



Original Research Article

Methicillin resistant Staphylococcus aureus infections in children: A prospective study

T Lineesh¹, Krishnan C^{1*}, Gireeshan VK.¹, Sasidharanpillai Sabitha¹,
Suresh Baboo V K², Ramesh Menon³

¹Dept. of Pediatrics, Government Medical College, Kozhikode, Kerala, India

²Dept. of Microbiology, Government Medical College, Kozhikode, Kerala, India

³Dept. of Pediatrics, All India Institute of Medical Sciences, New Delhi, India



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ABSTRACT

Introduction : Community acquired MRSA (CA MRSA) can cause invasive diseases posing a challenge to treating physicians. The knowledge about the disease load, clinical pattern, risk factors, outcome and susceptibility pattern in a given geo demographic context contribute crucially to the treatment outcome of MRSA infections in children.

Aim: To study the profile, clinical pattern, factors affecting the immediate outcome and antimicrobial susceptibility of MRSA infections in children

Materials and Methods: A prospective observational study was conducted in children between 2 months and 12 years admitted with MRSA infections, from January 2016 to December 2017 in the Institute of Maternal and Child Health, Government Medical College Kozhikode, Kerala state, India.

Results: Out of 431 children evaluated 83(19.3%) had MRSA infections with 44(53%) CA MRSA and 39(47%) hospital associated MRSA (HA MRSA). Twenty one (53.8%) of HA MRSA infections were hospital onset MRSA (HAHO MRSA) and 18(46.2%) community onset MRSA (HACO MRSA). There were 37 infants, 16 toddlers, 12 preschool children, 18 school children, 48 males and 35 females in the study population. Blood (50.6%), pus (33.7%), and body fluids (15.7%) were the sites of isolation. Skin and soft tissue infections (SSTI)(30.10%), pneumonia (28.90%), empyema (9.64%), meningitis (7.23%), septicaemia (12.05%), bone and joint infections (9.64%), peritonitis (2.41%) and septic shock (18.1%) were the clinical presentation. Mortality occurred in 9.9% and paediatric intensive care requirement in 45.8% patients. Anaemia and thrombocytopenia were identified as the risk factors for PICU admissions (corrected OR; 95% C I, 3.38; 1.02–11.18 and 8.35; 1.35–45.03 respectively). Thrombocytopenia was associated with mortality (corrected OR 43.74, 95% C I 3.86–495.9). Susceptibility to clindamycin, co-trimoxazole, amikacin and rifampicin were 79.5%, 73.5%, 68.7% and 90.4% respectively.

Conclusion: MRSA constituted a significant proportion of bacterial infections in children, the majority being community onset. Pneumonia and empyema predominate over SSTI. Thrombocytopenia was associated with mortality and PICU admission. Clindamycin, co-trimoxazole and amikacin can be utilised in the treatment of less severe MRSA infections

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1. Introduction

Methicillin resistant Staphylococcus aureus (MRSA) was first reported from the United Kingdom in 1961.¹ Initially it was considered as a nosocomial pathogen. Later in

* Corresponding author.

E-mail address: drkrishnanc@gmail.com (Krishnan C).

1980, community associated MRSA (CA MRSA) infection was reported in the United States.² Since then, prevalence has increased worldwide. In an Indian study by Joshi et al, MRSA constituted 42% and 40% of *Staphylococcus* infections during two consecutive years.³

The epidemiological characteristics of MRSA infections in children reported from developed countries are bacteraemia, musculoskeletal infections, skin and soft tissue infections (SSTI), pneumonia, central nervous system infections and endocarditis with a 78% of MRSA infections being community onset.⁴ In a study from South India, Kandasamy et al showed that MRSA was responsible for 44% of SSTI, 66% of empyema, 30% of bacteraemia and 13% of septic shock. In the above study, 80% of MRSA infections were community acquired (CA MRSA) whereas another Indian study reported a 54% incidence of CA MRSA.^{5,6}

Compared to the hospital associated MRSA (HA MRSA), CA MRSA is reported as more virulent,⁷ placing themselves capable of causing highly invasive, rapidly progressive and life-threatening diseases. These factors along with the increasing incidence of CA MRSA infections in children pose a challenge to the clinicians during the selections of empirical antimicrobial agents in suspected invasive infections. So knowledge about the disease load, clinical pattern, risk factors, outcome and antimicrobial susceptibility in a given geo demographic context can contribute crucially to the treatment outcome of MRSA infections in children. There is insufficient data on MRSA infections in children in this part of the country and the present study aims to analyse the profile, clinical pattern, factors affecting the immediate outcome and antimicrobial susceptibility of MRSA infections in children.

2. Materials and Methods

This prospective observational study was undertaken from January 2016 to December 2017 in the Institute of Maternity and Child Health, Government Medical College Kozhikode, Kerala state, India, which a tertiary hospital is catering for six districts. Institute Ethics Committee clearance was obtained (Reg. No.ECR/395/Inst/KL/2013). (Ref.NO. GMCKKD/RP 2016/IEC/20; dated 28.01.2016). Children aged between two months and 12 years having a documented fever $\geq 38.5^{\circ}\text{C}$ were evaluated for invasive bacterial infections by drawing the sample for blood culture by the standard procedure. They were examined for the symptoms and signs characteristics of systemic infections. Complete blood count, urinalysis, blood urea, creatinine and transaminase estimation were carried out in all the patients. Chest radiography, echocardiography and invasive procedures were performed as indicated. Culture samples from pus, body fluids, urine or bone marrow were collected selectively according to the clinical characteristics. Written informed consent was obtained from the parents. The

procedures followed were in accordance with the standards of institutional ethics committee.

The specimens for culture were subjected to bacteriological study as per the Clinical and Laboratory Standards Institute (CLSI) recommendations in the microbiology department.⁸ *Staphylococcus aureus* was identified using standard microbiological laboratory parameters. MRSA was defined when an isolate demonstrated a minimum inhibitory concentration (MIC) of $>4\ \mu\text{g}$ of oxacillin per mL. The MIC was determined by broth microdilution method using 0.0125 to 128 $\mu\text{g}/\text{ml}$ solution. Antimicrobial susceptibility testing was performed for gentamicin, amikacin, cotrimoxazole, linezolid, clindamycin and rifampicin with the disk diffusion method.⁸ Susceptibility to vancomycin was tested by the agar dilution method according to the CLSI guidelines.⁸ A minimum inhibitory concentration of $\leq 2\ \mu\text{g}/\text{ml}$ was the cut-off for vancomycin susceptibility. Methicillin resistance was tested using a cefoxitin disk on Mueller-Hinton agar by the modified Kirby Bauer disc diffusion method in which $\leq 21\ \text{mm}$ inhibition zone in 30 μg cefoxitin disc was taken as the cut off for resistance. All the discs used in our study were from HiMedia, Mumbai.

Once diagnosed, MRSA infection was treated with vancomycin for three weeks. If prolonged treatment was warranted, as in the case of empyema or bone and joint infections, parenteral or oral linezolid was used as switch over treatment. Each patient was monitored during their hospitalisation. Demographic, clinical, microbiological and laboratory data were documented in a structured proforma.⁹

Cases were defined as HA MRSA, when growth obtained on the Mueller-Hinton agar plate was ≥ 48 hours after hospitalisation or growth obtained < 48 hours of admission with any of the health care associated risk factors like i) a history of hospitalisation, surgery, dialysis, or residence in a long-term healthcare facility within 12 months prior to the culture date, ii) past history of MRSA infection or colonisation or iii) presence of an indwelling intravenous line, catheter, or any other percutaneous medical device at the time the culture was taken.¹⁰ HA MRSA was categorised into hospital onset type (HAHO MRSA) when growth was obtained ≥ 48 hours after hospitalisation, and community onset type (HACO MRSA), when culture was obtained < 48 hours after hospitalisation and had a health care associated risk factor.¹⁰ Patients with growth obtained within 48 hours with no health care risk factor were classified as CA MRSA infections.¹⁰ MRSA pneumonia was defined as patients with clinical and radiologic evidence of pneumonia with isolates of MRSA from blood. Empyema was defined as i) MRSA isolated from pleural fluid or ii) MRSA isolated from blood having loculated effusion identified by radiology and/or histologic evidence of empyema during pleural fluid study. MRSA septicaemia was diagnosed when patients were showing features of

systemic inflammatory response syndrome (SIRS) and MRSA growth from blood.¹¹ Peritonitis was defined as a symptomatic child with ascitic fluid study showing >100 leukocytes/mm³ with $\geq 50\%$ neutrophils and/or positive culture for MRSA from peritoneal fluid. Anaemia was defined as a haemoglobin level below the range for age and sex and leucocytosis when the white blood cell (WBC) count was >2 standard deviation above the mean for age and thrombocytopenia as a platelet count <1,50,000/cu mm. Prolonged hospital stay was defined as hospitalisation ≥ 14 days.

2.1. Statistical analysis

The statistical analysis was performed by using SPSS (<https://www.ibm.com/analytics/spss-statistics-software>) version 18.0. The chi-square test was used for comparing proportions. Univariate analysis was performed to find out the correlations of variables with PICU admission and mortality; further a multivariate model was set up to study the possible risk factors.

3. Results

A total of 431 children suspected with invasive bacterial infections were included in the study, out of which 83(19.3%) were diagnosed as MRSA infections. Blood (42, 50.6%), pus (28, 33.7%) and body fluids (13, 15.7%) were the sites of MRSA isolation. The body fluids were constituted by 6 cerebrospinal fluid, 4 joint fluid, 1 pleural and 2 peritoneal fluid samples. Cerebral palsy, nephrotic syndrome, hematologic malignancies, primary immunodeficiency, congenital cyanotic heart diseases and bronchiectasis were the co-morbidities associated. Among the MRSA infections, 44(53%) were CA MRSA and 39(47%) HA MRSA and 21(53.8%) of the HA MRSA infections were hospital onset type (HAHO MRSA) and 18(46.2%) were community onset type (HACO MRSA). The demographic data and clinical presentations of children with MRSA infections are described in Table 1. The clinical profile, haematological parameters and outcome of children with MRSA infection are shown in Table 2 and the antimicrobial susceptibility profile in Table 3. The analysis of risk factors for PICU admission and mortality in children with MRSA infections is given in Table 4.

4. Discussion

In this study we found that 19.3% of children suspected with severe bacterial infections were having MRSA infection, which was similar to the 24.8% incidence by Kandasamy et al in a South Indian study⁵ which underscores the importance of surveillance of sick children for MRSA infections. CA MRSA infection (44, 53%) was more common than HA MRSA (39, 47%) in our study which is in agreement with other studies^{6,12}, and 18 (46.2%)

Table 1: Demographic data and clinical presentations of children with MRSA infection (n = 83)

Variables	Number (%)
Infants	37 (44.6%)
Toddlers	16 (19.3%)
Preschool children	12 (14.5%)
School aged children	18 (21.7%)
Males	48 (57.8%)
Females	35 (42.2%)
Fever $\geq 38.5^\circ\text{C}$	83 (100%)
Cough & breathlessness	32 (38.6%)
Lethargy	13 (15.7%)
Altered sensorium	21 (25.4%)
Seizure	3 (3.7%)
Pyoderma/painful swelling	25 (30.2%)
Joint swelling	7 (8.5%)
Loose stools	6 (7.3%)
Persistent vomiting	24 (29.0%)

of HA MRSA infections were community onset. This shows that MRSA infections of community onset, which includes CA MRSA as well as community onset HA MRSA, constituted 74.7% of the MRSA infections. Similar findings were reported by previous studies also.^{5,11,12} This implies that clinician needs to consider MRSA as a possible pathogen during the evaluation of a sick child at the time of hospitalisation itself. CA MRSA and HA MRSA were found more in infants in this study similar to the other studies.^{10,12,13}

Intra thoracic infections (38.6%), constituted by pneumonia (29%) and empyema (9.7%) were the commonest MRSA infection in our study. This is in contrast with a previous Indian study in children between 0 and 12 years, which showed SSTI constituting 42% of MRSA infections.⁵ Similar to our findings, Gonzalez et al has reported pulmonary involvement as the commonest manifestation of MRSA infections¹⁴ and Kandasamy et al reported that 66% of empyema was caused by MRSA.⁵ Skin and soft tissue infection (SSTI) was the second most common (30.2%) MRSA infection in our study. A similar Indian study reported SSTI constituting 44% of MRSA infections.¹⁵ In accordance with other studies, SSTI was predominantly (72%) caused by CA MRSA in our study also.^{10,15} A significant proportion (15,18.1%) of children in our study population were having septic shock, which was more (53.4%) in CA MRSA compared to HA MRSA. Kandasamy et al showed a 13% incidence of septic shock and Menif et al was showing a 28.6% incidence in a study on CA MRSA infections in children.^{5,13}

Comorbidities were observed more in HA MRSA than CA MRSA (p value 0.01) in our study. Similar findings were reported earlier also.¹⁶ The increased mean hospital stay, PICU admission, requirement for ventilator support and mortality observed in HA MRSA patients compared to

Table 2: Clinical profile, haematological parameters and outcome of children with MRSA infection

Variables	Total(n=83)	CA MRSA(n=44)	^a HA MRSA(n=39)	^{**} p value
Comorbid conditions†	42(50.7%)	16(38.09%)	26(61.9%)	0.006
Septic shock	15(18.1%)	8(53.33%)	7(46.66%)	0.978
SSTI ⁺	25(30.2%)	18(72%)	7(28%)	0.038
Pneumonia	24(29.0%)	14(58.33%)	10(41.66%)	0.692
Empyema	8(9.7%)	2(25%)	6(75%)	0.095
Meningitis	6(7.3%)	2(33.33%)	4(66.66%)	0.316
Peritonitis	2(2.5%)	0(0%)	2(100%)	0.128
Bone and joint infections*	8(9.7%)	3(37.5%)	5(62.5%)	0.355
Septicemia	10(12.1%)	5(50%)	5(50%)	0.839
PICU care	38(45.8%)	18(47.37%)	20(52.63%)	0.344
Ventilator care	17(20.5%)	8(47.06%)	9(52.94%)	0.581
Prolonged hospital stay	48(57.8%)	21(43.75%)	27(56.25%)	0.048
Mortality	9(9.9%)	3(33.33%)	6(66.66%)	0.210
Anaemia	60(72.3%)	31(51.66%)	29(48.33%)	0.692
Neutrophilia	66(79.6%)	34(51.51%)	32(48.48%)	0.590
Thrombocytopenia	16 (19.3%)	6(37.5%)	10(62.5%)	0.166

Community Associated MRSA ^aHospital Associated MRSA ⁺Skin and Soft Tissue Infection *Septic Arthritis & Osteomyelitis ^{**} p value < 0.05 is taken as significant

Table 3: Antibiotic susceptibility pattern of MRSA (n = 83)

Antibiotics	Total(n=83)	CA MRSA(n=44)	^a HA MRSA (n=39)	P value
Vancomycin	83(100%)	44(100%)	39(100%)	NA*
Linezolid	83(100%)	44 (100%)	39(100%)	NA*
Gentamicin	26(33.3%)	19(73.07%)	7(26.92%)	0.01
Amikacin	57(68.7%)	31(54.38%)	26(45.61%)	0.71
Co-trimoxazole	61(73.5%)	33(54.09%)	28(45.9%)	0.75
Clindamycin	66(79.5%)	37(56.06%)	29(43.94%)	0.25
Rifampicin	75(90.4%)	37(84.1%)	38(97.5%)	0.04

Community Associated MRSA, ^aHospital Associated MRSA *NA - Not applicable

Table 4: Factors associated with PICU admissions and mortality in children with MRSA infections (n=83)

Variables	Number (%)	Odds Ratio	Corrected OR	(95% CI)	p value
Risk Factors for PICU admission					
CA MRSA(n=44)	18(41)	1.6	0.88	0.31 – 2.53	0.80
^a HA MRSA(n=39)	20(51)	2.2	0.39	0.88 - 5.10	0.30
Comorbidities(n=42)	23(55)	2.2	1.60	0.56 - 4.59	0.40
Anemia(n=60)	33(55)	4.5	3.38	1.02 - 11.18	0.04
Thrombocytopenia(n=16)	14(88)	12.6	8.35	1.55 – 45.03	0.02
Neutrophilia(n=66)	27(41)	0.4	0.43	0.11 – 1.72	0.24
Risk Factors for mortality					
CA MRSA(n=44)	3(7)	0.4	0.50	0.08 – 3.23	0.47
^a HA MRSA(n=39)	6(15)	2.5	0.11	0.56 – 10.70	0.11
Comorbidities(n=9)	6(67)	2.2	1.7	0.27 – 9.98	0.61
Thrombocytopenia(n=9)	7(78)	25.3	43.74	3.86 – 495.9	0.02
Anemia (n=9)	7(78)	1.4	0.20	0.02 – 2.54	0.30
Neutrophilia (n=9)	6(67)	0.5	0.59	0.16– 9.63	0.96

Community Associated MRSA, ^aHospital Associated MRSA

CA MRSA in our study seems contributed by the increased comorbidities associated with HA MRSA infections.

Six children in the study population were having meningitis due to MRSA, out of which two were CA MRSA and in all the patients, isolates were obtained from CSF. MRSA meningitis in previously healthy children has been reported sporadically.^{5,17}

We studied the risk factors for PICU admission and mortality in children with MRSA infections and found that anaemia and thrombocytopenia were correlating with PICU admission (OR, corrected OR; 95% C I: p value 4.5, 3.38; 1.02 – 11.18; 0.04 and 12.6, 8.35; 1.35 – 45.03; 0.02 respectively) whereas thrombocytopenia showed a strong correlation with mortality (OR 25.3, corrected OR 43.74, 95% C I 3.86 – 495.9 and p value 0.02)

There was no resistance documented against vancomycin and linezolid in our study, as shown in other Indian studies.^{3,5,18} Susceptibility to clindamycin (79.5%), co-trimoxazole (73.5%), amikacin (68.7%) and rifampicin (90.4%) were high, similar to the observations reported in other studies.^{5,12,18} These antimicrobials can be used for the empiric treatment of suspected MRSA infections which are less severe, so that vancomycin and linezolid can be safeguarded against the development of bacterial resistance. There was no significant difference in the susceptibility pattern between CA MRSA and HA MRSA, except for gentamicin. Susceptibility to gentamicin by CA MRSA was 73.07% compared to the 26.92% by HA MRSA. Similar findings were documented earlier also.¹⁵ The following conclusions were made from the present study. i) A significant proportion of invasive bacterial infections in children is caused by MRSA, majority being community onset type, ii) epidemiology of MRSA infections in children shows a change with predominance of pneumonia and empyema over SSTI, iii) clinician should consider MRSA as a potential etiologic agent during the management of septic shock and bacterial meningitis, iv) anaemia and thrombocytopenia are associated with adverse outcomes like PICU admission and/or mortality and v) clindamycin, co-trimoxazole and amikacin need to be utilised in the treatment of less severe MRSA infections. Limitations of the study were i) molecular characterization of the isolates not performed due to the lack of facilities and ii) the risk factors of MRSA infections not studied.

5. Conflicts of Interests

No conflicts of interests were disclosed.

6. Source of Funding

None.

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Sasidharanpillai Sabitha, Assistant Professor  <https://orcid.org/0000-0002-0391-3759>

Author biography

Suresh Baboo V K, Additional Professor

T Lineesh, Senior Resident

Ramesh Menon, Associate Professor  <https://orcid.org/0000-0002-1156-590X>

Krishnan C, Additional Professor  <https://orcid.org/0000-0001-6913-6692>

Gireeshan VK., Additional Professor

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