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Extremity chronic osteomyelitis in a population of North East India: epidemiology, clinical characteristics and management

Tashi G. Khonglah*, Bhaskar Borgohain, Wanlamkupar Khongwir, Kashif A. Ahmed

Department of Orthopaedics and Trauma, The North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India

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***Correspondence:**
Dr. Tashi G. Khonglah,
E-mail: tashigalen@gmail.com

ABSTRACT

Background: The purpose of this study was to review the epidemiology, clinical features and the management of extremity chronic osteomyelitis in a population of North East India and to provide evidenced based guidelines for early diagnosis and treatment.
Methods: We retrospectively reviewed patients who were diagnosed and treated for extremity chronic osteomyelitis at a tertiary care hospital at Shillong in North East India. Medical records for all patients were analysed and details on gender, age at incidence, anatomical site, infecting organisms, levels of inflammatory markers, and the various treatment modalities were evaluated.
Results: A total of 131 patients (96 males and 35 females) were included in this study. The median age at first diagnosis was 17 years for all. Infections caused by hematogenous osteomyelitis was found to be slightly more than those of traumatic origin. All patients had single site infections with a majority of lesions affecting the lower extremities. The tibia was the most common site in traumatic osteomyelitis while the femur was mostly involved in hematogenous osteomyelitis. The positive rate for all cultures was at 57.25% with the most commonly encountered organism being *Staphylococcus aureus*. Treatment methods used in our study included radical debridement with the use of local and systemic antibiotics and reconstruction of bony or soft tissue defects. The overall infection control rate was 96.18%.
Conclusions: The findings from this study can provide information for early diagnosis and treatment of this form of bone infection particularly in this part of the country.

Keywords: Extremity chronic osteomyelitis, Bone infection, North East India, Regional characteristics

INTRODUCTION

Infections of the skeleton have been chronicled since the earliest periods of humankind. Osteomyelitis is an ancient disease with proof of burned-out infection involving the skeleton and has been documented in hominid fossils (*Australopithecus africanus*).[1] Human osteomyelitis has been described as early as the 300s BC by Hippocrates.[2]

Osteomyelitis is a severe infection of the bone that results from various aetiologies and mechanisms.[3] It may be secondary to a contiguous focus of infection (after trauma, surgery, or insertion of a joint prosthesis); vascular insufficiency (in diabetic foot infections); or of haematogenous origin.[4] With the passage of time, the diagnosis and treatment of osteomyelitis has improved and this has been made possible by systematic classification and staging system helping to define the treatment plans.[5,6] Even as advances are made in the management of osteomyelitis, the epidemiology of the condition appears to have evolved over time. From the geographical perspective, it has been seen that in developed countries, the prevalence of chronic osteomyelitis has substantially decreased because of the

improvement in both socio-economic status and health care delivery. However, unfortunately, in developing countries the prevalence remains high.[7] From the time perspective, over the past decades, the clinical picture of chronic osteomyelitis has also markedly changed. In the industrialized countries, hematogenous osteomyelitis has been almost wiped out.[8] What use to be a sequela of acute hematogenous osteomyelitis is now a result of trauma, orthopaedic implants and diabetic foot. With the change in age structure and the growing use of orthopaedic implants, post-traumatic/post-operative forms of osteomyelitis are expected to further increase in the near future.[9] The burgeoning pervasiveness of diabetes and peripheral vascular disease also predisposes and complicates osteomyelitis which, if not treated effectively may result in undesirable consequences.[10] The emergence of multidrug-resistant microorganisms (e.g. methicillin-resistant *Staphylococcus aureus*, MRSA) in hospitals has been associated with increased rates of bacterial infections posing an uphill task in treating such pathogens.[11,12]

Chronic osteomyelitis, defined as long-standing infection that evolves over months and even years, is characterized by the presence of microorganisms, low-grade inflammation, and the presence of dead bone (sequestrum) and fistulous tracts.[13] The management of chronic osteomyelitis is a challenge, for both patient and surgeon demanding utmost perseverance from both to ensure eradication. Clinicians are required to make an early diagnosis and provide timely intervention in order to prevent recurrence and improve the overall quality of life of the patients. It is important therefore to understand the aetiology of the infection, as well as the pathophysiology of its chronicity.

To the best of our knowledge, there are no comprehensive studies describing the spectrum of extremity chronic osteomyelitis in the population of North East India. Therefore, this study was aimed to review the clinical features and management of extremity chronic osteomyelitis in patients of North East India.

METHODS

This study was conducted at the North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, a tertiary care hospital at Shillong in North East India. We retrospectively reviewed patients who were diagnosed with extremity chronic osteomyelitis and were treated at our hospital from 1 January 2013 to 31 December 2017. Patients' data was collected from the hospital medical records department. The information gathered from these patients included, gender, age at incidence, anatomical site, infecting organisms, levels of inflammatory markers, and the various treatment modalities. Due to the retrospective design of the present study, written consents of the patients were waived and prior to analysis their personal information was anonymised. This study was approved by the medical ethics committee of the hospital.

Eligible patients included in this study were those diagnosed with chronic osteomyelitis involving only the bones of the extremities. The clinical records of these patient were retrospectively studied using a predefined protocol, which included gender, age at first diagnosis, laterality and site of infection, intraoperative microorganism cultures, preoperative serum values of white blood cells (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the treatment modalities that followed. Those diagnosed with acute osteomyelitis or chronic osteomyelitis of non-extremity bones (e.g. clavicle, scapula, spine, and mandible) and diabetic foot were excluded from this study. Patients with a history of repeated hospitalization with multiple medical records had only their relevant records, gathered and analysed.

SPSS 17.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis. P value below 0.05 were considered significant.

RESULTS

The present study included 131 patients of whom 96 (73.28%) were males and 35 (26.72%) females giving a gender ratio of 2.74 for a male predilection. The median age on first diagnosis was 17 years while the mean age was approximately 21 years. The top three age groups involved were the periods from 1 to 20 years (59.5%), 21 to 40 years (27.5%), and 41 to 60 years (12.2%) respectively (Table 1). Gender ratios differed statistically among the types of infections ($p<0.001$) ranging from 2.4 (hematogenous osteomyelitis) to 3.2 (traumatic osteomyelitis). According to the Waldvogel classification, 68 (51.9%) cases of the total 131 cases were of hematogenous origin, the highest percentage 83.8% of which were in the 1 to 20 years age group. 63 (48.1%) cases were of post traumatic origin of which 44.4% of these patients were in the 21 to 40 years age group ($p<0.001$). The oldest patient in this study was a 66 years old male with traumatic osteomyelitis (Table 2).

Table 1: Age and gender of patients at the time of presentation.

Age (years)	Male	Female	%
1-20	55	23	59.5
21-40	27	9	27.5
41-60	13	3	12.2
61-80	1	0	0.8
Total N (%)	96 (73.3)	35 (26.7)	

All the patients had a single infection site, the right side accounted for 48.1% (63) of the total infection sites, and the left side accounted for 51.9% (68). None of the patients had bilateral involvement. 120 (91.6%) cases had a lesion in a lower limb while 11 (8.4%) cases involved the upper limb. The most frequent single site of infection was the femur (57 cases, 43.5%) followed by the tibia (51 cases, 38.9%), the calcaneus and the humerus (5 cases each, 32.2%), and metatarsals (4 cases, 12.9%) (Table 3). In

addition, the tibia was the most common site in traumatic osteomyelitis while the femur was the most common site for hematogenous osteomyelitis (Table 4).

Table 2: Types of infection according to age groups.

Age (years)	Hematogenous osteomyelitis N (%)	Traumatic osteomyelitis N (%)
1-20	57 (83.8)	21 (33.3)
21-40	8 (11.8)	28 (44.4)
41-60	3 (4.4)	13 (20.6)
61-80	0 (0.0)	1 (1.6)
Total	68 (51.9)	63 (48.1)

Table 3: The distribution and percentage of affected sites.

Site	Number (N)	%
Humerus	5	3.8
Radius	3	2.3
Ulna	1	0.8
Fingers	2	1.5
Femur	57	43.5
Tibia	51	38.9
Fibula	3	2.3
Calcaneus	5	3.8
Metatarsals	4	3.0

Table 4: Sites and types of infection.

Site	Hematogenous osteomyelitis N (%)	Traumatic osteomyelitis N (%)
Humerus	4 (5.8)	1 (1.6)
Radius	3 (4.4)	0 (0.0)
Ulna	1 (1.4)	0 (0.0)
Fingers	0 (0.0)	2 (3.2)
Femur	35 (51.4)	22 (34.9)
Tibia	21 (30.8)	30 (47.6)
Fibula	3 (4.4)	0 (0.0)
Calcaneus	1 (1.4)	4 (6.3)
Metatarsals	0 (0.0)	4 (6.3)

The laboratory cut-off values for the various serum inflammatory markers used in this study were WBC: 11×10^9/L, ESR: 20mm/1h and CRP: 5mg/l. A pre-operative comparison of the values of these 3 markers among the different types of osteomyelitis did not reveal any differences. While the mean WBC and CRP levels were found to be marginally elevated in the hematogenous type of osteomyelitis. In contrast, mean ESR levels were found to be elevated in traumatic infections. The overall positive rates for these three serum inflammatory markers showed that ESR was the highest (86.3%, 113/131) followed by CRP (65.6%, 86/131). Positive rates of WBC were the lowest (26%, 34/131). The positive rates for all three inflammatory markers was higher among the hematogenous osteomyelitis group than among the post-traumatic osteomyelitis group (Table 5).

Table 5: Mean serum levels of preoperative inflammatory markers.

Variables	Hematogenous osteomyelitis	Traumatic osteomyelitis
ESR[a] (mm/1h)	55.0	60.7
WBC[b] ($\times10^9$/l)	10.8	9.0
CRP[c] (mg/l)	13.6	11.2

[a]Erythrocyte sedimentation rate, [b]white blood cells, [c]C-reactive protein.

All 131 patients had records of organism cultures in our study. The positive rate for all was 57.25% (75 cases). A significant difference was identified regarding the positive rate of culture for the two different types of osteomyelitis ($p<0.001$). The most common bacteria to account for both hematogenous and traumatic infections was *Staphylococcus aureus* (44 cases, 33.58%), 9 of which were of MRSA strain. Other bacteria detected in more than five patients was *Escherichia coli* (9 cases, 6.87%) (Table 6).

Table 6: Common organisms found is positive cultures.

Organism	%
Staphylococcus aureus	33.58
***Streptococci* species**	3.81
***Pseudomonas* species**	3.05
Escherichia coli	6.87
Enterobacteriaceae	3.81
Acinetobacter buamannii	1.5
Klebsiella pneumoniea	2.3

Table 7: Treatment strategies for extremity chronic osteomyelitis.

Treatment strategies	Number
Radical debridement	84
Radical debridement and bone grafting	34
Radical debridement and bone transport	8
Limb amputation	1
Conservative treatment	4

Treatment methods for extremity chronic osteomyelitis used in our study included radical debridement with the use of local and systemic antibiotics and reconstruction of bony or soft tissue defects either with free bone grafts or using bone transport. Limb amputation was reserved only for those with severe infections. 84 patients underwent radical debridement alone, while 42 patients underwent repeated surgery with a radical debridement & free bone grafting (34 cases) or radical debridement and bone transport (8 cases) at a later stage. All 131 patients were

followed up for at least 18 months. The total infection control rate was 96.18% (126 cases). 4 cases were treated conservatively and had a satisfactory outcome, one patient had to undergo an amputation (Table 7).

The protocol for intravenous antibiotics followed at our institute consists of an average of 14 days followed by another 4 weeks of oral antibiotics. The most commonly used intravenous antibiotic in our study were cephalosporins (80 cases) followed by clindamycin and pipercillin-tazobactum (16 cases each).

DISCUSSION

The aetiology and morbidity of osteomyelitis is linked to many factors, including ethnicity, lifestyle and economic conditions.[14] Traditionally, chronic osteomyelitis has been thought of as a sequela of acute osteomyelitis. However, over the past decades; reports suggest that trauma, fracture-fixation devices/prothesis and diabetic foot infection are now the leading causes of chronic osteomyelitis.[15]

The present study involving 131 patients established a male predilection with a gender ratio of 2.74. This male preponderance was evident throughout all age groups. The highest (57.3%) was noted in the 1 to 20 years age group. In a recent study, Kremers et al also reported an annual incidence higher in men and this male dominance was evident in all ages.[16] In our study, the median age at first diagnosis was 17 years while the mean age was approximately 21 years. As mentioned by Kremers et al in their study, age was an important factor in determining the etiology because in children the cause for osteomyelitis would be hematogenous infection.[16] In our study, 73% of patients in the age group of 1 to 20 years with osteomyelitis of the extremities were of hematogenous onset. Of the 63 cases of post traumatic origin 44.4% of these belonged to the 21 to 40 years group. Our median reported age was much lower than those reported by both Kremers et al and Jiang et al.[16,17]

Unlike many other reported studies, the most frequent type of extremity chronic osteomyelitis in our group was that of hematogenous origin (51.9%) which was slightly higher than that of post traumatic origin (48.1%). Both Jiang et al and Wang et al reported 76.85% and 80.1% respectively reported post traumatic osteomyelitis as the predominant type.[14,17] We consider that the vast difference may be a consequence of the different age distributions of the osteomyelitis types in between the studies. Approximately 60% of our patients were below 20 years of age of which 70% of them had haematogenous osteomyelitis, comparable to a study by Perez et al.[13] Despite the predominance of post traumatic osteomyelitis, hematogenous osteomyelitis is still present in large proportions, particularly with a childhood and adolescent onset.

Though the most common site of extremity chronic osteomyelitis in our study was the femur (43.5%), the most common site for post traumatic osteomyelitis was the tibia while the femur remained the favoured site for hematogenous osteomyelitis. These findings were consistent with those of Wang et al.[14] The unique anatomical location of the tibia and its blood supply all contribute to its susceptibility. Adversely, the rich blood supply of the femur makes it more prone to hematogenous osteomyelitis.

Our positive rate of microbial culture was about 57% which closely compared to previous reports.[14] Several factors have been known to play a crucial role in deciding the positive rate of culture such as culture time and conditions, antibiotic use before culture, and biofilm associated bacterial strains.[18] A number of our patients 22% had undergone antibiotic treatment prior to admission, which may have led to changes in drug resistance. It has been recommended that before culture, patients suspected of chronic osteomyelitis should discontinue antibiotic use for at least 2 weeks, and at least 3 independent infection sites should be selected for culture. The regular culture time is normally 1 week for all cases, the duration of which may be extended to 2 weeks if the outcome obtained is negative. Culture conditions may be then changed for fungal and acid-fast bacillus.[17] Kremers et al in their study noted that *Staphylococcus aureus* infections were responsible for 44% of their cases, followed by *Staphylococcus epidermidis* (17%) and Streptococcus infections (16%).[16] Arias et al recognised in their study of 193 patients. *Staphylococcus aureus* (28.7%) as the most common organisms and 31% were of polymicrobial strain.[19] In our study, the most prevalent bacteria detected was *Staphylococcus aureus* (33.58%) including 9 strains of MRSA and approximately 20% were polymicrobial infections. Similar to the study by Wang et al, we found that among our patients with monomicrobial infection, the proportion of *Staphylococcus aureus* was higher 23.66% in the haematogenous osteomyelitis patients compared to post traumatic osteomyelitis patients 9.92%, while the rates of *Escherichia coli*, *Enterobacter cloacae* and *Pseudomonas aeruginosa* were elevated in the latter.[14]

The diagnosis of characteristic extremity chronic osteomyelitis ensuing patient history and examination is generally straightforward. To assist in the the diagnosis, there are pre-operative levels of serum inflammatory markers. In our study, we noted that the positive rates of these markers differed between the two categories of osteomyelitis. While the mean WBC and CRP levels were found to be marginally elevated in the hematogenous type of osteomyelitis. In contrast, mean ESR levels were found to be elevated in traumatic infections. It was seen that the positive rates for all three inflammatory markers were elevated among the hematogenous osteomyelitis group compared to the post-traumatic osteomyelitis group. The indefinite characteristic of these markers warrants a guarded approach when using them to diagnose the various

forms of osteomyelitis. Reports are confirming approximately 20% of patients still having infections even when all these markers were in their normal ranges.[20]

The management of extremity chronic osteomyelitis should be based on both systemic and local factors and hinges on the decision of the treating surgeon.[19] Treatment methods for extremity chronic osteomyelitis used in our study included radical debridement with the use of local and systemic antibiotics and reconstruction of bony or soft tissue defects either with free bone grafts or using bone transport. Though surgical intervention was the mainstay of our treatment, 4 patients with hematogenous origin were treated conservatively and had an acceptable outcome. The grounds for conservative management were mainly because patients opposed undergoing operative intervention. At an average follow-up of 18 months, the total infection control rate attained was 96.18%. It must be mentioned that of the 5 patients who relapsed, 3 were diagnosed with chronic osteomyelitis involving the bones of the feet. The lone amputee in our study was diagnosed with chronic osteomyelitis involving the metatarsal bone. Jiang et al described cure rates that differed with regards to diverse treatment strategies, ranging from 26.92% to 100%.[17]

The majority of our patients who were on intravenous antibiotics received cephalosporins. The frequent selection of cephalosporins is probably associated with their broad antimicrobial spectrum.[17] Antimicrobial therapy was administered for an average minimum of 6 weeks, 2 weeks intravenously. With regards to the duration of antibiotic therapy, several studies state that there is no evidence that antibiotic therapy for more than 4 to 6 weeks improving outcome compared to a shorter regimen.[21,22] As for the route of antibiotic administration (oral versus parenteral), Spellberg et al in their study concluded that oral therapy with a highly bioavailable agent was an acceptable and equally effective alternative to parenteral therapy.[21] A systemic review affirmed similar clinical efficacy between oral and parenteral antibiotics for the management of osteomyelitis provided the bacteria were sensitive to the antibiotic used.[23]

There are several notable limitations to this study. The study is retrospective with a small sample size. The study was conducted in a single hospital in North East India. Therefore, it may not well depict the extent of chronic extremity osteomyelitis in this part of the country. Thus, a large multi-centre prospective study should be performed to gain more precise information. Diabetic foot infections were also not treated in our department, and we did not have data which may have impacted the observation of the overall distribution of this form of osteomyelitis.

CONCLUSION

To summarize, our present study involving 131 patients observed that chronic extremity osteomyelitis largely involved males and was more common in the lower limbs. Osteomyelitis of hematogenous origin which was marginally higher than that of post traumatic origin and the most prevalent bacterial strain was *Staphylococcus aureus.* Results from this study can provide information for early diagnosis and treatment of this form of bone infection particularly in this part of the country. Further multi-centre research is warranted to replicate these findings in a larger population and this would help us gain better understanding about the burden of this disease.

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