Clinico-epidemiology and resistance pattern of Community and Hospital-acquired S*taphylococcus aureus* sepsis in children

Running Title: Clinicoepidemiology and Resistance Patterns of Pediatric *Staphylococcus aureus* Sepsis

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Abstract

Background: *Staphylococcus aureus* (*S. aureus*) is a pathogenic bacterium causing infections ranging from minor skin conditions to life-threatening sepsis. The rise of methicillin-resistant strains (MRSA), including hospital-acquired (HA-MRSA) and community-associated (CA-MRSA) variants, complicates treatment, particularly in pediatric sepsis. This study aimed to characterize *S. aureus* sepsis in children, compare community (CA-SA) and hospital-acquired (HA-SA) cases, and analyze antibiotic resistance.

Methods: This study was conducted from January 2021 to December 2022 in the Postgraduate Department of Pediatrics, Children's Hospital Srinagar, J&K, on patients aged one month to 18 years suspected of having *S. aureus* sepsis or disseminated disease. Culture of various samples was performed using standard methods (BacT Alert and Vitek II Compact). Continuous data was expressed as Mean ± Standard deviation, and categorical variables as proportions.

Results: Among 56 patients, 66.1% had CA-SA and 33.9% had HA-SA. Males (62.5%) and rural residents (71.43%) were predominant. Localized musculoskeletal symptoms (91.9%, *p* ≤ 0.05) were common. Pleuropulmonary disease was linked to HA-SA, while necrotizing soft tissue infections were associated with CA-SA. Pneumonia and abscesses were frequent presentations. Complications (septic shock, respiratory failure, multi-organ dysfunction) were more prevalent in HA-SA. Of 50 culture-confirmed cases, 96% were MRSA. Survival rates were 94.6% (CA-SA) and 89.5% (HA-SA).

Conclusions: The study highlights the high prevalence of MRSA in pediatric sepsis, necessitating urgent antimicrobial stewardship. Distinct clinical profiles of CA-SA and HA-SA underscore the need for tailored management in resource-limited settings.

Key words: *Staphylococcus aureus;* Sepsis*;* Methicillin; MRSA.

Introduction

Staphylococcus aureus (*S. aureus*) is frequently encountered as an asymptomatic colonizer on human skin and mucosal surfaces. The predominant colonization site is thought to be the anterior nares; however, the bacteria can also be detected on the skin or throat. Colonized people, either with their hands or through airborne droplets from the nose, can spread the germs to others. In hospitals, healthcare personnel's hands have been a major source of staphylococcal transmission. Risk factors for the development of infection is disruption of skin, including breaches from wounds, skin diseases such as eczema, epidermolysis bullosa or burns, ventriculoperitoneal shunts, and indwelling intravascular or intrathecal catheters (1). The spectrum of infections involves skin, bone and joint, and lungs. Invasive disease is frequently a complication of previous Skin Soft Tissue Infection or viral respiratory tract infection (especially influenza), but it can also occur spontaneously in otherwise healthy children with no known prior infections or risk factors (2). This pathogen causes both community and hospital-acquired infections (3). Staphylococcal infections, particularly those caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), have increased morbidity and mortality in patients (4, 5). Since the first case was reported in 1961 in the United Kingdom (6). MRSA has been linked to a variety of infections in patients exposed to nosocomial settings, a condition known as Healthcare-Associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA). The emergence of Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has resulted in a significant shift in the epidemiology of MRSA isolates over the last decade (7). *S. aureus* is the primary cause of sepsis necessitating pediatric intensive care unit hospitalization, with an incidence rate of 4 to 26 per 100,000 children per year (8, 9).

The goals of this prospective study were to define the demographic, clinical, and microbiological characteristics of invasive *S. aureus* infections in children. The secondary objectives are to determine their Intensive Care Unit (ICU) needs and to find out whether there is a change in resistance pattern.

Methods

This hospital-based descriptive study was conducted in a tertiary care Hospital, Srinagar, J&K, from January 2021 to December 2022 after obtaining ethical clearance from the institutional ethical committee, IEC no F (Minutes-BOPGS) Acad/KU/22. Informed consent was taken from the guardian of every patient in the local language before their inclusion in the study.

The study included patients aged 1 month to 18 years who met the following criteria: *S. aureus* sepsis was defined as Systemic Inflammatory Response Syndrome (SIRS) in the presence of culture-confirmed staphylococcal infection, with SIRS diagnosed according to the 2005 International Consensus Criteria on Pediatric Sepsis. These criteria included abnormal core temperature (>38.5°C or <36.5°C), cardiovascular abnormalities (mean heart rate >2SD above normal for age or, for infants under 1 year, bradycardia with mean heart rate below the 10th percentile for age), respiratory abnormalities (mean respiratory rate >2SD above normal for age or need for mechanical ventilation), and leukocyte count abnormalities (elevated or decreased white blood cell count for age or >10% immature neutrophils). Disseminated staphylococcal disease was defined as a pyogenic infection at two or more anatomically non-contiguous sites, along with clinical suspicion of staphylococcal disease, plus either culture-confirmed *S. aureus* from a sterile site or microscopic evidence of gram-positive cocci in clusters from sterile body fluid. Infections were classified as community-acquired MRSA (CA-MRSA) when symptoms began before hospitalization, with cultures obtained within 48 hours of admission, there was no prior history of

S. aureus infection (no previous positive cultures), and no history of hospitalization, surgery, or invasive medical devices in the preceding 12 months. Infections that did not meet these criteria were classified as hospital-acquired (10).

Culture for various samples was done by various standard methods. Blood culture, body fluids, and pus culture were done in BacT Alert blood culture bottles. Bottles that were flagged positive by the BacT Alert system were subcultured on standard media, and then growth proceeded for antimicrobial sensitivity on VITEK II Compact as well as manually by the Kirby Bauer method. Urine culture was done by semi-quantitative method on Hi-Chrome UTI Agar, and antibiotic sensitivity was done manually by Kirby Bauer method [11]. Cefoxitin disc (30mcg Himedia Labs India) was used to differentiate between MRSA and MSSA. Other antibiotics tested by the disc diffusion method were Linezolid 10mcg, Gentamicin 10mcg, Amikacin 30mcg, Cotrimoxazole 25mcg, and Clindamycin 2mcg (Himedia Labs India). Teicoplanin and Vancomycin MICs were tested on the Vitek II compact.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to the data editor of SPSS Version 25 (SPSS Inc., Chicago, Illinois, USA). Values for continuous data are expressed as Mean ± SD, and categorical variables are expressed as proportions. The chi-square test is used for qualitative data whenever two or more groups are used to compare. The level of significance was set at $P \leq 0.05$.

Results

Out of the 56 children with *staphylococcus* sepsis or disseminated *staphylococcus* infection, culture was positive in 50 (89.30%). 37 (66.10%) had CA infection and 19 (33.90%) HA infections. The ratio of CASS to HASS was 2:1 (66.1%: 33.9%). Further, it was observed that among 50 patients who had *S. aureus* sepsis in cultures, 48 (96%) were MRSA and 2 were MSSA. Linezolid, Vancomycin, and Teicoplanin showed 100% sensitivity. It was followed by Gentamicin, Amikacin, Cotrimoxazole, and Clindamycin with 70%, 60%, 50% and 30% sensitivity, respectively.

Out of 48 MRSA, 32 had community-acquired sepsis and 16 had hospital-acquired sepsis, whereas both MSSA had community-acquired sepsis. The majority of the patients were male, 35 (62.50%) and from a rural background, 40(71.43%). Trauma (21.42%) was thought to be the most common predisposing factor. Pustules (10.71%), fractures (5.35%), and burns (3.60%) also contributed to the infection.

The most common symptoms at admission were fever, localized musculoskeletal symptoms, cough, and altered sensorium. Only the localized musculoskeletal symptoms (91.90%) were significantly associated with community-acquired staph (Table 1). The most common signs at admission were tachypnoea, hypotension, tachycardia, crepitations, and feeble pulses; however, none of the signs was significantly associated with CAS or HAS (Table 1). The common organ system involvement at admission was Pleuropulmonary disease, Necrotising soft tissue disease, Osteoarticular disease, Meningitis, and Pericardial effusion. While as pleuropulmonary disease was significantly associated with HASS, necrotizing soft tissue disease was significantly associated with CASS (Table 2). The common disease presentation was pneumonia followed by abscess (Table 3). The presence of abscess was significantly associated with community-acquired staph sepsis.

Septic shock, respiratory failure, multi organ dysfunction and pneumothorax were among the common complications seen more often in HASS (47.4 %, 21.05 %, 15.8 %, 5.3% respectively)

as compared to CASS (37.8%, 5.4%, 5.4%, 2.7% respectively) but the difference did not acquire significance. Two patients with CASS had ARDS.
The presence of abnormal leucocyte count, platelet count, abnormal kidney function, liver function, coagulopathy, or anemia was not significantly associated with CA or HA infection (Table 4). LV dysfunction was seen in equal proportions (5.40% patients among CASS and 5.30% among HASS).
All patients were treated with anti-*Staphylococcal* antibiotics. Nasal prong oxygen, vasopressor support, incision drainage, packed cell transfusion, heated high flow nasal cannula, ventilator support, intercostal tube drainage, pericardiocentesis was needed in 33 (59%), 23 (41%), 20 (36%), 19 (34%), 16 (28%), 6 (11%), 9 (16%), 1 (0.02%) patients respectively.
There was a significant association between use of high flow in the population of HASS (p vlue0.025).
The Mean±SD hospital stay was 13.32 ± 4.26 days for CASS patients and 14.78 ± 5.53 for HASS patients. The difference was not significant. Mortality was higher in patients who developed HASS ie, 10.50% when compared to patients having CASS, 5.40% respectively, although this was not statistically significant

Discussion

The current study was conducted to find out the demographic, clinical, and microbial profile of *S. aureus* sepsis in infants and children in Post Graduate Department of Pediatrics, GB Panth Children Hospital, Srinagar, and Kashmir. 56 children were admitted to the Hospital, the majority of whom were male. This male predominance also exists in other Indian studies [Bathla A, *et al* (12) and Prachiti Karode *et al* (13)]. In the current study, the majority of the children (71.43%) were from rural areas. This could be attributed to the fact that most of the children in rural households are more likely to suffer from undernutrition, which in turn, increases their susceptibility to childhood infections (14).
Among the predisposing factors, trauma, skin infections, and fractures were the most common factor for sepsis. The history of trauma in a patient with staph sepsis is a common denominator. Trauma results in inoculation of bacteria in skin and soft tissues, causing bacteremia and its consequences. However, the relationship could be temporal. Baranwal et al., **(**15) also found pustules (26%), blunt trauma (15%), and injections (8%) as the most common predisposing conditions.
We found that the majority of the patients (66.10%) had community-acquired *S. aureus* sepsis. The proportion of CASS to HASS is reflective of the level of aseptic care provided in the hospital and the burden of *S aureus* in the community.
Fever (92.85%) was the most common symptom found in the studied population, followed by musculoskeletal symptoms. A similar finding was reported by Bathla A, et al (12) and Mathew *et al*. (16).
In our study, pneumonia was present in 73.70% of HASS and 56.80% of CASS. Hospitalized patients quickly develop oropharyngeal colonization with nosocomial flora and can subsequently manifest lower respiratory tract infections related to these organisms (17).
Necrotizing soft tissue disease, pleuro-pulmonary disease, pericardial effusion, osteoarticular disease, and meningitis are the most common organ system involvement in staph illnesses Baranwal *et al* (15). It was uncovered in our study that pleuropulmonary disease is significantly associated with HASS and necrotizing soft tissue disease with CASS.
Staphylococcal sepsis, if not treated on time, is associated with rapid deterioration and

complications like septic shock, respiratory failure, multi-organ dysfunction, and pyopneumothorax (18). We also encountered patients with similar complications.
We did not observe abnormal leucocyte count, platelet count, abnormal kidney function, liver function, coagulopathy, or anemia to be a significant predictor of CA or HA infection.
A significant number of patients ie, 31(55%) needed ICU care for vasopressors, heated high flow nasal cannula oxygen therapy, and ventilator support. There was a significant association between the use of high flow in the population of HASS, probably due to the high proportion of severe pulmonary disease in this subgroup. High flow therapy is used as the first line of therapy for various etiologies of acute respiratory distress with hypoxia in a pediatric intensive care unit in our setting.
In the current study, out of 50 patients who had *S. aureus* sepsis in culture, 48 were MRSA and 2 were MSSA. Out of 48 MRSA isolates, 32 were from the community and 16 were hospital-acquired acquired and both MSSA were community-acquired. A study was conducted in the same center by Qadri, I *et al*. in 2019 (19). In their observations, only 35% of specimens were reported as methicillin-resistant. Similarly, in an Iranian study, a high frequency of methicillin resistance (48%) was found in *S. aureus,* and all of these tested positive for the *mecA* gene (20). In another multicentre study done by Camacho-Cruz, J *et al*, 38% of isolates were found to be methicillin resistant (21). This reflects a change in resistance pattern in the community, probably due to misuse of antibiotics, and is being witnessed around the globe.
The limitations of our study were that MIC values were not available for all antibiotics, lack of molecular characterization, including *PVL* and *mecA* genes. Also proportionate carriage of *S. aureus* was not determined. Also, limitations due to cross cross-sectional nature of the study, like the establishment of causality of risk factors, could not be established.

Conclusion

Our findings indicate that community-acquired *S. aureus* sepsis remains more prevalent than hospital-acquired cases. Notably, the antimicrobial sensitivity pattern of *S. aureus*-both in our setting and globally-has shifted significantly, with a concerning rise in methicillin-resistant strains. This trend demands urgent attention to guide effective treatment strategies and infection control measures.

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Nil

Ethical statement

The study was approved by the Institutional Ethics Committee
IEC no F (Minutes-BOPGS) Acad/KU/22

Author contribution

Mohd suhail and umer qureshi conceived and designed the experiments. Rayees khanday wrote the main manuscript text. Sahar siddiqui collected samples and performed the experiments. Mohd suhail and umer qureshi analyzed the data and prepared the figures. All the authors reviewed and finalized the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability Statement

Yes, data is available

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Conflicts of Interest

The authors declare no conflicts of interest.

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Table 1. Distribution of studied population as per symptoms and signs at admission

Symptoms	Total (N)	Community acquired (n) (%)		Hospital acquired N (%)	P-Value
Fever	52	36	97.30	16 (84.20)	0.71795
Localized musculoskeletal symptoms	38	34	91.90	4 (21.10)	0.00001
Cough	16	10	27.00	6 (31.60)	0.960148
Altered sensorium	12	7	18.90	5 (26.30)	0.523013
Breathlessness	9	6	16.20	3 (15.80)	0.967161
Signs					
Tachypnea	30	18	48.60	12 (63.20)	0.30264
Hypotension	23	17	45.90	5 (26.30)	0.154414
Tachycardia	21	15	40.50	6 (31.60)	0.511912
Crepitation's	21	15	40.50	6 (31.60)	0.511912
Feeble pulses	20	13	35.10	7 (36.80)	0.899557

Table 2. Distribution of studied population as per organ involvement at admission

Disease spectrum	Total (N)	C.A. N (%)		H.A. (N) (%)	P-Value
Pleuropulmonary disease	41	24	64.90	17 (89.50)	0.048964
Necrotising soft tissue disease	38	30	81.10	8 (42.10)	0.003107
Osteoarticular disease	11	9	24.30	2 (10.50)	0.218506
Meningitis	6	2	5.40	4 (21.10)	0.07306
Pericardial effusion	1	1	2.70	0	1

Table 3. Distribution of studied population as per disease spectrum

Disease spectrum	Total (N)	C.A. (N) (%)	H.A. (N) (%)	P-Value
Pneumonia	35	21 (56.80)	14 (73.70)	0.2154
Abscess	30	26 (70.30)	4(21.10)	0.000471
Pleural effusion	9	5(13.50)	4(21.10)	0.467034
Empyema	7	4(10.80)	3(15.80)	0.59377
Septic arthritis	7	5(13.50)	2(10.50)	0.748947
Osteomyelitis	4	4 (10.80)	0	0.29
Cellulitis	8	4 (10.80)	4(21.10)	0.299731
Meningitis	6	2 (5.40)	4(21.10)	0.07306
Pericardial effusion	1	1(2.70)	0	1

Table 4. Distribution of studied population as per laboratory investigations

Lab. Investigations	Total (N)	Community acquired (N) (%)	Hospital acquired (N) (%)	P-Value
Leukocytosis	35	23 (62.20)	12 (63.20)	0.941907
Leukopenia	5	2 (5.40)	3(15.80)	0.196969
Thrombocytopenia	5	5 (13.50)	0	0.147
Anemia	23	15 (40.50)	8(42.10)	0.910276
Abnormal liver function tests	10	6(16.20)	4(21.10)	0.654571
Abnormal kidney function tests	8	5 (13.50)	3(15.80)	0.817745
Coagulopathy	6	2(5.40)	4(21.10)	0.07306