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Breakpoint values established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were applied for susceptibility interpretation (12). Methicillin resistance was determined via cefoxitin screening, with strains exhibiting minimum inhibitory concentrations (MICs) >4 mg/L classified as methicillin-resistant (12).

2.4 Definitions

SA-SSTI was defined as a culture-confirmed *S. aureus* infection from an abscess or wound site accompanied by clinical signs of infection. Hospital-acquired SSTI (HA-SSTI) was an infection occurring ≥48 hours after hospital admission or in patients with inpatient hospitalization within the previous year. Cases not meeting these criteria were classified as community-acquired SSTIs (CA-SSTIs) (13,14). SSTIs were categorized as either abscesses or infected wounds (15). Length of stay (LOS) due to infection was defined as the time between the first culture-confirmed detection of *S. aureus* and the completion of antimicrobial therapy and management of complications. Recurrence was defined as the re-detection of SA-SSTI between 14 days and 12 months after the initial culture positivity

(16,17). Definitive treatment duration was the interval from the first dose of culture-guided antibiotic therapy to the final dose. The primary outcome was the comparison of clinical outcomes between MRSA- and MSSA-associated skin and soft tissue infections (SSTIs). The secondary outcome was the comparison of clinical outcomes based on the specific antistaphylococcal agents administered.

2.5 Statistical analysis

All analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess normality. Non-normally distributed variables were compared using the Mann-Whitney U test. If applicable, comparisons of multiple antibiotic groups in MRSA cases were performed using the Kruskal-Wallis H test and Dunn's post hoc test. Results were expressed as medians (minimum–maximum). Categorical variables were analyzed using the Pearson chi-square test, Likelihood Ratio test, or Fisher's exact test, as appropriate, and reported as counts and percentages. A p-value <0.05 was considered statistically significant.

2.6 Ethical approval

The study protocol was approved by the xxx Hospital Clinical Research Ethics Committee (Decision No: E2-2022-2008; Date: June 22, 2022).

3. Results

3.1 Demographic, clinical and laboratory characteristics

A total of 89 pediatric patients with culture-confirmed *S. aureus*-associated skin and soft tissue infections (SA-SSTIs) were included in the study. The cohort consisted of 48.3% male patients, with a median age of 41.4 months (2–213 months). Methicillin-resistant *S. aureus* (MRSA) was identified in 39.3% of cases (n = 35), and hospital-acquired infections (HAIs) were observed in 76.4% (n = 68). Detailed demographic, clinical, laboratory, and treatment outcome data are presented in Table 1. The most common anatomical site for specimen collection was the head and neck region (42.6%). Risk factors such as indwelling central venous catheter (20.2%), trauma (40.4%), neurological disorders (18.0%), and hospitalization within the previous 12 months (39.3%) were more frequently observed in the MRSA group compared to the MSSA group, with statistically significant differences ($p = 0.012$, $p < 0.001$, and $p < 0.001$, respectively). No significant differences were found between the two groups for other epidemiological variables (Table 1). Overall, complications occurred in 14.6% of patients, with a higher incidence in the MRSA group (28.6%) compared to the MSSA group (5.6%) ($p = 0.003$). No significant differences were noted between the groups regarding other clinical outcome measures ($p > 0.05$).

Table 1. Comparison of the patients in terms of their demographic, clinical and laboratory characteristics

	TOTAL n=89 (%)	**MSSA-SSTI n=54 (60.7%)**	**MRSA-SSTI n=35 (39.3%)**	**p-value**
Demographic and Clinical Characteristics				
Age, months median (range)	41.4 (2-213)	34 (2-210)	72 (2-213)	0.133 ʊ
Gender, n, (%)				
Male	43 (48.3)	26 (48.1)	17 (48.6)	0.969 ʊ
Female	46 (51.7)	28 (51.9)	18 (51.4)	
Source of infection, n, (%)				
Community-acquired (CA)	21 (23.6)	16 (29.6)	5 (14.3)	0.096 ʊ
Hospital-acquired (HA)	68 (76.4)	38 (70.4)	30 (85.7)	
Source of bacterial growth, n (%)				
Abscess aspirate culture	44 (49.4)	28 (51.9)	16 (45.7)	0.571 ʊ
Wound swap culture	45 (50.6)	26 (48.1)	19 (54.3)	
Region of bacterial growth, n, (%)				**0.015 ɸ, a**
Cranium	5 (5.6)	1 (1.9)	4 (11.4)	
Face	10 (11.2)	6 (11.6)	4 (11.4)	
Neck	23 (25.8)	21 (38.9)	2 (5.7)	
Chest	14 (15.7)	5 (9.3)	9 (25.7)	
Abdomen	8 (9.0)	5 (9.3)	3 (8.6)	
Perineum	2 (2.2)	1 (1.9)	1 (2.9)	
back	1 (1.1)	0 (0.0)	1 (2.9)	
Upper extremity	8 (9.0)	5 (9.3)	3 (8.6)	
Lower extremity	15 (16.9)	8 (14.8)	7 (20.0)	
Multiple regions	3 (3.4)	2 (3.7)	1 (2.9)	
Invasive medical devices, n, (%)				
Central venous catheter	18 (20.2)	6 (11.1)	12 (34.3)	**0.010 ɸ**
Non-tunnelled CVC	5 (5.6)	2 (3.7)	3 (8.6)	**0.013 ɸ**
Tunnelled CVC	3 (3.4)	2 (3.7)	1 (2.9)	0.321 ɸ
Implantable port	10 (11.2)	2 (3.7)	8 (22.9)	0.012 ɸ
Ventriculoperitoneal shunt	4 (4.5)	1 (1.9)	3 (8.6)	0.207 ɸ
Implant	1 (1.1)	1 (1.9)	0 (0.0)	0.326 ɸ
Comorbidities, n (%)				**<0.001 φ,b**
Trauma	36 (40.4)	30 (55.6)	6 (17.1)	
Burns	10 (11.2)	6 (11.1)	4 (11.4)	

Hematologic-oncologic disorders	6 (6.7)	4 (7.4)	2 (5.7)	
Neurological disorders	16 (18.0)	4 (7.4)	12 (34.3)	
Immunological disorders	9 (10.1)	5 (9.3)	4 (11.4)	
Rheumatic diseases	2 (2.2)	2 (3.7)	0 (0.0)	
Surgical disorders	2 (2.2)	2 (3.7)	0 (0.0)	
Gastroenterological disorders	1 (1.1)	1 (1.9)	0 (0.0)	
Congenital heart disease	4 (4.5)	0 (0.0)	4 (11.4)	
Kidney diseases	2 (2.2)	0 (0.0)	2 (5.7)	
Prematurity, n, (%)	7 (7.9)	4 (7.4)	3 (8.6)	0.843 $^{\phi}$
Hospital stay within the previous 12 months, n (%)	35 (39.3)	13 (24.1)	22 (62.9)	**<0.001** $^{\circlearrowleft}$
Hospital stay up to bacterial growth, median days (range)	4 (1-46)	3.5 (1-24)	6 (1-46)	**0.045** $^{\tau}$
LABORATORY FINDINGS				
White blood cell count, /mm^3 median (range)	11000 (550-33000)	9590 (550-20700)	11990 (1280-33000)	**0.021** $^{\tau}$
Total neutrophil count, /mm^3 median (range)	6620 (30-26000)	5040 (30-14470)	7315 (350-26000)	**0.027** $^{\tau}$
CRP, mg/dL median (range)	27.5 (5-295)	24.50 (11-295)	48 (5-198)	0.190 $^{\tau}$
OUTCOMES				
Total length of hospital stay, days, median (range)	18 (7-184)	16.5 (7-184)	28 (8-157)	**0.002** $^{\tau}$
Infection-associated length of hospital stay, median days (range)	10 (5-35)	10 (5-35)	12 (7-35)	0.726 $^{\tau}$
PICU admission (n, %)	11 (12.4)	7 (13.0)	4 (11.4)	0.829 $^{\circlearrowleft}$
Need for surgery, n (%)	52 (58.4)	32 (59.3)	20 (57.1)	0.843 $^{\circlearrowleft}$
Time to CRP-negativity, days median (range)	7 (2-21)	6 (2-21)	7 (3-14)	0.829 $^{\tau}$
Recurrence, n (%)	9 (10.1)	3 (5.6)	6 (17.1)	0.077 $^{\circlearrowleft}$
Development of complication(s), n (%)	13 (14.6)	3 (5.6)	10 (28.6)	**0.003** $^{\circlearrowleft}$
Complications developed, n (%)				
Bacteremia	6 (6.7)	1 (1.9)	5 (14.3)	**0.022** $^{\phi}$
Septic arthritis	3 (3.4)	2 (3.7)	1 (2.9)	**0.826** $^{\phi}$
Osteomyelitis	4 (4.5)	0 (0.0)	4 (11.4)	**0.024** $^{\phi}$

Abbreviations: *MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-susceptible Staphylococcus aureus: SSTI: Skin and soft tissue infection; $^{\phi}$: Likelihood Ratio Test; $^{\circlearrowleft}$: Pearson Chi Square test; $^{\Theta}$: Kruskal Wallis H test; $^{\tau}$: Mann- Whitney U Test*

a: In the MSSA group, high rates of bacterial growth were observed in culture materials obtained from patients with SSTIs of the neck region (38.9%), whereas in the MRSA group, high rates of bacterial growth were observed in the patients with SSTIs of the cranial region (11.4%), chest and lower extremities. b: In the MSSA group, traumatic lesions were observed, while in the MRSA group, neurological disorders and congenital heart disease were observed at a higher rate.

3.2 Antibiotic Susceptibility Profile

Antibiotic susceptibility testing revealed that all isolates (100%) were susceptible to glycopeptides (vancomycin, teicoplanin), linezolid, daptomycin, fosfomycin, and tigecycline. Clindamycin susceptibility was 74.1% in MSSA and 60.0% in MRSA isolates. Inducible clindamycin resistance (IRC) was identified in 25.9% of MSSA and 40.0% of MRSA isolates. No statistically significant difference was found between the two groups for clindamycin susceptibility or IRC rates.

Erythromycin resistance was 70.4% in MSSA and 82.4% in MRSA isolates, while tetracycline resistance was 62.9% in MSSA and 60.0% in MRSA isolates. Trimethoprim-sulfamethoxazole susceptibility remained high in both groups—94.4% for MSSA and 88.6% for MRSA isolates. Fluoroquinolone resistance (ciprofloxacin and levofloxacin) was more frequent in MRSA isolates ($p = 0.005$ for both agents). These data indicate a higher antimicrobial resistance profile in MRSA compared to MSSA isolates. Antibiotic susceptibility patterns and inducible clindamycin resistance rates are summarized in Figure 1 below.

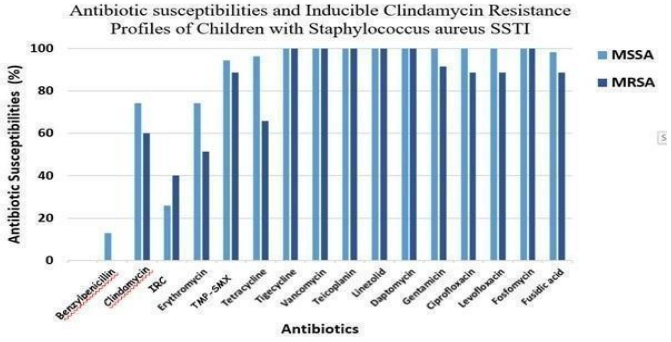

Figure 1. *Antibiotic susceptibilities and inducible clindamycin resistance rates of the isolates*
Abbreviations: *SSTI: skin and soft tissue infection, IRC: Inducible clindamycin resistance, TMP-SMX: Trimethoprim-sulfamethoxazole*

3.3. Comparison of Clinical Outcomes According to Parenteral Antibiotics Used for MRSA-SSTIs

No significant differences were found in clinical outcomes between patients treated with vancomycin and those treated with teicoplanin. However, patients who received clindamycin had a significantly shorter median infection-related hospital stay (7 days) compared to those treated with vancomycin (21 days) and teicoplanin (12 days) (p = 0.002). No statistically significant differences were observed between the three treatment groups regarding other clinical outcome parameters. The comparison of parenteral antibiotics used in MRSA-SSTIs in terms of clinical outcomes is summarized in Table 2.

Table 2. Comparison of parenteral antibiotics used in MRSA-SSTIs in terms of clinical outcomes

	All antibiotics used				Glycopeptide subgroup antibiotics		
	Clindamycin (n=7)	Vancomycin (n=14)	Teicoplanin (n=14)	p-value	Vancomycin (n=14, %)	Teicoplanin (n=14)	p-value
Infection-related length of hospital stay, median days (range)	7[c] (7-10)	21[a] (7-35)	12[b] (7-28)	0.002 $^{\Theta}$	21 (7-35)	12 (7-28)	0.125 $^{\tau}$
PICU admission n (%)	0 (0.0)	3 (21.4)	1 (7.1)	0.210 $^{\sigma}$	3 (21.4)	1 (7.1)	0.596 $^{\varphi}$
Recurrence, n (%)	0 (0.0)	4 (28.6)	2 (14.3)	0.147 $^{\phi}$	4 (28.6)	2 (14.3)	0.648 $^{\varphi}$
Development of complication(s), n (%)	0 (0.0)	5 (35.7)	5 (35.7)	0.068 $^{\phi}$	5 (35.7)	5 (35.7)	1.00 $^{\varphi}$

$^{\Theta}$: Kruskal Wallis H test ^{abc}: Different letters written as superscripts indicate differences between columns (Dunn's test for intergroup analysis);
$^{\varphi}$: Fisher Exact Test; $^{\sigma}$: Pearson Chi-Square test; $^{\tau}$: Mann-Whitney U Test; $^{\phi}$: Likelihood Ratio Test.
***Abbreviations:** PICU: pediatric intensive care unit; MRSA: Methicillin-resistant Staphylococcus aureus; SSTI: Skin and soft tissue infection*

3.4. Clinical Outcomes of Parenteral Antibiotics Used for MSSA-SSTIs

In the MSSA group, clinical outcomes were assessed through two distinct analyses. The first analysis, presented in Table 3, compared outcomes between patients who received clindamycin in combination and those who did not. The second analysis, detailed in Table 4, focused on a subgroup of MSSA-SSTI patients who did not receive clindamycin and compared those treated with β-lactam/β-lactamase inhibitor combinations to those treated with third-generation cephalosporins. Both analyses revealed no significant difference in clinical outcomes across the compared treatment groups. Supplementary material includes detailed data on SSTI-related complications as presented in Table S1, surgical interventions in Table S2, PICU admissions in Table S3, clindamycin combination therapy in MSSA-SSTIs in Table S4, piperacillin-tazobactam use in MSSA cases in Table S5, and antibiotic regimens used in the MRSA group in Table S6

Table 3. Comparison of different empirical antibiotic regimens used in MSSA-SSTIs, including clindamycin combinations, in terms of clinical outcomes

	MSSA group			Not combined with clindamycin (n=30)			Combined with clindamycin (n=24)		
	Not combined with clindamycin (n=30)	Combined with clindamycin (n=24)	P value	BL-BLİ** (n=24)	3. generation CS* (n=6)	P value	BL-BLİ (n=21)	3. generation CS (n=3)	P value
Infection-related length of hospital stay, median days (range)	10 (5-35)	10 (5-21)	0.768 $^{\tau}$	10 (5-21)	8.5 (5-14)	0.273 $^{\tau}$	10 (5-21)	10 (5-14)	1.00 $^{\tau}$
PICU admission, n (%)	4 (13.33)	2 (8.33)	0.682 $^{\varphi}$	4 (16.7)	1 (16.7)	1.00 $^{\varphi}$	1 (4.8)	1 (4.8)	0.239 $^{\varphi}$
Recurrence, n, (%)	2 (6.7)	1 (4.2)	1.00 $^{\varphi}$	2 (8.3)	0 (0.0)	1.00 $^{\varphi}$	1 (4.8)	0 (0.0)	1.00 $^{\varphi}$
Development of complications	3 (10.00)	0 (0.0)	0.245 $^{\varphi}$	2 (8.3)	0 (0.0)	1.00 $^{\varphi}$	1 (4.8)	0 (0.0)	1.00 $^{\varphi}$

$^{\tau}$: Mann-Whitney U Test, $^{\varphi}$: Fisher Exact Test;
**3rd generation cephalosporins: ceftriaxone, cefotaxime*
***Abbreviations.** PICU, pediatric intensive care unit; BL, beta-lactam; BL-BLI, beta-lactam/beta-lactamase inhibitor combination; CS, cephalosporin; MSSA, methicillin-susceptible Staphylococcus aureus*

This table includes all MSSA-SSTI cases regardless of clindamycin use. Clindamycin combination therapies are also included and compared to monotherapies.

Table 4. Subgroup analysis of MSSA-SSTI patients treated without clindamycin: comparison of BL-BLI combinations versus third-generation cephalosporins in terms of clinical outcomes

	BL+BLİ subgroup (n=24)			**3rd generation cephalosporin subgroup (n=6)**		
	Ampicillin-sulbactam (n=16)	**Piperacillin-tazobactam (n=8)**	**p**	**Ceftriaxone (n=3)**	**Cefotaxime (n=3)**	**p**
Infection-associated hospital stay (days: median (range)	10 (5-14)	11 (10-21)	0.320 [τ]	7 (5-10)	14 (7-14)	0.200 [τ]
PICU admission, n (%)	3 (18,8)	1 (12,5)	0.333 [φ]	1 (33,3)	0 (0,0)	1.00 [φ]
Recurrence, n (%)	0 (0,0)	2 (25,0)	0.101 [φ]	0 (0.0)	0 (0.0)	N/A
Development of complications, n (%)	0 (0,0)	2 (25,0)	0.101 [φ]	0 (0.0)	0 (0.0)	N/A

[φ]: Fisher Exact Test; [τ]: Mann Whitney U Test;
**Third-generation cephalosporins: ceftriaxone, cefotaxime*
Abbreviations: *PICU, pediatric intensive care unit; BL-BLI, beta-lactam/beta-lactamase inhibitor combination; N/A, not applicable*

This analysis only includes MSSA-SSTI patients who were not treated with clindamycin. The aim is to compare clinical outcomes between patients treated with β-lactam/β-lactamase inhibitor combinations and those receiving third-generation cephalosporins.

4. Discussion

This study presents detailed findings on the clinical outcomes of parenteral antibiotics used to treat *Staphylococcus aureus*-associated skin and soft tissue infections (SA-SSTIs) in hospitalized pediatric patients. These findings contribute valuable insights to the limited pediatric literature addressing this topic.

4.1. Demographic, Clinical, and Laboratory Characteristics

The epidemiological and clinical characteristics of pediatric patients with SA-SSTIs can vary depending on multiple factors. The high incidence of SSTIs in children aged 6 months to 5 years has been associated with factors such as increased exposure to communal environments (e.g., daycare), close physical contact, suboptimal hygiene, and a decline in maternally acquired passive immunity after infancy (10,11). Although MSSA is classically considered less virulent, hospital-acquired MSSA (HA-MSSA) strains may act as nosocomial pathogens in pediatric SSTIs (18,19). The severity of SSTIs has been linked to the presence of Panton-Valentine leukocidin (PVL) genes, detected in 8.4–49% of MSSA strains (6,18,20) and 31–73% of MRSA strains (2,21), suggesting a potential genetic overlap and shared virulence between MRSA and MSSA isolates (13). In line with previous pediatric studies, most infections in our cohort originated from abscesses or infected wounds, particularly in the head and neck region and lower extremities (10,11). Known risk factors, such as central venous catheters, comorbidities, previous hospitalizations, and *S. aureus* colonization, were also observed in our study population (5,6,9). Unlike previous studies (2,20,21) where community-acquired MRSA (CA-MRSA) was predominant, most of our cases were hospital-acquired and MSSA-associated. These previous studies were predominantly conducted in community settings and in pediatric populations, particularly in regions with high CA-MRSA prevalence (2,20,21). The observed difference in our cohort may reflect regional variations in hospital microbiota, as well as the fact that our study focused on hospitalized children, many of whom had comorbidities or recent healthcare exposure. This shift in epidemiology raises the possibility of PVL-positive methicillin-susceptible *Staphylococcus aureus* (MSSA) strains, warranting future molecular analysis. Median hospital stay durations of approximately 10 days, as reported in the literature (11,22), were consistent with our findings, although they were prolonged in patients with complications or comorbidities. Rates of recurrence (19–63%), complications (4–16%), and bacteremia (2.1–12.5%) reported previously (5,10,11,16,23) were also reflected in our cohort. Among patients requiring PICU admission, nearly all had significant comorbidities, and a notable proportion required surgical intervention, especially abscess drainage. Although PVL testing was not conducted, the severity of clinical presentation supports the need for further molecular studies.

4.2 Antibiotic Susceptibility Profile

Clindamycin susceptibility, including inducible resistance, remains a key consideration in empirical treatment decisions (24). In pediatric studies, nearly all isolates have been reported to be susceptible to glycopeptides, linezolid, daptomycin, and tigecycline (17,46,47). In our cohort, all *S. aureus* isolates demonstrated full susceptibility (100%) to glycopeptides (vancomycin and teicoplanin), linezolid, daptomycin, fosfomycin, and tigecycline, aligning well with previous literature. However, high resistance rates have previously been reported for trimethoprim-sulfamethoxazole (78.4–98.6%), clindamycin (34.2–88.1%), inducible clindamycin (4.5–26.5%), and tetracycline (80.8–89.7%) (17,46,47). In our study, clindamycin resistance was detected in 40.0% of MRSA and 25.9% of MSSA isolates, while inducible clindamycin resistance was observed in 40.0% and 25.9% respectively, indicating higher resistance rates than typically reported for inducible forms. MRSA isolates are generally more resistant to clindamycin and tetracycline than MSSA (25,26). Consistent with this, we observed higher erythromycin and tetracycline resistance among MRSA isolates (82.4% and 60.0%) compared to MSSA isolates (70.4% and 62.9%). Trimethoprim-sulfamethoxazole susceptibility remained relatively high, at 88.6% for MRSA and 94.4% for MSSA isolates, suggesting it may be a viable option in selected MRSA-SSTI cases. Among fluoroquinolones, ciprofloxacin and levofloxacin resistance was more common in MRSA isolates in our study, again consistent with previous findings of broader resistance in this group. These findings emphasize the higher antimicrobial resistance profile of MRSA isolates and support the continued necessity of local susceptibility data to guide empirical antibiotic choices in pediatric SSTIs. While clindamycin and doxycycline may still be considered for targeted therapy, their empirical use should be approached with caution in settings where resistance is common. When glycopeptides are contraindicated, linezolid and daptomycin represent valuable alternatives. However, further prospective studies are needed to confirm their safety and effectiveness in pediatric *S. aureus*-related SSTIs.

4.3 Clinical outcomes of parenteral antibiotics used for MRSA-SSTIs

The potential for resistance development during clindamycin treatment should be considered, especially in the presence of inducible or erythromycin resistance (27). Vancomycin remains the standard of care for complicated methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections (SSTIs) (8). Pediatric studies comparing clindamycin and glycopeptides are lacking; however, adult studies suggest comparable outcomes (28). Teicoplanin, which offers the advantages of once-daily intramuscular dosing, reduced toxicity, and no need for therapeutic drug monitoring, may be a viable alternative to vancomycin (29,30). In our study, clindamycin was mainly preferred in uncomplicated or CA-MRSA infections, while glycopeptides were reserved for more severe, hospital-acquired, or clindamycin-resistant cases. Although hospital stay was longer in patients treated with glycopeptides, clinical outcomes were similar between teicoplanin and vancomycin, consistent with the literature. Furthermore, Turkey's lack of a liquid clindamycin suspension may contribute to the preference for parenteral formulations in hospitalized children.

4.4 Clinical outcomes of parenteral antibiotics used for MSSA-SSTIs

Ampicillin-sulbactam is widely accepted as a first-line agent for MSSA-SSTIs, with efficacy comparable to cefazolin (31–33). Pediatric studies directly comparing ampicillin-sulbactam with piperacillin-tazobactam or cephalosporins are lacking. Adult studies have shown no differences in clinical outcomes among ampicillin-sulbactam, antistaphylococcal penicillins, and cephalosporins (34–37). Some reports suggest a shorter hospital stay with ampicillin-sulbactam than piperacillin-tazobactam (38), though this finding is inconsistent (39). Piperacillin-tazobactam remains a recommended empirical choice for more complicated SSTIs (40). No pediatric studies have assessed the effect of clindamycin combination therapy in MSSA-SSTIs. Studies in adults have shown no added benefit of combining clindamycin with standard agents (41–43), and such combinations may increase adverse events such as diarrhea (43). Our cohort utilized clindamycin combinations in complicated methicillin-susceptible *Staphylococcus aureus* (MSSA) cases involving large abscesses or wounds. However, no significant differences in outcomes were observed between the combination and monotherapy groups. Similarly, no outcome differences were found between beta-lactamase inhibitors and third-generation cephalosporins. Piperacillin-tazobactam was more frequently used in patients with complicated MSSA-SSTIs.

This study has several limitations. Its retrospective, single-center design and modest sample size limit the generalizability of the findings. Molecular

testing for virulence genes such as PVL was not performed. Additionally, adverse effects related to antibiotic treatment were not recorded, and culture results from wound swabs may be subject to contamination bias. Despite these limitations, the study has several strengths. It includes a well-characterized pediatric cohort with a high proportion of hospital-acquired infections. Importantly, the study provides comparative outcome data for different antistaphylococcal antibiotics in managing pediatric SA-SSTIs, an area that remains understudied.

Although susceptibility differences were observed between MRSA and MSSA isolates, particularly for clindamycin, inducible clindamycin resistance (IRC), erythromycin, and tetracycline, these differences did not translate into meaningful differences in clinical outcomes such as recurrence, complication, or PICU admission rates. In the MRSA group, clinical outcomes were comparable between patients treated with vancomycin and teicoplanin, despite variable susceptibility patterns. Similarly, in the MSSA group, clinical outcomes did not significantly differ between patients treated with beta-lactam/beta-lactamase inhibitors and third-generation cephalosporins, even though resistance profiles slightly varied. These findings suggest that while resistance patterns are critical for guiding empirical therapy, they may not always predict clinical progression, especially when definitive treatment is guided by susceptibility results.

5. Conclusion

Given the comparable clinical outcomes, Teicoplanin is a reasonable alternative to vancomycin in treating MRSA-associated skin and soft tissue infections (MRSA-SSTIs). For MSSA-SSTIs, ampicillin-sulbactam and third-generation cephalosporins demonstrated satisfactory efficacy and may serve as appropriate therapeutic options. Additionally, combining clindamycin with other antibiotics did not improve clinical outcomes in cases of MSSA, suggesting that routine combination therapy may not be necessary for these infections. Considering this study's retrospective and single-center design, further prospective, multicenter investigations are warranted to validate these findings and provide stronger evidence for treatment recommendations in pediatric SA-SSTIs.

Abbreviations

CA: Community-acquired

HA: Hospital-acquired

MSSA: Methicillin-susceptible *Staphylococcus aureus*

MRSA: Methicillin-resistant *Staphylococcus aureus*

SSTI: Skin and soft tissue infection

SA-SSTI: *Staphylococcus aureus*-associated skin and soft tissue infection

LOS: Length of stay

MIC: Minimum inhibitory concentration

PVL: Panton-Valentine leukocidin

PICU: Pediatric intensive care unit

SPSS: Statistical Package for the Social Sciences

BL-BLI: Beta-lactam/beta-lactamase inhibitor

EUCAST: European Committee on Antimicrobial Susceptibility Testing

MALDI-TOF MS: Matrix-assisted laser desorption ionization-time of flight mass spectrometry

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