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Clinical and Biologic Characteristics of *Kingella kingae*-Induced Septic Arthritis of the Knee in Young Children

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Background and Objectives: Septic arthritis of the knee is presumed to be the most frequent form of *Kingella kingae*-induced osteoarticular infection. This study aimed to report on the clinical course, biological parameters, and results of microbiological investigations among children with *K. kingae*-induced septic arthritis of the knee. It also assessed the modified Kocher–Caird criteria's ability to predict *K. kingae*-induced septic arthritis of the knee.

Methods: The medical charts of 51 children below 4 years old with confirmed or highly probable *K. kingae*-induced arthritis of the knee were reviewed. Data were gathered on the five variables in the commonly-used Kocher–Caird prediction algorithm (body temperature, refusal to bear weight, leukocytosis, erythrocyte sedimentation rate, and C-reactive protein level).

Results: Patients with *K. kingae*-induced arthritis of the knee usually presented with a mildly abnormal clinical picture and normal or near-normal serum levels of acute-phase reactants. Data on all five variables were available for all the children: 7 children had zero predictors; 8, 20, 12, and 4 children had 1, 2, 3, and 4 predictors, respectively; no children had 5 predictors. This gave an average of 1.96 predictive factors and a subsequent probability of ≤ 62.4% of infectious arthritis in this pediatric cohort.

Conclusions: Because the clinical features of *K. kingae*-induced arthritis of the knee overlap with many other conditions affecting this joint, the Kocher–Caird prediction algorithm is not sensitive enough to effectively detect *K. kingae*-induced septic arthritis of the knee. Excluding *K. kingae*-induced arthritis of the knee requires performing nucleic acid amplification assays on oropharyngeal swabs and joint fluid from those young children presenting with effusion of the knee, even in the absence of fever, leukocytosis, or a high Kocher–Caird score.

Keywords: septic, arthritis, *Kingella kingae*, children, knee, NAAA (nucleic acid amplification assay), PCR (polymerase chain reaction)

(*Pediatr Infect Dis J* 2023;42:195–198)

Accepted for publication November 10, 2022

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The authors have no conflicts of interest to disclose.

AR and BC conceptualized and designed the study, collected the data in Geneva, drafted the initial manuscript, and reviewed and revised the manuscript. GDM, BC, OV, NG, CS, and RD treated the patients, collaborated in collecting the data, and critically reviewed the manuscript for important intellectual content. ATF participate in data representation, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ISSN: 0891-3668/23/4203-0195
DOI: 10.1097/INF.0000000000003797

INTRODUCTION

Since the beginning of the 2000s, a clinician's ability to efficiently detect small quantities of bacterial DNA using nucleic acid amplification assays (NAAAs) has improved. Indeed, the introduction and widespread use of NAAAs has decreased the rates of osteoarticular infections (OAIs) that had previously returned as culture-negative.

Cases of osteoarticular infections attributed to *Kingella kingae* increased during the same period. More extensive use of NAAAs has provided evidence that *K. kingae* has become the most common pathogen responsible for OAIs in children below 4 years old.[1–4] Septic arthritis is the most common form of the osteoarticular disease caused by *K. kingae*. This infection tends to involve above all the lower limb limbs and the knee joint most frequently.[5–12] The clinical and biological aspects of septic arthritis of the knee can, unfortunately, be less obvious when *K. kingae* is responsible for the infection.[13] In addition, synovial fluid white blood cell (WBC) examinations in children with culture-proven arthritis due to *K. kingae* revealed counts of less than 50,000 WBC/ml in a quarter of cases, and Gram stain testing was usually negative.[14–16] Thus, an afebrile presentation, mild clinical symptoms, and the absence or slightly altered laboratory data in *K. kingae* arthritis do not meet the criteria for diagnosing a septic joint.[13]

Many conditions can present a similar clinical picture to pediatric septic arthritis, including inflammatory arthritis, reactive arthritis, transient synovitis, or even Lyme arthritis. Since 1999, some authors have tried to identify predictive factors that could help to differentiate septic arthritis of the hip from transient synovitis.[17–19] A few studies have also tested the predictive value of these factors for septic arthritis of the knee.[20–22]

This study's primary objectives were to define the clinical and biological characteristics of *K. kingae*-induced septic arthritis of the knee, and appreciate whether the modified Kocher–Caird criteria could effectively identify septic arthritis of the knee with this specific pathogen.

MATERIALS AND METHODS

After approval by the Children's Hospital Ethics Review Committee (CE 14-102R), we conducted a retrospective, cross-sectional, case series analysis of pediatric patients from 0–4 years old who had been evaluated within the hospital for suspected septic arthritis of the knee between January 2007 and December 2021. Our 111-bed tertiary pediatric hospital serves the city of Geneva and surrounding areas; it is the only facility providing inpatient and specialized medical services for pediatric osteoarticular infections (OAI) to the region's 460,000 inhabitants. January 2007 was chosen as the study's start date, as this was when our institution began to use real-time PCR assays specific for *K. kingae*.[23,24]

The criteria established by Morrey were used to estimate children's risks of a joint infection.[25,26] From our overall patient

cohort, we extracted all those children with confirmed or highly probable *K. kingae*-induced septic arthritis. Cases with positive MRI results and positive blood and/or joint fluid PCR assays specific for *K. kingae* were categorized as cases of confirmed *K kingae*-induced septic arthritis. Cases with positive MRI results, clinical and laboratory data typical of an osteoarticular infection due to *K. kingae*, and a positive PCR assay from an oropharyngeal specimen were categorized as highly probable *K. kingae*-induced septic arthritis.[27] This group had not undergone joint-fluid aspiration.

The following data fields were recorded for each *K. kingae* patient: sex, age, temperature at admission, weight-bearing ability, WBC count, platelet count, C-reactive protein value (CRP), erythrocyte sedimentation rate (ESR), and detailed results of the bacteriological investigations. We used the classic cutoff values for the five modified Kocher–Caird variables considered as having a predictive value for infection parameters in clinical practice: fever, defined as an oral temperature of >38.5°C; inability to bear weight; WBC > 12,000 leukocytes/mm^3; CRP > 20 mg/l; and ESR > 40 mm/h.[17–19] The following exclusion criteria were used to avoid any information bias associated with incomplete data analysis and selection bias associated with the inclusion of patients with presumptive and inconsistent diagnoses: (I) no bacteriological diagnosis obtained, (II) no laboratory data available, or (III) the patient was not ultimately managed with the administration of antibiotics. No native and non-hematogenous arthritis-osteoarthritis were excluded from the study.

Microbiologic Methods

Blood cultures have been used systematically to isolate the microorganisms responsible for septic arthritis. Our institution used the BACTEC 9000 blood culture medium before 2009 and subsequently a BD BACTEC FX automated blood culture system. Joint fluid was sent to the laboratory for Gram staining, cell count, and immediate inoculation onto Columbia blood agar (incubated under anaerobic conditions), CDC anaerobe 5% sheep blood agar (incubated under anaerobic conditions), chocolate agar (incubated in a CO_2-enriched atmosphere), and brain–heart broth. These media were incubated for 10 days. Two PCR assays were also used for bacterial identification when standard cultures were negative. Initial aliquots (100–200 µl) were stored at −80°C until processing for DNA extraction. A universal, broad-range PCR amplification of the 16S rRNA gene was performed using BAK11w, BAK2, and BAK533r primers (Eurogentec, Seraing, Belgium). As of 2007, our institution also used a real-time PCR assay targeting the *K. kingae* gene's rtx toxin and was designed to detect two independent gene targets from the *K. kingae* rtx toxin locus, namely rtxA and rtxB11. This assay was used to analyze different biological samples, such as synovial fluid or peripheral blood. Since September 2009, we have also been carrying out oropharyngeal swab PCR assays for children from 6 months to 4 years old. This simple technique for detecting *K. kingae* rtx toxin genes in the oropharynx provides strong evidence that this microorganism is responsible for OAI or even stronger evidence that it is not.

Statistical Analyses

Patient demographics and clinical characteristics were reported as mean, with standard deviations (mean (SD)) for continuous variables, and frequencies with percentages (*n* (%)) for categorical variables.

RESULTS

During the period studied, our clinic evaluated 68 children below 4 years old for septic arthritis of the knee, 51 of whom were considered to have *K. kingae*-induced septic arthritis. The study included 47 children with confirmed *K. kingae*-induced septic arthritis and 4 of whom this was considered highly probable. In 48 cases, infection of the knee presented as septic arthritis, whereas septic arthritis with concomitant osteomyelitis was noted in 3 cases.

Septic arthritis affected 28 males and 23 females, and the mean age at admission was 15.3 ± 5.9 months old. Clinically, 45 children were afebrile at admission, and 33 were unable to bear weight on the affected limb (64%). WBC count was normal (<17,000/mm3) in 46 children (90%), with a mean of 12,728 ± 3407/mm3, and a left-band shift was never noted; WBC count was below 12,000/mm3 in 26 children (51%). At the initial blood evaluation, the CRP level was normal (≤ 10 mg/l) in 14 children (27%) and averaged 27.9 ± 20.5 mg/l over the entire study population. In parallel, the mean ESR was 31.2 ± 16.3 mm/h, and it was above 40 mm/h in 12 cases (24%). Mean platelet count was 425.5 ± 118.3/microliter and showed normal values in 22 cases (43%) (Table 1).

From a bacteriological point of view, *K. kingae* was recovered from classic blood cultures in 6 cases, in one case this pathogen was revealed by *K. Kingae*-specific real-time PCR assay in peripheral blood. In 45 cases, *K. kingae*-specific real-time PCR assays were performed on joint fluid, resulting in 44 positive cases (99.7%). Finally, all 45 *K. kingae*-specific real-time PCR assays performed on throat swabs were positive (100%). Children sustained classical cultures of the articular fluid.

Next, the five modified criteria predictive of septic arthritis were evaluated, as defined by Kocher and Caird (i.e., fever > 38.5°C, inability to bear weight, serum WBC count > 12,000/mm^3, ESR > 40 mm/h, and CRP level > 20 mg/l). Inability to bear weight was found in 33 children (64%) and was the most frequently noted risk factor for childhood *K. kingae*-induced septic arthritis. WBC count > 12,000/mm3 was found in 25 children (49%), a CRP level > 20 mg/l was found in 23 patients (45%), an ESR > 40 mm/h was found in 14 cases (24%), and a fever > 38.5°C was noted in 6 infants (12%) (Figure 1). When all the predictive risk factors were analyzed together, we noted that 7 infants with *K.kingae*-induced septic arthritis had none of them; 8 children had 1 factor, 20 had 2 factors, 12 had 3 factors, and 4 had 4 factors. None of the children was positive for all 5 risk factors. The average number of risk factors per patient was 1.96, corresponding to a less than 62% probability of infectious arthritis in this patient cohort with *K. kingae*-induced septic arthritis (Figure 1).

DISCUSSION

To the best of our knowledge, the present work represents the largest consecutive case series on *K. kingae*-induced septic arthritis in infants younger than 4 years old. It provides important data about this infection in terms of epidemiology and clinical and biological presentations.

Clinically, only 11.7% of patients with *K. kingae*-induced septic arthritis had a body temperature >38.5°C at admission, but

TABLE 1. Population Description (*n* = 51)

	Descriptive data
Age, mean (SD)	15.3 (5.9) months
Gender	28 males/23 females
Septic arthritis (knee)	48/51 (94%)
Septic arthritis with concomitant osteomyelitis	3/51 (6%) °
K. kingae–induced septic arthritis confirmed	47/51 (92%)
K. kingae–induced septic arthritis highly probable	4/51 (8%)

SD, standard deviation.

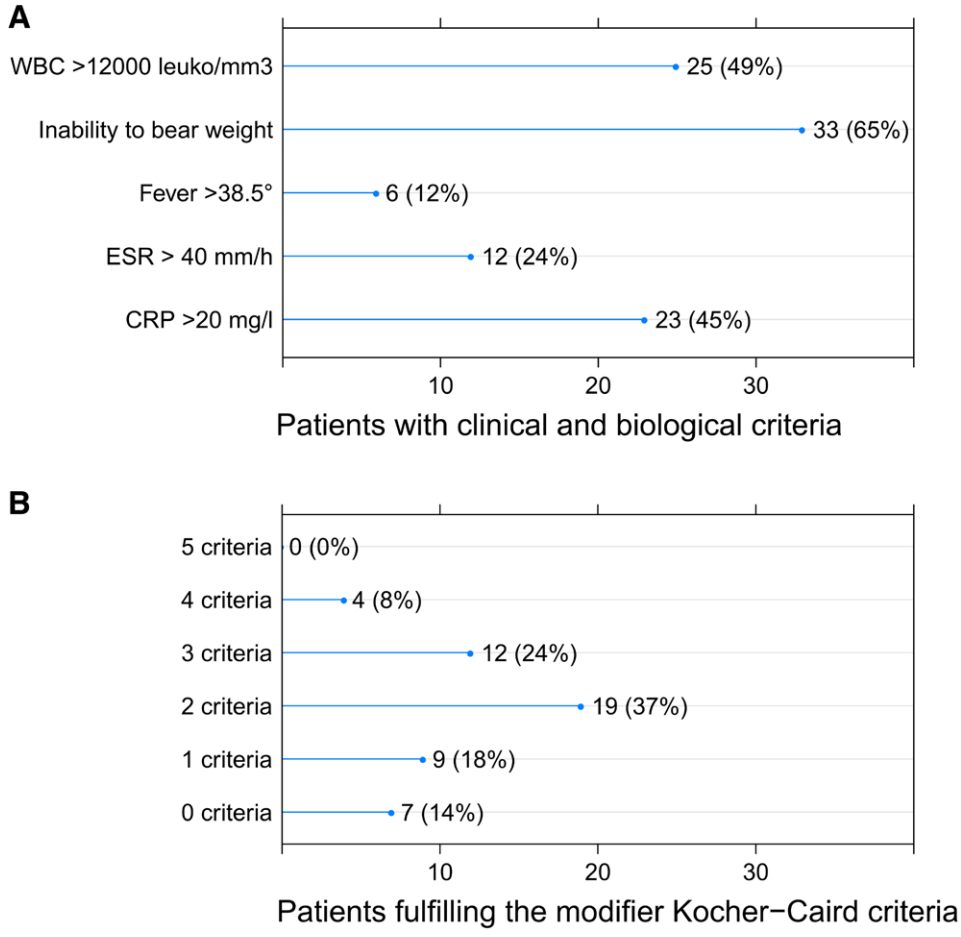

FIGURE 1. (A) Number of patients with clinical and biological criteria; (B) Number of patients fulfilling the modifier Kocher–Caird criteria. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell. full color online

64% of them were unable to bear weight on the affected limb. The study also highlighted that there might be few moderate laboratory findings in cases of *K. kingae*-induced septic arthritis. Indeed, our infant cohort only presented with mild-to-moderate clinical and biological inflammatory responses to an infection, and thus they fulfilled few, if any, of the usual criteria suggestive of an osteoarticular infection: 88% of infant patients with *K. kingae*-induced septic arthritis had normal WBC counts of ≤17,000/mm^3, and half had WBC counts below 12,000/mm^3; 55% of the infants had CRP levels below 20 mg/l, and 76% of them had an ESR below 40 mm/h. In this context, faced with a more benign clinical picture, we insist on the need for diagnostic arthrocentesis. Our results were thus in line with existing published data.

More interestingly, this was the first study to examine whether the modified Kocher–Caird criteria could effectively predict *K. kingae*-induced septic arthritis of the knee However, applying those modified criteria in children younger than 4 years to identify *K. kingae*-induced septic arthritis has only demonstrated fair predictability. We noted that 35 patients (69%) with *K. kingae*-induced septic arthritis of the knee only had two or fewer criteria suggestive of septic arthritis, which is similar to a 62.4% probability of septic arthritis.[19] Our results fit with those of *Yagupsky et al*., who demonstrated that the Kocher predictive algorithm was not sensitive enough to differentiate *K. kingae*-induced septic arthritis of the hip.[28]

Moreover, our results seem to confirm the conclusions of a few studies that noted that applying the modified Kocher–Caird criteria to identify septic arthritis of the knee was less accurate than for identifying septic arthritis of the hip. *Obey et al*. studied a cohort of pediatric patients with septic arthritis of the knee and demonstrated that the original Kocher criteria were less reliable for identifying this than they were for septic arthritis of the hip. Those authors estimated that the presence of three of the four Kocher criteria had 48.5% predictive sensitivity for septic arthritis of the knee compared to the 73% to 93% sensitivity for septic arthritis of the hip patients found by *Kocher* et al.[17,18] Similarly, *Joshy* et al. compared pediatric patients who underwent arthrotomy for suspected septic knee or hip joints.[22] These authors concluded that children with septic arthritis of the knee could not be associated with the Kocher criteria in the same way that children with septic arthritis of the hip could.

In the same way, a recent study concluded that the modified Kocher–Caird criteria had more limited utility in predicting septic arthritis of the knee than septic arthritis of the hip. In their experience, an inability to bear weight combined with an elevated CRP level had an 89.7% positive predictive value for septic arthritis of the knee, with the inability to bear weight being the strongest independent risk factor for this.

As an alternative to the original Kocher criteria, *Baldwin et al*. evaluated the notion of episodes of fever, pain within an arc of

motion below 30 degrees, a CRP level ≥4.0 mg/l, and age below 2 years old to be positive predictive factors able to help distinguish septic arthritis of the knee from non-septic conditions such as Lyme disease. These authors found that by increasing the number of criteria, they got higher predictive values; in their experience, pain within a short arc of motion had the greatest adjusted odds ratio, at 67.3.[29,30]

CONCLUSION

Septic arthritis of the knee is one of the most frequently observed forms of *K. kingae*-induced joint infection. As with the other osteoarticular infections due to *K. kingae*, septic arthritis induced by this pathogen is reported to present with a milder clinical picture than pyogenic pathogens. The modified Kocher–Caird criteria only have a limited utility in predicting *K. kingae*-induced septic arthritis of the knee, but this is also the case for knee infections caused by other pathogens. However, as several previous studies have suggested, we believe the inability to bear weight is probably the strongest independent risk factor for septic arthritis of the knee, especially when *K. kingae* is the microorganism responsible, and we insist that to have a clear diagnosis, an arthrocentesis should be considered.

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