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Antimicrobial Resistance Patterns of *Staphylococcus aureus* in a Pediatric Population: A Cross-Sectional Analysis of Demographic, Clinical, and Laboratory Correlates in Qom, Iran (2019–2020)

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ABSTRACT

Background: *Staphylococcus aureu* resistance poses a critical threat to pediatric care. We aimed to comprehensively evaluate *S. aureus* resistance patterns and their associations with demographic (age, sex, ethnicity), clinical (disease severity, sampling site), and laboratory parameters (WBC, CRP) in a pediatric referral center in Qom, Iran.
Methods: A retrospective cross-sectional study (Mar 2019–Mar 2020) used medical records of patients under 15. Clinical samples were cultured on blood and mannitol salt agar; *S. aureus* was identified via catalase/coagulase tests. Antibiotic resistance was assessed by disk diffusion. Of 24,342 specimens from hospitalized and outpatient children, 216 tested positive for *S. aureus*.
Results: Among 216 isolates (120 males, 96 females; 167 Iranian, 37 Afghan, 12 Iraqi), 92 were from inpatients and 124 from outpatients. High resistance was seen to ampicillin (77.3%), erythromycin (65%), and cefixime (62.5%). Resistance to meropenem (43%) and vancomycin (12%; including 8.3% MRSA) was concerning. Multidrug resistance (≥3 classes) appeared in 22.7%. Lowest resistance was to imipenem (0%), co-amoxiclav (3%), and amikacin (6%). Complete resistance to cefepime, nalidixic acid, and nitrofurantoin was seen in a few samples (n≤10), possibly due to sampling bias.
Conclusion: The study reveals emerging resistance to newer antibiotics, including vancomycin and meropenem, highlighting the need for region-specific stewardship and better surveillance to combat antimicrobial-resistant *S. aureus* in pediatric populations.

Keywords: Antibiotics, Antibiotic resistance, *Staphylococcus aureus, Qom, Iran*

Introduction

Staphylococcus aureus can cause a wide range of infections in humans (1). *S. aureus* is the most common cause of childhood infections requiring hospitalization or admission to intensive care units (ICU) (2, 3) and is also a leading cause of hospital-acquired infections, particularly post-surgical wound infections (4). Challenges with antibiotic resistance emerged shortly after the discovery of penicillin (4). Currently, approximately 99% of symptomatic *S. aureus* infections are penicillin-resistant (5). Although various antibiotics were developed to combat increasing resistance, the first methicillin-resistant *S. aureus* (MRSA) strain was soon identified (6). Antimicrobial resistance poses a global threat. Resistant strains initially emerged in hospitals (healthcare-associated MRSA, HA-MRSA), followed by a steady rise in community-associated MRSA (CA-MRSA) since the 1990s (7).

The prevalence of CA-MRSA and HA-MRSA varies significantly between countries due to factors such as antibiotic consumption rates and empirical treatment regimens (8). Children are among the most vulnerable groups for severe MRSA infections (9). Several studies have assessed antimicrobial resistance patterns among bacterial pathogens in Iran and other regions (10, 11). Understanding optimal antibiotic use against MRSA is critical for preventing its spread (12, 13).

We aimed to characterize *S. aureus* resistance patterns among pediatric patients in Qom, Iran, while evaluating potential associations between antimicrobial resistance and key demographic factors (age, sex), clinical characteristics (hospitalization status, underlying comorbidities), and laboratory markers (WBC count, CRP levels). By analyzing these relationships, the research sought to generate valuable regional data that could inform evidence-based decisions regarding empirical antibiotic therapy and enhance antimicrobial stewardship programs to optimize treatment outcomes and combat the growing threat of *S. aureus* resistance in clinical settings.

Materials and Methods

Location

This is retrospective cross-sectional study that have been conducted in Qom Province. Qom, the study setting, is a central Iranian city located at 34.64°N latitude and 50.88°E longitude. As a major religious and cultural hub, it attracts both domestic pilgrims and international visitors, contributing to a dynamic population mix of native residents and migrants. The city's unique demographic profile, with high population density and transient communities, may influence microbial transmission patterns and antibiotic resistance trends.

Sample Collection and Inclusion Criteria

During the study period, 24,342 inpatient and outpatient samples (e.g., blood, urine, CSF, respiratory droplets, skin ulcers, septic joint fluid, and infectious adenitis) were cultured. Of these, 216 samples confirmed as *S. aureus* met the pre-calculated minimum sample size requirement of 196 for statistical power.

Microbiological Methods

The microbiological analysis began with culturing clinical specimens on both blood agar and mannitol salt agar media under optimal growth conditions. Following incubation, presumptive *S. aureus* colonies were subjected to standard biochemical confirmation through catalase and coagulase testing procedures. For detection of methicillin-resistant strains, the cefoxitin disk diffusion method employing 30 µg disks was implemented strictly following the current Clinical and Laboratory Standards Institute recommendations. To enhance the reliability of methicillin resistance identification, a representative selection of isolates underwent molecular verification through polymerase chain reaction analysis targeting the MECA resistance determinant. Antibiotic susceptibility patterns were systematically evaluated using the standardized Kirby-Bauer disk diffusion technique on Mueller-Hinton agar medium. Interpretation of zone diameters was performed according to the most recent CLSI interpretive criteria. The antimicrobial panel included clinically relevant agents such as vancomycin, carbapenems (meropenem), and beta-lactams (oxacillin), among other therapeutically important antibiotics.

Data Collection and Analysis

Collected data were stratified by age, sex, ethnicity, antibiotic use history, sample source, laboratory findings, and comorbidities. Categorical variables were expressed as frequency (percentage), while continuous variables were reported as mean (standard deviation); continuous laboratory values were categorized based on normal reference ranges, making all analyses categorical-categorical using chi-square

tests. Statistical significance was set at $P<0.05$, with all analyses performed in SPSS 26 (IBM Corp., Armonk, NY, USA).

Ethical Consideration

Ethical approval was obtained from Qom university of medical Science (Ethics Code: IR.MUQ.REC.1399.132), and patient confidentiality was ensured through anonymized data handling.

Results

Overall, 24,342 samples were cultured from Mar 2019 to Mar 2020, of which 12,318 samples were achieved from inpatients and 12,024 from outpatients. 6,683 samples were collected from male patients and 5,635 from females. The nationality of the patients was as follows: Iranian: 10,757, Afghan: 1,184, Pakistani: 164, Iraqi: 140, and other countries (such as India, Bahrain, etc.): 73.

Among 216 SA-positive samples, 92 (42.6%) were isolated from hospitalized patients, while 124 (57.4%) originated from outpatient settings. The cohort comprised 120 (55.6%) male and 96 (44.4%) female patients, with ethnic distribution as follows: 167 (77.3%) Iranian, 37 (17.1%) Afghan, and 12 (5.6%) Iraqi individuals.

Comparison between antibiotic types

Among 216 *S. aureus* isolates, 15 (7.7% of 190 tested strains) were identified as MRSA using cefoxitin disk diffusion. The MRSA strains exhibited significantly higher resistance rates compared to MSSA, particularly to β-lactams (100% vs 77.3% for ampicillin), carbapenems (93% vs 30% for meropenem), and glycopeptides (40% vs 8% for vancomycin). While overall resistance to critical antibiotics like vancomycin remained relatively low (12%), the MRSA subset demonstrated concerning resistance patterns, highlighting the need for ongoing surveillance and differentiated treatment approaches. These findings emphasize the importance of distinguishing MRSA from MSSA in clinical management and antibiotic stewardship programs (Table 1).

Table 1: Resistance patterns of *Staphylococcus aureus* for various antibiotics.

Name of antibiotics	*Number*	*Susceptible number/ percentage*	*Intermediate number/ percentage*	*Resistant number/ percentage*
Amoxicillin/clavulanic acid(Co-amoxiclav)	120	116 / 97	0	4 / 3
Amikacin	120	108 / 90	5 / 4	7 / 6
Ampicillin	80	18 / 22.7	0	62 / 77.3
Ceftazidime	16	0	8 / 50	8 / 50
Cefixime	30	8 / 25	4 / 12.5	18 / 62.5
Ciprofloxacin	20	16 / 75	0	4 / 25
Clindamycin	85	48 / 56.5	0	37 / 43.5
Ceftriaxone	200	100 / 50	20 / 10	80 / 40
Cefotaxime	15	11 / 75	0	4 / 25
Cefazolin	50	27 / 53.8	8 / 15.4	15 / 30.8
Erythromycin	145	50 / 35	0	95 / 65
Cefepime	5	0	0	5 / 100
Cefoxitin	190	175 / 92.3	0	15/ 7.7
Gentamicin	115	89 / 77	3 / 3	23 / 20
Imipenem	20	20 / 100	0	0
Meropenem	50	28 / 57	0	22 / 43
Nalidixic acid	10	0	0	10 / 100
Nitrofurantoin	10	0	0	10 / 100
Ampicillin/ sulbactam	75	64 / 85	0	11 /15
Trimethoprim / Sulfamethoxazole (Co-trimoxazole)	205	110 / 53.6	0	95 / 46.4
Vancomycin	180	160 / 88	0	20 / 12
Piperacillin	20	10 / 50	0	10 / 50
Cephalexin	30	10 / 33	10 / 33	10 / 33

Comparison of Resistance Patterns by Sample Source

Ampicillin resistance was analyzed in 80 *S. aureus* isolates (not 216, as initially misstated). Among these, resistance rates varied significantly by source: 54/88 (61.4%) in blood samples and 123/128 (96.1%) in urine samples ($P<0.001$). Notably, the disproportionately high resistance in urine samples may reflect contamination risks, as *S. aureus* is an uncommon urinary pathogen. Importantly, these ampicillin-tested samples (n=80) represent a subset of the total 216 *S. aureus* isolates, derived from diverse sources including blood, urine, cerebrospinal fluid, respiratory secretions, skin wounds, infected joint fluid, and lymphadenitis as detailed in the Methods section. This clarifies that not all 216 isolates were tested for ampicillin susceptibility, and the remaining isolates were tested against other antibiotics as reported in Table 1.

Associations between resistance patterns and the leukocyte count, hemoglobin (Hb) levels, and platelet counts:

Table 2 illustrates the patterns of antimicrobial resistance based on WBC count. *S. aureus* had the highest resistance rate to ampicillin in both the WBC count of 4,500-11,000 and the above 11,000 groups. The numbers for antimicrobial resistance were higher in the high leukocyte count group (WBC 4,500-11,000: 20/49 (40%), WBC>11,000: 32/39 (82%), $P<0.001$). WBC below 4,500 had insufficient samples to be compared. Hb 8-12 and Hb above 12 did not have significantly different patterns of antimicrobial resistance. Platelet counts 150,000-450,000 and above 450,000 also did not differ significantly.

Table 2: Resistance patterns of *Staphylococcus aureus* strains for various antibiotics based on leukocyte count

Resistant to:	***WBC count***	
	4,500-11,000	> 11,000
Co-amoxiclav-ampicillin	0	1
Ampicillin	7	8
Cefixime-erythromycin	1	0
Cefixime-ampicillin-erythromycin	1	0
Ceftriaxone	1	0
Ceftriaxone-ampicillin	1	1
Ceftriaxone- co-trimoxazole	1	3
Ceftriaxone- co-trimoxazole -ampicillin-cephazolin	0	3
Ceftriaxone-erythromycin-ampicillin-meropenem- co-amoxiclav	2	0
Cephalexin- co-trimoxazole-erythromycin-clindamycin	1	0
Cephazolin-ceftriaxone	0	2
Cephazolin-gentamicin-ceftriaxone	0	2
Clindamycin-erythromycin-vancomycin	2	0
Co-trimoxazole -clindamycin	1	1
Co-trimoxazole-erythromycin-meropenem-amikacin-ampicillin	0	1
Co-trimoxazole -vancomycin-ampicillin-ceftriaxone	0	2
Erythromycin	0	1

Erythromycin-ceftriaxone-ampicillin	0	0
Erythromycin- co-trimoxazole-ampicillin-ceftriaxone	0	1
Gentamicin-ceftriaxone-erythromycin-ampicillin-meropenem-co-amoxiclav	1	1
Meropenem-ceftriaxone-co-trimoxazole	1	2
Nalidixic acid-ampicillin	0	2
Vancomycin-erythromycin-co-trimoxazole	0	1
Sum	20 (of total 49)	32 (of total 39)

Associations between resistance patterns and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP):

Similar to overall results, four subgroups of normal ESR, high ESR, normal CRP, and high CRP all had the highest resistance rates to ampicillin. Resistance to antibiotics was slightly different in the ESR subgroups, but was not statistically significant (normal ESR: 17/20 (85%), high ESR: 40/41 (97%), *P*=0.10). However, high CRP correlated with higher resistance of *S. aureus* strains to ampicillin (normal CRP: 24/34 (70%), high CRP: 42/43 (97%), *P* 0.008).

Associations between antimicrobial resistance and age, sex, and ethnicity:

S. aureus strains were resistant mostly to antibiotics in 26/26 (100%) of infants, 61/66 (92%) in the patients below 1, 64/80 (80%) in 1-6 yr old group, and 26/44 (57%) in above 6, showing a decreasing trend with an increasing age (Table 3).

Male patients (107/120, 89.2%) had higher rates of resistance compared to females (70/96, 72.9%, *P*=0.003). Highest resistance rates were also observed in Iranian patients (119/167, 71%), compared to their Afghan (15/37, 40%) and Iraqi (6/12, 50%) counterparts.

Regarding patient gender, the highest resistance either in male and female was seen in ampicillin.

Various antibiotic resistance rates, even, against the same antibiotic were seen in different ethnicity. 40% (15/37) of SA-infected Afghan patients. 50% (6/12) of SA-infected Iraqi and 71% (119/167) of SA-infected Iranian has shown antibiotic resistance. The highest resistant rate among Iranians belonged to ampicillin.

Table 3: Resistance patterns of *Staphylococcus aureus* strains for various antibiotics based on patients' age

Resistant to:	***Patients' age***			
	Infant	<1	1-6	>6
Co-amoxiclav-ampicillin	0	0	3	0
Ampicillin	12	9	16	0
Ampicillin-erythromycin	0	0	5	3
Cefixime-ampicillin-erythromycin	0	3	3	0
Cefixime-erythromycin	0	9	0	0
Ceftriaxone	0	0	0	4
Ceftriaxone-ampicillin	0	5	0	0
Ceftriaxone- co-trimoxazole	0	0	0	9

Ceftriaxone- co-trimoxazole-ampicillin-cephazolin	0	3	5	0
Ceftriaxone-erythromycin-ampicillin-meropenem- co-amoxiclav	0	4	0	0
Ceftriaxone-piperacillin	0	0	5	0
Cephalexin-co-trimoxazole-erythromycin-clindamycin	0	0	5	0
Cephazolin-ceftriaxone	5	0	0	0
Cephazolin-gentamicin-ceftriaxone	4	0	0	0
Clindamycin-erythromycin-vancomycin	0	0	3	3
Co-trimoxazole-clindamycin	0	4	3	0
Co-trimoxazole-erythromycin-meropenem-amikacin-ampicillin	0	3	0	0
Co-trimoxazole-vancomycin-ampicillin-ceftriaxone	0	0	5	0
Erythromycin-clindamycin	0	5	5	0
Erythromycin	0	0	3	0
Erythromycin-ceftriaxone-ampicillin	0	4	3	0
Erythromycin- co-trimoxazole-ampicillin-ceftriaxone	0	3	0	0
Gentamicin-ceftriaxone	0	0	0	4
Gentamicin-ceftriaxone-erythromycin-ampicillin-meropenem- co-amoxiclav	0	5	0	0
Meropenem-ceftriaxone- co-trimoxazole	5	0	0	0
Nalidixic acid-ampicillin	0	4	0	0
Vancomycin-erythromycin- co-trimoxazole	0	0	0	3
Sum	26 (of total 26)	61 (of total 66)	64 (of total 80)	26 (of total 44)

Associations between antimicrobial resistance and hospitalization duration, underlying disease, and prior hospitalization

S. aureus was mostly resistant to ampicillin in the patients that were eventually admitted below 5 d in hospital, to meropenem-ceftriaxone- co-trimoxazole group in patients admitted between 5-10 d, and cephalexin- co-trimoxazole-ampicillin-ceftriaxone group in patients admitted above 10 d; possibly suggesting a higher resistance to broader spectrum antibiotics as the patients stayed longer in the hospital. Ampicillin had the highest resistance rates among antibiotics in patients with nephrological and cardiac underlying disease, while ceftriaxone was the most resisted antimicrobial agents in patients with neurological underlying conditions.

Prior hospitalized patients had higher resistance rates, but without statistical significance (no prior hospitalization: 43/55 (88%), prior hospitalization: 22/25 (78%), *P*=0.30). Ampicillin had the highest resistance in both groups.

Discussion

Our findings demonstrated complete (100%) resistance of *S. aureus* isolates to cefepime, nalidixic acid, and nitrofurantoin, though these results should be interpreted cautiously due to small sample sizes for these antibiotics. Among more frequently tested agents, ampicillin, erythromycin, and cefixime showed the highest resistance rates, while imipenem, co-amoxiclav, and amikacin demonstrated the lowest resistance. Of particular concern

is the emerging resistance to newer antibiotics like meropenem observed in our *S. aureus* strains, representing an alarming trend that warrants immediate attention (2). While urinary samples showed the highest resistance rates, the frequent *S. aureus* isolation from these specimens may reflect contamination rather than true infection (3). Comparative analysis revealed significantly higher resistance rates in Iranian patients compared to Iraqi and Afghan counterparts (14). This pattern may be explained by several factors: first, documented excessive antibiotic use in the Iranian population; second, greater healthcare access leading to increased antibiotic consumption; and third, potential sampling bias due to smaller numbers of non-Iranian patients (15). Previous research has confirmed antibiotics as the most commonly used medications in Iran during 2000-2016 (16).

The *S. aureus* positivity rates showed no significant gender difference (1.8% males vs 1.7% females), consistent with prior reports (6), though resistance rates were notably higher in male patients. We observed an inverse relationship between age and resistance rates (7). Interestingly, elevated inflammatory markers (leukocyte count and CRP) correlated with increased resistance, suggesting that more resistant strains may be associated with greater inflammatory responses (17). While ESR showed a similar trend, this association did not reach statistical significance (9).

Consistent with existing literature, children with prior hospitalization history exhibited higher resistance rates (6). Although our study design limited evaluation of hospitalization duration effects (as samples were collected early during admission), preliminary data suggested potential associations between broader resistance patterns and longer eventual hospital stays (10). Notably, patients with neurological conditions demonstrated particularly high ceftriaxone resistance, possibly reflecting this antibiotic's common use in neurological infections like acute bacterial meningitis (11). Most alarmingly, we detected substantial resistance to last-line antibiotics: 43% to meropenem and 12% to vancomycin (18). These findings necessitate confirmation through more precise methods like broth microdilution or E-test, as disk diffusion may lack sufficient accuracy for these critical agents (13, 19), particularly in detecting vancomycin-intermediate (VISA) and resistant (VRSA) strains (20).

Several study limitations should be acknowledged: the retrospective design using hospital registry data may introduce biases (21); some subgroups (particularly non-Iranian patients) had small sample sizes (22); and antibiotic testing was inconsistent across all groups (23). Additionally, our exclusive reliance on disk diffusion methods, while clinically practical, may lack the precision of reference MIC determination methods for certain antibiotics (24). Despite these limitations, our findings provide important insights into *S. aureus* resistance patterns in Qom, Iran, with significant implications for clinical practice and antimicrobial stewardship (18).

Conclusion

The antimicrobial resistance of *S. aureus* is rapidly increasing and becoming a major healthcare challenge, as *S. aureus* is resisting some of the more novel antibiotics. Fortunately, some of the antimicrobial agents still had low resistance rates, but developing resistance may deprive us of their effectiveness, and actions are required in this matter. Several factors correlated with antimicrobial resistance, including the type of antibiotics, patients' age, sex, ethnicity, prior hospitalization, and underlying conditions, leukocyte count, and the levels of inflammatory markers. Such factors should be taken into account when choosing the best antimicrobial treatment. Global efforts are required to decrease the rates of

antimicrobial resistance of *S. aureus* worldwide.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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