Factors associated with dissemination and complications of acute bone and joint infections in children

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Abstract

Background

Paediatric bone and joint infections remain common in low- and middle-income countries (LMICs) and may have devastating long-term sequelae. There is a paucity of data from LMICs where the true incidence might be underreported, and delayed presentation is common. Our study aimed to determine the complication rate and incidence of disseminated infection in paediatric bone and joint infections in an LMIC setting. Secondly, we aimed to elucidate factors associated with complications and disseminated disease.

Methods

We retrospectively reviewed our paediatric orthopaedic database for children that presented with bone and joint infections between September 2015 and March 2019. Data were extracted from medical records, laboratory results and radiological investigations to identify factors that were associated with the development of complications and disseminated infection at a median follow-up of four months.

Results

We analysed 49 children. The median age at presentation was 6 years (range 1 month to 12 years). Locally advanced disease, with combined acute haematogenous osteomyelitis (AHOM) and septic arthritis (SA), was present in 13 children (27%). The remaining 36 children were evenly divided (18/49 each, 37%) between isolated AHOM and SA, respectively. Disseminated disease was present in 16 children (33%) and was associated with locally advanced disease, an increase in the number of surgeries and an increased length of stay. Twenty-six complications were documented in 22 (45%) children. Chronic osteomyelitis developed in 15/49 (31%) cases, growth arrest in 5/49 (10%), and pathological fracture, DVT and septic shock in 2/49 (4%) each. Complicated disease was associated with locally advanced disease, a higher number of surgeries, disseminated disease and an increased length of stay. *Staphylococcus aureus* was the infecting pathogen in 65% of cases (31 MSSA, 1 MRSA), while 25% (12/49) were culture-negative infections. While the median time from admission to surgery was one day, the median time from onset of symptoms to surgery was seven days.

Conclusion

We found a high complication rate despite a short follow-up period. More than a quarter of patients had locally advanced disease, and this was associated with the development of complications and disseminated disease. Further studies are needed to be able to predict which children will have poor outcomes.

Level of evidence: Level 4

Keywords: acute haematogenous osteomyelitis, septic arthritis, bone and joint infections, low-and middle-income countries, developing world, resource-constrained

Introduction

Paediatric bone and joint infections are a major burden in low- and middle-income countries (LMICs). Acute haematogenous osteomyelitis (AHOM) has been shown to have an incidence of 8 to 10 per 100 000 in high-income countries while in LMIC countries the incidence is reported to be much higher at 80 per 100 000.[1,2] The true incidence may still be underreported. Data from the United States of America (USA) revealed a 2.8-fold increase in the incidence of AHOM from 1982 to 2008, while that of SA has remained unchanged.[3] According to a study from South Africa by Nunn and Rollinson in 2007, the incidence of haematogenous pyogenic bone and joint sepsis in the Ngwelezane catchment area was estimated to be 1:4 000.[4] This suggests a higher incidence of musculoskeletal infections in children in South Africa when compared to the international figures.

Some of the concerns with musculoskeletal infection include a protracted course of infection leading to severe disease and a poor outcome. Popescu et al. performed a retrospective study to identify the patients with AHOM who are at risk of a poor outcome. They found that a negative outcome was associated with a young age, male sex, rural residence, repeated negative cultures and delayed surgery.[5] There was no statistically significant association between negative outcomes and infection entry site, organism and location of the infectious process.[5]

In Southeast Asia, investigators have found that poor outcomes are associated with a prolonged course of antibiotics (> 30 days), symptom duration of more than one week, younger age, hip joint infection, infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and delayed administration of antibiotics.[6,7] In sub-Saharan Africa, a study by Mamo et al. in Ethiopia found that poor outcomes were associated with the presence of a comorbidity and the use of combination antibiotics (ceftriaxone and metronidazole).[8] Mue et al. in Nigeria suggested that complications in their cohort of patients may be due to a long duration of symptoms and delay in treatment, underlying systemic and immunosuppressive illnesses, joint site (especially hip and shoulder), and the virulence of the organisms (e.g., *Staphylococcus aureus* and Gram-negative bacilli).[9] Unfortunately, no univariate analyses were performed on these proposed associations.

As described earlier, the severity of the infection influences the outcomes. We, therefore, aimed to determine the complication rate and incidence of disseminated infection in paediatric bone and joint infections. Secondly, we aimed to identify factors associated with complications and disseminated disease, and, by extension, the severity of infection. Our results will contribute to the literature that is available in LMICs.

Methods

After obtaining approval from the relevant institutional medical research ethics board, we reviewed our paediatric orthopaedic database to identify all children who presented with acute bone and joint infections, between September 2015 and March 2019, to our paediatric orthopaedic unit. A retrospective review of case medical records, laboratory results and radiological investigations was done, and data were extracted to identify factors that were associated with the development of complications or disseminated disease.

We included all children who were 12 years or younger at the time of presentation with a diagnosis of AHOM and/or SA. We excluded children with acute reactivation of chronic osteomyelitis, pyomyositis without bone or joint involvement, hand infections, pre-patellar abscesses and musculoskeletal tuberculosis (TB).

The following data were recorded from the folders: HIV status, immunisation status, time from onset of symptoms to presentation, length of hospital stay (LOS), intensive care unit (ICU) admission, time from presentation to surgery, diagnosis (septic arthritis and/or acute haematogenous osteomyelitis), initial vitals, inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], white cell count [WCC]), and the cultured organism. The number of surgeries was recorded, as well as the development of any complications (e.g., chronic osteomyelitis, pathological fracture, growth arrest, deep vein thrombosis and septic shock). All radiographs were accessed and analysed using our picture archiving and communication system (PACS).

Complications were defined as the development of any of the following conditions: septic shock, deep venous thrombosis, growth arrest, chronic osteomyelitis or pathological fracture. The presence of septic shock was diagnosed using the criteria of the 2005 Pediatric Sepsis Consensus Conference (PSCC).[10] The presence of disseminated infection was diagnosed by the involvement of an organ system other than the musculoskeletal system (e.g., pneumonia, infective endocarditis or septic shock), or another distant musculoskeletal site. (e.g., combined distal femur and proximal humerus AHOM). Locally advanced disease was defined as adjacent AHOM and SA.

Management

The patients were managed according to our departmental protocol on the management of musculoskeletal infection in children. A clinical diagnosis of AHOM and/or SA was made by history and clinical examination. Biochemical inflammatory markers (WCC, CRP and ESR) and X-ray imaging were obtained to confirm the suspected diagnosis and monitor the response to treatment. Ultrasound was used when available to identify joint effusion and/or the location of subperiosteal or other abscess collections. Initial management included empiric intravenous antibiotic treatment with either an anti-staphylococcal penicillin (cloxacillin) or a first-generation cephalosporin (cefazolin), and gentamycin was added in patients aged ≤ 12 months and younger. Analgesia, splinting, emergent surgical drainage, debridement and biopsy also formed part of the initial management strategy. Debridement involved draining any subperiosteal pus collections and removing infected tissues. In cases where there was no subperiosteal collection, an oval window was drilled in the bone to drain any intramedullary collections. Samples (pus, periosteal tissue) were sent for Gram staining, and microscopy, culture and antibiotic sensitivity analysis. Directed antibiotics were started as soon as culture results became available, and intravenous antibiotics were changed to an oral equivalent depending on the clinical response and the CRP level demonstrating a downward trend and dropping to below 20 mg/L.[11] In uncomplicated SA and uncomplicated AHOM, oral antibiotics were given for a total of three and six weeks, respectively.

Statistical analysis

Statistical analysis was performed using jamovi version 1.2.18.0 open-source software.[12] Normally distributed continuous variables were reported as means with standard deviations (SD) and ranges. Non-parametric data were reported as medians with interquartile ranges (IQR) [Q25–Q75] and total ranges. Continuous variables were reported as percentages and numbers. The Shapiro–Wilk test was used to analyse the distribution of data. Normally distributed data were compared with the use of the unpaired Student's t-test, while the Mann–Whitney test was used for non-parametric data. Categorical data were analysed using the chi-squared test unless the expected value in any cell was below 5 when Fisher's exact test was used. All tests were two-sided, and the level of significance was set at $p < 0.05$.

Table I: Nature and anatomical distribution of musculoskeletal infections

Distribution	n	%
Acute haematogenous osteomyelitis		
Tibia	9	50
Femur	5	28
Radius	2	10
Fibula	1	6
Calcaneus	1	6
Total	**18**	**100**
Septic arthritis		
Knee	9	50
Hip	6	33
Elbow	3	17
Total	**18**	**100**
Locally advanced disease		
Ilium and hip	3	22
Proximal femur and hip	2	15
Proximal tibia and knee	2	15
Pan-femoral, hip, knee	1	8
Pan-tibial, knee, ankle	1	8
Distal femur and knee	1	8
Distal fibula and ankle	1	8
Proximal humerus and shoulder	1	8
Proximal radius and elbow	1	8
Total	**13**	**100**

Results

We identified 66 children who were admitted and treated for AHOM and/or SA at our institution during the study period. We were unable to retrieve the records of 17 children and they were excluded. We analysed the records of 49 children.

Table II: Bacteriology

Organism	n	%
Staphylococcus aureus (MSSA)	31	63
Staphylococcus aureus (MRSA)	1	2
Klebsiella pneumoniae	1	2
Staphylococcus lugdenusis	1	2
Bacillus species	1	2
Morganella morganii	1	2
No organism grown	12	24
No results	1	2
Total	**49**	**100**

Thirty-two (65%) of the 49 children were male. The median age of the children was 6 years (IQR 3–9 years, range 1 month to 12 years). Forty-five of the 49 children had a record of their HIV status available in the nursing charts. The recorded HIV infection prevalence was 4% (2/45). The median time between the onset of symptoms and presentation to our institution was seven days (IQR 4.5–13.8 days, range 1 to 30 days).

The median CRP was 104 mg/L (IQR 32–193 mg/L, range 1–315 mg/L). Locally advanced disease (combined SA and osteomyelitis) was present in 27% (13/49) of children, while the remaining 36 children were evenly divided between locally isolated AHOM and SA (18/49, 37% each) (*Table I*). The median CRP in children with locally advanced disease was 152 mg/L, compared to 74 mg/L in children with isolated AHOM or SA (p = 0.060). Disseminated disease was present in 33% (16/49) of children. The median ESR was 92 mm/hr (IQR 59–108 mm/hr, range 7 to 122 mm/hr). The median WCC was 14.2 x 109/L (IQR 9.0–19.2 × 109/L, range 4.9 to 34.7 × 109/L). Two (3.8%) patients met the Pediatric Sepsis Consensus Conference (PSCC) criteria for septic shock. Fourteen per cent (7/49) of patients were admitted to the intensive care unit (ICU) with a mean ICU stay of 8.1 days (SD 7.6 days, range 2–23 days).

While the median time to surgery from admission was one day (IQR 0–1 day, range 0–7 days), the median time to surgery from

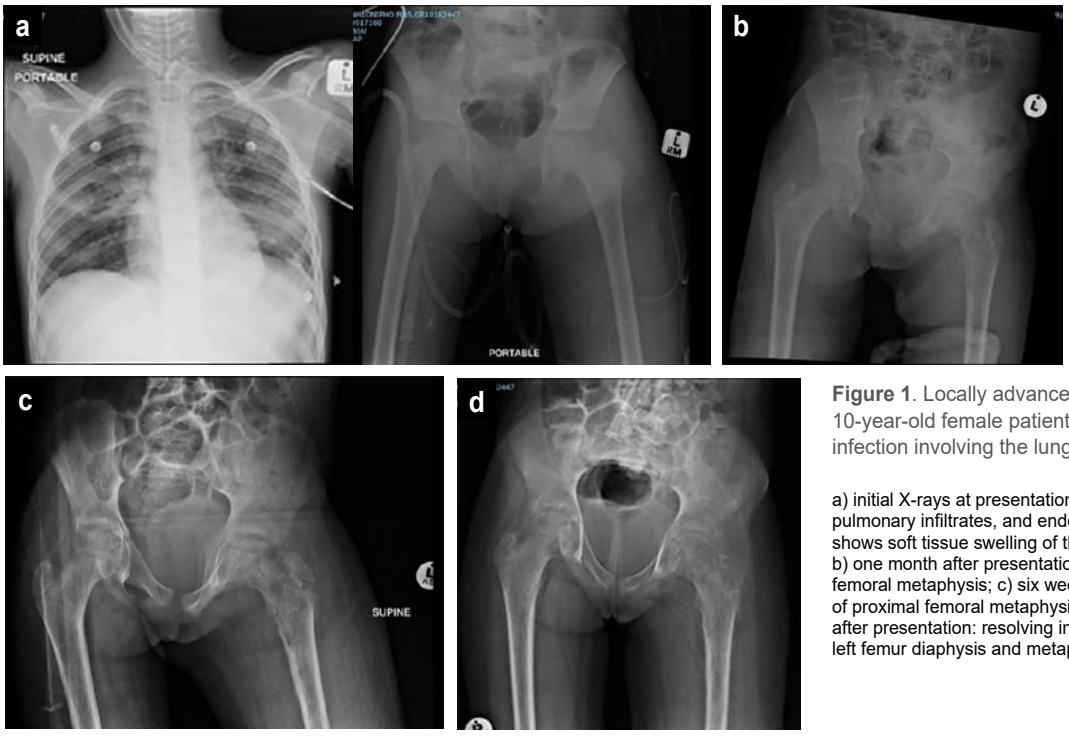

Figure 1. Locally advanced and disseminated infection in a 10-year-old female patient – disseminated staphylococcal infection involving the lungs, left proximal femur and left hip.

a) initial X-rays at presentation: chest X-ray (CXR) revealing bilateral pulmonary infiltrates, and endotracheal tube in situ; pelvis X-ray (PXR) shows soft tissue swelling of the left thigh with no obvious bony changes; b) one month after presentation: rarefaction involving the proximal left femoral metaphysis; c) six weeks after presentation: extensive destruction of proximal femoral metaphysis extending into the diaphysis; d) ten weeks after presentation: resolving infection, with a periosteal reaction around the left femur diaphysis and metaphysis

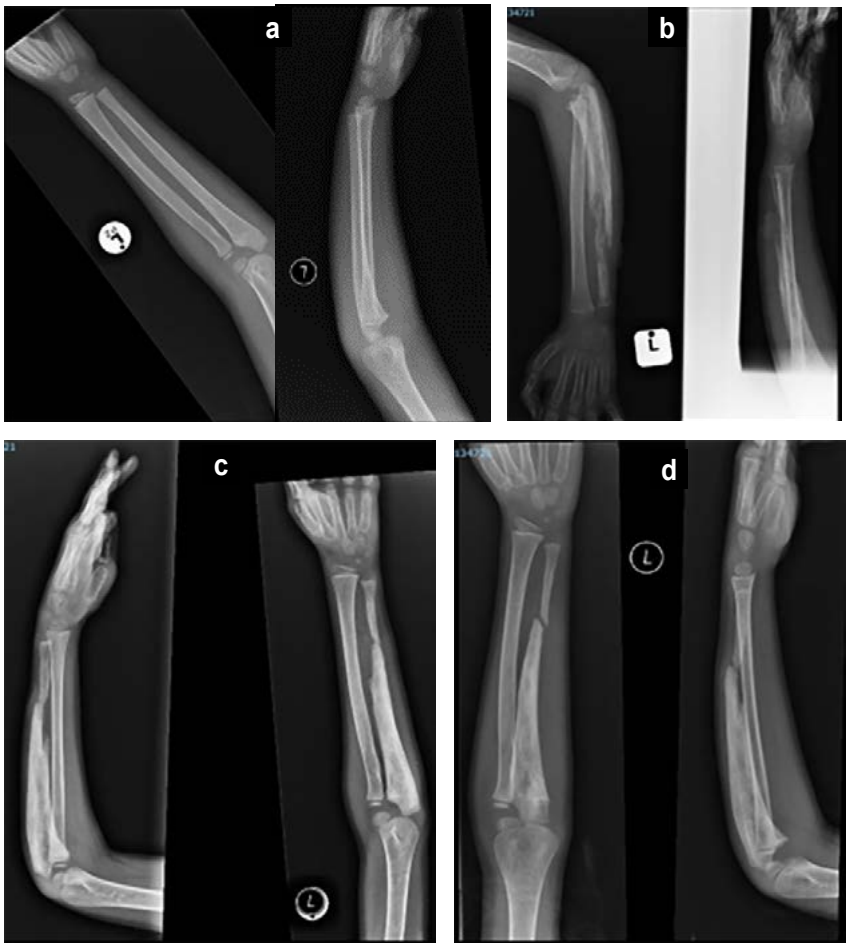

Figure 2. Complicated infection in a 4-year-old male patient with left ulna acute haematogenous osteomyelitis secondary to methicillin-resistant *Staphylococcus aureus* (MRSA).

a) initial X-rays at presentation with no bony changes; b) two months after presentation, showing extensive destruction of ulna shaft with sequestrum and involucrum; c) and d) five and six months after presentation, showing dense, sclerotic proximal ulna with loss of intramedullary canal and nonunion with the distal third ulna shaft

the onset of symptoms was seven days (IQR 4–14 days, range < 24 hours to 42 days). The median number of surgical procedures required was one (IQR 1–2, range 1–4). The median length of stay (LOS) was 12 days (Q25 7 to Q75 16 days, range 4–82 days). The median follow-up was four months (IQR 1–11 months, range 1–43 months).

Staphylococcus aureus was responsible for 32/49 (65%) of cases (*Table II*). There was no statistically significant associa-tion between *Staphylococcus aureus* and complicated (p = 0.247) or disseminated disease (p = 0.343).

During the hospital stay and follow-up period, 26 complications in 22/49 (45%) patients were documented. Twenty patients developed a single complication, and two patients had three complications. The most common complication was chronic osteomyelitis (n = 15) (*Figures 1 and 2*).

We found a statistically significant association between complicated disease and the presence of locally advanced disease, disseminated disease and the number of surgeries performed (*Table III*). Patients who developed complicated disease also had a longer hospital stay (median 15 vs 8 days, p = 0.004). Disseminated disease was associated with locally advanced disease, a higher number of surgeries performed, as well as an increased LOS (*Table IV*).

Discussion

This study aimed to describe bone and joint infections in a cohort of paediatric patients from an LMIC. Furthermore, it aimed to identify factors associated with the development of complications or disseminated disease, and, by extension, the severity of infection.

The median age of our patients was 6 years, similar to Horn et al., but higher than the 2.5 years reported by Robertson et al.[13,14] We found a male predilection (65%) for bone and joint infections in our study population. Although Arkader et al. stated that the prevalence is equally distributed among the sexes, our finding was similar to other South African reports and international publications.[4,15,16] It has been speculated that this may be due to increased exposure to microtrauma in males.[16]

The HIV prevalence in our study group was 4% (2/45). This was comparable to the reported HIV prevalence of 2.7% in children between 0 and 14 years in South Africa in 2017.[17] The rate is much lower than the 21.6% reported by Robertson et al. in 2012.[13] The reduced rate may be the result of an effective prevention of mother-to-child transmission programme (PMTCT), as the HIV prevalence reported in women of childbearing age (15–49 years) was 26.3% in 2017.[17] The PMTCT programme consists of antenatal HIV-testing, effective maternal viral load suppression with anti-retroviral drugs, safe childbirth practices and appropriate infant feeding.

Table III: Factors associated with complicated musculoskeletal infection

Variable	No complications	Complications	p-value
Age	5.6 yr (1 mo–11 yr)	5.9 yr (1 mo–12 yr)	0.832
Sex	63% male (17/27)	68% male (15/22)	0.703
Symptom duration	7 days (range 1–21)	8 days (range 1–30)	0.194
Time to surgery	7 days (range 0–22)	7.5 days (range 0–42)	0.709
Surgical procedures	**1 (range 1–4)**	**2 (range 1–4)**	**< 0.001**
CRP (mg/L)	117 (range 1–315)	79 (range 5–291)	0.904
ESR (mm/hr)	78 (SD 36)	87 (SD 33)	0.437
WCC	16.1 × 10^9/L (SD 8.23)	14.4 × 10^9/L (SD 6.72)	0.501
Locally advanced disease	**15% (4/27)**	**41% (9/22)**	**0.040**
Disseminated disease	**19% (5/27)**	**45% (10/22)**	**0.042**
Length of stay	**7 days (range 4–31)**	**15.5 days (range 4–82)**	**0.004**

Table IV: Factors associated with disseminated musculoskeletal infection

Variable	No disseminated disease	Disseminated disease	p-value
Age	6 yr (1 mo–11 yr)	5.5 yr (1 mo–12 yr)	0.983
Sex	70% male (23/33)	56% male (9/16)	0.354
Symptom duration	7 days (range 1–30)	8 days (range 3–30)	0.061
Time to surgery	7 days (range 0–42)	8.5 days (range 0–31)	0.137
Surgical procedures	**1 (range 1–2)**	**2 (range 1–4)**	**0.004**
CRP (mg/L)	69 (range 1–291)	152 (range 9–315)	0.096
ESR (mm/hr)	85 (range 7–120)	117 (range 20–122)	0.099
WCC	13.7 × 10^9/L (4.93–33.0)	20.7 × 10^9/L (7.9–34.7)	0.107
Locally advanced disease	**9% (3/33)**	**63% (10/16)**	**< 0.001**
Length of stay	**9 days (range 4–31)**	**18.5 days (range 6–82)**	**< 0.001**

The median CRP on admission was 104 mg/L. This value was similar to Robertson et al. but lower than the median 223.6 mg/L reported by Horn et al.[13,14] Rosenfeld et al. found a significantly higher CRP in children with SA and adjacent osteomyelitis.[18] In our study, the median CRP of the patients with locally advanced disease was higher than the median CRP of children with isolated AHOM or SA, but there was a significant overlap in the ranges, and the association was not statistically significant. Roine et al. found an association between a higher CRP and the occurrence of complications.[19] We, together with Horn et al., did not confirm this association in our study group.[14]

The children in our study were symptomatic for a mean of seven days prior to surgery at our institution. This was a longer period than the symptom duration of three days (range 1–7 days) and five days (range 1–42 days) in the studies by Robertson et al. and Horn et al., respectively.[13,14] Nunn and Rollinson reported that in their series the majority of their patients had surgery beyond the recommended five and seven days of symptoms for SA and osteomyelitis respectively. A major finding in their study was a significantly longer duration of symptoms prior to surgery in the children with complications when compared to those without complications.[4] Dartnell et al. in a systematic review similarly warned against delayed treatment, reporting a study by Cole et al. which showed a decreased cure rate from 92% to 25% when treatment was delayed beyond five days.[20,21] This intuitively seems correct but was not corroborated by our study or by Robertson et al.[13] In the study by Robertson et al., there were no patients that had surgery after seven days, which may have skewed their results. In our study, several of the children with prolonged symptom duration had treatment before presentation, including the prescription of oral antibiotics, which may have influenced their presentation and outcome. Another consideration is that infectious disease severity is influenced by organism virulence and host defence, which may result in those children with more severe disease who present earlier having a similar complication rate to those children with moderate disease that present late. Further studies with comprehensive data capturing and accurate disease severity classification are essential to study the association between symptom duration prior to treatment and outcome. Despite our findings, we maintain the recommendation that efforts to improve early recognition and referral of children with suspected musculoskeletal infection for definitive treatment should be strengthened. We base this on our finding of a relatively long duration of symptoms before surgery in a condition taught to be an orthopaedic emergency.

Staphylococcus aureus was the pathogen found in most of our bacterial cultures (65%) with MSSA predominating (97%) and only one case (3%) of community-acquired MRSA. The low rate of MRSA was similar to the previous studies from South Africa (0–2.4%).[13,14] This rate is much lower than the rates of 25% and 29% reported in the USA.[22,23] There was a high culture-negative rate in our study (25%, 12/49). Several factors could have contributed, including the fact that a blood culture was not done on admission in all cases, a failure to collect a viable bacterial sample intraoperatively, and the possibility of *Kingella kingae* infection. Literature has shown an increasing trend in the prevalence of Kingella osteoarticular infections in children between 6 months and 4 years of age.[24] A systematic review by Wong et al. identified *K. kingae* in 48% of musculoskeletal infections in children aged less than 48 months.[25] This is mainly due to the improvement in detection and isolation methods with real-time PCR (RT-PCR) being more sensitive and specific compared to microbiological culture. Ceroni et al. identified *K. kingae* in 82% of cases using RT-PCR.[26] Notably, Gram staining and traditional culturing methods were all negative. In our study, 4/12 (33%) of the culture-negative patients were aged 4 years and below. Only microbiological culture was performed on the samples, and none were sent for RT-PCR. Further research using improved detection methods is required to determine the true incidence of *K. kingae* infection in our setting.

Children with acute musculoskeletal infection present on a spectrum of severity.[27] Several attempts have been made to devise scoring systems to predict more severe infection. Variations in the definition of severe infection make these difficult to interpret. Copley et al. used length of stay (LOS) as a surrogate measure of disease severity, while Mignemi et al. classified infection severity into three groups: inflammation, local infection and disseminated infection.[28,29] More severe infection was associated with higher inflammatory markers and specifically the CRP, increased number of surgical procedures and an increased LOS.[29,30] Disseminated infection included infection in multiple compartments (e.g. subperiosteal abscess), as well as in children with a combination of SA and osteomyelitis (defined anatomically as complex infections in their study).[29] This makes this classification less applicable in our environment where most cases of osteomyelitis have subperiosteal abscess formation at presentation. The classic teaching that the physis presents a barrier to epiphyseal and articular infection spread after the age of 1 year is based on the vascular studies of Trueta.[31] The exception to the rule is where the metaphysis extends beyond the capsular insertion, such as in the proximal humerus, femur and radius, and the distal fibula.[32]

A more recent observational study based on MRI investigations found that transphyseal spread is considerably more common than once thought.[33] This is supported by Nunn and Rollinson who found a 44% (35/80) incidence of combined SA of the knee with distal femur or proximal tibial osteomyelitis.[4] We found a 27% (13/49) incidence of combined SA and adjacent osteomyelitis (defined as locally advanced disease). There was a 10% (5/49) incidence of knee SA with adjacent osteomyelitis (in two of these cases the hip and ankle were respectively also affected). Rosenfeld et al.

developed an algorithm to predict adjacent infections in children diagnosed with SA based on age, CRP, duration of symptoms and neutrophil count.[18] Other authors were not able to validate this algorithm in different geographic regions.[20,34] We found an association between locally advanced disease and a higher rate of complications, as well as a higher rate of disseminated disease, highlighting the importance of this diagnosis as a marker of increased disease severity. A timely diagnosis of concomitant SA and osteomyelitis will assist with appropriate management of both sites at the index operation, thus reducing the bacterial burden early and potentially reducing the number of surgeries and positively impact the outcome. Griswold et al. showed that routine MRI investigation in children with suspected musculoskeletal infection reduced repeat surgery from 50% of cases to < 27% ($p = 0.009$).[35] Further research is required to develop indicators to predict which children are at risk of locally advanced disease to inform the appropriate use of MRI investigation in a resource-limited environment.

Children in our study who developed complications were more likely to have locally advanced disease, disseminated disease, a longer LOS and more surgical procedures. Similarly, children with disseminated disease were more likely to have locally advanced disease, a longer LOS and a higher number of surgical procedures. Further research is required to develop a locally applicable disease severity classification and to identify factors associated with increased disease severity at presentation.

Our study found a 45% (22/49) complication rate within a median follow-up period of four months (range 1–43 months). The most common complication was chronic osteomyelitis. This relatively high complication rate was similar to the 48% complication rate reported by Horn et al.[14] The follow-up period in our study was too short to detect all cases of chronic osteomyelitis, pathological fracture and growth arrest, and it is likely to have underrepresented the actual complication rate.

Our study had several limitations. First, we had a small sample size. Contributing to the small sample size, and another limitation impacting the interpretation of our results, was the exclusion of 17 patients. We also did not analyse adolescents between the ages of 13 and 18 years with musculoskeletal infections because they were not managed by our paediatric unit. Our findings may not be representative of all children with musculoskeletal infection, as only the cases referred to our institution that underwent surgical drainage were included in this study. Thirdly, we were unable to record the time to the first dose of antibiotics, as antibiotics were often started at the base hospitals before referral. Another limitation of our study was the short follow-up period. This was because children with an uncomplicated course of infection often failed to attend scheduled follow-up appointments. Despite the short follow-up period, we reported a relatively high complication rate, emphasising the serious consequences of musculoskeletal infections and the importance of further research.

Conclusion

Septic arthritis and acute haematogenous osteomyelitis remain a relevant concern in the developing world. We found a high complication rate despite a short follow-up period. More than a quarter of patients had locally advanced disease, involving combined SA and AHOM, and this was associated with the development of complications and disseminated disease. Further, adequately powered, studies are still needed to be able to predict which children will have poor outcomes.

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Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd world Conference on Research Integrity in Singapore, 2010.
Prior to commencement of the study, ethics approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00001084/2020).
All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

VSM: study conceptualisation, data collection, data analysis, manuscript preparation and revision
PHM: study conceptualisation, study design, data analysis, manuscript review and revision
LCM: data review and revision, manuscript review and revision

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