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Original Article

Orthopaedics Section

Microbiological Evaluation of Paediatric Chronic Haematogenous Osteomyelitis in a Tertiary Care Hospital in Northern India and its Association with Radiological Appearance: A Retrospective Study

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ABSTRACT

Introduction: Chronic osteomyelitis in the paediatric age group is a frequent complication of improperly treated acute haematogenous osteomyelitis, leading to devastating complications such as pathological fractures and deformities in affected children. There is a growing need to comprehend the disease process and develop improved treatment strategies.

Aim: To evaluate bacterial culture and antibiotic sensitivity patterns in children and adolescents with chronic haematogenous osteomyelitis in North India and to explore associations between radiological patterns and antibiotic sensitivity.

Materials and Methods: The present retrospective study was conducted in the Department of Orthopaedics of tertiary care centre, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, North India, from July 2018 to June 2020. Total 100 children and young adolescents with chronic osteomyelitis who reported to OPD of hospital with pus discharge from an extremity persisting for more than six weeks, along with radiological features indicative of chronic osteomyelitis. Parameters such as site of infection, illness duration, blood parameters, bacteriological culture reports, etc., were examined. Radiological evaluation was performed using the Beit CURE (BC) classification. Data were analysed and represented in the form of frequencies and percentages. The Chi-square test was used to compare proportions, with significance set at p-value <0.05.

Results: The median age of the study population was 13 years, there were 32 (32%) females and 68 (68%) males. The majority of cases (70%) belonged to the B1-B3 group. *Staphylococcus aureus* was responsible for 86 (86%) cases, followed by *Pseudomonas aeruginosa* in 7 (7%) cases. Out of the 86 *Staphylococcus aureus (S. aureus)* isolates, 58 (67.44%) were Methicillin-resistant *Staphylococcus aureus* (MRSA). Multidrug resistance was observed among gram-negative species, as well. *Pseudomonas aeruginosa* showed resistance to fluoroquinolones in 4 (57%) cases, aminoglycosides in 2 (28%) cases, and carbapenem in 1 (14%) case, which is considered highly effective in treating serious infections caused by multidrug resistant Gram-negative species. No significant association was found between drug sensitivity patterns and radiological features in the present study.

Conclusion: *Staphylococcus aureus* remains the most predominant organism isolated from deep tissue cultures. Among *S. aureus* isolates, MRSA was the most frequently identified. Identifying the causative organism may be challenging in some cases. Among cases where the offending microbe was identified, drug resistance was widespread among both Gram-negative and Gram-positive specimens. No significant relationship was found between the radiological appearance of infected bone and the pattern of antibiotic resistance.

Keywords: Aminoglycosides, C-reactive protein, Fluoroquinolones, *Staphylococcus aureus*

INTRODUCTION

Chronic osteomyelitis is an inflammatory bone condition that progresses due to microorganisms, leading to bone destruction and the formation of sequestrum [1,2]. The incidence rate of this condition is 10-14 per 100,000 children annually [3,4]. But significantly higher rates of 76 per 100,000 have been reported in Maori children in New Zealand, and much lower rates of 3 per 100,000 have been reported in Scotland [5,6]. Infection sources can include a contiguous focus of infection (such as infected decubiti), remote penetrating trauma, surgery, or a late complication of acute haematogenous osteomyelitis. Chronic haematogenous osteomyelitis is a consequence of acute osteomyelitis, where inadequate management leads to residual disease that can result in disability. Its treatment requires prolonged care, multiple surgical procedures and frequent hospitalisations [7].

Chronic osteomyelitis can be a consequence of inadequately treated acute osteomyelitis and is characterised by low-grade bone infection [7,8]. This is more prevalent in third-world nations where healthcare resources are insufficient, posing risks to the health and quality of life of patients and their caregivers. Treatment for chronic osteomyelitis is often lengthy, involving multiple surgeries and extended hospital stays [8]. In the paediatric population, chronic osteomyelitis is more common than in adults, and its sequelae affect children more frequently [3]. Treatment typically involves an interdisciplinary approach combining systemic and/or local antibiotics with surgical-orthopaedic procedures. Procedures like sequestrectomy, radical surgical debridement, and plastic reconstructive techniques such as flap coverage, skin grafting, and negative pressure wound therapy are often necessary. The primary goal of chronic osteomyelitis management is to restore function early and eradicate the infection [9].

The most common microorganism causing chronic osteomyelitis is known to be *Staphylococcus aureus*, with a 60-70% frequency rate globally in both developing and developed countries [3-5]. However, due to varied presentations, a more diverse microbiology is observed with chronic haematogenous osteomyelitis. Unfortunately, there is

a lack of comprehensive studies to guide orthopaedic surgeons in treating this complex disease in the paediatric population [10,11]. Therefore, the present study was aimed primarily to evaluate bacterial culture and antibiotic sensitivity patterns in children and adolescents with chronic osteomyelitis and to explore associations between radiological patterns and antibiotic sensitivity among the patients.

MATERIALS AND METHODS

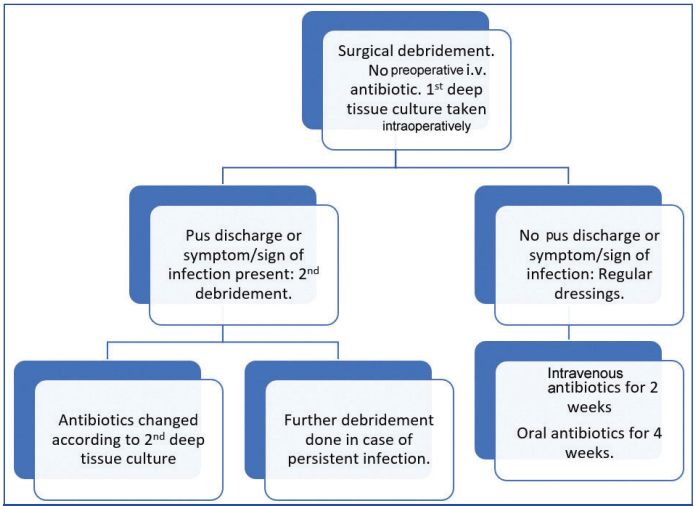
This was a retrospective review of patients visiting conducted in the Department of Orthopaedics OPD, Himalayan Institute of Medical Sciences (tertiary care institution), Dehradun, Uttarakhand, North India, from July 2018 to June 2020. The Institutional Ethics Board reviewed and approved the study (HIMS/RC/2018/204), and informed consent was obtained from participants. A total of 100 cases were included using a random convenience sampling method.

Inclusion criteria: Children and young adolescents visiting the hospital's OPD with pus discharge from an extremity for more than six weeks, along with radiological features of chronic osteomyelitis, were included in the study.

Exclusion criteria: Patients with features of acute osteomyelitis or non haematogenous chronic osteomyelitis were excluded from the study.

Study Procedure

The patient's demographics, clinical presentation, hospital course (duration of stay, antibiotics before admission, site of infection, surgical and medical management), blood reports {Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive Protein (CRP)}, radiological findings {X-ray, Magnetic Resonance Imaging (MRI)}, culture report (bacterial), Beit CURE classification [12], histopathology report, antibiotics given (i.v./Oral) along with duration were noted. The Beit CURE classification is a radiological classification used to grade paediatric chronic osteomyelitis, classifiable as A, B1-B4, C and unclassifiable, with type A being mild and type C indicating the most severe involvement [Table/Fig-1].



[Table/Fig-1]: Flowchart describing the treatment protocol used in the study.

All the patients were treated according to a fixed hospital in-patient protocol. Surgical debridement was performed, and the first deep tissue culture was taken intraoperatively. Antibiotics were stopped in all cases prior to the first surgery to improve the chances of isolating the offending microorganism, and they were started only after taking the first deep tissue culture intraoperatively. Regarding empirical antibiotic therapy, piperacillin-tazobactam (100 mg/kg piperacillin, 10 mg/kg tazobactam) was given parenterally to all patients who had not received any antibiotics before presenting. Furthermore, for patients already taking antibiotics, the same regimen were continued empirically. After the first procedure, if the patient had a discharge from the suture line or persistence of any symptoms/ signs of infection, the patient was planned for a second debridement, and a second deep tissue culture was again taken intraoperatively. Antibiotics were continued for a period of six weeks or changed, if discharge or signs of infection were present according to culture sensitivity. Antibiotic bone cement was used for patients requiring multiple debridements and for dead space management. All cases were followed for a period of one year [Table/Fig-2].

Classification	Radiological appearance of bone segment
A	Abscess type, osteolytic areas, no sequestrum, no involucrum
B1	Peripheral, localised cortical sequestrum, minimal/no involucrum
B2	Sequestrum present, stable normal looking cortical involucrum
B3	Sequestrum present, stable sclerotic cortical involucrum
B4	Sequestrum present, unstable, inadequate involcrum
C	No sequestrum present visible on X-rays, densely, diffusely sclerotic bone segment; abscess may be present
Unclassifiable	Inadequate X-rays/disease onset >6 months/previous surgery

[Table/Fig-2]: Beit CURE classification [12].

STATISTICAL ANALYSIS

Data analysis was done using MS Excel. All categorical data were presented in the form of frequencies and percentages. The difference between MRSA and non MRSA was observed using a Chi-square test. The p-value less than 0.05 were considered statistically significant.

RESULTS

Out of a total of 100 patients, there were 60 (60%) children between 12 years and 18 years of age, 38 (38%) children between two years and 12 years of age, and 2 (2%) children below two years of age, while the median age was 13 years. There were 32 (32%) females and 68 (68%) males in the present study. The tibia was involved in 38 (38%) patients, the femur in 28 (28%), the humerus in 12 (12%), the radius in 4 (4%) patients, and other bones in 18 (18%) patients. The duration of illness before seeking treatment varied from less than two months in 28 (28%) cases to 2-12 months in 60 (60%) cases and more than one year in 12 cases [Table/Fig-3]. The number of debridements needed before clearance (at least two subsequent negative cultures) was one in 34 cases, two in 42 cases, three in 12 cases and more than three in 12 cases.

Variables	n (%)
Median age (years) (Range)	13 (10-15.75)
Gender	
Males	68 (68)
Female	32 (32)
Site involved:	
Tibia	38 (38)
Femur	28 (28)
Humerus	12 (12)
Radii	4 (4)
Other bones	18 (18)
Number of surgeries required (≥2), n	66
Median duration of symptoms on presentation (months)	6
Median WBC at presentation	11.03 (8.80-13.63)
ESR at presentation	42.5 (25-54)
CRP at presentation	4.12 (1.45-11.52)

[Table/Fig-3]: Overall characteristics of study population.
WBC: White blood cells; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein

Beit CURE (BC) classification was used on preoperative X-rays for evaluation. Most of the cases (70%) belonged to the B1-B3 group [Table/Fig-2]. In this group, cases classified as B1 required the least number of surgical procedures, while B3 and B4 had to undergo the maximum number of debridements. Type C also required an equivalent number of surgical procedures as type B2 [Table/Fig-4]. The first

culture taken among the present study population was positive in 68 patients and negative for any growth in 32 patients. Out of these 100, 66 required a 2nd debridement due to the persistence of discharge or symptoms/signs of infection. Thus, a 2nd intraoperative deep tissue culture was taken in these 66 patients, and it was positive for 34 patients. Among the initial 32 patients that were culture negative, 10 had discharge from the suture line or symptoms and signs of infection, leading to the need for repeat debridement. Among these 10, eight patients had positive cultures, and *Staphylococcus aureus* was isolated in six of them [Table/Fig-5].

Beit CURE classification	No. of cases, n	Mean number of surgeries, n
A	2	1
B1	20	1.7
B2	26	2.3
B3	24	2.7
B4	8	3
C	8	2.4
Unclassifiable	12	2.5

[Table/Fig-4]: Distribution of cases according to Beit CURE classification and mean number of surgical procedures required.

Organism	1st culture, n (%)	2nd culture, n
Staphylococcus aureus	58 (58)	22+6 (earlier negative for *S. aureus*)
Pseudomonas aeruginosa	4 (4)	2+1 (earlier negative for *P.aeuroginosa*)
Streptococcus	2 (2)	-
Acinetobacter	2 (2)	-
Proteus mirabilis	2 (2)	-
Enterococcus	-	3
Total	68	34

[Table/Fig-5]: Distribution of cases according to organism isolated in both the cultures.

Based on the culture and sensitivity patterns, *Staphylococcus aureus* was the most predominantly identified organism. Other isolated organisms included *Pseudomonas aeruginosa* (*P. aeruginosa*), 4 (4), streptococcus, 2 (2%), acinetobacter, 2 (2%), *Proteus mirabilis*, 2 (2%) and enterococcus (found in three patients after the 2nd debridement). Out of the 86 *S. aureus* isolates, 58 (67.44%) were MRSA. Maximum resistance was observed against ciprofloxacin (72% of cases with *S. aureus*). Vancomycin resistance was observed in 10 cases (11.62%) with *S. aureus*, while all the isolates were sensitive to linezolid and teicoplanin, 86 (100) (with *S. aureus*). High susceptibility was observed with tetracycline, 66 (76.74%) and clindamycin, 74 (86.04%). Other Gram-positive bacteria (streptococcus and enterococcus) were sensitive to a large number of antibiotics; however, they showed 100% susceptibility to vancomycin, linezolid and teicoplanin. Pseudomonas (4 out of 7) isolates were resistant to ciprofloxacin (57.14%), while they showed good sensitivity to gentamycin, cefoperazone-sulfbactum, and imipenem [Table/Fig-6].

Furthermore, based on the difference in proportion in culture patterns with Beit CURE X-ray classification, no association was observed between the presence of MRSA and a more severe Beit CURE X-ray grade. However, the maximum number of MRSA was observed for grade B2-C, 34 (58.62%) and only 4 (6.89%) for grade A-B1 [Table/Fig-7].

Regarding the clinical outcome, 24 out of 100 required three or more debridements. Antibiotic-bone cement was used in 18 cases, 11 of which underwent bone grafting for dead space management after the subsidence of infection. Overall, 16 patients did not show clinical and radiological improvement; nine of them were multidrug-resistant, and seven underwent amputation.

DISCUSSION

Chronic osteomyelitis is a persistent disease, difficult to treat or eradicate completely. In the absence of early diagnosis and prompt treatment, or in cases of antibiotic therapy failure due to the development of drug resistance, chronic osteomyelitis becomes an important cause of high morbidity, especially in developing countries [9].

Epidemiological data described in recent articles were validated [13,14]. In the present study, the maximum number of patients were in the age group of 12-18 years (60%), with the majority being males (68%), and involving lower limb long bones in 66% of cases [15]. Children presented with raised White Blood Cells (WBC) count, ESR and CRP, with the sensitivity of ESR and CRP being higher compared to leucocytosis. The WBC count was elevated in 46% of patients with a mean value of 9.5; ESR and CRP were elevated in >90% of cases, aligning with previous literature [16]. For preoperative

Antibiotics	*S. aureus* (n=86)	*Pseudomonas aeruginosa* (n=7)	Beta-haemolytic streptococcus (n=2)	*Proteus mirabilis* (n=2)	Enterococcus species (n=3)
Cloxacillin/penicillin	31 (36.04%)	-	2 (100%)	-	2 (66.66%)
Cefuroxime	37 (43.02%)	-	1 (50%)	1 (50%)	2 (66.66%)
Ciprofloxacin	21 (24.41%)	3 (42.85%)	-	2 (100%)	-
Cotrimoxazole	63 (73.25%)	-	1 (50%)	1(50%)	-
Gentamycin	-	5 (71.42%)	-	1 (50%)	-
Tetracycline	66 (76.74%)	-	0 (0%)	1 (50%)	3 (100%)
Linezolid	86 (100%)	-	2 (100%)	-	3 (100%)
Vancomycin	76 (88.37%)	-	2 (100%)	-	3 (100%)
Teicoplanin	86(100%)	-	2 (100%)	-	3 (100%)
Clindamycin	74 (86.04%)	-	2 (100%)	-	2 (66.66%)
Ceftriaxone	33 (38.37%)	-	2 (100%)	1 (50%)	2 (66.66%)
Cefoperazone-sulfbactum	-	5 (71.42%)	2 (100%)	2 (100%)	2 (66.66%)
Impinem	-	6 (85.71%)	-	2 (100%)	-

[Table/Fig-6]: Antibiotic susceptibility of bacteria isolated including both 1st and 2nd culture.

Beit CURE grade	Non MRSA n (%)	MRSA n (%)	Chi-square test	p-value
A	0	2 (100)	1.18	0.235
B1	4 (20)	16 (80)	2.72	**0.006**
B2	14 (53.8)	12 (46.2)	0.352	0.724
B3	10 (41.7)	14 (58.3)	0.954	0.339
B4	4 (50)	4 (50)	0.337	0.735
C	6 (75)	2 (25)	0.718	0.473
Unclassifiable	4 (33.3)	8 (66.7)	1.30	0.192
Total	58 (58)	42 (42)	1.6	0.109

[Table/Fig-7]: Association between % of MRSA and Beit CURE classification. Chi-square test; The p-value in bold font indicates statistically significant value

X-ray evaluation, the Beit CURE classification was utilised. It is the only classification designed solely for chronic haematogenous osteomyelitis. It is simple, reliable, and reproducible, requiring just plain radiographs, which are widely available throughout the developing world [12]. The maximum number of cases according to this classification belonged to the B3 group, while group A had the least. Previous literature supports this result [17]. Type A and B1 required the least surgical input, while types B2, B3, B4 and C required a higher number of surgeries, with B4 topping the group. Thus, a correlation of the classification grade with the number of procedures required can be established, which would further aid in resource allocation and developing a strategic treatment plan [12,17]. Regarding the most common bone involved, the results reflect previous studies, with the tibia being the most commonly affected bone followed by the femur and humerus [18,19]. This is likely due to the poor soft tissue cover around the tibia, leaving the periosteum vulnerable to infection.

Despite drastic improvements and recent advances in the diagnosis and treatment of the disease, sepsis continues to be a major cause of morbidity and mortality in the paediatric population, especially in developing countries. The microbiological profile and their antibiotic susceptibility pattern show wide variations, presenting a challenging task in eliminating the infection. The appropriate treatment of chronic osteomyelitis requires a culture-directed approach [20,21]. Recent literature suggests that deep tissue or bone specimen cultures are more reliable than superficial swab cultures for identifying the correct etiological organism [21,22]. Studies by Tong SY et al., and Lobati F et al., and many others conducted in various countries, particularly in developing nations, draw a conclusion that *Staphylococcus aureus* causes 80-90% of cases of chronic haematogenous osteomyelitis in children [23,24]. Authors hereby found *S. aureus* to be responsible for 86% of cases, followed by *Pseudomonas aeruginosa* (7%). A large study on this subject was conducted in Malawi with 167 children suffering from chronic haematogenous osteomyelitis, in which 61.7% of the isolates were Staph aureus [25].

A large proportion of the identified *S. aureus* specimens were Methicillin-resistant (36.04%), while 100% sensitivity was observed with teicoplanin and linezolid. High levels of susceptibility were observed with cotrimoxazole (73.25%) and clindamycin (86.04%), which have been found to achieve high levels of bone concentration (50% with cotrimoxazole and 70-80% with clindamycin) and are as effective as vancomycin [26]. Other Gram-positives, streptococcus and enterococcus showed excellent sensitivity to clindamycin, vancomycin, linezolid and teicoplanin (100%). Multidrug resistance was observed with Gram-negative species. *Pseudomonas aeruginosa* was resistant to fluoroquinolones in four out of seven cases and to aminoglycosides in two out of seven cases, while it even showed resistance to carbapenem in one case, which is considered the most potent in treating serious infections caused by multi-drug-resistant Gram-negative species. This is in contrast with the study by Mthethwa P and Marais L which the carbapenem group [27]. Multidrug resistance was also noted with other Gram-negative bacteria isolated, such as Proteus mirabilis. Infection with multidrug-resistant MDR organisms poses a serious challenge for the clinician. Delayed empirical antibiotic therapy or inappropriate antibiotic therapy leads to the worsening of the disease, further increasing morbidity and the financial burden on the patient. The present study supports the conclusion drawn by Banerjee B et al., that piperacillin-tazobactam along with clindamycin can be an effective empirical treatment regime, which can be modified after a culture report. However, considering the high incidence of MRSA, vancomycin can also be considered in place of clindamycin [26].

Furthermore, regarding clinical outcome, the authors observed that those patients whose culture grew MDR organisms had a much more severe infection in terms of X-ray presentation, duration of hospital stay, number of debridements required and late sequelae of chronic osteomyelitis. About 58.62% of MRSA belonged to the B2-C Beit CURE group, requiring more surgical intervention and having a poorer prognosis.

Limitation(s)

Due to the retrospective nature of the study, recall bias was inevitable. The present study was conducted on a sample of 100 patients who presented to the OPD of a tertiary care hospital. Therefore, a study with a larger sample size and a prospective study design will further corroborate the results.

CONCLUSION(S)

Chronic haematogenous osteomyelitis in children is not a rare disease in developing countries and causes substantial morbidity. Regarding microbiology, *S. aureus* is definitely the most prevalent; however, the aetiology is diverse, and the presence of multidrug-resistant organisms further complicates the treatment. An association between higher levels of drug resistance and a worse X-ray picture was postulated while designing the study, but no association was found between drug sensitivity patterns and radiological pictures among this group of patients.

Authors contribution: CP: Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing-review and editing. RR: Conceptualisation; Data curation; Formal analysis; Funding acquisition; Visualisation; Roles/writing- original draft. DPS: Writing and Validation. AJ: Validation and supervision.

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