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Characteristics of bone and joint infections in paediatric patients complicated with disseminated sepsis

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Abstract
Background: The bone and joint infections in the pediatric population account for one of the major causes of childhood morbidity and when complicated with sepsis, the results can be devastating. Hence the, timely diagnosis and appropriate treatment are cardinal to minimize complications and improve outcomes. This study aims to evaluate the prevalence of septic arthritis and osteomyelitis in children with sepsis, the organisms implicated, and their antibiotic sensitivities.
Patients and Methods: During one year period, 21 patients with bone and joint infection complicated with sepsis, severe sepsis, and septic shock were included in our study. Demographical details were collected from these patients with clinical features suggestive of septic arthritis and acute osteomyelitis, after proper clinical examination and appropriate investigations.
Results: Twenty-one patients with bone and joint infections complicated with sepsis, severe sepsis, and septic shock were included, of which 13 patients were males and 8 were females. The median age at presentation was 6.7 years. The median interval between symptom onset and hospital admission was 8 days. Septic arthritis was seen in 14 patients, and osteomyelitis was seen in 7patients. Multiple sites were involved in 2 patients. The most common joint was the knee (28.5%), followed by the hip (19%), and the most common bone involved was the femur (23.8%), followed by the tibia (9.5%). C-reactive protein (CRP) was raised among all patients with a median of 96 mg/L (range 48-170mg/L].14 [66.6%] cases were culture positive and Staphylococcus aureus (MRSA) was detected either in their blood or aspirate in 12 [85.6%] of such patients.
Conclusion: Acute osteomyelitis and septic arthritis are relatively common serious bacterial infections that can progress to disseminated sepsis and septic shock. A multidisciplinary approach, including the consideration of combined medical and surgical management, should be considered in these patients.

Keywords: Disseminated sepsis, acute osteomyelitis, septic arthritis, *Methicillin-resistant* staphylococcus aureus

Introduction
Pediatric bone and joint infection account for one of the major causes of childhood morbidity and mortality, with the incidence being up to 200 for osteomyelitis and 10-20 for septic arthritis per 1 lakh individuals in developing countries and mortality of up to 1% and morbidity up to 29% [1, 2, 3].
In children, these infections are most often caused by the dissemination of the pathogenic bacteria through blood [3]. Acute osteomyelitis [AO] can be a devastating disease unless it is diagnosed promptly and treated appropriately [3]. Septic arthritis [SA] causes morbidity due to the destruction of articular cartilage and underlying epiphysis with long-term complications [4]. Timely diagnosis and appropriate treatment are cardinal to minimize complications and improve outcomes.
Staphylococcus aureus is an important cause of AO and Septic arthritis in children and is incriminated as an important cause of disseminated sepsis [5, 6], which has led to significant mortality and morbidity in the pediatric age group. The emergence of *Methicillin-resistant* Staphylococcus aureus (MRSA) has become a challenge in deciding the empirical treatment in such patients. Limited data is available from our region regarding acute bone and joint infection [AO and Septic arthritis] that complicates as disseminated sepsis and shock in children.

Materials and Methods

Our study was a prospective study conducted in the tertiary care hospital of Kashmir. All the children admitted from October 2018 to October 2019 who had any form of acute bone and joint infection [AHO and SA] complicated with sepsis, severe sepsis, and septic shock were included in our study.

Sepsis is a systemic inflammatory response syndrome due to infection. Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Septic shock is defined as hypoperfusion and hypotension despite adequate resuscitation [7].

Demographical details were collected and patients with clinical features suggestive of septic arthritis (fever, general malaise, painful passive joint motion) and acute osteomyelitis (fever, general malaise, local pain, and tenderness) during their entire stay in the hospital were considered after appropriate clinical examination and investigation.

All the patients were subjected to a panel of blood tests, including a complete blood count, Kidney function test, Liver function test. Septic panel including C-Reactive protein, ESR, and blood culture. Bone and/or joint aspiration was done, and aspirated material was sent for gram stain, aerobic bacterial culture, TB culture, and fungal culture, and sensitivity. Roentgenograms and an ultrasonographic examination were carried out as per indication. Patients with severe sepsis and septic shock were managed in the Intensive care unit of our hospital. Specific management included antimicrobial therapy, thorough surveillance to search for collections and their surgical drainage. Supportive care included maintenance of blood pressure, fluid and electrolyte balance, analgesia, prevention of bed-sores, physiotherapy, asepsis, and early enteral nutrition [8].

As per the institutional protocol, empirical antibiotic therapy included a combination of intravenous vancomycin and ceftriaxone. Empiric use of Glycopeptide Antibiotics in children with disseminated sepsis is because we have a high incidence of Methicillin resistance staphylococcus aureus in an intensive care unit.

Results

During the defined period of one year from, 21 patients with bone and joint infection complicated with sepsis, severe sepsis, and septic shock were admitted to our hospital, of which 13 patients were males and 8 were females. The median age at presentation was 6.7 years [IQR 6.3-8.6years]. The median interval between symptom onset and hospital admission was 8 days (IQR: 6-11.5). The predisposing injury was present in 5 (23.8%) patients (3-trauma and 2-skin infection /cellulitis). Patients had a history of non-significant trauma to the extremities. [Table 1]

Table 1: Demographic profile of patients

	N=21[%]
Male	N=13
Female	N=8
The median age of presentation	6.7 years [range 6.3-8.6years]
The median time between the onset of symptoms and treatment	8 days [range 6-11.5days]
Predisposing factors	5[23.8%]
Non-significant trauma	3[14.2%]
skin abscess /boil/cellulitis	2[9.5%]

Thirteen patients had fever on presentation. Local symptoms of decreased joint movements and pain were seen in 11patients. Swelling and redness and warmth were the presentation at admission in 5 patients each. Predominantly systemic manifestation with generalized malaise was present in 8. Hypotension with cold extremities was present in 2 patients, whereas another 2 patients were admitted with altered sensorium. [Table.2]

Table 2: Presenting signs and symptoms of patients

A. **Fever**	13
B. **Local signs and symptoms**	
1. Decreased range of movements, painful movements	11[52.3%]
2. Redness and warmth	5[23.8%]
3. Localized swelling	5[23.8%]
C. **Systemic signs and symptoms**	
1. Generalised malaise and fatigue	8[38.1%]
2. Altered sensorium	2[9.5%]
3. Hypotension	2[9.5%]

Septic arthritis was seen in 14 patients, and osteomyelitis was seen in 7patients. Multiple sites were involved in 2 patients. The most common joint was the knee (28.5%), followed by the hip (19%), and the most common bone involved was the femur (23.8%), followed by the tibia (9.5%). [Table 3]

Table 3: Pattern of Musculoskeletal involvement

1. Osteomyelitis	7[33.3%]
a) Femur	5[23.8%]
b) Humerus	-
c) Tibia	2[9.5%]
2. Septic arthritis	14[66.6%]
a) Hip	4[19%]
b) Knee	6[28.5%]
c) Shoulder	1[4.7%]

d) Ankle	1[4.7%]
e) Elbow	-
3. Multifocal	2[9.5%]

The median total leukocyte count (TLC) was 18,970/mm 3, with interquartile range [13,400 -22,750]. C-reactive protein (CRP) was raised among all patients with a median of 96 mg/L (range 48-170mg/L]. The median erythrocyte sedimentation rate was 44mm/hr [range 23.5 -49]. [Table 4].

Table 4: Septic screening /laboratory parameters of all patients [N=15]

Total leucocyte count	18,970 (median)	13,400-22,750 (IQR)
Platelet count	2,50,700	190350-340600 (IQR)
C reactive protein	96 mg/dl (median)	48-170 mg/dl[IQR]
ESR	44 mm/hr	[23.5-49 mm/hr]

The microbiological confirmation was obtained by performing a blood culture and culture of the aspirate. 14 [66.6%] cases were culture positive, of which 7 [33.3%] had positive culture of aspiration fluid.5 [23.8%] patients had microbial growth in blood and in 2 patients [9.5%], organisms were isolated both from blood and aspiration fluid. [Table 4]. Staphylococcus aureus (MRSA) was detected either in their blood or aspirate in 12 [85.6%] patients. Escherichia coli and Coagulase-negative Staphylococcus Aureus was isolated in 1[7.1%] patient each.

Table 4a: Microbiological confirmation

	N =21[%]
Blood culture positive	5[23.8%]
Joint culture positive	7[33.3%]
Both blood and joint culture positive	2{9.5%]
Culture negative	7 [33.3%]

Table 4b: Microbiological distribution

Organisms	**N= 14[%]**
Methicillin-Resistant Staphylococcus Aureus (MRSA)	12[85.7%]
Escherichia coli	1[7.1%]
Coagulase-negative Staphylococcus Aureus	1[7.1%]

Treatment

All the patients received intravenous antibiotic therapy. Empiric antibiotics were vancomycin and a third-generation cephalosporin. Our intensive care unit has a very high incidence of oxacillin resistance henceforth, vancomycin is started empirically. The average duration of intravenous antibiotics was 4 to 6 weeks. Intravenous antibiotics were stopped depending on the improved clinical parameters such as fever, improved joint range of motion, and reduced inflammatory markers like TLC, ESR, and CRP. After IV antibiotics, oral antibiotics were given for 2 weeks. Intravenous inotropes and fluid resuscitation were done for patients presenting with hypotension and shock as per protocol. Four patients were on ventilatory support, of which 3 were extubated and 1 patient expired due to disseminated sepsis. One patient with coagulase-negative staph sepsis echocardiography revealed large vegetation and was managed as infective endocarditis. Surgical intervention was done in 19 patients that included arthrotomy of the affected joint and incisional drainage with bone drilling in cases with acute osteomyelitis.

Discussion

Despite many studies of septic arthritis and osteomyelitis in children, there is a paucity of studies regarding the clinical profile and risk factors that lead to disseminated sepsis in these children.

Our study confirms epidemiological data previously well described in the literature [9]: AO and septic arthritis is more commonly reported in males and young children, and the patient's history is commonly positive for a recent trauma or a febrile episode. In our study, the median age of presentation is 6.7 years which is in concordance with previous studies where young age was found to be a risk factor for complicated bone and joint infections [10]. This is possibly related to delays in the diagnosis and initiation of treatment, as well as differences in the response of younger children to antibiotic therapy. In our study, the median time between initial symptoms and treatment was 8 days. Besides, in our part of the world, the lack of education and low socio-economic factors cause a delay in seeking medical attention.

In our study, fever at admission was present only in 61.9% of children. This finding is similar to that one reported by Dartnell *et al.* [11] who observed fever as the presenting symptom only in 61.7% of children. Local symptoms of decreased joint movements and pain were seen in 52.3%patients. Swelling and redness and local warmth were present in 23.8%. Systemic symptoms of generalized fatigue and severe malaise were seen in 38.1%. Altered sensorium and hypotension were present in 9.5%, respectively. The pleuropulmonary disease was seen in 68% of patients in a study by Sodavarapu *et al.* [12]. Paterson noted in his study that systemic involvement in form of pneumonia and empyema were detected in 87% and 53%, respectively, among the 38 patients with osteoarticular infection with the disseminated staphylococcal disease [13].

The knee (42.8%) and hip (28.5%) were the most common joints involved in septic arthritis. For osteomyelitis, the femur was most commonly involved (71.4%). Previous studies also ascertained this finding, with the hip and knee are common sites for septic arthritis and the femur was found to be the most common site among osteomyelitis [14]. Paterson found out that hip was commonly involved among septic arthritis (55.5%), and the involvement of tibia (48.8%) and femur (41.4%) was higher in osteomyelitis among the patients of disseminated staphylococcal disease in his study [13].

Our study revealed a median leucocyte count of 18,970. Median CRP 96 mg/dl and median ESR of 44mm/hr. Leucocytosis was less remarkably seen in patients than markedly elevated C-reactive protein and ESR. In the study by Chiappini *et al.* [15] the high CRP and ESR were associated with complicated osteomyelitis, In a study of culture-positive AO and SA, the reported sensitivity of CRP at diagnosis was 95% (CI 91% to 97% CI). ESR and CRP both peaked on day the 2 of presentation, with the level of CRP normalizing in 10 ± 0.5 days. In this cohort of 265 children with confirmed osteoarticular infections, all had an elevated CRP and/or ESR within 3 days of admission [16].

Microbiological confirmation was done by performing a blood culture and culture of aspirate. [Table 4a, 4b]. Culture positivity of either blood or aspirate was seen in 14[66.6%]. Culture negative results may be due to less virulent organisms, due to slow-growing organisms, due to the low burden of disease, or due to the administering of antibiotics, A microbiological diagnosis is achieved in barely more than half

of all cases. In their systematic review, Dartnell *et al*. reported that microbiological diagnosis is achieved in approximately 50% of all cases of musculoskeletal infection [11].

In our experience, Gram-positive cocci represented 85.7% of all isolates. Escherichia coli from 2 [18.1%] isolates and 1 [9.09%] revealed Klebsiella. S. aureus is a major cause of acute osteomyelitis in children. Methicillin resistance among S. aureus isolates has become an emerging problem in pediatrics. The prevalence of MRSA varies among countries as well as among hospitals. MRSA strains are typically viewed as hospital pathogens, but this image is now changing. Outbreaks of community-acquired MRSA infections have recently been described worldwide, mainly in previously healthy children with no recognizable risk factors [17]. In a recent study in a tertiary care center in India, MRSA was the predominant isolate in 13% of young infants with septic arthritis [18].

In our series, all patients received antibiotic treatment, and 19 [66.6%] also needed open surgical drainage, which include either arthrotomy of the affected joint or incisional drainage and bone drilling in cases with osteomyelitis. The median duration of treatment was 4 to 6 of Intravenous antibiotics and two weeks of oral antibiotics. Vancomycin, along with third-generation cephalosporin, can be the preferred choice of antibiotic in cases of disseminated disease with suspected osteoarticular infection, as all cases of Staphylococcus aureus were sensitive to vancomycin in our study, but further studies are required to ascertain its use before recommending it as a first choice drug as suggested by other studies [19].

Conclusion

Acute Osteomyelitis and Septic Arthritis are relatively common serious bacterial infections of children that can progress to disseminated sepsis and septic shock. Early diagnosis and initiation of appropriate antibiotics is a sine qua non in preventing life-threatening complications like endocarditis. While this disease can be caused by a wide variety of pathogens, *S. aureus* is the predominant etiology. MRSA is emerging as community-acquired bacteria. A multidisciplinary approach including the consideration of combined medical and surgical management should be considered in these patients.

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