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Original Research Article

Antibiotic resistance pattern of *Staphylococcus aureus* infections in children

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ABSTRACT

Background: Methicillin resistant *Staphylococcus aureus* (MRSA) is endemic in India and is a dangerous pathogen for hospital acquired infections. Analysing antibiotic susceptibility pattern of Staphylococcus helps us to overcome the therapeutic difficulties created by the rising anti-microbial resistant bacteria and guide us in choosing appropriate antibiotics. Hence, this study was conducted.
Methods: Children with confirmed *S. aureus* infection between the age group of 0-12 years were classified into MSSA and MRSA subgroups. Isolates were identified as *S. aureus* using standard microbiological methodologies at diagnostic bacteriology laboratory, in the Microbiology department. Basic demographic variables and antibiotic resistance patterns were compared between MRSA and MSSA subgroups.
Results: Majority of *S. aureus* were isolated from pus followed by blood culture. Prevalence of community acquired MRSA in present study (80%, with 95% CI from 68.56% to 91.44%) was significantly higher when compared to another studies (p value=0.004). Resistance to gentamicin and ciprofloxacin among the MRSA isolates was more than that in methicillin sensitive *S. aureus* (MSSA) (P<0.001).
Conclusions: It is prudent to include MRSA coverage in empirical antibiotic regimens in settings where a significant proportion of patients hospitalized for *S. aureus* infection have MRSA.

Keywords: Antibiotic resistance, MRSA, *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is the most virulent among all staphylococcal species. It has demonstrated its versatility by remaining a major cause of morbidity and mortality despite the availability of numerous effective anti-staphylococcal drugs.[1] *Staphylococcus aureus* causes skin and soft-tissue infection, pneumonia, osteomyelitis, septic arthritis, bacteremia and other invasive diseases in adults and children.[2] The emergence of methicillin-resistant *S. aureus* (MRSA) has complicated the treatment of such infections.[3] For many years, cases of MRSA infection were confined to hospitalized patients.[4] However, the recent emergence of community-associated MRSA (CA-MRSA) infections has expanded the realm of MRSA infections to include *S. aureus* infections with a fundamentally different epidemiology than that of hospital-associated MRSA (HA-MRSA) infections.[5] CA-MRSA infections often occur in individuals without a history of health care exposure and most commonly manifest as skin and soft-tissue infections.[6] *Staphylococcus aureus* was naturally susceptible to virtually every antibiotic that has ever been developed. Resistance is often acquired by horizontal transfer of genes from outside sources. Chromosomal mutation and antibiotic selection are also other important methods of resistance.[7] This exquisite susceptibility of *S. aureus* led to Alexander Fleming's discovery of penicillin, ushering

in the "antibiotic era." Penicillin was truly a miracle drug. Uniformly fatal infections were cured with the administration of this antibiotic. First wave began in the mid-1940s as the proportion of infections caused by penicillin-resistant *S. aureus* rose in hospitals. These strains produced a plasmid encoded penicillinase that hydrolyzes the beta-lactam ring of penicillin essential for its antimicrobial activity.[7] Introduction of methicillin marked the onset of the second wave of resistance in 1961. Methicillin-resistant *Staphylococcus aureus* (MRSA), popularly known as a type of superbug, has been a serious challenge for animal and human health. S. aureus has developed methicillin resistance mainly by expression of β-lactamase and PBP2a, which is regulated by the blaZ-blaI-blaR1 and mecA-mecI-mecRI systems. The evolution of the staphylococcal cassette chromosome mec determines the epidemiological risk of MRSA.[8] Descendants of the archaic MRSA clone and other highly successful MRSA lineage/s emerged constituting the third wave of antibiotic resistance in 1980. The MRSA invasion of the community constitutes the fourth and latest wave of antibiotic resistance in 1990.[9]

METHODS

This descriptive study titled 'antibiotic resistance pattern of *Staphylococcus aureus* infections in children' was done in the Department of Pediatrics in collaboration with the Department of Microbiology from August 2016 to July 2018 after obtaining ethical clearance from the Institute Ethics Committee (IEC).

Inclusion criteria

- A total of 104 children in the age group of 0 to 12 years who underwent treatment for confirmed *Staphylococcus aureus* infection were included in the study.

MRSA strains were subcategorized as health care associated (HA-MRSA) and community acquired (CA-MRSA). A suspected staphylococcal infection was diagnosed as CA-MRSA in the outpatient setting or by a culture growing MRSA within 72 hours of hospital admission, obtained from a patient with no medical history of MRSA infection or colonization; no medical history in the past year of 1) hospitalization 2) admission to a nursing home 3) surgery; and, no permanent indwelling catheters or medical devices that pass through the skin. All other MRSA infections were considered as hospital acquired (HA-MRSA).[10] Isolates were identified as *S. aureus* using standard microbiological methodologies at diagnostic bacteriology laboratory, in the Microbiology Department. For detection of Methicillin resistance, Oxacillin screen agar was used as culture medium, which is Mueller Hinton Agar supplemented with 6µg/ml of Oxacillin Sodium and 4% NaCl as per CLSI (Clinical and Laboratory Standards Institute) recommendations. A 0.5 Mc Farland suspension of the strain to be tested was prepared and it was inoculated using a 1µl loop to make a spot on the surface of the agar. If more than one colony of the strain grew on Oxacillin screen agar after 24 hour incubation at 35°C, it was considered Methicillin resistant. The plate was read in transmitted light. Control strains (MSSA and MRSA) were also inoculated on the plate.

Statistical analysis

Data was entered into Epi-Info version 2.3. Univariate analysis was performed to compare the demographic variables, site of infection, and medical history between the MRSA and MSSA cases. Fisher's exact test or χ^2 tests where appropriate were used to compare categorical variables. Unpaired Student t test was used for continuous data. All tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

RESULTS

Children ≤12 years with culture proven *Staphylococcus aureus* infection were included in the study. They were sub-classified into MRSA and MSSA subgroups.

Table 1: Frequency of Staphylococcus species infection.

Variables	N (%)
MRSA	46 (44)
Hospital-acquired	9 (9)
Community-acquired	37 (35)
MSSA	52 (50)
Coagulase negative *Staphylococcus aureus* (CONS)	6 (6)
Total	104 (100)

In MRSA subgroup, 80% (37) of *S. aureus* culture isolates were community-acquired and remaining 20% (9) were hospital-acquired.

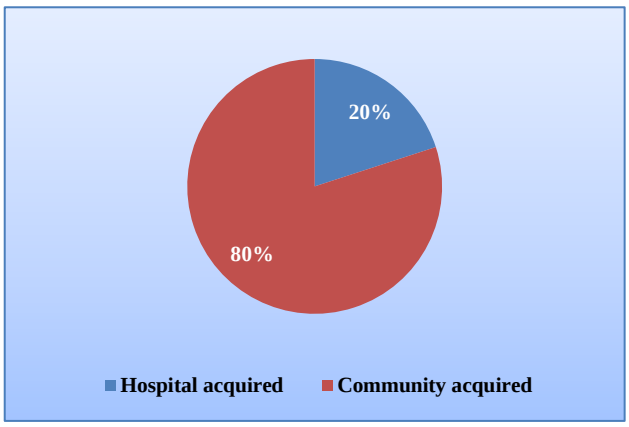

Figure 1: Source of MRSA infection.

It was observed that the prevalence of community-acquired MRSA in present study (80%, with 95% CI from 68.56% to 91.44%) was significantly higher when

compared to another study where prevalence of MRSA was 60% (p value=0.004).

Table 2: Age distribution of MRSA and MSSA.

Age group	MRSA N (%)	MSSA N (%)	p-value
0-1 month	11 (24)	9 (17)	0.418
>1 month-5 years	30 (65)	32 (62)	
>5-12 years	5 (11)	11 (21)	
Total	46 (100)	52 (100)	

Median age of *S. aureus* infection was 10 months. In MRSA group, 1month to 5 years age group children constituted 65% and in MSSA group they constituted 62%.

Table 3: Gender distribution.

Gender	MRSA N (%)	MSSA N (%)	p-value
Male	28 (61)	30 (58)	0.749
Female	18 (39)	22 (42)	
Total	46(100)	52(100)	

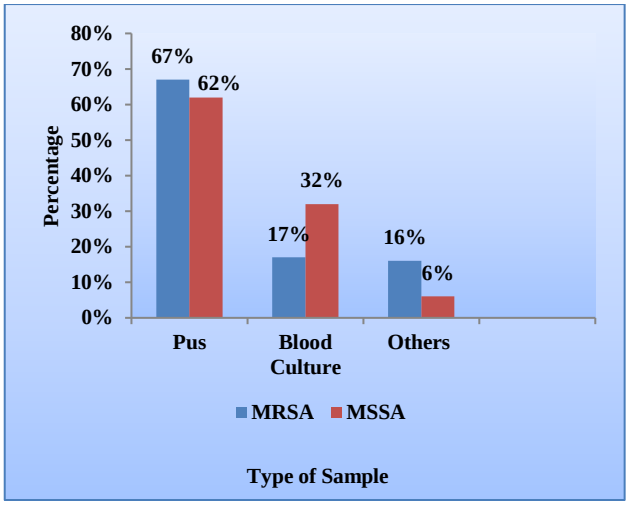

Figure 2: Type of samples.

In both MRSA and MSSA subgroup, males were more affected than females. Among the 46 children in MRSA subgroup, 61% (28) were males and 58% (30) were males in MSSA subgroup of 52 patients.

Table 4: Antibiotic susceptibility of *Staphylococcus aureus*.

Antibiotic	Strain-MRSA n=46, MSSA n=52	Sensitive N (%)	Resistant N (%)	p-value
Gentamicin	MRSA	21 (46)	25 (54)	<0.001
	MSSA	44 (85)	8 (15)	
Ciprofloxacin	MRSA	14 (30)	32 (70)	<0.001
	MSSA	40 (77)	12 (23)	
Erythromycin	MRSA	25 (54)	21 (46)	0.129
	MSSA	36 (69)	16 (31)	
Clindamycin	MRSA	29 (63)	17 (37)	0.393
	MSSA	37 (71)	15 (29)	
Tetracycline	MRSA	37 (80)	9 (20)	0.520
	MSSA	39 (75)	13 (25)	
Vancomycin	MRSA	46 (100)	0 (0)	NA
	MSSA	52 (100)	0 (0)	

Table 5: Comparison of antimicrobial resistance of CA MRSA and HA MRSA.

Antibiotic	MRSA sub-group (N=46)	Sensitive N (%)	Resistant N (%)	p-value
Gentamicin	CA	17 (46)	20 (54)	0.999
	HA	4 (44)	5 (56)	
Ciprofloxacin	CA	13 (35)	24 (65)	0.318
	HA	1 (11)	8 (89)	
Erythromycin	CA	20 (54)	17 (46)	0.999
	HA	5 (56)	4 (44)	
Clindamycin	CA	25 (68)	12 (32)	0.365
	HA	4 (44)	5 (56)	
Tetracycline	CA	31 (84)	6 (16)	0.470
	HA	6 (67)	3 (33)	
Vancomycin	CA	37 (100)	0 (0)	NA
	HA	9 (100)	0 (0)	

Majority of *S. aureus* were isolated from pus (67% in MRSA and 62% in MSSA) followed by blood culture (32% in MSSA and 17% in MRSA). However, the differences were not statistically significant (p=0.105).

Antibiotic susceptibility testing data for gentamicin, ciprofloxacin, erythromycin, clindamycin, pencillin, tetracyclin and vancomycin were compared. There was no resistance documented against vancomycin. Resistance to gentamicin and ciprofloxacin among the MRSA isolates was more than that in methicillin - sensitive *S. aureus* (MSSA) (P<0.001). However, for other antibiotics the differences were statistically not significant.

All isolates in both CA-MRSA and HA-MRSA were sensitive to vancomycin. Ciprofloxacin resistance was higher (89%) in HA-MRSA when compared to 65% in CA-MRSA. However, the difference was statistically not significant.

Table 6: Outcome of *Staphylococcus aureus* infection.

	MRSA N (%)	MSSA N (%)	p-value
Recovery	43 (93)	50 (96)	0.883
Death	3 (7)	2 (4)	
Total	46(100)	52(100)	

Average length of hospitalization in MRSA and MSSA subgroup was 20.4±7.14 days and 15.6±6.725 days respectively. Three children (7%) in MRSA subgroup and two in MSSA (4%) subgroup had expired and the differences were not statistically significant.

DISCUSSION

Age and gender distributions of children with MRSA infections were comparable to those with MSSA infections. Children in the age group of 1 month to 5 years formed the highest proportion in both MRSA and MSSA subgroups (65% vs 62%). Similarly, Alvarez et al in 2012 in a study from India, had reported that proportion of MRSA in children<5 years were 73.7%.[11] A study by Mallick et al from central India in 2010 found that the prevalence of MRSA and MSSA was 51.8% and 48.2% respectively.[12] Skin and soft tissue infections (SSTI) were the predominant infection in both MRSA (42%) and MSSA (46%) subgroups, followed by blood stream infection. Similarly, a study by INSAR (Indian network for surveillance of antimicrobial resistance) group noted that majority of *S. aureus* isolates (40%) were obtained from the patients with skin and soft tissue infections followed by those suffering from blood stream infections (BSI) and respiratory infections.[13] In this study, data on antibiotic susceptibility testing for gentamicin, ciprofloxacin, erythromycin, clindamycin, penicillin, tetracycline, oxacillin and vancomycin were compiled. There was no resistance documented against vancomycin. Susceptibility of methicillin resistant *S. aureus to* gentamicin was 46%, ciprofloxacin was 30%, erythromycin was 54%, clindamycin was 63%, tetracycline was 80%, and vancomycin was 100%. Resistance to gentamicin and ciprofloxacin amongst the MRSA isolates was significantly more than that in methicillin sensitive *S. aureus* (MSSA) (*P*<0.001). Similar study by INSAR group reported the susceptibility of methicillin resistant *S. aureus* to gentamicin was 41.7%, ciprofloxacin was 20.7%, erythromycin was 29.2%, clindamycin was 53.4%, vancomycin and linezolid was 100%.[13] In this study, MRSA isolates were more multi-drug resistant (resistant to 3 antibiotics in 20% children and to 4 antibiotics in 9% children) when compared with the MSSA isolates. Vancomycin continues to remain the most sensitive drug for MRSA infections.

Antimicrobial susceptibility pattern of community-acquired vs hospital-acquired methicillin resistant *S. aureus* was 35% vs. 11% for ciprofloxacin, 68% vs 44% for clindamycin and 84% vs 67% for tetracycline. Hence in this study, despite the similarities that occurred between strains of CA and HA-MRSA in relation to antibiotic susceptibility, strains of HA-MRSA were more resistant to certain types of antimicrobials (ciprofloxacin, clindamycin and tetracycline), as compared to CA-MRSA strains. Similar to present study, Jung et al in Korea (2006) reported that CA-MRSA isolates were more susceptible for clindamycin (46% vs 12%; P=0.01), ciprofloxacin (43% vs 11%; P=0.01), and gentamicin (43% vs 6%; P=0.01) than were the HA-MRSA isolates.[14] A study conducted by Abdallah et al in Kuwait in 2013 showed that CA-MRSA has different characteristics from those of HA-MRSA similar to this study.[15] These differences can be attributed due to high virulence nature of HA-MRSA when compared to CA-MRSA as evidenced by chambers et al in 2005.[16]

Five children in this study expired as a result of *S. aureus* infection; 3(7%) of these children were infected with MRSA, and 2(4%) were infected with MSSA infection. Mortality was comparable in both the subgroups. Similar to this study, Miller et al in 2008 reported that there was no compelling evidence that MRSA in general was more virulent than MSSA.[17] Average length of hospitalization in MRSA subgroup was 4.8days more when compared to MSSA subgroup, though this was statistically not significant.

CONCLUSION

From an infection-control perspective, this data suggests that 80% of *S. aureus* (p value=0.004) from the community being MRSA, contact isolation should be given to all the patients with suspected *S. aureus* infection and should be continued until pathogens are identified. Thus, from a clinical standpoint, it is prudent to include MRSA coverage in empirical antibiotic regimens in settings where a significant proportion of patients hospitalized for *S. aureus* infection have MRSA.

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REFERENCES

1. Miller LG, Diep BA. Clinical practice: colonization, fomites, and virulence: rethinking the pathogenesis of community-associated methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008;46:752-60.
2. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339:520-32.
3. Cosgrove SE, Fowler VG Jr. Management of methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008;46Suppl 5:S386-93.
4. Deurenberg RH, Vink C, Kalenic S, Friedrich AW, Bruggeman CA, Stobberingh EE. The molecular evolution of methicillin-resistant Staphylococcus aureus.Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2007;13:222-35.
5. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008;46Suppl 5:S344-9.
6. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant Staphylococcus aureus. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008;46Suppl 5:S368-77.
7. Chambers HF, Deleo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. Nat Rev Microbiol. 2009;7:629-41.
8. Hao H, Dai M, Wang Y, Huang L, Yuan Z. Key genetic elements and regulation systems in methicillin-resistant Staphylococcus aureus. Future Microbiol. 2012;7:1315-29.
9. Udo EE, Pearman JW, Grubb WB. Genetic analysis of community isolates of methicillin-resistant Staphylococcus aureus in Western Australia. J Hosp Infect. 1993;25:97-108.
10. Clinical and Laboratory Standards Institute. 2013. Performance standards for Antimicrobial susceptibility testing; twenty third Informational supplement. M100-S23.
11. Alvarez-Uria G, Reddy R. Prevalence and Antibiotic Susceptibility of Community-Associated Methicillin-Resistant Staphylococcus aureus in a Rural Area of India: Is MRSA Replacing Methicillin-Susceptible Staphylococcus aureus in the Community? ISRN Dermatol. 2012;2012:248951.
12. Mallick SK, Basak S. MRSA--too many hurdles to overcome: a study from Central India. Trop Doct. 2010;40:108-10.
13. Ray P, Manchanda V, Bajaj J, Chitnis DS, Gautam V, Goswami P, et al. Methicillin resistant Staphylococcus aureus (MRSA) in India: prevalence and susceptibility pattern. Indian J Med Res. 2013;137(2):363-9.
14. Jung SI, Shin DH, Park KH, Shin JH. Antimicrobial susceptibility and clonal relatedness between community- and hospital-acquired methicillin-resistant Staphylococcus aureus from blood cultures. J Microbiol Seoul Korea. 2006;44:336-43.
15. Abdallah SA, Al-Asfoor KK, Salama MF, Al-Awadi BM. Prospective analysis methicillin-resistant Staphylococcus aureus and its risk factors. J Glob Infect Dis. 2013;5:19-25.
16. Chambers HF. Community-associated MRSA--resistance and virulence converge. N Engl J Med. 2005;352:1485-7.
17. Miller LG, Quan C, Shay A, Mostafaie K, Bharadwa K, Tan N, et al. A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible Staphylococcus aureus skin infection. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007;44:483-92.

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