

## Microbiological spectrum of osteomyelitis in children and adolescents from rural population of kashmir valley.

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**Cite this paper:** Reyaz Ahmad Dar, Bushra Rashid Sahaf, Talat Masoodi, Azhar Shafi, Adil Hussain Shah(2024) Microbiological spectrum of osteomyelitis in children and adolescents from rural population of Kashmir valley. *Frontiers in Health Informatics*, 13 (3), 9877-9488

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### ABSTRACT

**Introduction:** Osteomyelitis in children can prove detrimental in terms of morbidity if left untreated or undertreated. This study describes the microbiological spectrum of osteomyelitis and the antimicrobial susceptibility of its causative agents in children in a predominant rural population. Further it helps guide the choice of empirical antibiotics for this condition in children and adolescents, so as to reduce chances of osteomyelitis requiring drainage or it getting complicated by the timely institution of the treatment.

**Aims:** The aim of the study is to look into the microbiologic spectrum of osteomyelitis in children and adolescents in rural population of Kashmir, so that the pattern of their susceptibility to antibiotics is also known, thereby helping in the institution of empirical antibiotics.

**METHODS:** This is a retrospective analysis of the children who had been treated for the acute osteomyelitis and whose records were available for the study. This study was carried in the Department of Orthopaedics and Microbiology, SKIMS Medical college Hospital Srinagar which caters to the most rural areas around Srinagar. Records of 102 patients with osteomyelitis who were treated in our hospital from October 2015 to October 2023 contributed to this study. Patients with known immunodeficiency syndromes were excluded.

**RESULTS:** *Staphylococcus aureus* was recovered in almost 80% of the cases of osteomyelitis in both infants and children and most of them were Methicillin Sensitive *Staphylococcus aureus* (MSSA) and thus were sensitive to Cefazolin, Amikacin and Clindamycin. About one third of these cases were Methicillin Resistant *Staphylococcus aureus* (MRSA) accounting for about 26% of the total number of isolates and 33% of the staphylococcus group. This was followed by *Escherichia coli* which accounted for about 4.5% of the total isolates. Distal end of femur and upper end tibia were the most common sites of infection. Boys were more infected than girls with male female ratio of 2.7:1 and the age group of 6-15 comprise 70% of the cases.

**CONCLUSION:** The pathogenesis of haematogenous osteomyelitis in children is a process that is influenced by characteristics of the growing skeleton. Bacteria, principally *Staphylococcus aureus* causes the majority of cases of acute osteomyelitis in children. A single organism is responsible for most of the infections. Most of the patients were infected by MSSA. We suggest that any patient in the said age group with osteomyelitis in our set

*up be put empirically on a combination of Cefazolin and Amikacin till the culture sensitivity report comes, as the combination is synergistic and less likely to cause adverse reactions.*

**KEY WORDS:** *Osteomyelitis, children, haematogenous, Community acquired Methicillin sensitive Staphylococcus aureus (CA-MSSA) and Community acquired Methicillin resistance Staphylococcus aureus (CA-MRSA).*

## INTRODUCTION

Osteomyelitis is strictly defined as any form of inflammation involving bone and/or bone marrow, but it is almost exclusively the result of infection. It is usually bacterial in origin [1]. The provisional diagnosis of bone infection is made on basis of clinical history and examination along with laboratory findings (Total leucocyte count, C reactive protein etc) and radiological evaluation. This is followed by surgical intervention and the diagnosis is confirmed on histopathological evaluation and microbiological identification of pathogen on culture [2]. The culture is followed by finding out the sensitivity of the organism grown to different antibiotics.

Microorganisms can be introduced into bone in three ways: Haematogenous delivery, Direct inoculation (usually traumatic, but also surgical) and Local invasion from a contiguous infection. Acute osteomyelitis in children is usually caused by haematogenous spread. Anatomic characteristics of the growing skeleton affect the site of infection, pathogenesis, and clinical features of the disease in patients of acute haematogenous osteomyelitis. Non haematogenous osteomyelitis is not common in children. Open fracture, puncture wounds, implanted orthopaedic hardware are some of the risk factors for Non-haematogenous osteomyelitis. Staphylococcus aureus is the major cause of acute haematogenous osteomyelitis in an otherwise healthy paediatric population, accounting for 70 – 90% of cases [3, 4, and 5]. Community-acquired (CA) methicillin-resistant S. aureus (MRSA) infections are now common worldwide [6]. Although the spectrum of illnesses caused by CA-MRSA remains confined primarily to skin and soft tissue infections, similar to that of CA-methicillin-susceptible S. aureus (MSSA), however over the past decade, CA-MRSA has been increasingly responsible for invasive infections with considerable morbidity and mortality in children [7,8]. Acute haematogenous osteomyelitis typically arises in the metaphysis of long tubular bones, with approximately two-thirds of all cases involving the femur, tibia or humerus [9, 10]. The pathogenesis of haematogenous osteomyelitis differs with different age groups. In children, hematogenous osteomyelitis begins with bacterial deposition in the metaphysis because of stasis of blood in hair pin like arrangement of blood vessels, deficiency of reticuloendothelial cells at metaphysis, high vascularity at metaphysis and predisposition to trauma. Infection with inflammation develops in the bone marrow from foci in the metaphysis. In the absence of therapy, necrosis of cortical bone and marrow occurs [11].

Histopathological diagnosis is performed by examining the tissue reaction pattern like leucocyte infiltration, osseous changes and soft tissue changes.

To our knowledge, there are no data on the incidence, disease morbidity, and outcomes of Staphylococcus aureus or MRSA invasive disease (including musculoskeletal infections) in the rural population of Kashmir valley.

## MATERIAL AND METHODS

All paediatric patients who had been treated for acute osteomyelitis in the Department of Orthopaedics, SKIMS Medical college Hospital Srinagar, and whose records were available from October 2015 to October 2023, were included in this study. All patients with known immunodeficiency syndromes were excluded. A total of 102 such patients with osteomyelitis were included in the study. As a part of treatment protocol, specimen collections

were meticulously performed to avoid contamination. Antibiotic administration was withheld until specimen's cultures were collected whenever possible, except in those who were very sick at presentation or the site was not accessible easily without causing pain and discomfort to the patients. Specimen collections were accomplished by needle aspiration, wherever an abscesses had formed and were accessible, and bone drilling when pus had not come out into the soft tissues. Of the total samples about 36 patient's specimens were also sent for histopathological analysis. Samples were cultured on Brain Heart Infusion (BHI) broth, Blood agar and chocolate Agar (incubated for 24 hours at 37° C in presence of 5% CO<sub>2</sub>) and MacConkey Agar plates and incubated aerobically at 37°C for 18-24 hrs. The clinical isolates were identified by standard biochemical tests and procedures [12]. Antibiotic susceptibility testing was done on Mueller Hinton agar by Kirby Bauer disc diffusion method. Detection of MRSA was done by Cefoxitin disc diffusion test by using Clinical and Laboratory Standard Institute guidelines: CLSI GP17A3:2012 and M02-A12:2015[13]. Antibiotic discs (HiMedia Laboratories) used were: Ampicillin (10mcg), Amoxicillin/Clavulanic acid (20/10 mcg), Gentamicin (10mcg), Amikacin (30mcg), Ciprofloxacin(5mcg), Cotrimoxazole (1.25mcg/23.75mcg), Tetracycline (30 mcg), Cefoxitin (30mcg), Cefazolin (30mcg), Erythromycin (5mcg), Clindamycin (2mcg), Linezolid (30mcg), Teicoplanin (30mcg), Vancomycin (30mcg). Methicillin sensitive *Staphylococcus aureus* (MSSA) ATCC 25923 was used as antibiotic quality control. This is the Gram-Positive panel of antimicrobials. For the Gram negative bacteria the following antibiotics were tested: Ampicillin (10 mcg), Amoxicillin/Clavulanate 20/10 mcg), Piperacillin-Tazobactam (100/10 mcg), Cefoperazone-salbactam 975/10 mcg), Ceftazidime (30 mcg), Cefepime (30 mcg), Aztreonam (30 mcg), Gentamicin (10 mcg), Amikacin (30 mcg), Tobramycin (10 mcg), ciprofloxacin (10 mcg), Cotrimoxazole (1.25/23.75 mcg), Imipenem (10 mcg), Meropenem (10 mcg), Polymixin B (300 units), Tigecycline (15 mcg).

## RESULTS

From our analysis of results we found that the most common organism involved in osteomyelitis was *Staphylococcus aureus* which was isolated from 72 patients (80%) out of which MRSA was isolated from 24 patients (33%). Other bacterial isolates were *Escherichia coli* (4.5%), *Klebsiella*, *Proteus*, *Pseudomonas*, *Acinetobacter*, *Enterococcus* and Coagulase negative staphylococcus (2.3% each). 12 Samples showed no growth after 48 hours of aerobic incubation, of which osteomyelitis was later confirmed on histopathology in four specimens.

All *Staphylococcus aureus* isolates were 100% sensitive to Linezolid, Teicoplanin and Vancomycin. The percentage sensitivity of the Gram negative and Gram positive organisms to various antimicrobial agents is shown in Table 3 and Table 4 respectively.

Maximum patients belonged to age group 6 to 10 (37%) followed by age group 11 to 15 (33%). Least number of patients were from age group 16 to 18 (7%). Among 102 patients, 74 (73%) patients were male and 28 (27%) were female. Male to female ratio was 2.7:1

Predominant involvement was of the lower limbs, with femur comprising of (35%) of patients, tibia (33%) whereas iliac bone, calcaneus and humerus comprised 6.6% each. Foot and hand bones accounted for 5% of the cases. Other less common sites included vertebrae, clavicle and fore arm bones.

Among the 36-specimen sent for histopathological examination, 8 were from femur, 20 were from tibia, 2 from bones of foot, 4 from humerus and 2 from forearm bones. The samples were obtained by bone drilling. Depending upon the tissue reaction pattern, the osteomyelitis was classified as acute or chronic form. Acute osteomyelitis was noted in 32 cases which on histopathology showed mixed inflammation rich in neutrophils along with necrotic osseous tissue showing absence of osteocytes, ragged margins and basophilia. The four

cases, which included two from humerus and two from forearm bones showed features of chronic inflammation having mononuclear inflammatory infiltrate rich in lymphocytes, histiocytes and plasma cell along with necrotic bone(sequestrum) as well as areas of bone neogenesis (involucrum).

TOTAL NO OF SAMPLES	GROWTH	NO GROWTH
102	90	12

TABLE 1 SHOWING DISTRIBUTION OF GROWTH AND NO GROWTH IN SAMPLES

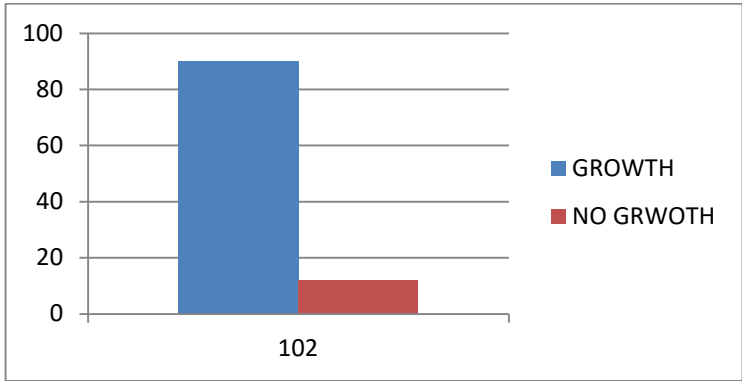


FIGURE 1 SHOWING DISTRIBUTION OF GROWTH AND NO GROWTH IN SAMPLES

S.no	Organism Distribution	Total No
01.	MRSA	24
02.	MSSA	48
03.	ESCHERCHIA COLI	04
04.	KLEBSIELLA	02
05.	PROTEUS	02
06.	PSEUDOMONAS	02
07.	ACINETOBACTER	02
08.	CONS	02

09.	ENTEROCOCCUS	02
10.	CITROBACTER	01
11.	ENTEROBACTER	01

TABLE 2 SHOWING ORGANISM DISTRIBUTION IN CULTURES.

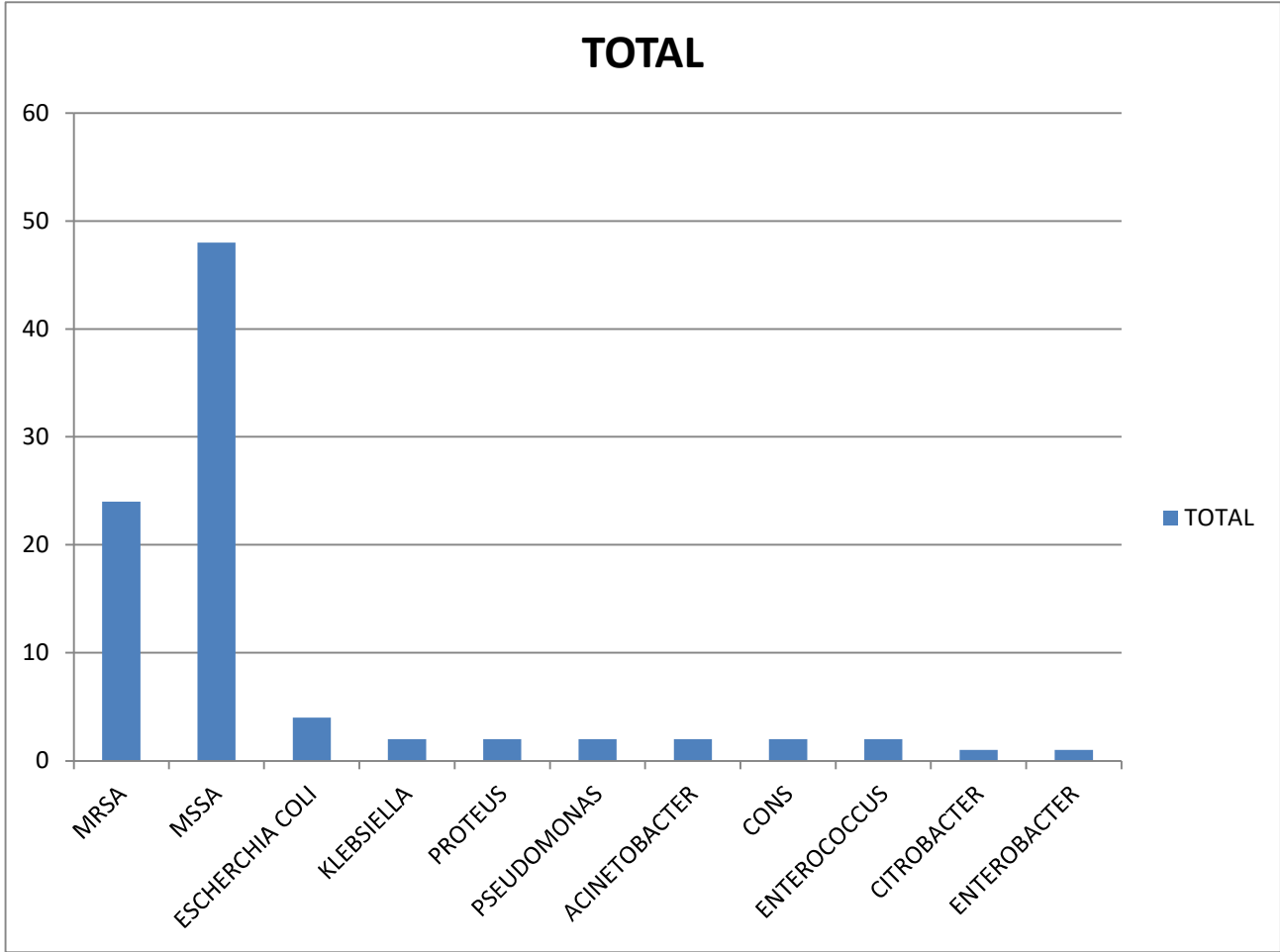


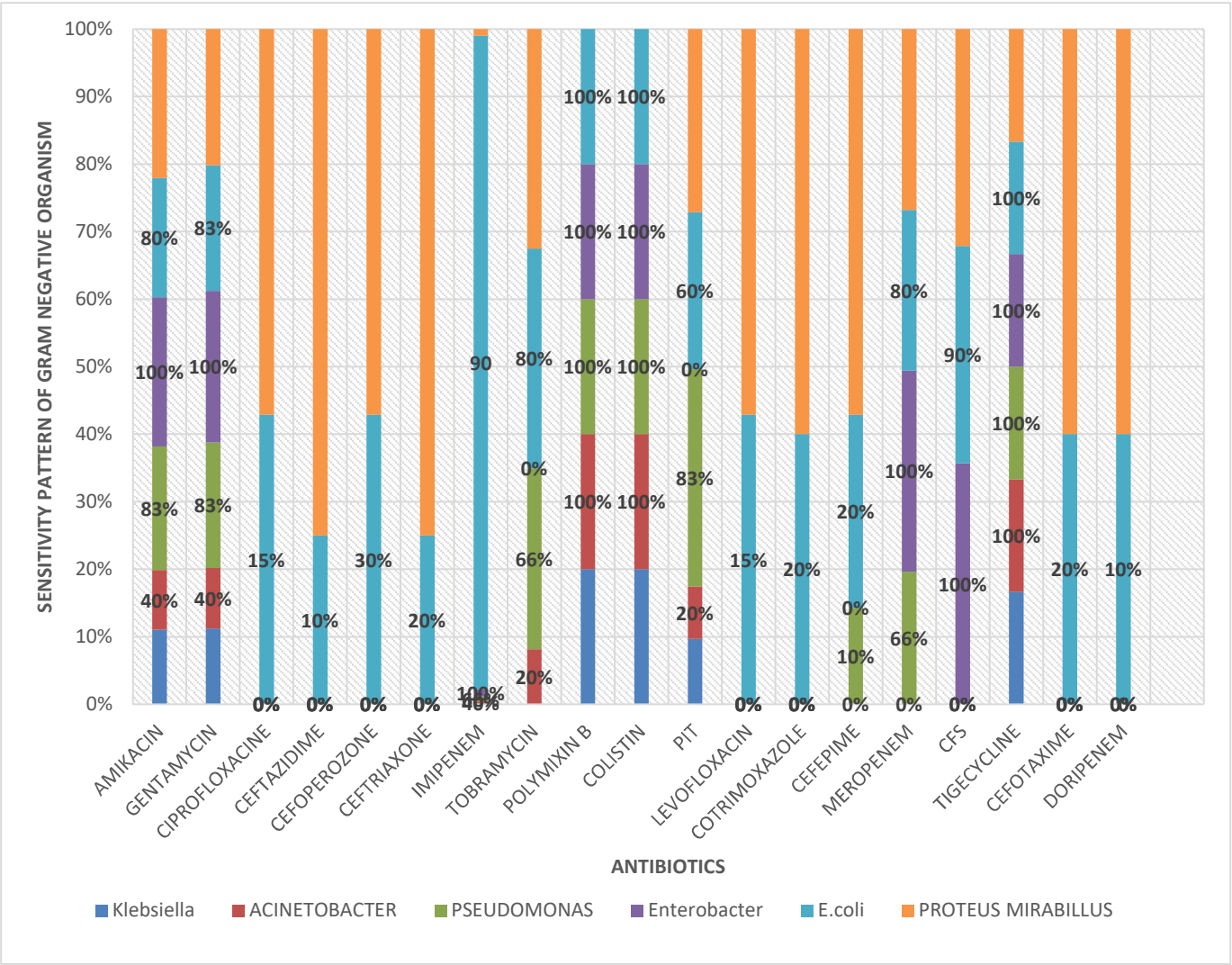
Figure 2: SHOWING ORGANISM DISTRIBUTION IN CULTURES.

S/n o.	Antibiotics: Percentage sensitivity	GRAM NEGATIVE ORGANISMS						
		<i>Klebsiella spp</i>	<i>Acinetobacter spp</i>	<i>Pseudomonas spp</i>	<i>Enterobacter spp</i>	<i>Escherichia coli</i>	<i>proteus</i>	<i>citrobacter</i>
1	Amikacin (AK)	50%	40%	83%	100%	80%	100%	80%
2	Gentamycin(G)	50%	40%	83%	100%	83%	90%	80%
3	Ciprofloxacin (CIP)	0%	0%	0%	0%	15%	20%	50%
4	Ceftazidime (CAZ)	0%	0%	0%	0%	10%	30%	20%
5	Cefoperazone (CPZ)	0%	0%	0%	0%	30%	40%	30%
6	Ceftriaxone (CTR)	0%	0%	0%	0%	20%	60%	50%
7	Imipenem (IMP)	0%	40%	66%	100%	90	90%	50%
8	Tobramycin (TOB)	0%	20%	66%	0%	80%	80%	60%
9	Polymyxin B (PB)	100%	100%	100%	100%	100%	0%	100%
10	Colistin (CL)	100%	100%	100%	100%	100%	0%	100%
11	Piperacillin Tazobactam (PIT)	25%	20%	83%	0%	60%	70%	60%
12	Levofloxacin(LE)	0%	0%	0%	0%	15%	20%	30%
13	Cotrimoxazole (COT)	0%	0%	0%	0%	20%	30%	50%
14	cefepime	0%	0%	10%	0%	20%	40%	30%
15	meropenem	0%	0%	66%	100%	80%	90%	70%
16	Cefoperazone sulbactam	0%	0%	0%	100%	90%	90%	80%

17	Tigecycline	100%	100%	100%	100%	100%	100%	100%
18	Cefotaxim	0%	0%	0%	0%	20%	30%	15%
19	Dorepenem	0%	0%	0%	0	10%	15%	10%

TABLE 3 : SHOWING SUSCEPTIBILITY OF GRAM NEGATIVE ISOLATES TO VARIOUS ANTIMICROBIALS.

FIGURE 3: SHOWING THE PERCENTAGE SENSITIVITY OF THE GRAM NEGATIVE ISOLATES TO VARIOUS ANTIMICROBIAL AGENTS.



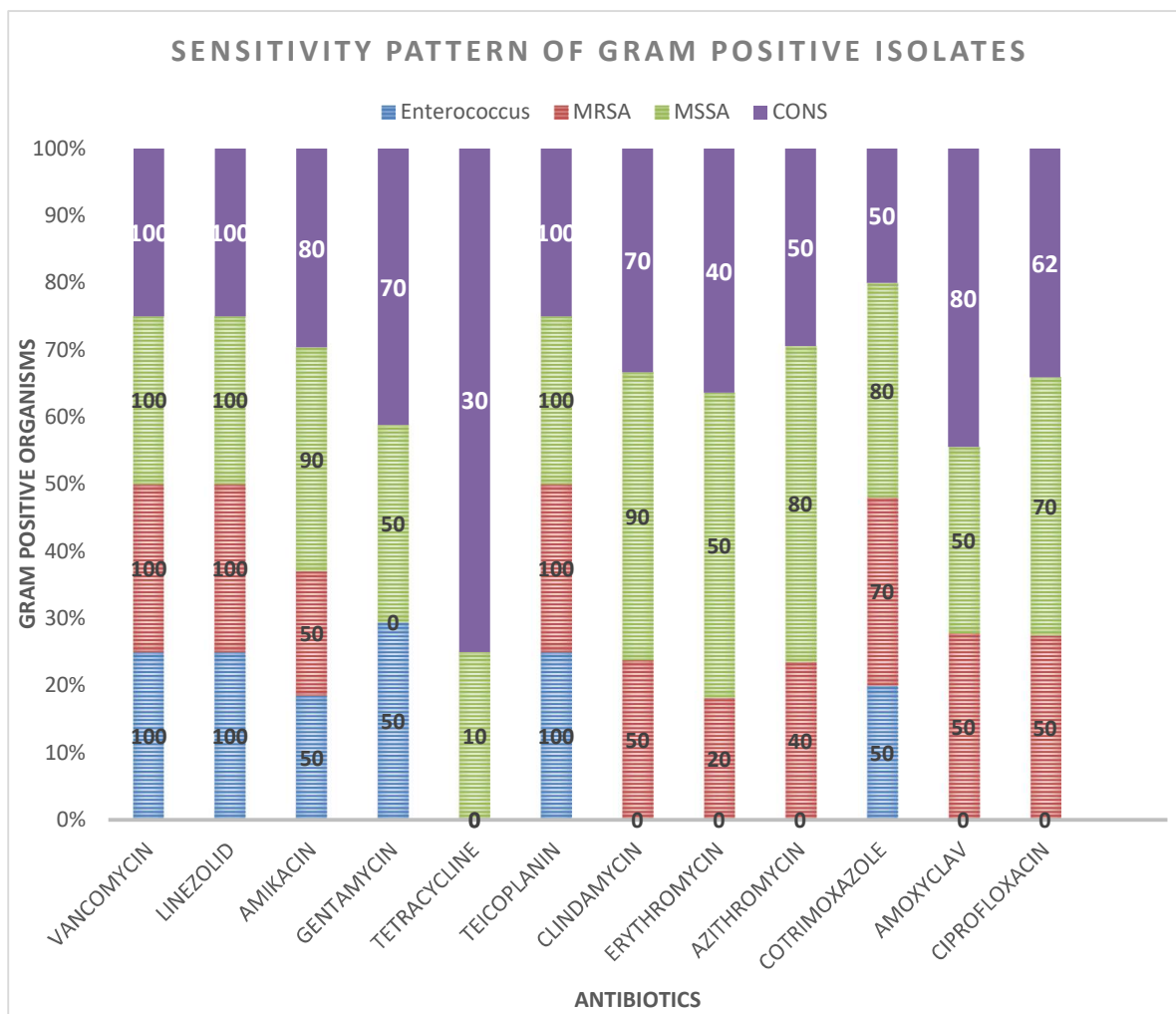


SNo	Antibiotic Susceptibility %ge	GRAM POSITIVE ORGANISMS			
		Enterococcus	MRSA	MSSA	CONS
1	Vancomycin (VA)	100%	100%	100%	100%
2	Linezolid (LZ)	100%	100%	100%	100%
3	Amikacin (AK)	50%	50%	90%	80%
4	Gentamycin (GEN)	50%	0%	50%	70%
5	Tetracycline (TE)	0%	0%	10%	30%
6	Teicoplanin (TEI)	100%	100%	100%	100%
7	Clindamycin	0%	50%	90%	70%
8	Erythromycin	0%	20%	50%	40%
9	Azithromycin	0%	40%	80%	50%
10	Cotrimoxazole	50%	70%	80%	50%
11	Amoxyclav	0%	50%	50%	80%
12	Ciprofloxacin	0%	50%	70%	60%

**TABLE 4: SHOWING SUSCEPTIBILITY PATTERN OF GRAM POSITIVE ISOLATES TO VARIOUS ANTIMICROBIAL AGENTS.**



**FIGURE 4 SHOWING SUSCEPTIBILITY PATTERN OF GRAM-POSITIVE ISOLATES TO VARIOUS ANTIMICROBIAL AGENTS.**



## DISCUSSION

Haematogenous osteomyelitis is an inflammation of bone and bone marrow, usually caused by bacterial infections, but occasionally caused by fungi, viruses or parasites (13). Osteomyelitis may cause growth changes or pathological fractures (14,15). Acute haematogenous osteomyelitis is usually defined as a history of relevant signs or symptoms of less than 14 days, and sub-acute haematogenous osteomyelitis as a history of such signs or symptoms of more than 14 days (16,17). In the current study, the male to female ratio is 2.75:1. Most studies (18,19,20,21) invariably demonstrated a predominance of male gender. Zaoutis et al (22), for example, found that boys were affected in 62% of the cases. In the current study, femur is involved in 35% of the cases and tibia is involved in 33% of the cases. In agreement with other studies in the literature, the most frequently affected sites were the long bones, with the femur in 34% of the cases, the tibia in 28% and the humerus in 14%. According to Weichert et al (23), the femur is affected in 36% of the cases, the tibia in 33%.

The histopathology evaluation was done on 36 specimens, out of which 32 had acute osteomyelitis (88.8%) while 4 had chronic osteomyelitis (11.1%). In a study by Tiemann et al, they found 19% cases of acute

osteomyelitis, 0.09% cases of acute exacerbated chronic osteomyelitis and 71% chronic osteomyelitis [2].

In the current study, 80 % of the cases were infected with *Staphylococcus aureus*. Other studies have also found that *staphylococcus aureus* is the most common isolate in osteomyelitis which was accounting from 50% to 82 % (24,25,26). Our study showed 26% of MRSA among the 72 *staphylococcus aureus* isolates which were lower compared to other studies by Mita et al. (40%) but higher as compared to Senneville et al. (11%) (26,27,28). In our study, Linezolid, Teicoplanin and Vancomycin were showing 100% effectivity against *Staphylococcus aureus*, other studies also revealed the same results (29,30,31,32).

Based on the above findings, current study showed that two third of the staphylococcal isolates were found sensitive to cefazolin and amikacin and majority to Clindamycin, the isolates were sensitive either to all the three antibiotics in most cases or to at least one of them in a few. Hence it is logical to empirically start treatment for osteomyelitis with cefazolin and amikacin till culture report comes and if sensitivity is confirmed to these antibiotics they can be continued for two weeks and after that patients would receive oral clindamycin or would continue with intravenous cefazolin if the child can't swallow the capsules of clindamycin for six to eight weeks (32,33) Both these antibiotics are easily available and are low cost and safe without many serious adverse reactions. In case of MRSA, Linezolid may be given to the patient.

## CONCLUSIONS

Osteomyelitis is a serious infection among children, particularly those in pre-school or school. Community acquired Methicillin sensitive *Staphylococcus aureus* was found to be the most common organism involved and most of them were sensitive to cefazolin, amikacin and clindamycin. Therefore it is reasonable to empirically start treatment for osteomyelitis with cefazolin and amikacin till the culture report comes. Henceforth, even in this era of multi drug resistance, first generation Cephalosporins can still be used for the empirical treatment of osteomyelitis in the rural population of India where drug abuse, indiscriminate use of broad spectrum antibiotics are less compared to the urban areas.

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