



Methicillin-Resistant And Methicillin-Susceptible Community-Acquired *Staphylococcus Aureus* Infection Among Children Of Age Group 2 To 5 Years In Pediatric Ward Of General Hospital.

Dr.MilanNimbalkar., Asst Prof. Department of Microbiology, L.A.D & Smt.R.P.College for Women,
Shankar Nagar, Nagpur. Maharashtra,. India.

Abstract: Over the past few decades, infection due to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has been reported worldwide.¹ CA-MRSA has been observed in many patient groups, and healthy children are also susceptible. Cases of CA-MRSA infection affecting children without established risk factors started emerging in 1990s.³ Mostly, CA-MRSA infection has been associated not only with skin/soft tissue infections (SSTIs), but also with invasive infections, which require aggressive treatment and hospitalization.⁴ The risk of severe disease caused by CA-MRSA is a real concern among researchers. This study attempted to describe the characteristics of CA-SA infections among children in a tertiary care center. We found no relevant differences on baseline characteristics or on the outcome of patients infected with CA-MRSA or CA-MSSA strains. In addition, the evidence presented herein supports the occurrence of genuine CA-MRSA in our region. Although it is clinically still significant to classify CA-SA as MSSA and MRSA, the clinicians should be aware of the broad epidemiology of *S. aureus* infections.²⁹ Both CA-MRSA and CA-MSSA strains may result in life-threatening disease or lethal events.

Index Terms - Antibacterial agents, Community-acquired infection, Methicillin resistance, Staphylococcal infections, *Staphylococcus aureus* antimicrobial resistance.

I. INTRODUCTION

Over the past few decades, infection due to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has been reported worldwide.¹ CA-MRSA has been observed in many patient groups, and healthy children are also susceptible.² Cases of CA-MRSA infection affecting children without established risk factors started emerging in 1990s.³ Mostly, CA-MRSA infection has been associated not only with skin/soft tissue infections (SSTIs), but also with invasive infections, which require aggressive treatment and hospitalization.⁴ The risk of severe disease caused by CA-MRSA is a real concern among researchers. In Minnesota and North Dakota, between 1997 and 1999, four pediatric deaths were associated with CA-MRSA strains.⁵ Many institutions have reported their experience with community-acquired *S. aureus* (CA-SA) infection in children. In a previous study conducted in a pediatric center in Northeast Brazil 4.9% of isolated CA-SA strains were resistant to methicillin.⁶ Several studies have shown differences between MRSA and methicillin-susceptible *S. aureus* (MSSA) infections even after controlling for confounding variables such as nosocomial infection.⁷ A three-year surveillance of CA-SA infections at the Texas Children's Hospital documented a greater percentage of CA-MSSA isolates (8.2%) than CA-MRSA isolates (4.4%) which were collected from patients with invasive infections.⁸ Recently, a report of CA-SA pneumonia among hospitalized children in Hawaii revealed the occurrence of pulmonary complications more frequently in MRSA

infected patients.⁹ The objectives of this investigation were to describe the spectrum of community-acquired disease presented by patients infected with *S. aureus* and to compare the patients infected with MSSA or MRSA strains.

II. Materials and methods

Design and study population

The study was carried out with the special permission of parents with their hospitalized wards, medical staff, concern doctors which was a retrospective cohort conducted in the same hospital. Cultures in which *S. aureus* were isolated from pediatric patients (<8-years-old) between 2017 and 2018 were identified in the Bacteriology Laboratory log-book and the respective medical records were reviewed. CA-MRSA infections were selected by applying the following items, according to the Centers for Disease Control and Prevention (CDC) criteria last updated in December 2, 2010: diagnosis of MRSA in a outpatient setting or by culture within 48 h after admission to the hospital, with no history of MRSA infection or colonization; the patient must not have experienced any of the following conditions during the year before infection: hospitalization, admission to a nursing home, skilled nursing facility, or hospice; dialysis; or surgery. Furthermore, the patient must be without permanent indwelling catheters or medical devices that pass through the skin into the body.¹⁰ *S. aureus* isolates obtained after 48 h of admission from patients with clinical evidence of disease prior to admission were also included.⁸ CA-MSSA cases were considered eligible for the study if they met the same criteria of CA-MRSA cases, that is lack of the previously cited healthcare-associated risk factors.¹⁰

III. Microbiological procedures Cultures were performed manually up to 1999; in 2000, the automatic process was implemented. Both of them were in accordance with standardized procedures previously described.¹¹ *S. aureus* was identified by routine procedures, including catalase and coagulase tests. Antimicrobial resistance was examined by the disc-diffusion method according to the Clinical and Laboratory Standards Institute.¹¹ In order to test for resistance to methicillin, a 1 µg oxacillin disc was applied to Mueller-Hinton agar containing 5% sodium chloride and incubated at 35 °C.¹² Additionally, only fluids from which *S. aureus* was the only isolated pathogen were included.

IV. Data collection and analysis

For each case of CA-SA infection, the following medical information was retrieved: demographics (age, gender); diagnosis; infection sites; length of hospitalization, nutritional evaluation, underlying illnesses, treatment; patients' outcomes (stay at a pediatric intensive care unit [ICU], sequela and death). Additional information about healthcare-associated risk factors, as proposed by the CDC in 2010,¹⁰ at the time of *S. aureus* infection, and sequela was collected by a phone call to the patient's families between October 2017 and June 2018, after receiving oral informed consent. Nutritional evaluation was performed by using the software Anthro; malnutrition and severe malnutrition were defined as Z-score for weight-for-age.¹³ Infections were classified as SSTIs, such as abscess, cellulitis, or impetigo, and deep-seated (or invasive) infection which included bacteremia, meningitis, osteomyelitis, pneumonia, septic arthritis, endocarditis or another illness in which *S. aureus* was isolated from normally sterile body fluids. If a patient had both SSTIs and deep-seated infection, the infection was defined as deep-seated.¹⁴

V. Results

Ninety cases of CA-SA were detected; 59 (66%) patients were male and the age was two years (5.4 months–6.2 years). The majority (87%) of the patients were hospitalized. Chronic underlying illnesses were detected in 27 (30%) cases: skin (44.4%), heart (25.9%) respiratory tract (11.1%), and central nervous system (3.7%). Additionally, sickle cell disease, AIDS, prematurity, and trauma were diagnosed (3.7% each). Twelve (13.3%) cases presented malnutrition, out of which two (16.7%) were severely malnourished. Overall, 34 (37.8%) patients had SSTIs (abscess [44.1%], pyodermitis [41.2%], cellulitis [5.9%], conjunctivitis [2.9%], tonsillitis [2.9%], sinusitis [2.9%]) and 56 (62.2%) patients had deep infection (pneumonia [26.8%], arthritis [17.9%], pyodermitis [14.3%], abscess [14.3%], osteomyelitis [8.9%], adenitis [5.4%], sepsis [5.4%], endocarditis [3.6%], cellulitis [1.8%], urinary tract infection [1.8%]). *S. aureus* was recovered from skin lesion (47.1%), skin abscess (41.2%), ocular secretion and nasopharyngeal or oropharyngeal swab (5.9% each) in patients with SSTIs and from blood (71.4%), abscess (10.7%), pleural effusion (5.4%), synovial fluid (5.4%), urine, pericardial effusion, fistula secretion and intra-abdominal lymph node (1.8% each) in patients with deep-seated infections.

Among the 78 hospitalized cases, two (2.6%) died and the length of hospitalization for the others was 14 (7–22), range 1–53. All were discharged after improvement. Among the 12 outpatients studied, one (8.3%) was hospitalized for seven days and discharged; all of them also improved. Four (5.1%) patients were transferred to the ICU and their mean stay (days) there was 3 to 5 days, r The mean interval (days) between

hospitalization and admission to the ICU was 2.5 (1.3), range (1–4). Complications were detected in 17 (18.9%) cases including pleural effusion (41.2%), osteomyelitis (23.5%), sepsis (17.6%), respiratory insufficiency (11.8%), arthritis, cellulitis, fistula, pericarditis, septic shock (5.9% each). Three patients presented more than one complication. None had sequelae and one patient with arthritis was not followed-up after being discharged.

Approximately 93% of the cases had received systemic antibiotics. Initially, 59 (65.5%) patients were treated with oxacillin or cefalotin, to whom aminoglycosides ($n = 20$), ceftriaxone ($n = 2$), aqueous penicillin G ($n = 1$) were also given. Twenty-five cases (28%) used other antibiotic regimens: other penicillins (e.g. aqueous penicillin G, benzathine penicillin or amoxicillin) [13.3%], aminoglycosides [5.6%], trimethoprim-sulfamethoxazole (TMP-SMX) [5.6%], ceftriaxone, vancomycin and a combination of ceftriaxone and aminoglycoside [1.1% each]. Twenty-three (27.4%) children had their first antimicrobial regimen changed to: vancomycin (43.6%) or oxacillin (34.8%), erythromycin (8.7%), TMP-SMX, ceftriaxone and clindamycin (4.3% each). Only one patient had the antibiotic regimen changed for the second time; in this case oxacillin was switched to vancomycin. Six (6.7%) MRSA strains were detected according to the aforementioned microbiologic criteria. shows the comparison between the patients with MRSA or MSSA infection. Four patients did not use vancomycin as a therapeutic option, even though MRSA was isolated from their blood. The clinical features of these four cases were studied very closed which showed that not all four bacteremic patients infected with MRSA who improved despite not receiving vancomycin. It is important to state that in spite of the recognized virulent nature of MRSA bacteremia, not all bacteremic patients experience complications.

VI. Discussion

In the present study, we did not observe higher morbidity or mortality rates among patients with CA-MRSA infection when they were compared with patients who had CA-MSSA infection. In Korea, MRSA was not found to be significantly associated with higher mortality among adults.¹⁵ However, other studies have described the association between CA-MRSA strains and worse outcomes. A prior report documented the presence of CA-MRSA isolates causing necrotizing pneumonia and severe sepsis.¹⁶ Another investigation demonstrated that CA-MRSA osteomyelitis had a longer duration of hospitalization compared with osteomyelitis caused by CA-MSSA strains in children.¹⁷ Furthermore, it is important to emphasize that CA-MSSA infections are also found to be prevalent among life-threatening staphylococcal infections. This statement is consistent with some published data suggesting that CA-MSSA isolates are more likely than CA-MRSA isolates to be associated with invasive infections.⁸ Nevertheless, a recent analysis showed severe clinical course in both CA-MSSA and CA-MRSA pneumonia. Days of oxygen requirement and intubations were similar between MRSA and MSSA infected children.⁹ It is increasingly recognized that Panton-Valentine leukocidin-positive *S. aureus* is associated with highly aggressive disease, irrespective of antimicrobial resistance.¹⁸

Interestingly, we found four bacteremic patients infected with MRSA who improved despite not receiving vancomycin. It is important to state that in spite of the recognized virulent nature of MRSA bacteremia, not all bacteremic patients experience complications.¹⁹ A risk-scoring system was created to estimate the likelihood of developing complications among patients with *S. aureus* bacteremia.²⁰ Persistent fever at 72 h, positive result of follow-up blood culture at 48–96 h, skin findings of acute systemic infection and community-acquired infection are the individual risk factors included in the score. Except for the *S. aureus* community origin, all other factors were not present among those four bacteremic cases summarized in [Table 2](#). It is useful to classify CA-SA infections as MRSA and MSSA, but this is not necessarily predictive of *S. aureus* virulence.²¹

In this context, one can suspect that several of our MRSA strains were not really resistant to methicillin. However, the disc-diffusion method as outlined by the Clinical and Laboratory Standards Institute (CLSI) was used to detect antimicrobial resistance and methicillin resistance was confirmed by the ability of the isolates to grow on Mueller-Hinton agar supplemented with 5% sodium chloride and 1 µg oxacillin, incubated at 35 °C.¹² The CLSI defines the disc-diffusion test with oxacillin as a reliable method to detect MRSA. Other techniques are also available, such as the cefoxitin disc screen test and the latex agglutination test for PBP2a. When used correctly, all three methods usually can detect MRSA strains accurately.^{22, 23}

In our analysis, MRSA was isolated from 6 (6.7%) of 90 eligible CA-SA cases. Data reported in other studies showed higher frequency (37%) of CA-MRSA strains.²⁴ The use of healthcare-associated risk factors in the inclusion criteria in studies of CA-MRSA epidemiology may explain these disparate results. A previous meta-analysis including different CA-MRSA publications documented that the prevalence of MRSA isolates among people without risk factors (genuine CA-MRSA) remains low, which is consistent

with our finding.²⁵ So, it must be emphasized that in some studies found in the literature the majority of those MRSA isolates were not really CA strains.²⁶ In the present report, we were able to contact patients' families with CA-MRSA to verify any healthcare risk factor that might have been missed in medical records. Thus, we can assure the genuine community origin of isolates enrolled in this investigation according to the updated 2010 CDC definition.¹⁰

SSTIs are by far the most common clinical manifestations of CA-SA infections in children and adults.^{27, 28} However, this finding has not been demonstrated in our analysis. SSTIs were responsible for 34 (37.8%) cases of CA-SA infections. The great majority of our patients have experienced invasive infections (62.2%). It is important to note that this investigation was conducted in a tertiary care center and children admitted to our institution might have presented the worse spectrum of disease, which required hospitalization.

The limitations of this study must be emphasized. Firstly, the retrospective design had intrinsic limitations, including incomplete medical charts. This was overcome by telephone contact. Secondly, the number of patients with CA-MRSA infection was small. This finding may have been influenced by the strict criteria used for the classification of CA-SA infection¹⁰ with the purpose of detecting genuine CA-SA infection. Moreover, it is a finding by itself. Thirdly, during the analysis, we did not address additional bacterial characteristics, including clonal types and virulence factors of the strains. This further investigation could add to the understanding of the distinct clinical course and therapeutic response of *S. aureus* strains, especially in invasive infections.⁴ Fourthly, recall bias may have occurred because the phone call was performed between October 2010 and July 2011 and the patients had *S. aureus* isolated between 1995 and 2004. But as the phone call searched for sequelae and sequelae are permanent, it is not probable that recall bias have occurred in regard to sequelae. Concerning healthcare-associated risk factors (any of the following conditions during the year before infection: hospitalization, admission to a nursing home, skilled nursing facility, or hospice; dialysis; or surgery; the patient must be without permanent indwelling catheters or medical devices that pass through the skin into the body) that were also searched for in the previous year to *S. aureus* isolation, they are not usually easy to be forgotten. Therefore, recall bias is unlikely.

In conclusion, this study attempted to describe the characteristics of CA-SA infections among children in a tertiary care center. We found no relevant differences on baseline characteristics or on the outcome of patients infected with CA-MRSA or CA-MSSA strains. In addition, the evidence presented herein supports the occurrence of genuine CA-MRSA in our region. Although it is clinically still significant to classify CA-SA as MSSA and MRSA, the clinicians should be aware of the broad epidemiology of *S. aureus* infections.²⁹ Both CA-MRSA and CA-MSSA strains may result in life-threatening disease or lethal events.

References

- 1.M.J. Rybak, K.L. LaPlante, Community-associated methicillin-resistant *Staphylococcus aureus*: a review. *Pharmacotherapy*, 25 (2005), pp. 74-85
- 2.C.A. Sattler, E.O. Mason Jr., S.L. Kaplan. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. *Pediatr Infect Dis J*, 21 (2002), pp. 910-916
- 3.R.M. Mera, J.A. Suaya, H. Amrine-Madsen, *et al.* Increasing role of *Staphylococcus aureus* and community-acquired methicillin-resistant *Staphylococcus aureus* infections in the United States: a 10-year trend of replacement and expansion. *Microb Drug Resist*, 17 (2011), pp. 321-328
- 4.K. Mongkolrattanothai, S. Boyle, M.D. Kahana, R.S. Daum. Severe *Staphylococcus aureus* infections caused by clonally related community-acquired methicillin-susceptible and methicillin-resistant isolates. *Clin Infect Dis*, 37 (2003), pp. 1050-1058.
5. Morb Mortal Wkly Rep, 48 (1999), pp. 707-710. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*: Minnesota and North Dakota, 1997-1999. Centers for Disease Control and Prevention
- 6.C.M. Nascimento-Carvalho, T.G. Lyra, N.N. Alves, R.M. Caldas, M.G. Barberino. Resistance to methicillin and other antimicrobials among community-acquired and nosocomial *Staphylococcus*

aureus strains in a pediatric teaching hospital in Salvador, Northeast Brazil. *Microb Drug Resist*, 14 (2008), pp. 129-131.

7.S.E. Cosgrove, G. Sakoulas, E.N. Perencevich, M.J. Schwaber, A.W. Karchmer, Y. Carmeli. Comparison of mortality associated with methicillin-resistant and methicillin susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis*, 36 (2003), pp. 53-59.

8.S.L. Kaplan, K.G. Hulten, B.E. Gonzalez, *et al.* Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. *Clin Infect Dis*, 40 (2005), pp. 1785-1791

VII. 9.K.A. Len, L. Bergert, S. Patel, M. Melish, C. Kimata, G. Erdem. Community-acquired *Staphylococcus aureus* pneumonia among hospitalized children in Hawaii. *Pediatr Pulmonol*, 45 (2010), pp. 898-905.

10.CDC. Diagnosis & Testing of MRSA|MRSA Infections [CDC web site]

11.C. Nascimento-Carvalho, L.S. Freitas-Souza, O.A. Moreno-Carvalho, *et al.*

Invasive pneumococcal strains isolated from children and adolescents in Salvador. *J Pediatr (RioJ)*, 79 (2000), pp. 209-214.

12.Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing approved standard M100-S17. (2007) Wayne, PA, USA

13.M. de Onis, A.W. Onyango, E. Borghi, C. Garza, H. Yang, WHO Multicentre Growth Reference Study Group Comparison of the World Health Organization (WHO) child growth standards and the National Center for Health Statistics/WHO international growth reference: implications for child health programmes. *Public Health Nutr*, 9 (2006), pp. 942-947

14.D.M. Sievert, M.L. Wilson, M.J. Wilkins, B.W. Gillespie, M.L. Boulton. Public health surveillance for methicillin-resistant *Staphylococcus aureus*: comparison of methods for classifying health-care and community-associated infections. *Am J Public Health*, 100 (2010), pp. 1777-1783

15.C.I. Kang, J.H. Song, D.R. Chung, *et al.* Clinical impact of methicillin resistance on outcome of patients with *Staphylococcus aureus* infection: a stratified analysis according to underlying diseases and sites of infection in a large prospective cohort. *J Infect*, 61 (2010), pp. 299-306

16.U. Seybold, E.V. Kourbatova, J.G. Johnson, *et al.* Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections *Clin Infect Dis*, 42 (2006), pp. 647-656.

17.G. Martinez-Aguilar, A. Avalo, Mishaan, K. Hulten, W. Hammerman, E.O. Mason Jr., S.L. Kaplan. Community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* musculoskeletal infections in children. *Pediatr Infect Dis J*, 23 (2004), pp. 701-706

18. Thomas, A. Pugalenthi, M. Chilvers,. Pleuropulmonary complications of PVL-positive *Staphylococcus aureus* infection in children. *Acta Paediatr*, 98 (2009), pp. 1372-1375.

19. G.R. Corey. *Staphylococcus aureus* bloodstream infections: definitions and treatment. *Clin Infect Dis*, 48 (2009), pp. S254-S259

20.V.G. Fowler Jr., M.K. Olsen, G.R. Corey, *et al.* Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*, 163 (2003), pp. 2066-2072.

21.E.H. Ibrahim, G. Sherman, S. Ward, V.J. Fraser, M.H. Kollef. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*, 118 (2000), pp. 146-155.

22.J.H. Jorgensen. Mechanisms of methicillin resistance in *Staphylococcus aureus* and methods for laboratory detection. *Infect Control Hosp Epidemiol*, 12 (1991), pp. 14-19.

23.S.S. Taiwo. Methicillin resistance in *Staphylococcus aureus*: a review of the molecular epidemiology, clinical significance and laboratory detection methods. *West Afr J Med*, 28 (2009), pp. 281-290

24.K. Mongkolrattanothai, J.C. Aldag, P. Mankin, B.M. Gray.Epidemiology of community-onset *Staphylococcus aureus* infections in pediatric patients: an experience at a Children's Hospital in central Illinois. BMC Infect Dis, 9 (2009), pp. 1-7

25.C.D. Salgado, B.M. Farr, D.P. Calfee. Community-acquired methicillin resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors.Clin Infect Dis, 36 (2003), pp. 131-139

26.D.V. Folden, J.A. Machayya, A.E. Sahnoun, *et al.*

Estimating the proportion of community-associated methicillin-resistant *Staphylococcus aureus*: two definitions used in the USA yield dramatically different estimates.J Hosp Infect, 60 (2005), pp. 329-332.

27.L.G. Miller, S.L. Kaplan. *Staphylococcus aureus*: a community pathogen.Infect Dis Clin North Am, 23 (2009), pp. 35-52

28.D.Wu, Q. Wang, Y. Yang, *et al.*Epidemiology and molecular characteristics of community-associated methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* from skin/soft tissue infections in a children's hospital in Beijing, China.Diag Microb Infect Dis,67(2010), pp. 1-8.

29.H.F. Chambers.The changing epidemiology of *Staphylococcus aureus*. Emerg Infect Dis, 7 (2001), pp. 178-182

