ORIGINAL RESEARCH PAPER
Volume-8 | Issue-9 | September - 2019 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PREVALENCE OF MRSA BACTERAEMIA AND THE ASSOCIATED RESISTANCE PATTERN IN CHILDREN AT A TERTIARY CARE PAEDIATRIC HOSPITAL

Microbiology

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ABSTRACT

Introduction: Severe metastatic or complicated infections are associated with Staphylococcus aureus (S. aureus) bacteraemia. Multidrug resistant (MDR) strains of S. aureus, particularly Methicillin Resistant S. aureus (MRSA) cause hard to treat infections, thus making the first line drugs ineffective.
Methodology: Retrospective data was collected from all MRSA bacteraemia events in children (0- 16 years) from Jan 2019 to June 2019 at Bai Jerbai Wadia Hospital, a tertiary care pediatric hospital in Mumbai.
Results: The overall prevalence of methicillin resistance during the study period was 79.55 %. The overall prevalence of methicillin resistance during the study period was 79.55 %. No isolates were found to be resistant to Vancomycin, Teicoplanin, Linezolid or Tigecycline.
Conclusion: The study showed alarmingly high level of bacteraemia, due to MRSA in the pediatric population. Multiple-non-β-lactam agents have also become ineffective against the newer strains isolated.

KEYWORDS

MRSA, bacteraemia

INTRODUCTION:

Staphylococcus aureus is recognized as an important cause of infection in children. It can cause simple superficial skin and soft tissue infections to life threatening pneumonia, bloodstream, bone and joint, respiratory, gastrointestinal and genital tract infections [1,2].

The pre-antibiotic era, was defined by poor results in patients with S. aureus infections [1]. However, the discovery of penicillin to treat infections caused by *S. aureus* significantly changed the prognosis of patients with severe infections [1-3]. Nevertheless, due to antibiotic abuse, *S. aureus* strains resistant to penicillin begun to surface [3]. Penicillin resistance was due to the production of *penicillinase* by the bacteria, an enzyme which could inactivate the antibiotic, rendering it inactive against the bacteria.

To counter these penicillinase producing *S. aureus* Methicillin was introduced in clinical practice [4]. But by 1961, resistance to Methicillin was also reported. Methicillin resistance in *S. aureus* emerged due to the addition of the *mec*A gene on a mobile genomic island designated staphylococcal chromosome cassette mec (SCC*mec*) by methicillin-susceptible *S. aureus*. The presence of *mec*A gene enabled the bacterium to synthesize a novel penicillin-binding protein known as penicillin-binding protein 2a, which decreased its binding affinity for penicillin and cephalosporins. Thus, MRSA strains became resistant to all β-lactam antibiotics, making them an important cause of healthcare-associated infections globally. [5,6]

Consequently, to tackle the MRSA strains newer antibiotics such as streptomycin, tetracycline, erythromycin, and chloramphenicol were developed [7]. However, as they were put into clinical use, resistance to them too appeared, thereby laying a red carpet for the emergence of strains that were resistant to multiple antibiotics. Today Vancomycin remains last man standing, for treating MRSA infections. [8,9].

The growing frequency of MRSA bacteraemia is an urgent medical problem due to its poor associated outcome in children. However, to my knowledge population-based data on these infections in children are limited.

METHODOLOGY:

A six months retrospective study (January 2019 to June 2019) was conducted in the Department of Microbiology at Bai Jerbai Wadia Hospital, a tertiary care hospital in Mumbai. Blood isolates growing S. aureus, that were resistant to oxacillin (MIC ≥4 µg/mL) or cefoxitin (≥8 µg/mL) were included in this study. Clinical samples were processed at our microbiology laboratory according to standard operating procedures. Blood was collected in BACTEC Peds Plus/ F blood culture bottle (BD Diagnostics) for pathogen and Vitek 2 system (bioMérieux) was used for identification and antibiotic susceptibility testing.

RESULTS:

A total of 3696 blood cultures were studied from children (0 – 16 years) from January 2019 to June 2019 and 175 strains of S. aureus were isolated. The prevalence of MRSA was 79.55 %.

Table 1: Phenotypes detected

PHENOTYPES DETECTED	NUMBER	%
mecA gene	70	79.55
MLSB Inducible	35	39.77
Partial resistance to Quinolones	74	84.09
ICR	39	44.32
Resistance to Kanamycin, Tobramycin, Gentamicin	38	43.18

The above table shows the various phenotypes associated with the MRSA isolates in the study. Inducible MACROLIDE – LINCOSAMIDE – STRETOGRAMIN B (MLSB) (39.77%), Inducible Clindamycin Resistance (44.32%), resistance to Kanamycin, Tobramycin, Gentamicin (43.18%) and Partial resistance to Quinolones (84.09%) were prevalent.

Table 2: Antibiotic Susceptibility Pattern

ANTIBIOTICS	SENSITIVE	%
AZITHROMYCIN	23	26.14
CIPROFLOXACIN	06	6.82
CLARITHROMYCIN	23	26.14
CLINDAMYCIN	41	46.59
DAPTOMYCIN	81	92.05
ERYTHROMYCIN	26	29.55
GENTAMICIN	76	86.36
LEVOFLOXACIN	06	6.82
LINEZOLID	88	100.00
PENICILLIN	01	1.14
TEICOPLANIN	88	100.00
OFLOXACIN	06	6.82
RIFAMPIN	85	96.59
COTRIMOXAZOLE	65	73.86
TETRACYCLINE	81	92.05
TIGECYCLINE	88	100.00
VANCOMYCIN	88	100.00

Susceptibility to Penicillin (1.14%), Ciprofloxacin, Levofloxacin and Ofloxacin (6.82% each) was less than 10%. Less than 30% of isolates are susceptible to Azithromycin, Clarithromycin (26.14% each) and Erythromycin (29.55%). Only 46.59% of the isolates were sensitive to Clindamycin. No isolate were found to be resistant to Vancomycin, Teicoplanin, Linezolid or Tigecycline.

DISCUSSION:

S aureus bacteraemia (SAB) continues to be a significant disease affecting the paediatric population and above that MRSA infection in children if of greater concern.

MRSA is now endemic in India. The prevalence of MRSA also varies in between regions and even hospitals in the same region. In western parts of India, [10] the incidence of MRSA is reported up to 25 per cent, while it is 50 per cent in South India [11]. The overall MRSA prevalence in our study was 79.55% per cent which is worrisome. Age is an important determinant of SAB incidence; with either extremes of life being most affected [12]. Studies have homogenously shown high rates in the first year of life, a low incidence through young adulthood, and a gradual upsurge in cases with advancing age. Our hospital being a tertiary reference centre for paediatric diseases, the cases admitted are all serious infections. This probably explains the high prevalence of MRSA bacteraemia in our study.

All MRSA strains in our study were sensitive to Vancomycin, Linezolid, Teicoplanin and Tigecycline. This is in accordance with other studies [13, 14]. However, vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA and VRSA) strains have also been reported recently from other parts of the country [15, 16]. The high prevalence of MRSA, leads to increase in the use of glycopeptides. Both these factors enforce the emergence of VRSA strains, making the widespread dissemination of these organisms an alarming and realistic possibility.

Tackling MRSA bacteraemia has become a *Catch – 22*. We barely *dodged a bullet* and the association of multidrug resistance with MRSA adds to the problem [17]. The susceptibility to Ciprofloxacin, Levofloxacin, Ofloxacin, Azithromycin, Clarithromycin, Erythromycin and Clindamycin was found to be less than 50 % in this study. Phenotypes like iMSLB, ICR and resistance to Kanamycin, Tobramycin, and Gentamicin were detected in nearly 40% of the isolates. Partial resistance to Quinolones was reported in as high as 80% of the isolates. Vidhani S *et al*. reported marked differences in sensitivity patterns of MRSA and Methicillin sensitive S. aureus (MSSA) isolates [18]. Majumder D *et al*. also agrees with the findings of our study [19].

There are several issues that limit the utility of an antimicrobial agent. Vancomycin has its own limitations like slow bactericidal activity, low tissue penetration, and increasing reports of resistance and failure [20]. Although Daptomycin acts against MRSA bacteraemia, emergence of non-susceptible strains is concerning [21], Evidence suggests Daptomycin resistance in *S. aureus* has occurred in those who have been previously treated with Vancomycin [22].

Given the limitations of currently approved treatments, there is a need to identify alternative agents for the treatment of MRSA bacteraemia.

Alternative antimicrobial agents like Ceftaroline, Linezolid, and Quinupristin/dalfopristin (Q/D) are being evaluated but none have been approved for treatment of MRSA bacteraemia [23]. A multi centric study reported that nearly 70% of patients with MRSA bacteraemia were successfully treated with Ceftaroline, when used as a salvage therapy alone or in combination with another antistaphylococcal antibiotic [24]. Linezolid, a bacteriostatic agent is indicated for use in pneumonia and complicated and uncomplicated skin and skin structure infections caused by *S. aureus*, but a study reported that it was effective as a salvage therapy for MRSA bacteraemia as well [25]. Q/D is indicated for treatment of skin infections caused by MSSA, but is known to have in vitro activity against MRSA. In a study Q/D was used as a salvage therapy in 12 Vancomycin non responsive patients with MRSA infections. 5/12 patients had successful outcomes [26]. Cotrimoxazole has also been suggested as an alternative treatment; but it failed to meet the necessary non inferiority criteria as compared to vancomycin in many a trials of severe MRSA infections, including SAB [27]. Telavancin another drug is currently being evaluated for treatment of *S. aureus* bacteraemia and is in phase 3 trial.

Combination therapy is another angle that needs to be explored. Davis et al. [28] used a combination of vancomycin plus flucloxacillin to treat 60 MRSA bacteraemia patients. Duration of bacteraemia was reported to be decreased by 1 day in comparison to those on mono therapy. A combination of Daptomycin and Ceftaroline has shown to retain their bactericidal effect on isolates with increased MIC to Daptomycin [29].

Further clinical trials are still needed to evaluate benefits of combination therapies against the probable effects on the intestinal flora, development of multidrug-resistant microorganisms, and possibly defying the protocols established by antimicrobial stewardship programs.

CONCLUSION:

A 100% sensitivity of MRSA to vancomycin suggests its prudent use and continuous monitoring of MIC levels so that we may not fall back into pre-antibiotic era. Glycopeptides must be kept reserved for life-threatening infections caused by drug resistant strains of MRSA.

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