Title

A clinical decision tool for septic arthritis in children based on epidemiologic data of atraumatic swollen painful joints in South Africa

Journal

International Orthopaedics, 44(12)

ISSN

0341-2695

Authors

Upfill-Brown, Alex
Bruins, Marie-Fien
Dix-Peek, Stewart
et al.

Publication Date

2020-12-01

DOI

10.1007/s00264-020-04815-3

Peer reviewed

Published: 28 September 2020

A clinical decision tool for septic arthritis in children based on epidemiologic data of atraumatic swollen painful joints in South Africa

Alex Upfill-Brown, Marie-Fien Bruins, Stewart Dix-Peek, Maritz Laubscher, Nicholas M. Bernthal & Michael Held

International Orthopaedics (2020)Cite this article

Abstract

Background

In settings with limited access to specialist services, differentiating septic arthritis—a surgical emergency—from non-infectious atraumatic arthropathy in paediatric patients is challenging, especially in a setting with a high burden of tuberculosis (TB). We aimed to investigate the aetiologies of swollen, painful joints in an urban setting in South Africa and determine how clinical and laboratory findings varied with diagnosis.

Patients and methods

A retrospective review of patients aged 12 or younger presenting to a paediatric hospital in Cape Town, South Africa, with atraumatic swollen, painful joints was conducted over a two year period from 2013 to 2015. Children were excluded if they did not have tissue culture or analysis conducted at our facility. Aetiology was classified as non-infectious, TB septic arthritis, or pyogenic arthritis from other bacterial causes.

Results

One hundred and four children met inclusion criteria. Arthritis was classified as non-infectious in 43 (41%), TB in 15 (14%), and pyogenic in 40 (38%), with six (6%) patients never receiving a final diagnosis. Mean C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WCC) were all significantly higher in pyogenic infectious arthritis compared with TB and non-infectious arthritis. There were no significant differences in these parameters between non-infectious and TB arthritis. Using cut-point analysis, thresholds were identified predictive of the presence of pyogenic arthritis versus TB or non-infectious arthritis; these included the presence of fever, CRP > 50 mg/L, ESR > 65 mm/h and WCC > $12x10^9$/L. The absence of all of these criteria

resulted in a negative predictive value of 100% for pyogenic infection; the presence of three to four criteria resulted in a positive predictive value of 71%.

Conclusions

Despite insignificant differences in their clinical presentation compared with non-infectious arthidities, 15% of children were diagnosed with tissue-confirmed TB infection. Predictive values of clinical criteria are reduced in our population due to elevated levels of inflammatory markers in all patients. Synovial biopsy to rule out TB is recommended in all patients in a high-burden setting given clinical similarity to non-infectious aetiologies.

Introduction

Differentiating septic arthritis (SA) from non-infectious atraumatic arthropathy in paediatric patients is challenging, especially in settings with limited access to specialist services and advanced diagnostic modalities. Delayed or inappropriate management of SA can lead to significant joint destruction and subsequent morbidity for the patient which underlines the importance of assessing the epidemiology [1, 2].

Other causes of joint effusion in children include non-infectious conditions such as juvenile idiopathic arthritis, acute or chronic synovitis, or malignancy. Previous research has sought to identify laboratory serum studies to help clinicians differentiate infectious from non-infectious causes of swollen painful joints. To date, C-reactive protein (CRP) and procalcitonin have shown promise in this regard [3, 4]. Yet, for southern Africa, there is limited evidence on the utility of serum studies in differentiating causes of joint effusion in children.

In southern Africa, distinguishing septic arthritis from non-infectious aetiologies of joint effusion is complicated by the high burden of tuberculosis (TB) and human immunodeficiency virus (HIV), which can lead to nonclassical presentations of septic arthritis [5,6,7]. Commonly, children with TB arthritis often present with subacute or chronic monoarticular joint pain, stiffness, and antalgic gait [8]. Without tissue biopsy, infections can be confused with inflammatory arthropathies, such as juvenile idiopathic arthritis (JIA), sarcoidosis, or malignancy [5, 9, 10]. TB, known as a notorious mimicker of other conditions, can often lead to delayed diagnosis and poor clinical outcomes [7].

In the USA, clinical criteria first developed by Kocher and colleagues as a means of differentiating septic arthritis from transient synovitis of the hip have come to be used as means of differentiating between septic arthritis and other non-infectious causes of arthritis [11, 12]. These criteria include fever greater than 38.5 °C, non-weight-bearing, white cell count (WCC) greater than 12.0×10^9 L, and ESR greater than 40 mm/h [11, 12]. Since the development of C-reactive protein (CRP), a criterion of CRP greater than 20 mg/L has been proposed [13]. It is unknown if these criteria are useful in an urban setting in southern Africa.

In this study, we aim to assess the main causes of swollen painful joints in southern African children, describe the microbiology of infected joints, and evaluate the utility of common serum studies in differentiating between aetiologies.

Patients and methods

Patients

We conducted a retrospective review of consecutive paediatric patients, 12 years of age or younger, who presented with swollen, painful joints to the Red Cross War Memorial Children's Hospital in Cape Town, South Africa, from April 2013 to April 2015. Children admitted to our hospital are usually from low-income household and live in densely populated areas, which increases the risk of exposure to TB.

The included children underwent open biopsy to test for TB as part of the routine clinical workup. Children were excluded from our study if they were older than 13 years of age on admission, or if they did not have tissue culture or analysis conducted at our facility. Tests conducted on these samples included histology, microbiology, culture, and PCR Xpert MTD/RIF assay (Cepheid, Sunnyvale, California) [14]. The PCR Xpert technique has been described in detail previously [15]. TB infection was defined as TB culture positive, Xpert MTD/RIF positive, or histology positive for acid fast bacilli, or histologic evidence of granulomatous inflammation, and Langerhans cells. Pyogenic infection was defined as positive bacterial culture or gram stain. Improvement was measured for at least one month while on appropriate therapy. Clinical notes, laboratory results, and histological findings were combined into a single database for analysis.

Statistical analysis

Two-tailed Student's *t* tests and Mann–Whitney U tests were used to analyze differences within normally and non-normally distributed variables, respectively. Chi-squared and Fisher's exact tests were used to test for independence in contingency tables. Logistic regression techniques were used to evaluate relationships between measured covariates and different outcomes. Variables independently associated with outcomes were evaluated in multivariate models. Cut-point analysis was utilized to determine the optimal threshold in hematological parameters to distinguish between different diagnostic categories. A p-value of < 0.05 was considered to be significant. Analysis was carried out in R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [16].

Results

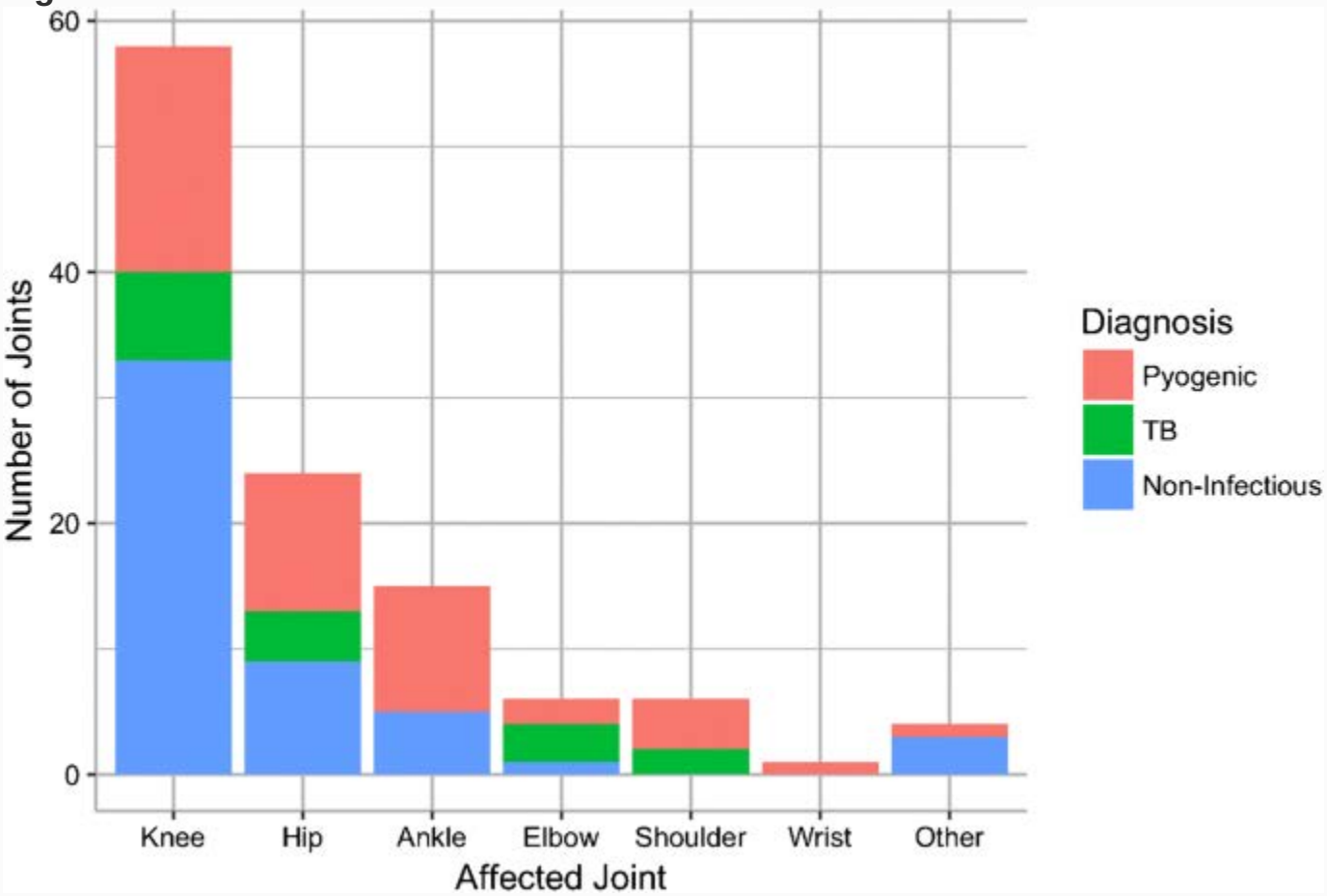
Patient demographics

Of the 104 patients, 61 males were included (Table 1). Forty (38%) children were diagnosed with a pyogenic infection, 15 (14%) with TB, and 43 (41%) with a non-infectious cause. Here, acute synovitis was the most common diagnosis. Four children were diagnosed with TB before presentation, and only one of these children was subsequently

diagnosed with TB arthritis. Most patients presented with monoarticular arthritis (93%). The knee was the most commonly affected joint (54%), followed by the hip (23%) (Fig. 1).

Table 1 Summary of patient characteristics

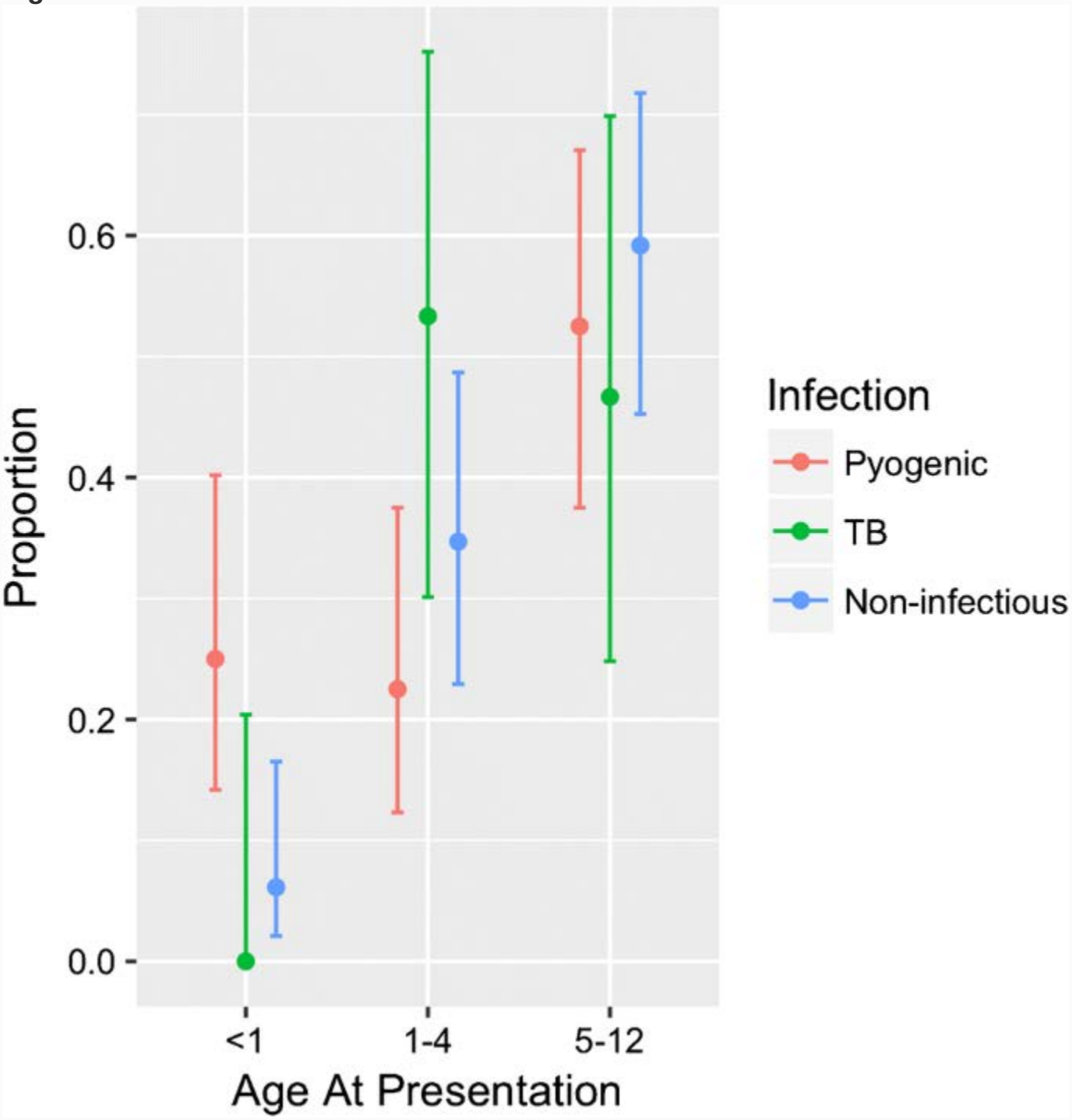
Fig. 1



Distribution of the location of swollen, painful joint by final diagnosis

Age at diagnosis varied significantly between the three diagnostic categories ($p = 0.023$, Fig. 2). Of the 13 children under one year old, 10 (77%) were diagnosed with pyogenic arthritis and three (23%) with non-infectious arthritis. In the 57 children between five and 12 years old, 21 (37%) were diagnosed with pyogenic arthritis, seven (12%) with tuberculosis arthritis, and 29 (51%) with non-infectious arthritis.

Fig. 2



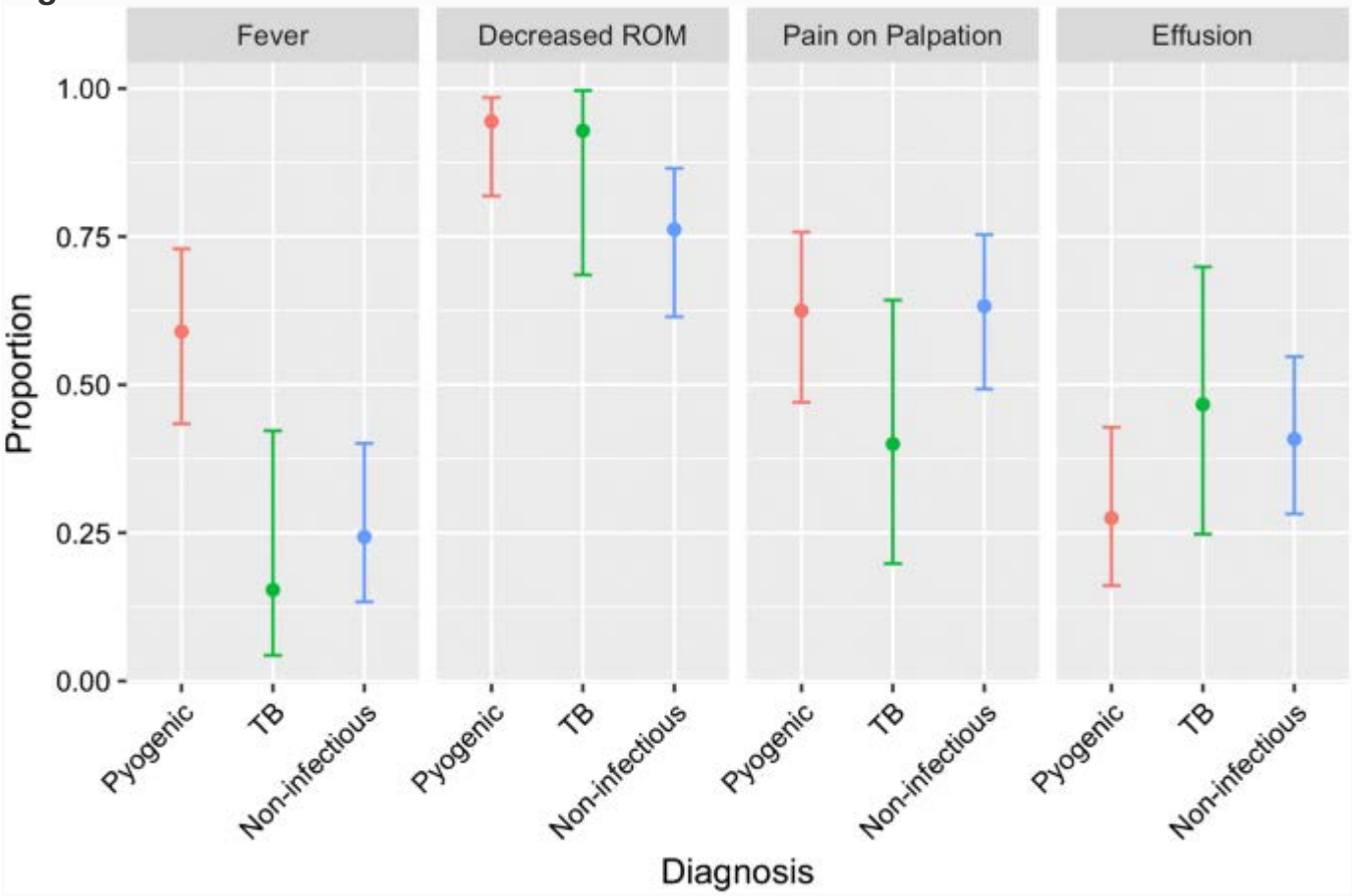
Age at presentation by final diagnosis. Error bars represent 95% confidence intervals

Clinical characteristics

Clinic characteristics were collected from the chart, including the presence of fever (temperature > 38 °C), decreased range of motion (ROM) on exam, pain on palpation, and a clinically appreciable effusion (Fig. 3). Significantly more patients with pyogenic arthritis presented with pyrexia (59%) compared with non-infectious arthritis (24%) or TB (15%) ($p = 0.001$). Although not significant, there was a trend of decrease in ROM ($p = 0.05$), in patients with pyogenic arthritis (94%) and TB (93%) patients, compared with non-

infectious arthritis (76%). Differences between groups with regard to pain on palpation (p = 0.25) and effusion (p = 0.29) were insignificant.

Fig. 3



Presenting symptoms by final diagnosis. Error bars represent 95% confidence interval

Pathogens

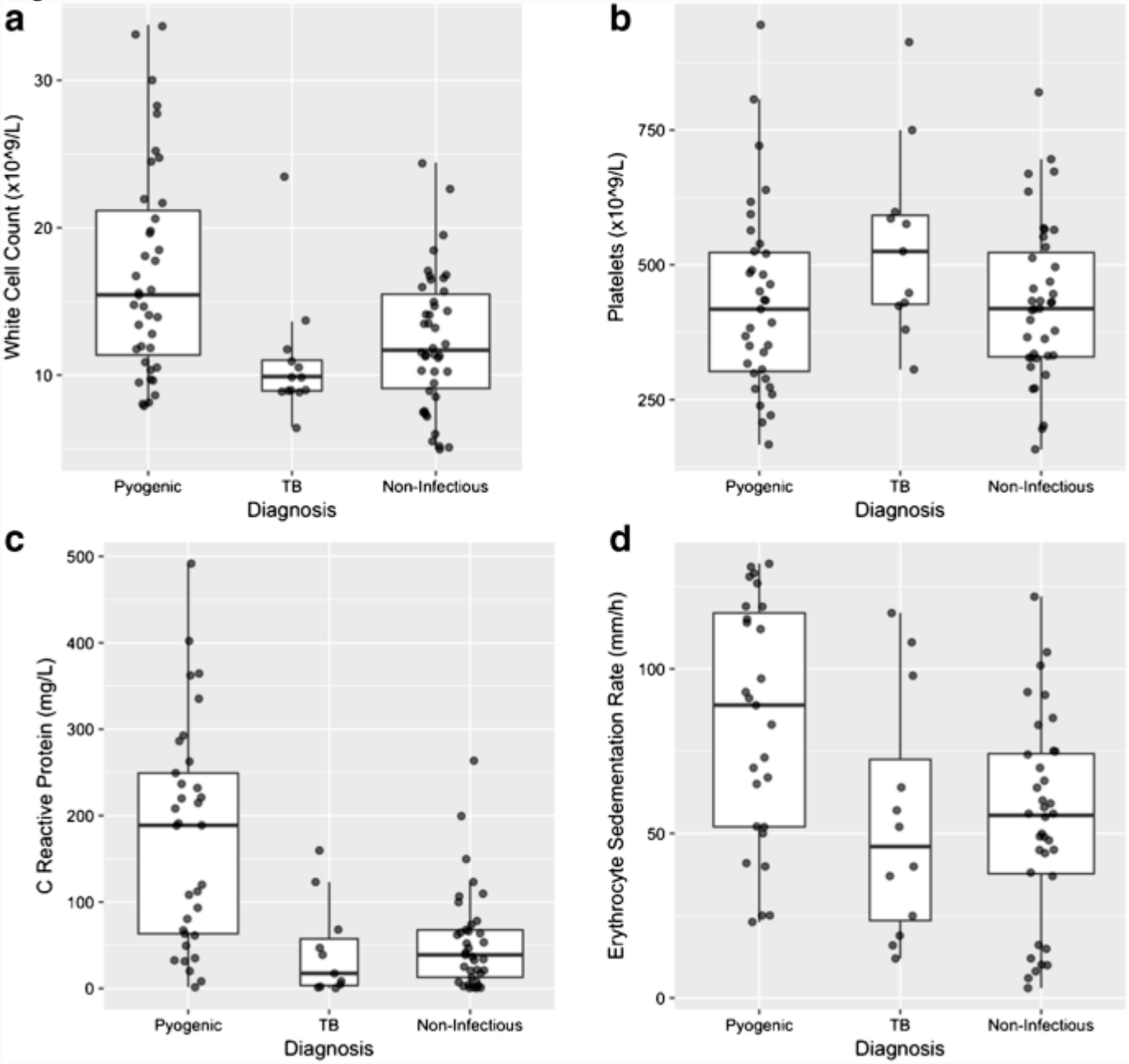
Most infections were due to *Staphylococcus* species (23 *S. aureus*, 2 *S. epidermidis*), followed by *Mycobacterium tuberculosis*, *Streptococcus* species (4 *S. pyogenes*, 3 *S. pneumoniae*), Gram-negative rods (1 *E. coli*, 1 *Klebsiella*, 1 *Pseudomonas*, 1 *Salmonella*), and *Bacillus* species (Table 2). In two patients, final speciation was not possible. There was no significant variation in the distribution of pathogens by primary location of infection (p = 0.22, Table 2).

Table 2 Distribution of infectious pathogens identified and anatomical distribution

Haematological parameters

Four different laboratory studies were examined for their relationship with aetiologies of arthritis: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white cell count (WCC), and platelet count. While there was substantial variability within groups (Fig. 4), significant differences emerged (Table 3).

Fig. 4



Distribution of haematological parameters by the final diagnosis for (A) white cell count, (B) platelet count, (C) C-reactive protein, and (D) erythrocyte sedimentation rate

Table 3 Distribution of haematological parameters by final diagnosis

The mean CRP for pyogenic infections was 177 mg/L, while the mean CRP was 43 for TB arthritis and 54 for non-infectious causes ($p < 0.001$). The mean ESR was similarly elevated in pyogenic arthritis (84 mm/h) compared with TB arthritis (54) and non-infectious arthritis (54, $p = 0.002$). WCC was elevated in pyogenic arthritis to 17.0 × 10^9/L, 10.9 in TB arthritis, and 12.3 in non-infectious arthritis ($p < 0.001$). The difference in platelet counts between groups was not significant ($p = 0.13$).

Clinical criteria decision tool

Cut-point analysis was conducted comparing ESR, CRP, and WCC in pyogenic septic arthritis and the clinically similar categories of non-infectious and TB arthritis. Optimal cut-

points were estimated to maximize sensitivity for detecting pyogenic infections. For CRP, the calculated cut-point was approximately 50 mg/L, with a sensitivity of 0.82, and a specificity of 0.60. The estimated cut-point for WCC was approximately 12.0 × 10^9/L with a sensitivity of 0.74 and a specificity of 0.60. The optimal cut-point for ESR was approximately 65 mm/h with a sensitivity of 0.70 and a specificity of 0.69.

Next, we evaluated the utility of a clinical score derived as a sum of criteria met using clinical and laboratory data supported by the current analysis. The four parameters included were (1) presence of fever, (2) WCC greater than 12 × 10^9/L, (3) CRP greater than 50 mg/L, and (4) ESR greater than 65 mm/h. As a comparison, a modified version of the Kocher criteria was also evaluated. The refusal to bear weight was not included in this evaluation as this was not available in our study. The Kocher criteria evaluated were (1) presence of fever, (2) WCC greater than 12.0 × 10^9/L, (3) CRP greater than 20 mg/L, and (4) ESR greater than 40 mm/h.

Table 4 summarizes the results of these exercises. If children met three or four of the four criteria developed from this study, there was a positive predictive value (PPV) of 71% (15/21), compared with a PPV of 59% (19/32) using the modified Kocher criteria described above. If children met zero or one of the criteria developed here, the negative predictive value (NPV) was 83% (20/24), compared with 92% (12/13) using the modified Kocher criteria. The estimated area under the curve (AUC) for the receiver operating characteristic (ROC) for our clinical criteria scoring system was 0.81, compared with 0.78 for the modified Kocher criteria. The Pearson chi-squared test for trend indicated a strong relationship between an increasing number of criteria met and the likelihood of having pyogenic arthritis for both modified Kocher and criteria developed here ($p < 0.001$).

Table 4 Utility of clinical criteria for predicting pyogenic septic arthritis in study cohort

Discussion

The correct diagnosis of swollen, painful joints in children is crucial in preventing future morbidity. A low density of specialists and limited resources make primary healthcare workers the main contact for most children with these symptoms in southern Africa, and initial diagnostic tools need to be simple, objective, and reproducible.

In this study, we describe the epidemiology of large joint arthidities in children from an urban area in South Africa. The main finding was a high rate (15%) of TB arthritis among children with swollen painful joints. Importantly, these children did not differ in their clinical presentation with regard to both symptoms and laboratory studies compared with non-infectious arthropathies. Classical clinical guidelines or criteria for identifying children with septic arthritis can therefore not be applied to this cohort of patients. In areas with high population burden of TB, more invasive clinical studies—including joint aspiration and synovial biopsy—are necessary in order to eliminate TB as a cause of a paediatric swollen

painful joint. TB has notoriously poorer sensitivity for fluid tested compared with tissue, although newer methods (such as PCR) are improving accuracy [14]. TB is often paucibacillary in children and the tissue response assessed with histology is key in the diagnosis. We therefore routinely collect representative synovial tissue specimen through an open surgical approach. Where open biopsy is not feasible, aspiration should still be done under sterile conditions, ideally in the OR to avoid inoculation and contamination with skin commensal. In view of a high TB infection rate, protocols should be implemented to protect staff from exposure; this should include access to the appropriate respirators and special precautions taken during intubation and extubation.

Up to 20% of all TB patients can have extrapulmonary involvement [5]. Musculoskeletal manifestations may account for 10–15% of this specific group but have also been described to go up to 35%—accounting for 1–5% of all cases of tuberculosis infection [7, 17,18,19]. In the paediatric patient population, almost a third develops extrapulmonary disease, and 7% will be affected by bone and joint involvement (32). In children, the spinal column is also most commonly affected (50%), followed by the hip (20%), knee (10%), foot and ankle (5%), wrist and hand (3%), elbow (2%), and shoulder (1%) (33). Of the 15 children with a confirmed TB joint infection, the knee was the most common joint affected (47%), followed by the hip (27%), and the elbow (20%). Spinal column infections were not included in this study.

In total, 39% of our cohort were diagnosed with pyogenic joint infections. Pyrexia and certain lab-based parameters showed significant differences when comparing pyogenic with TB or inflammatory arthritis. These were combined to a new clinical decision tool which had a higher predictive value than Kocher's clinical criteria. The majority of pyogenic infections in our study were caused by *S. aureus* (58%), consistent with epidemiologic studies of septic arthritis from the USA [1]. Group A strep and *S. pneumoniae* were the next most common causes of septic arthritis at 10 and 8%, respectively. Again, this is roughly consistent with epidemiologic studies from the USA [2]. We identified no cases of *Kingella kingae* infection, an increasingly identified cause of septic arthritis in young children in Europe [1]. This organism is very difficult to culture and also results in more benign presentations than those resulting from other pathogens, making it difficult to detect [20]. This is similar to TB joint infections identified in this study. Given the difficulty isolating *K. kingae* in standard bacterial culture, it is possible that some patients in this study diagnosed with non-infectious arthritis were infected with *K. kingae* and cleared their infections without antibiotics.

As expected, pyogenic infections differed significantly from non-infectious aetiologies with regard to clinical presentation. Children with pyogenic infections were more likely to present with fever (59%) compared with children with non-infectious aetiologies (24%). Children with pyogenic infections also had higher average WCC, ESR, and CRP on presentation. Importantly, children with TB arthritis were indistinguishable with regard to fever, WCC, ESR, and CRP from those with non-infectious arthritides. Clinically, this poses a challenge as criteria, such as the Kocher criteria, cannot be effectively used to distinguish infected joints from uninfected joints in populations with high burdens of TB.

Overall, we found that the laboratory study thresholds used in the Kocher criteria developed with a cohort from Boston, USA, were too low for our population from Cape Town, South Africa, for CRP and ESR. In our assessment of modified Kocher criteria, we found a high NPV for the absence of pyogenic injection if only 0 or 1 of criteria were met (92%). However, there was a lower positive predictive value if 3 or 4 (59%) criteria were met compared with the original published studies (93%) [11, 12]. Using cut-point analysis methods, we identified higher thresholds for CRP and ESR to be used in our clinical criteria-based decision tool. These resulted in a slightly higher PPV when 3–4 (71%) criteria were met at the expense of a lower NPV when 0–1 (84%) criteria were met compared with the Kocher criteria. Importantly, if no criteria were met, the NPV was 100% in this study. A possible explanation for the higher inflammatory markers in South African children compared with those in the USA is that children presented to our hospital later in the course of their disease process than those in the USA.

There are limitations to this study. First, it is retrospective in nature, and as a consequence, a standardized set of clinical assessments and laboratory studies was not available for all patients. Second, this study represented a specific urban population in South Africa. While TB prevalence is high nationwide, this study is not representative of rural communities. Third, this study is relatively small. The number of patients limits the confidence in the clinical criteria developed here and prevented further statistical analysis.

In conclusion, this is an epidemiological study on tissue-confirmed pediatric arthritis in urban southern Africa. A total of 15% of children were diagnosed with tissue-confirmed TB septic arthritis, and these children were indistinguishable from those with non-infectious arthritis with regard to clinical presentation and laboratory values. Overall, fever and decreased range of motion were more commonly noted in patients with pyogenic joint infections compared with joint swelling. Predictive value of clinical criteria developed in the USA to identify children with pyogenic joint infections appears to be reduced in our cohort as inflammatory markers were much higher overall. The proposed clinical criteria are a valuable decision tool for prioritization, especially to primary healthcare providers, who are often the point of first contact in southern Africa. Although this is useful to decide on the urgency of treatment and referral, a synovial biopsy is still recommended, even if cut-off points are not reached, to rule out TB arthritis in populations with high burdens of TB.