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Antimicrobial Susceptibility in Methicillin Resistance Staphylococcus aureus causing Acute Haematogenous Osteomyelitis in Paediatric Age Group

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Abstract

Introduction: Acute haematogenous osteomyelitis (AHO) in the paediatric group is an important condition confronting surgeons. Osteomyelitis by methicillin-resistant Staphylococcus *aureus* is on the rise.

AIM: The study aimed to evaluate the antimicrobial susceptibility among MRSA causing acute haematogenous osteomyelitis.

Material and methods: Using a prospective study design, patients with acute haematogenous osteomyelitis were recruited after obtaining consent from their parents or guardians. All the clinical samples received were processed by the BD Phoenix system (BD Diagnostics, Sparks, MD, USA). The bacterial antimicrobial susceptibility results were interpreted using breakpoints established by the Clinical Laboratory Standards Institute (CLSI).

Results: Of the 120 paediatric patients of AHO, 78 (65%) and 42 (35%) cases were males and females respectively. The majority (42 (35%) of cases were in 9-12 years age group. The site of AHO involvement was femur in 40 (33.3%) and proximal tibia in 21 (17.5%). In 84 (70%) cases the total leucocyte count was > 10000 per microliter. In 80 (67%) and 32 (26.7%) of cases, C-reactive proteins was in the range of 61-100 mg/dl and ESR was > 100mm/H respectively. 87.0% and 69.2% of MRSA strains were resistant to rifampicin and levofloxacin. All the cases of MRSA were sensitive to linezolid and vancomycin; 87% were sensitive to clindamycin.

Conclusions: The majority of MRSA infections were in the 9-12 years age group. Vancomycin, linezolid and clindamycin were effective against MRSA. Rifampicin and erythromycin were the least effective antimicrobials. The study emphasizes the need to regulate antimicrobials dispensing, and discourage the use of over-the-counter sales of antimicrobials.

Keywords: Acute haematogenous osteomyelitis; Antimicrobial Sensitivity; Methicillin Resistance Staphylococcus aureus

Introduction

Osteomyelitis is a painful inflammatory disease of bone, often of bacterial origin that results in the death of bone tissue[1]. Osteomyelitis is characterized by sudden onset of localized symptoms with a history of fever of less than two weeks of duration. The various factors that predispose to osteomyelitis include trauma with coincident bacteraemia, sickle cell anaemia, indwelling vascular catheters, distant foci of infection, compound fractures, grossly contaminated wounds, immunodeficiency and sepsis.

Worldwide, the incidence of acute haematogenous osteomyelitis (AHO) in the paediatric age group ranges from 1 per 1000 to 1 per 20,000[2] with the majority in children under five years. The factors affecting the epidemiology of AHO include the

increased awareness, immunization patterns, and modification of clinical course by antibiotics[3]. Microorganisms can enter bone by the haematogenous route, direct introduction from the contiguous focus of infection or from a penetrating wound. The initial changes in bone after the inoculation of bacteria are alterations in pH and capillary permeability that contribute to regional oedema, cytokine release, tissue breakdown, leukocyte recruitment, and decreased oxygen tension. Increased local pressure cause its extension into the cortex by Haversian and Volkman canals with subsequent spread into the sub-periosteal space and finally to the periosteum and adjacent soft tissue.

In any age group, the most frequent pathogen responsible for osteomyelitis and septic arthritis is staphylococcus *aureus*. It is responsible for up to 70% to 90% of confirmed cases[4]. The worrying trend over the past years is the emergence of methicillin-resistant strains of S. *aureus*. There has been an increase in AHO caused by methicillin-resistant strains of S. *aureus* (MRSA) in paediatric patients that should be considered when choosing an imperial antimicrobial treatment. The incidence of MRSA AHO has increased from 4% to 40%. In the above context, the current study was carried out to evaluate the antimicrobial resistance of MRSA causing AHO in the paediatric age group.

Patients And Methods

This prospective observational study was conducted in the post-graduate departments of orthopaedics in collaboration with the department of microbiology, government medical college Srinagar from November 2018, to October 2020. The study prospectively enrolled 120 children with community acquired AHO. Patients of either sex with suspected community acquired acute haematogenous osteomyelitis, aged < 16 years and in whom pus or altered fluid could be drained were included in the study. Patients with symptom duration of more than two weeks, past history of same site osteomyelitis, recent history of hospitalization or compound fracture of the affected limb and intravenous drug abusers were excluded from the study.

Study Procedure

A detailed history was taken from each patient with special emphasis on the history of trauma, similar episodes in the past, duration of symptoms, previous hospitalization and history of any treatment, especially antibiotics used and their duration. Besides, general and systemic examination, investigations like ESR, quantitative CRP, blood culture and radiographs were conducted.

Under aseptic precautions, needle aspiration was carried out using16G or 18G spinal needle. A bone marrow biopsy needle was used in older children. Aspiration was done at the site of maximum tenderness and sent for culture and sensitivity. The BD Phoenix system (BD Diagnostics, Sparks, MD, USA) was used for bacterial identification and antimicrobial sensitivity. The bacterial antimicrobial susceptibility results were interpreted using breakpoints established by the Clinical Laboratory Standards Institute (CLSI)[5].

Empiric treatment was started in the form of cefazolin or cefuroxime plus amikacin in neonates and cefazolin or cefuroxime in older patients. Incision and drainage of pus were carried out at accessible sites. Patients were monitored clinically and blood counts, CRP and USG were repeated after 48 hours. Inability to improve clinically after 48 hours of mandated surgery. Patients showing clinical improvement and where laboratory measurements normalized were discharged on appropriate antibiotics based on the antibiogram.

Ethics and consent

This study protocol was approved by the institutional review board of Bone and joints hospital vide no 2436 dated 2020. All the parents/guardian of the paediatric patients were explained about the study. The purpose and procedure of the study was explained to each parents/guardian of the paediatric patients' in local language. All the guardian signed the consent paper in the presence of the two independent witnesses.

Statistical Analysis

The data obtained was evaluated using Microsoft Excel 2011and then analysed in Statistical Package for the Social Sciences (SPSS) version 16.1 (Chicago IL). The frequencies and percentages were calculated.

Results

In all, 120 paediatric patients were enrolled; 78 (65%) were males and 42 (35%) were females. The

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majority (42 (35%) of patients were in the age group of 9-12 years followed by 33 (27.5%) in the age group of 5-8 years. The distal femur was involved in 40 (33.3%), proximal tibia in 21 (17.5%) and calcaneum in 5(4.2%) of cases. High-grade fever was observed in 30 (25%) of cases. The total leucocyte count was in the range of 4000-21000 per microliter with 84 (70%) cases having > 10000 per microliter. In 80 (67%) cases C-reactive proteins were in the range of 61-100 mg/dl and in 32 (26.7%) cases ESR was above 100mm/H. The methicillin-resistant Staphylococcus *aureus* was cultured from 78 (65%) samples (Table 1).

Table 1 Demographic, clinical and laboratory profile of paediatric acute haematogenous osteomyelitis cases (n=120).

Characteristic	Number (n)	Percentage (%)
Gender		
Male	78	65.0
Female	42	35.0
Age group (years)		
< 1	4	3.3
1-4	13	10.9
5-8	33	27.5
9-12	42	35.0
13-16	28	23.3
Site of osteomyelitis		
Distal femur	40	33.3
Proximal tibia	21	17.5
Distal tibia	19	15.9
Distal fibula	10	8.3
Proximal femur	7	5.8
Proximal humerus	7	5.8
Calcaneum	5	4.2
Other sites	11	9.2
Fever		
High grade (104.1-106)	30	25.0
Mild & moderate (100.5-104)	90	75.0
Total leucocyte count		
<7000	10	8.3
7001-10000	26	21.7
10001-13000	38	31.6

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13001-16000	23	19.2
>16000	23	19.2
C-Reactive proteins (mg/dl)		
40	1	0.8
41-60	19	15.7
61-80	40	33.5
81-100	40	33.5
>101	20	16.5
ESR (mm/hour)		
≤ 100	88	73.3
>100	32	26.7
Organisms recovered		
MRSA	78	65.0
MSSA	24	20.0
E-coli	1	0.8
No growth	17	14.2

MRSA Methicillin Resistance Staphylococcus *aureus*; MSSA; Methicillin sensitive Staphylococcus *aureus*

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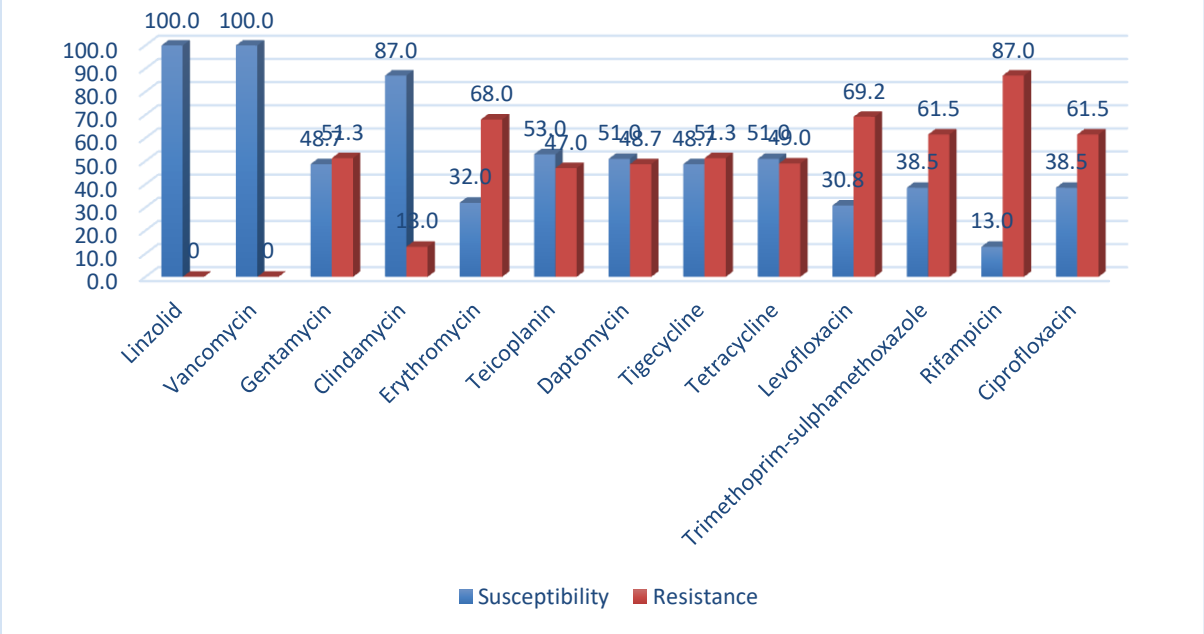

Figure1 Antimicrobial resistance in methicillin resistance staphylococcus aureus.

All cases of MRSA were sensitive to linezolid and vancomycin. MRSA was highly resistant to rifampicin (87.0%) followed by levofloxacin (69.2%).

Discussion

Overall, 120 cases of AHO in the age group 0-16 years were included in the study. The mean age of patients was 8.7 years with most (35%) of the patients in the age group of 9-12 years. Guiterrezk[6] reported 50% of all osteomyelitis patients in under 5 years age group. Furthermore, Trifa M[7] reported majority of cases in the age range of 4 to 8.5 years, however, PopescuB[8] observed a higher incidence in 11-13 years. The observation of AHO in the higher age group in our study can be attributed to maximum skeletal growth and abundant metaphyseal blood flow at this age. The mean age in our study is higher as compared to the earlier studies could be probably due to exclusion of patients who required surgery. A severe infection has been reported in this age group by an earlier study by Martin A et al[9].

In our study, we observed a male predominance with a male to female ratio of 1.86:1. This is consistent with previous studies conducted by Trifa M[7] (M:F ratio =1:0.94) and Bogdan et al [10] (M:F ratio = 2:1). Repeated micro-traumas play an important role in osteomyelitis and male children are more prone to such trauma. This phenomenon might explain the higher occurrences of AHO in males[11]. The role of trauma is also highlighted by the fact that more than one-third of children have a history of recent injury[12].

In the present study, 47 (39.2%) cases presented with the involvement of femur, 39 (33.3%) in tibia and 5 (4.2%) in calcaneum. 33.3% and 17.5% cases presented with distal femur and proximal tibia involvement which is consistent with the literature[13]. The frequent involvement of metaphysical regions is a result of typical arrangement of vascular supply that form the loops around metaphysis. Trueta proposed that this anatomic configuration results in slow, turbulent blood flow favouring circulating bacteria to localise[14].

Of the 120 cases, the total leukocyte count showed a wide variation from 4000 per microliter to 21000 per microliter. Only ten patients had TLC < 7000 per microliter, the majority of patients had TLC of > 10000 per microliter. From this observation, it can be postulated that TLC count is not specific for diagnosing AHO in the paediatric patients. In a study conducted by Popescu B et al[8] maximum patients had TLC count greater than 15000/dl.

ESR and quantitative CRP was elevated in all patients. 107 patients had elevated ESR of greater than 40mg/H. ESR has great predictive value in establishing the diagnosing of AHO. Riise R et al

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(2008)[15] have reported an ESR of > 40mm/H with an elevated CRP as highly diagnostic of AHO. In the present study, all patients had a CRP value of greater than 40mg/dl (normal value<5mg/dl), 20 (16.6%) patients had CRP greater than 100mg/dl. The patients responding well to empirical antibiotic therapy and incision and drainage showed a decrease in CRP. CRP has also been seen as an important prognostic factor and the patients responding well to treatment have shown decreasing CRP levels within 6-8 days. In a study conducted by the HARIK NS and SMELTER Ms[16], it was reported that ESR and CRP were elevated in patients with AHO and were found to be organism-specific, more elevated in MRSA infected cases than MSSA. These reports support our observation of elevated values of ESR and CRP in MRSA compared to MSSA cases.

In the present study, MRSA was 100% sensitive to vancomycin and linezolid and 87% sensitive to clindamycin. Previous studies also reported a similar susceptibility pattern of MRSA towards these antibiotics[17, 18]. Most of the MRSA were resistant to rifampicin, levofloxacin, erythromycin, ciprofloxacin, trimethoprim/sulpha-methoxazole among tested antibiotics. Although MRSA was 100% sensitive to both linezolid and vancomycin, strains resistant to these antibiotics are also reported by some authors [19]. There should be regular monitoring of antimicrobial sensitivity patterns to prevent the rapid emergence of resistance.

Conclusion

In conclusion, the 9-12 years age group had frequent MRSA infections. The distal femur and proximal tibia were commonly involved. MRSA was resistant to frequently used antibiotics, vancomycin, linezolid and clindamycin were effective against MRSA. MRSA infections are a serious challenge in hospital settings and cause major issues in treatment outcome. Antimicrobial dispensing should be strictly regulated, and over-the-counter sales of antimicrobials should be discouraged.

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