Distinguishing Lyme From Septic Knee Monoarthritis in Lyme Disease–Endemic Areas

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ABBREVIATIONS
ANC—absolute neutrophil count
CI—confidence interval
CRP—C-reactive protein
ED—emergency department
ESR—erythrocyte sedimentation rate
Ig—immunoglobulin
WBC—white blood cell count

WHAT’S KNOWN ON THIS SUBJECT: Children with Lyme and septic arthritis of the knee may present similarly, although septic arthritis requires prompt treatment initiation to avoid joint destruction. Clinicians must make initial management decisions without Lyme serology and bacterial culture results.

WHAT THIS STUDY ADDS: Our clinical prediction rule accurately identified patients at low risk for septic arthritis in a Lyme disease–endemic area. In the appropriate clinical context, low-risk patients may be spared invasive testing such as diagnostic arthrocentesis.

abstract

OBJECTIVE: Because Lyme and septic arthritis may present similarly, we sought to identify children with knee monoarthritis at low risk for septic arthritis who may not require arthrocentesis.

METHODS: We performed a retrospective study of children with knee monoarthritis presenting to 1 of 2 pediatric centers, both located in Lyme disease–endemic areas. Septic arthritis was defined by a positive result on synovial fluid culture or synovial fluid pleocytosis with a positive blood culture result. Lyme arthritis was defined as a positive Lyme serologic result or physician-documented erythema migrans rash. All other children were considered to have other inflammatory arthritis. A clinical prediction model was derived by using recursive partitioning to identify children at low risk for septic arthritis, and the model was then externally validated.

RESULTS: We identified 673 patients with knee monoarthritis; 19 (3%) had septic arthritis, 341 (51%) had Lyme arthritis, and 313 (46%) had other inflammatory arthritis. The following predictors of knee septic arthritis were identified: peripheral blood absolute neutrophil count $\geq 10 \times 10^3$ cells per mm$^3$ and an erythrocyte sedimentation rate $\geq 40$ mm/hour. In the validation population, no child with a absolute neutrophil count $< 10 \times 10^3$ cells per mm$^3$ and an erythrocyte sedimentation rate $< 40$ mm/hour had septic arthritis (sensitivity: 6 of 6 [100%], 95% confidence interval [CI]: 54–100; specificity: 87 of 160 [54%], 95% CI: 46–62). Overall, none of the 19 children with septic arthritis were classified as low risk (10%, 95% CI: 0–17).

CONCLUSIONS: Laboratory criteria can be used to identify children with knee monoarthritis at low risk for septic arthritis who may not require diagnostic arthrocentesis. Pediatrics 2013;131:e695–e701

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Children with acute knee monoarthritis commonly present to the emergency department (ED) for evaluation. In Lyme disease–endemic areas, many of these children will have Lyme arthritis.1–2 Most of these children present without other clinical manifestations of Lyme disease.3,4 Rarely, children may have a bacterial infection of the joint space (septic arthritis), which must be differentiated from other types of arthritis because it requires prompt treatment to avoid chondrolysis and joint destruction.5–7 Clinicians face a challenge in determining the appropriate diagnostic evaluation and empirical treatment of children with acute knee arthritis given the often overlapping clinical and laboratory features of Lyme and septic arthritis.3,4,8–13 Although highly sensitive and specific for Lyme arthritis, confirmatory Lyme serology can take several days for results.14 Arthrocentesis, the diagnostic gold standard for children with septic arthritis, is an invasive procedure that may require procedural sedation, especially in younger children. The Kocher criteria, a validated clinical prediction rule to identify children at low risk for septic arthritis of the hip, is in widespread clinical usage.15–18 Although this model was derived to distinguish septic arthritis from transient synovitis in children undergoing hip arthrocentesis, the Kocher criteria have been applied to children with knee arthritis rather than hip arthritis and to children residing in Lyme disease–endemic areas.2,19 However, the accuracy of this approach has not been investigated. We sought to identify children with knee monoarthritis who are at low risk for septic arthritis. To this end, we assembled a retrospective cohort of children with knee monoarthritis evaluated at 1 of 2 pediatric centers, both located in Lyme disease–endemic areas. Our primary aim was to derive and validate a clinical prediction rule to identify children at low risk for septic arthritis who may safely avoid diagnostic arthrocentesis. Our secondary aim was to compare the predictive ability of the resulting model with the Kocher criteria.15

METHODS

Study Design
We performed a retrospective cohort study of children ages 1 to 18 years who presented with knee monoarthritis to the ED at 1 of 2 urban, tertiary-care, pediatric centers located in Lyme disease–endemic areas. The study protocol was approved by the institutional review board of the 2 participating centers with a waiver of informed consent.

Derivation Population
Children who presented to the ED of Boston Children’s Hospital between January 1, 2000, and January 31, 2012, were included in the derivation population. Derivation patients were identified by using a 2-step process. First, potential patients were identified with a computer-assisted screening tool using regular expressions, a technique that provides a more comprehensive search than key word searches by allowing inclusion of possible misspelled and mistyped variations of the key words of interest. This approach has previously been shown to enhance case detection when compared with either chief compliant or discharge diagnosis coding.20,21 We then manually reviewed the medical records of all potential study patients to determine if the child met study criteria. To avoid missing any children with confirmed septic arthritis who may not have been identified in our initial search algorithm, we reviewed all synovial fluid cultures that grew bacterial pathogens during the study period. Additional cases of septic arthritis of the knee were identified by screening synovial fluid cultures between January 1, 1995, and December 31, 1999.

Validation Population
In the validation population, we included children who presented to the ED of Yale–New Haven Hospital between January 1, 1992, and April 1, 2009, with a joint effusion and who had a knee aspiration performed. Patients were identified by using screening microbiology logs for synovial fluid samples obtained during the study period (study procedures have previously been described in detail).2

Inclusion and Exclusion Criteria
For the derivation cohort, we included children with physician-documented knee monoarthritis on physical examination who either were evaluated for Lyme disease or who had septic knee arthritis. For the validation cohort, we used the same criteria although not all patients had Lyme serology obtained. Patients were excluded if they met any of the following criteria: recent history of significant knee trauma or penetrating injury, knee surgery within the past 30 days, previous arthritis of any joint, history of rheumatologic disease or an immunocompromised state, multiple joint involvement, knee cellulitis or other overlying infection, or critical illness (defined as hypotension requiring vasoactive medications or respiratory distress requiring assisted ventilation).

Data Collection
We reviewed the complete medical records of all study patients and abstracted demographic, historical, physical examination findings, laboratory studies, and microbiology results. We defined antibiotic pretreatment as any antibiotic given within 72 hours of initial ED evaluation. Synovial fluid and Lyme serology results were included if sent during the ED initial encounter or
within 3 days of initial evaluation. Subsequent medical encounters were reviewed to help determine final arthritis diagnosis. The derivation cohort data were collected and managed by using REDCap electronic data capture tools hosted at Boston Children’s Hospital.22

**Outcome Measures**

A case of septic arthritis was defined as a child with a synovial fluid culture result positive for a bacterial pathogen or by a synovial fluid pleocytosis (synovial fluid white blood cell count [WBC] ≥40,000 cells per µL) with a positive blood culture result for a bacterial pathogen.13 Bacterial cultures that grew *Bacillus* species, *Corynebacterium*, *Streptococcus viridans*, and *Staphylococcus non-aureus* were regarded as contaminants. Children with confirmed osteomyelitis but without bacterial growth from the blood culture with an associated synovial fluid pleocytosis or a positive synovial fluid culture result were not considered to have septic arthritis.

A case of Lyme disease was defined according to the Centers for Disease Control and Prevention definition as a patient with either a history of a physician-documented erythema migrans rash or clinical manifestations of Lyme disease with evidence of infection with *Borrelia burgdorferi* (defined by positive Lyme serology).23,24 A positive Lyme serology was defined as a positive Lyme immunoglobulin (Ig) G on Western blot according to reference laboratory definitions. Study patients who did not meet the septic arthritis or Lyme arthritis case definitions were defined as having other inflammatory arthritis (referred to as “other” arthritis). In the validation cohort, patients with negative bacterial cultures who did not have Lyme testing performed were assumed to have other inflammatory arthritis.

### K Analysis

To test the reliability of the medical record review process, we randomly selected ~10% of derivation patients for abstraction of the historical and examination findings by a second study investigator. K statistics were calculated for each potential predictor to measure the interrater reliability of the chart abstraction process. We considered clinical predictors with a lower end of the 95% confidence interval (CI; >0.4) to have moderate agreement.25,26

**Statistical Analysis**

In this analysis, we first described the characteristics of patients with septic, Lyme, and other inflammatory arthritis in the derivation population by using proportions for categorical variables and medians for continuous predictors. Second, we selected candidate predictors for inclusion in the multivariate model with biologic plausibility, minimal missing data, and moderate agreement for chart abstraction. Third, we derived a clinical prediction rule for septic arthritis by using binary recursive partitioning with Gini splitting rules by using CART v6.6 (Salford Systems, San Diego, CA). Because our goal was to identify children at low risk for septic arthritis, we aimed to maximize the rule sensitivity and the negative predictive value. To achieve this goal, we assigned a misclassification cost of 100:1 for the classification of a child with septic arthritis as low risk. A 10-fold internal cross-validation was used to avoid model overfitting.

**External Validation**

Our clinical prediction rule was then applied to the external validation population. Children with neither of the high-risk clinical predictors were considered to be low risk for septic arthritis. Children with either of the high-risk predictors were considered not at low risk. Otherwise, we did not apply the prediction models to children missing either of the included predictors. We report the test performance for clinical prediction rules with 95% CIs by using exact methods. Given the differences between the derivation and validation populations, we report the sensitivity and specificity but not the predictive values in the validation cohort.

**The Kocher Criteria**

The Kocher criteria included the following 4 high-risk predictors: history of fever ≥38.5°C, inability to bear weight on affected joint, WBC ≥12,000 cells × 10^3 per mL, and erythrocyte sedimentation rate (ESR) ≥40 mm/hour.15 We applied this prediction model to the study derivation and validation cohorts. Children with none of the high-risk predictors were considered at low risk for septic arthritis and those with ≥1 high-risk predictors were not at low risk. Otherwise, other children missing ≥1 of the included predictors were not classified. We compared the performance of our septic arthritis clinical prediction rule with the Kocher criteria by using the χ^2 test.

For all other analyses, PASW Statistics version 18.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) was used.

**RESULTS**

We identified 729 patients, of whom 56 (8%) were excluded for the reasons provided in Fig 1. Of the 673 study patients with knee monoarthritis, 19 (3%) had septic arthritis, 341 (51%) had Lyme arthritis, and 313 (46%) had other inflammatory arthritis. The derivation population included 474 children (70% of the study population), and the validation population comprised 199 children (30%).

Of the 19 children with septic arthritis, all had a positive synovial fluid culture result and 2 patients also had positive blood culture results for the same bacterial pathogen that grew from the...
Five (39%) of the children with knee septic arthritis had a positive synovial fluid Gram stain. Septic arthritis cases were caused by the following bacterial pathogens: methicillin-sensitive *S aureus* (12 patients), group A streptococcus (4), *Streptococcus pneumoniae* (2), and *Enterobacter agglomerans* (1). In the derivation cohort, 4 additional cases of septic arthritis were identified by reviewing microbiology logs from 1995 and 1996.

Of the 341 children with Lyme arthritis, all had positive Lyme serologic results. Of these, 194 (57% of patients with Lyme arthritis) had a positive IgG alone and 147 (43%) had both positive IgM and IgG. In addition to positive serologies, 14 children (4% of those with Lyme arthritis) also had a history of physician-documented erythema migrans rash. Of the 257 patients with Lyme arthritis who had arthrocentesis performed, 48 had a Lyme polymerase chain reaction test obtained from synovial fluid; 23 (48% of those tested) had positive results. None of the children with positive Lyme serology had septic arthritis.

Of the 474 children in the derivation population, the median patient age was 7.5 years (interquartile range: 4.6–11.3 years), and 295 (62%) were male. We compared the clinical and laboratory findings for children with septic, Lyme, and other inflammatory arthritis (Table 1). Children with septic arthritis had overlapping clinical and laboratory features to those with Lyme arthritis. However, patients with septic arthritis had both higher ESR and C-reactive protein (CRP) than those with Lyme or other inflammatory arthritis. Of note, CRP was obtained in only 77% of these patients. The proportion of patients undergoing arthrocentesis differed by arthritis type (septic [n = 13] 100% vs Lyme [n = 154] 64% vs other arthritis [n = 70] 32%; P < .001). Children with septic, Lyme, and other inflammatory arthritis presented throughout the year (Fig 2).

The proportion of patients presenting during peak Lyme disease season (June–October) did not differ by arthritis type (P = .90).

In the derivation cohort, we measured the interrater reliability of the chart abstraction for potential historical and physical examination clinical predictors (Table 2). All of the selected candidate predictors had moderate agreement except joint pain, and history of fever which were not included in the multivariate model. The following candidate predictors were selected for testing in the multivariate analysis: duration of symptoms, ability to bear weight on the affected joint, peripheral WBC, absolute neutrophil count (ANC), and ESR. We identified the following independent predictors of septic arthritis: ANC ≥10 × 10³ cells per mm³ and ESR ≥40 mm/hour (Table 3).
We applied our knee septic arthritis clinical prediction rule to our derivation and validation populations (Table 4). In the validation population, no child with a peripheral blood ANC, $10^3$ cells per mm$^3$ and an ESR, 40 mm/hour had septic arthritis (sensitivity: 6 of 6 [100%), 95% CI: 54–100; specificity: 87 of 160 [54%], 95% CI: 46–62).

Overall, none of the 19 children with septic arthritis from the derivation and validation cohorts were classified as low risk according to our knee septic arthritis prediction model (95% CI: 0–20). Next, we applied the Kocher criteria to our external validation cohort (Table 3). The Kocher criteria also identified all the children with septic arthritis.

We conducted a retrospective cohort study of all children with knee monoarthritis who presented to 1 of 2 pediatric centers, both located in Lyme disease–endemic areas. In our study population, most children had Lyme or other inflammatory arthritis whereas septic arthritis was rare. Lyme arthritis, a late manifestation of Lyme disease, presented throughout the year. We identified ANC $\geq 10 \times 10^3$ cells per mm$^3$ and ESR $\geq 40$ mm/hour as predictors of septic arthritis. More than one-half of the study patients were classified as low risk and may not in the appropriate clinical context, require diagnostic arthrocentesis. Our septic arthritis clinical prediction rule had the same sensitivity but higher specificity than the Kocher criteria in both derivation and validation populations.

Previous studies have shown that the majority of patients with Lyme arthritis have evidence of systemic inflammation, with elevated peripheral WBC and inflammatory markers (ESR or CRP). In addition, the synovial fluid leukocyte count can also be elevated in Lyme disease, making it sometimes difficult to differentiate from septic arthritis even after arthrocentesis. Similar to previous investigations, we found that children with Lyme arthritis and those with septic arthritis had signs of systemic inflammation as well as elevated synovial fluid WBC.

A recent meta-analysis of adults evaluated for septic arthritis sought to determine clinical and laboratory factors that could identify cases of septic arthritis at presentation. Septic arthritis was defined as a positive synovial fluid culture result or Gram stain, positive blood culture result, pus aspirated from the joint, or response to antibiotics. They identified the following clinical and laboratory predictors: pain in the affected joint, history of
swelling, fever, and elevated peripheral WBC, ESR, and CRP. However, these studies did not include either children or adults with Lyme arthritis, which limits the applicability of these findings to children who reside in Lyme disease–endemic areas.

Two previous studies identified predictors to distinguish Lyme from septic arthritis in children presenting for care to centers located in Lyme disease–endemic areas. Knee involvement and history of fever were predictors of Lyme arthritis in both studies. In the more recent study, inability to bear weight as well as elevated peripheral and synovial fluid WBC were correlated with septic arthritis. However, both of these studies included children with any joint arthritis (or multiple joints), all of whom had arthrocentesis performed. In our derivation population, we included children with knee monoarthritis regardless of whether arthrocentesis was performed to inform clinical decision-making about the necessity of this procedure.

In our study cohort, septic arthritis of the knee was a rare diagnosis, with only 19 cases detected over a 17-year period at 2 large pediatric referral centers. Our clinical prediction model identifies children with knee monoarthritis who are at very low risk of having septic arthritis with the goal of assisting clinical decision-making. Clinicians can safely bypass arthrocentesis, hospital admission, parenteral antibiotics, and surgical joint irrigation for children at low risk for septic arthritis, avoiding unnecessary invasive procedures, patient discomfort, and additional health care expenditure. Similar to previously reported experience, a number of study patients who underwent surgical joint irrigation had Lyme arthritis. Although the Kocher criteria also identified all children with septic arthritis, the model specificity was considerably lower than that of our septic arthritis prediction model. This lower specificity translates to fewer children with knee monoarthritis being classified as low risk, which reduced the potential model impact.

Our study has several important limitations. First, it was performed at a single tertiary care hospital in a Lyme disease–endemic area. Our findings, therefore, may be less applicable to areas of the country where Lyme disease is not prevalent. Second, our study was retrospective, and clinical predictors were abstracted from information available in the medical record. We attempted to minimize the potential bias inherent in this type of study by selecting candidate predictors with high interrater reliability for chart abstraction. Third, Lyme testing was performed by several different commercial laboratories at the 2 institutions over the study period. Although we were unable to standardize these interpretations, we relied on the reference standards of the testing laboratory. Fourth, we could not ensure complete identification of all children with septic arthritis because we included children who had been pre-treated with antibiotics and children who did not have arthrocentesis performed. However, the models performed similarly if we limited analysis to the subgroups who had not received antibiotic pretreatment or who had arthrocentesis performed (data not shown). Fifth, CRP was missing in a substantial proportion of patients and, therefore, could not be included in the multivariate model. However, future study may demonstrate the discriminative ability of this inflammatory marker. Last, our external validation population included a small number of children with septic arthritis. However, given the rarity of septic arthritis of the knee, a larger multiinstitutional study would be required to identify a substantial number of children with septic arthritis.

**CONCLUSIONS**

In Lyme disease–endemic areas, children with septic and Lyme arthritis

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**TABLE 3** Clinical Prediction Rule for Septic Arthritis of the Knee

<table>
<thead>
<tr>
<th>Septic Arthritis High Risk Clinical Predictors</th>
</tr>
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<tbody>
<tr>
<td>ANC ≥10 × 10³ cells/mm³</td>
</tr>
<tr>
<td>ESR ≥40 mm/hour</td>
</tr>
</tbody>
</table>

**TABLE 4** Performance of Study Septic Arthritis Prediction Model and the Kocher Criteria for the Identification of Septic Arthritis in the Derivation and Validation Cohorts

<table>
<thead>
<tr>
<th>Model/Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivation cohort</td>
<td>13/13 (100) (73–100)</td>
<td>251/402 (62) (58–67)</td>
<td>251/251 (100) [99–100]</td>
<td>13/164 (8) [4–13]</td>
</tr>
<tr>
<td>Validation cohort</td>
<td>6/6 (100) (54–100)</td>
<td>87/150 (54) (46–62)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kocher criteria</td>
<td>13/13 (100) (73–100)</td>
<td>103/390 (27) (22–31)</td>
<td>103/103 (100) [98–100]</td>
<td>13/299 (4) [23–73]</td>
</tr>
</tbody>
</table>

Data are presented as n/N (%). NA, not appropriate; NPV, negative predictive value; PPV, positive predictive value.

* Septic arthritis prediction model applied to 415 (86%) of the 474 patients in the derivation cohort.
* Septic arthritis prediction model applied to 166 (83%) of the 199 validation patients.
* Kocher criteria applied to 402 (85%) of 474 patients in the derivation cohort.
* Kocher criteria applied to 185 (83%) of the 199 validation patients.
have overlapping clinical presentations. Because both Lyme serologies and bacterial cultures take several days to return results, clinicians must make initial management decisions based on clinical presentation and laboratory findings. Children with ANC $< 10 \times 10^3$ cells per mm$^3$ and ESR $< 40$ mm/hour are at low risk for septic arthritis and, in the right clinical context, may not require diagnostic arthrocentesis. Our septic arthritis prediction model had the same sensitivity and higher specificity than the published Kocher criteria and can be used to assist clinical decision-making for the care of children with knee monoarthritis in Lyme disease-endemic areas. Future large validation studies are needed before widespread implementation of our septic arthritis prediction model.33

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REFERENCES

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