Lyme Arthritis in the Pediatric Knee
Clinical and Magnetic Resonance Imaging Differentiators

Yi-Meng Yen, MD, PhD, Ryan M. Sanborn, BA, Kyna Donohue, MD, Patricia E. Miller, MS, Matthew D. Milewski, MD, and Kirsten Ecklund, MD

Investigation performed at Boston Children’s Hospital, Boston, Massachusetts

Background: Lyme disease is the most prevalent tick-borne illness in the United States, especially endemic in the Northeast and Upper Midwest. Distinguishing Lyme arthritis (LA), the most common manifestation of the disease in children, from septic arthritis (SA) can be challenging because of overlap in clinical presentations. This study examined the role of magnetic resonance imaging (MRI) as an adjunct to clinical and laboratory features used to differentiate between LA and SA in children and adolescents.

Methods: The medical records and MRI scans of children who presented between 2009 and 2019 with an acute knee effusion ultimately diagnosed as LA or SA were retrospectively reviewed. Data collection included clinical information on the modified Kocher criteria (weight-bearing, fever, blood serology including white blood-cell [WBC] count, C-reactive protein [CRP], and erythrocyte sedimentation rate [ESR]), MRI findings, and serology confirmation of LA or bacterial SA. A total of 87 cases of confirmed LA and 9 cases of SA were identified.

Results: The 2 cohorts had substantial clinical overlap with regard to the ability to bear weight, fever, and joint aspirate WBC count. Differences between the 2 groups in several MRI characteristics, specifically vastus lateralis myositis, subcutaneous edema, and lymphadenopathy, were significant. A multivariate analysis demonstrated that weight-bearing, CRP of <3 mg/L, absence of subcutaneous edema, myositis of multiple muscles including the vastus lateralis, and lymphadenopathy were predictive of LA.

Conclusions: LA should be strongly suspected in endemic areas of the United States when children present with a knee effusion. The addition of MRI criteria to clinical and laboratory findings significantly improved the predictive value for identifying LA.

Level of Evidence: Diagnostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Lyme disease is the most common tick-borne illness in the United States and is caused by the spirochete *Borrelia burgdorferi*. Lyme disease is a multisystem disorder with dermatologic, cardiac, neurologic, and musculoskeletal manifestations. Since its discovery in children and adults in Lyme, Connecticut, the incidence of Lyme disease has been increasing steadily. Children are nearly twice as likely to develop arthritis as adults are as a result of late-stage Lyme disease and are also more likely to have arthritis as the initial manifestation of the disease.

The reported cases of Lyme disease have risen over the past decade, although cases in 2018 declined compared with 2017 according to the U.S. Centers for Disease Control and Prevention (CDC). Lyme disease is considered endemic in Connecticut, Delaware, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin. The arthritis due to *B. burgdorferi* induces mononuclear cell infiltration into the synovial tissue, which is responsible for the accumulation of neutrophils, immune complexes, and cytokines in the synovial fluid that causes the acute arthritis. Bacterial septic arthritis (SA) stimulates leukocytes, synovial cells, and chondrocytes to release proteases, peptidases, and collagenases that can lead to chondral destruction. Despite similar clinical presentations, Lyme arthritis (LA) does not cause the precipitous joint destruction that may occur with SA and, thus, urgent surgical management is not indicated. Rapid accurate diagnosis in children presenting with acute monoarthritis of the knee allows for proper triage to emergency surgical treatment for SA compared with antibiotic therapy for LA.

LA diagnosis typically requires a peripheral blood enzyme immunoassay or immunofluorescent assay followed by a Western blot. Although these tests have been shown to have high sensitivity and specificity, results can take up to several days to return, which

Disclosure: The Disclosure of Potential Conflicts of Interest forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A443).
can delay the diagnosis and lead to unnecessary surgical intervention. Several prior studies have examined predictive models for distinguishing LA from bacterial SA. In the study by Thompson et al., elevated C-reactive protein (CRP) and a fever history were found to be negative predictors of LA, with a sensitivity of 88% and a specificity of 82% when combined. In contrast, Milewski et al. found that CRP and fever were similar in the 2 groups of patients and refusal to bear weight was the strongest predictor of bacterial SA compared with LA. Baldwin et al. found that a short range-of-motion arc, fever, high CRP, and younger age were predictive of SA.

Magnetic resonance imaging (MRI) is widely used for the assessment of musculoskeletal infectious and inflammatory disorders. Many have recommended immediate MRI for the workup of knee infections specifically. SA frequently does not occur in isolation, and concomitant osteomyelitis may be seen in up to 60% to 80% of cases. Patients with associated osteomyelitis had worse outcomes than those with isolated SA. A timely preoperative MRI can add value and prevent second trips to the operating room by identifying concomitant bone infection that can be addressed at the index procedure. The use of MRI in the setting of SA is becoming more routine in many centers. Additionally, in the elective clinical setting, a knee with an effusion often has a workup that includes the use of MRI. In 2005, Ecklund et al. compared MRI features in a small number of children with LA with those in children with bacterial SA. Myositis, popliteal adenopathy, and lack of subcutaneous edema were suggestive of LA. These results also led our institution to acquire MRI scans in most patients who present with acute monoarthritis of the knee in both the emergency room setting and an elective clinical setting. We undertook a retrospective review of the medical records and MRI scans of a large group of children who presented with a swollen joint to a children's hospital in a Lyme disease-endemic state. We sought to examine the clinical presentation and MRI findings of LA to develop a clinical pathway to obtain a presumed diagnosis and begin treatment.

Materials and Methods

Patients

After institutional review board approval at a single, large, pediatric hospital in a Lyme disease-endemic region, a query was performed using an institutional imaging database to identify all patients (mean age, 9.7 years [range, 1.5 to 17 years]) with symptomatic knee effusion who had MRI between January 2009 and November 2019 and were subsequently diagnosed with SA or LA. The resulting cohort consisted of 96 patients (9 patients with SA and 87 patients with LA). Patients <1.5 years of age were excluded because of the low likelihood of LA. Patients with postoperative SA and those with MRI performed after operative irrigation and debridement were excluded.

Patient Characteristics

Demographic, clinical, and laboratory data were retrospectively collected from patients' medical records. Demographic data included age at presentation, sex, height, and weight. Clinical and laboratory information was collected to assess the Kocher criteria. Clinical data included maximum temperature, fever, and refusal to bear weight. Blood serology included serum white blood-cell (WBC) count, CRP, and erythrocyte sedimentation rate (ESR). The joint aspiration fluid WBC count was also recorded for patients who underwent joint aspiration. The results of blood, tissue, fluid, and wound cultures were collected, along with the resulting microbe, if applicable. The results of Lyme disease serology, including enzyme-linked immunosorbent assay (ELISA), immunoglobulin G (IgG), immunoglobulin M (IgM), and polymerase chain reaction (PCR), were collected for all patients with an LA diagnosis.

MRI Protocols and Analysis

All 96 patients underwent imaging of the involved knee on one of several 1.5-T or 3-T MRI scanners (Siemens Medical Systems). The imaging protocols varied because of the >10-year length of the study period, but all included sagittal and axial fluid-sensitive (T2-weighted with fat suppression or inversion recovery) and long axis T1-weighted sequences. Seventy-seven patients (8 with SA and 69 with LA) also underwent postcontrast axial and sagittal T1-weighted fat imaging with fat suppression.

A pediatric musculoskeletal radiologist with >20 years of experience reviewed all MRI scans and was blinded to the ultimate diagnosis of LA or SA. To establish interrater and intrarater reliability, an orthopaedic surgeon reviewed a random subset consisting of 54 MRI scans twice, approximately a month apart. MRI scans were reviewed for specific features. Subcutaneous edema was categorized as involving <25%, 25% to 50%, 51% to 75%, or >75% of the circumference of the knee (Fig. 1). Myositis, defined as increased fluid signal edema, was assessed within the popliteus, vastus medialis, vastus lateralis, biceps femoris, medial gastrocnemius, lateral gastrocnemius, and tibialis anterior muscles (Fig. 2). The total number of popliteal lymph nodes and the length of the long axis of the largest lymph node were noted (Fig. 3). All patients had a joint effusion, but posterior extension of fluid medially or laterally (defined as popliteal fluid) and the presence of synovial thickening and of intra-articular hemosiderin were assessed (Fig. 4). The extent of soft-tissue inflammation was categorized as absent, confined to the region around the knee, extending 10 to 15 cm superior or inferior from the joint, or extending >15 cm from the joint.

Statistical Analysis

Demographic, clinical, laboratory, and imaging characteristics were summarized for all knees in the study. Categorical characteristics were summarized by frequency and percentage, and continuous characteristics were summarized by mean and standard deviation. Univariable and multivariable logistic regressions using penalized maximum likelihood were used to compare clinical and MRI characteristics between diagnostic groups. Continuous or ordinal MRI factors were dichotomized at a value with the best ability to differentiate a diagnosis of LA from SA, as determined from the Youden index in a receiver operating characteristic (ROC) curve analysis, when applicable.
The Youden index identifies the optimal point on the ROC curve that maximizes both sensitivity and specificity simultaneously. The MRI factors that were found to be associated with the diagnostic outcome were combined into a simplified probability algorithm to estimate the likelihood of a diagnosis of LA given the number of MRI factors present. The Kocher criteria, with the addition of CRP, were assessed for their diagnostic utility for distinguishing between SA and LA. Lastly, model selection techniques were used to identify a combination of clinical and MRI characteristics that could best distinguish between SA and LA.

The MRI scans show differences in edema patterns between SA and LA. The axial and sagittal views of the knee demonstrate the extent and location of edema, which is a key diagnostic feature in Lyme arthritis. The presence of myositis is also evident on the MRI scans, which is another distinguishing feature between SA and LA.

**Fig. 1**
- **Fig. 1-A** Axial, T2-weighted, fat-saturation MRI scan showing extensive medial subcutaneous edema (white arrows) in a 10-year-old boy with SA of the knee.
- **Fig. 1-B** Sagittal, T2-weighted, fat-saturation MRI scan of the same boy showing anterior subcutaneous edema (white arrows).
- **Fig. 1-C** Axial, T2-weighted, fat-saturation MRI scan without any subcutaneous edema in a 5-year-old girl with LA.

**Fig. 2**
- **Fig. 2-A** Axial, T2-weighted, fat-saturation MRI scan showing a feathery edema of the vastus lateralis (thin white arrow) and subtle edema of the vastus medialis (thick white arrow).
- **Fig. 2-B** Sagittal, T2-weighted, fat-saturation MRI showing myositis of the biceps femoris (white arrow).
diagnoses in this cohort. The area under the ROC curve (AUC), along with a 95% confidence interval (CI), was estimated to quantify the diagnostic utility of each set of diagnostic criteria. Interpretations of the AUC were based on the study by Swets: 0.9 to 1.0 indicated excellent, 0.80 to 0.89 indicated good, 0.70 to 0.79 indicated fair, 0.60 to 0.69 indicated poor, and 0.50 to 0.59 indicated failure.

Intrarater and interrater reliability for all MRI measurements in the study were assessed on a random subsample of 56 knees. Two independent raters (1) read the 56 deidentified MRI scans, and 1 rater (2) repeated the measurements on the same sample, re-randomized, approximately 1 month later. Interrater and intrarater reliability were assessed for categorical characteristics by estimating the S (concordance) statistic, along with a 95% CI, and for continuous characteristics by estimating the intraclass correlation coefficient (ICC), along with a 95% CI. An ICC (2,2) model was used for interrater reliability, and an ICC (3,1) model was used for intrarater reliability. Interpretations of reliability estimates were based on the scale from Fleiss and Cicchetti and Sparrow: <0.40 indicated poor, 0.40 to 0.59 indicated fair, 0.60 to 0.74 indicated good, and >0.74 indicated excellent.

Power analysis determined that our final sample sizes of 9 patients with SA and 87 patients with LA provided >80% power, with alpha set to 5%, to test for AUC values of at least 0.85 compared with a null AUC of 0.60 using 1-sided tests. Having a higher null value gives better precision on the test result: if we drop the null value to 0.5, the power would be >80% for tests of AUC values of at least 0.75. The final sample size also provided >80% power, with alpha set to 5%, to detect an odds ratio as small as 3 using binary logistic regression for the model using the final criteria.

Source of Funding
None of the authors received financial support related to this study.

Results
The blinded MRI data were assessed for interrater and intrarater reliability (Table I). There was good to excellent concordance for intrarater reliability. The interrater reliability was good to excellent for myositis, intra-articular hemosiderin, synovial thickening, and popliteal node size and number, but was only fair for subcutaneous edema and popliteal fluid.

Table II illustrates the differences and similarities between the SA and LA cohorts in their clinical presentation, laboratory values, and MRI findings. Clinically, there was no significant difference with respect to the presence of fever, refusal to bear weight, or WBC count in the joint aspirate. There were significant differences in serum CRP and WBC count between groups. MRI findings demonstrated no difference in the presence of myositis, except specifically for the vastus lateralis, which was more...
prevalent in the LA group. Subcutaneous edema was more prevalent in the SA group, and the presence of >2 lymph nodes was seen in the LA group. All patients showed synovitis of the joint.

Table III shows the culture results from blood, tissue, wound, or knee aspirations from both groups. The Western blot data from the LA cohort are also shown, with a 99% rate of IgG positivity and a 40% rate of IgM positivity. All 9 patients with SA underwent emergency irrigation and debridement of the knee in the operating room and were administered appropriate antibiotics. Seven of the 9 patients with SA had positive cultures: 4 with methicillin-sensitive *Staphylococcus aureus* (MSSA), 1 with methicillin-resistant *S. aureus* (MRSA), 1 with group A streptococcus, and 1 with gram-negative rods. Fourteen (16%) of the patients eventually diagnosed with LA underwent operative irrigation and debridement for a presumed clinical diagnosis of SA. The patients with LA were treated with 1 month of antibiotics.

Based on the results of the univariate analyses, multivariate analysis was used to assess a set of potential diagnostic criteria. The results are shown in Table IV. We included the traditional Kocher criteria (fever, weight-bearing, ESR, and high synovial WBC count) plus CRP (“Kocher+ criteria”) and the MRI criteria, including the presence of subcutaneous edema, myositis, and lymphadenopathy (at least 2 lymph nodes measuring >1 cm in their long axis). Multivariate analysis using the Kocher+ criteria alone yielded a marginal AUC of 0.74, and the MRI criteria alone yielded an improved AUC of 0.88. Combining the MRI and Kocher+ criteria and using a forward and backward model selection method yielded a more stringent selection of clinical and MRI characteristics. As depicted in Figure 5, this yielded an excellent AUC of 0.93. The most robust criteria predictive of LA were ability to bear weight, serum CRP of <3 mg/L, absence of subcutaneous edema, myositis (with >1 muscle involved and involvement of the vastus lateralis), and lymphadenopathy as assessed by MRI. The probability of LA was 35% if 1 factor was present, 92% with 3 factors present, and 100% with 5 or all 6 factors present (Table V).

**Discussion**

Lyme disease in children has continued to rise in endemic regions of the United States, specifically the Northeast, Upper Midwest, and Pacific Northwest. When a child presents with an acute arthritis, the most pressing question is whether or not the joint is bacterially septic, which requires antimicrobial treatment as well as emergency surgical drainage. The arthritis caused by the *B. burgdorferi* spirochete is distinct from bacterial SA in that it does not cause the rapid articular cartilage destruction and therefore does not typically require emergency surgical drainage. Distinguishing between LA and SA can be particularly challenging because of considerable clinical overlap. Patients with LA can present with fever, inability to bear weight, elevated CRP and ESR, and high synovial WBC count from an arthrocentesis, which can mimic a bacterial SA. The standard approach to diagnose Lyme disease is a 2-tier test for serum antibodies. The first tier is an ELISA to measure the quantity of IgM and IgG against *B. burgdorferi*. However, there is cross-reactivity with antibodies against other pathogens that can give a false positive test. Consequently, if the assay is positive, a second-tier test using a Western immunoblot to surface proteins of *B. burgdorferi* is used to provide a confirmatory assay with higher specificity. However, these tests can take a considerable amount of time. Nigrovic et al. recently reported on the use of a more rapid C6 enzyme immunoassay (EIA) test with a turnaround of a couple of hours, but this still requires validation.

The Kocher criteria were originally established to distinguish SA of the hip from transient synovitis using 4
| Characteristic                        | SA Group (N = 9) | LA Group (N = 87) | P Value† |
|--------------------------------------|------------------|------------------|----------|
| Demographic                          |                  |                  |          |
| Age at presentation‡ (yr)            | 8.6 ± 4.4        | 10.6 ± 3.9       | 0.17     |
| Male sex§                            | 7 (78%)          | 60 (69%)         | 0.69     |
| Height‡ (cm) (n = 79)                | 131.1 ± 26.3     | 146.6 ± 22.0     | 0.06     |
| Weight‡ (kg)                         | 31.9 ± 15.7      | 38.9 ± 17.8      | 0.26     |
| Presented to the emergency room§     | 7 (78%)          | 56 (64%)         | 0.43     |
| Clinical symptoms                    |                  |                  |          |
| Maximum temperature‡ (°C) (n = 90)   | 38.6 ± 0.9       | 37.6 ± 1.4       | 0.02     |
| Had fever§ (n = 94)                  | 6 (75%)          | 38 (44%)         | 0.12     |
| Refused to bear weight§              | 4 (44%)          | 18 (21%)         | 0.12     |
| Laboratory values                    |                  |                  |          |
| First serum WBC count‡ (n = 90) (x10^3/mL) | 11.9 ± 4.8 | 9.5 ± 2.6 | 0.03 |
| Maximum serum WBC count‡ (n = 90) (x10^3/mL) | 13.6 ± 4.4 | 9.8 ± 2.7 | **0.003** |
| First serum CRP‡ (n = 74) (mg/L)     | 8.1 ± 7.9        | 3.7 ± 4.1        | 0.04     |
| Maximum serum CRP‡ (n = 85) (mg/L)   | 10.9 ± 8.3       | 4.3 ± 4.6        | **0.005** |
| First serum ESR‡ (n = 84) (mm/hr)    | 69.1 ± 35.8      | 36 ± 23.1        | **0.005** |
| Maximum serum ESR‡ (n = 90) (mm/hr)  | 84.5 ± 34.7      | 44.4 ± 29.2      | **0.003** |
| Underwent joint aspiration§ (n = 91) | 8 (89%)          | 50 (61%)         | 0.13     |
| Joint fluid WBC count‡ (x10^3/mL)    | 76.2 ± 3.1       | 60.0 ± 3.9       | 0.30     |
| MRI measures                         |                  |                  |          |
| Subcutaneous edema§                  | 0.003            |                  |          |
| Absent                               | 1 (11%)          | 50 (58%)         |          |
| <25% of circumference                | 2 (22%)          | 22 (25%)         |          |
| 25% to 50% of circumference          | 4 (44%)          | 12 (14%)         |          |
| 51% to 75% of circumference          | 2 (22%)          | 2 (2%)           |          |
| >75% of circumference                | 0 (0%)           | 1 (1%)           |          |
| Myositis§                            | 7 (78%)          | 74 (85%)         | 0.47     |
| No. of muscles involved‡             | 1.4 ± 1.3        | 2.3 ± 1.5        | 0.12     |
| Type of muscle§                      |                  |                  |          |
| Popliteus                            | 4 (44%)          | 42 (48%)         | 0.83     |
| Vastus medialis (n = 95)             | 3 (33%)          | 40 (47%)         | 0.45     |
| Vastus lateralis (n = 95)            | 3 (33%)          | 63 (73%)         | **0.02** |
| Biceps femoris (n = 95)              | 2 (22%)          | 23 (27%)         | 0.77     |
| Medial gastrocnemius (n = 95)        | 0 (0%)           | 13 (15%)         | 0.99     |
| Lateral gastrocnemius (n = 95)       | 1 (11%)          | 9 (11%)          | 0.95     |
| Tibialis anterior (n = 95)           | 0 (0%)           | 8 (9%)           | 0.99     |
| No. of popliteal lymph nodes‡ (n = 94)| 2 ± 1.3         | 4.1 ± 1.6        | **0.001** |
| Longest popliteal lymph node§ (n = 94) (mm) | 9.3 ± 3.6 | 12.5 ± 5.2 | 0.08 |
| Popliteal fluid present§             | 4 (44%)          | 49 (56%)         | 0.50     |
| Hemosiderin present§                 | 0 (0%)           | 6 (7%)           | 0.99     |
| Synovial thickening present§ (n = 95)| 9 (100%)        | 85 (99%)         | 1.00     |
| Tissue inflammation                  | 0.92             |                  |          |
| Confined to area around knee§ (n = 95)| 4 (44%)        | 42 (49%)         |          |
| Extends superiorly or inferiorly >10 but ≤15 cm§ (n = 95) | 3 (33%)        | 23 (27%)         |          |
| Extends >15 cm§ (n = 95)             | 2 (22%)          | 21 (24%)         |          |

*The n values in parentheses represent the total number of subjects with available data for the given category. †Bold values in this column are significant. ‡The values are given as the mean and the standard deviation. §The values are given as the number of patients, with the percentage in parentheses.
independent variables: (1) history of fever, (2) weight-bearing status, (3) ESR of >40 mm/hr, and (4) serum WBC count of >12,000 cells/mL. Use of these 4 diagnostic variables plus CRP of >2 mg/dL has been validated. Although the Kocher criteria have been applied to several other joints, the criteria have not been validated for the knee and were not intended to be used for Lyme disease. The SA cohort that Kocher studied consisted of patients with a synovial WBC count of >50,000 cells/mL regardless of bacterial culture results. LA quite frequently presents with synovial WBC counts of >50,000 cells/mL, which confuses the clinical picture. We examined the Kocher criteria and were able to demonstrate that, as the number of positive factors increased, the likelihood of SA increased, but the AUC of the ROC graph was 0.74, which is only fair. The Kocher criteria alone were not sufficient to distinguish between LA and pyogenic arthritis, which is comparable with the result reported by Obey et al.

There have been several prior studies that have sought to identify predictive factors to distinguish LA from SA. Thompson et al. studied 179 patients with an acute monoarticular arthritis and found fever history and elevated CRP to be negative predictors of LA and knee involvement to be a positive predictor, with a model sensitivity of 88% and specificity of 82%. However, there was still too much overlap to create a useful model. Milewski et al. compared 123 patients with LA with 51 patients with culture-positive SA and concluded that refusal to bear weight was the factor that was most predictive of SA. Additionally, their multivariate analysis showed that fever, serum WBC count of >12,000 cells/mL, and synovial cell count of >100,000 cells/mL were weak predictors. Deanehan et al. specifically examined knee monoarthritis and found that ESR of >40 mm/hr and neutrophil count of >10,000 cells/mL predicted SA. Baldwin et al. examined 189 patients with knee monoarthritis and identified 4 independent

| TABLE III Culture Results by Outcome Group |
|-------------------------------------------|
| Characteristic*                          | SA Group (N = 9) | LA Group (N = 87) |
| Initial Lyme ELISA††                     | 0.6             | 4.1 ± 1.1         |
| Maximum Lyme ELISA††                     | 0.6 ± 0.3       | 4.2 ± 1.2         |
| Positive Lyme IgG† (n = 82)              | 80 (98%)        |                  |
| Positive Lyme IgM† (n = 82)              | 35 (43%)        |                  |
| Positive Lyme PCR† (n = 33)              | 17 (52%)        |                  |
| Blood culture taken††                    | 6 (67%)         | 36 (41%)         |
| Positive                                | 2 (33%)         | 1 (3%)           |
| Tissue culture taken†† (n = 42)         | 2 (22%)         | 0 (0%)           |
| Positive                                | 2 (100%)        |                  |
| Fluid culture taken††                   | 9 (100%)        | 44 (51%)         |
| Positive                                | 4 (44%)         | 0 (0%)           |
| Wound culture taken††                   | 7 (78%)         | 2 (2%)           |
| Positive                                | 5 (71%)         | 0 (0%)           |
| Microbe†† (n = 41)                      | 0 (0%)          | 33 (97%)         |
| None                                    | 1 (14%)         | 0 (0%)           |
| MRSA                                    | 4 (57%)         | 0 (0%)           |
| MSSA                                    | 1 (14%)         | 1 (3%)           |
| Group A streptococci                    | 1 (14%)         | 0 (0%)           |
| Gram-negative rods                      | 1 (14%)         | 0 (0%)           |

*The n values in parentheses represent the total number of subjects with available data for the given category. ††The values are given as the mean, with or without the standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

| TABLE IV Diagnostic Criteria |
|-----------------------------|
| Variable*                   | SA Group† (N = 9) | LA Group† (N = 87) | P Value† |
| Clinical                    |                 |                   |         |
| Fever (n = 94)              | 6 (75%)         | 38 (44%)          | 0.12    |
| Refusal to bear weight      | 4 (44%)         | 18 (21%)          | 0.12    |
| Serum WBC count of >12 (×10³/mL) (n = 90) | 4 (50%)         | 16 (20%)          | 0.06    |
| Serum ESR of ≥40 mm/hr (n = 90) | 7 (88%)         | 39 (48%)          | 0.06    |
| Serum CRP of ≥3 mg/L (n = 85) | 8 (100%)        | 58 (75%)          | 0.003   |
| MRI                         |                 |                   |         |
| Subcutaneous edema present  | 8 (89%)         | 37 (43%)          | 0.03    |
| Myositis ≤1 muscle involved | 6 (67%)         | 27 (31%)          | 0.045   |
| Myositis of vastus lateralis muscle not involved | 6 (67%) | 23 (26%) | 0.02 |
| ≤2 popliteal nodes (n = 94) | 6 (67%)         | 12 (14%)          | 0.001   |
| Longest popliteal node ≤1 cm (n = 94) | 7 (78%)         | 37 (44%)          | 0.07    |

*The n values in parentheses represent the total number of subjects with available data for the given category. †The values are given as the number of patients, with the percentage in parentheses. ††Bold values in this column are significant.
predictive factors for SA: (1) CRP of >4 mg/L, (2) age of <2 years, (3) history of fever, and (4) short arc of motion. The risk of SA was 45% with 2 of these factors, 84% with 3 of these factors, and 100% with all 4 of these factors.

In this study, we assessed the predictive value of MRI as an aid in identifying LA. MRI can be an expensive modality and may require the use of sedation in patients, although we have been able to acquire quality images in patients as young as 4 years of age without anesthesia. However, the utility of MRI can be invaluable; MRI has been increasingly used to evaluate musculoskeletal infections because of its sensitivity in examining bone marrow, soft tissues, and joints. MRI findings in septic joints have been described to be abnormal after 24 hours from the onset of infection. MRI is used to identify osteomyelitis and abscesses in the setting of SA and can avoid additional surgical procedures if complete debridement can be performed. Additionally, patients who present to the clinic with a swollen knee often undergo MRI scans to evaluate monoarthritis. Ecklund et al. identified 3 MRI features, specifically myositis, lymphadenopathy, and lack of subcutaneous edema, that were strongly associated with LA compared with SA. We used these criteria as well as clinical and laboratory values in order to facilitate a model to identify LA.

The intrarater and interrater reliability of MRI measurements were examined first. The most reliable criteria were the presence of myositis, synovial thickening, and lymphadenopathy, with concordance of >0.70 for both intrarater and interrater reliability. Subcutaneous edema was more difficult to interpret and the variability was likely due to the timing of the MRI, either before or after an arthrocentesis was performed. If the MRI was acquired after arthrocentesis, the MRI scans may show subcutaneous fluid related to the procedure rather than to the underlying pathology. Edema may have been suspected to be due to the procedure and thus discounted by one reader and not by the other reader. Use of MRI criteria alone to predict LA compared with SA yielded an excellent AUC of 0.88 and supports the use of MRI to aid in the diagnosis of LA.

Presentation with SA is rarer than presentation with LA in areas in which LA is endemic. In a recent study from New England, Nigrovic et al. showed that the prevalence of Lyme disease in acute monoarthritis was 23% compared with 1% for SA. In the study by Milewski et al. of a group of 391 children presenting

| Algorithm | SA Group* (N = 9) | LA Group* (N = 87) | Probability of LA |
|-----------|------------------|-------------------|------------------|
| Best criteria variables | | | |
| Weight-bearing | 5 (56%) | 69 (79%) | |
| CRP of <3 mg/L | 0 (0%) | 19 (22%) | |
| Subcutaneous edema absent | 1 (11%) | 50 (57%) | |
| Myositis >1 muscle involved | 3 (33%) | 60 (69%) | |
| Myositis of vastus lateralis muscle involved | 3 (33%) | 63 (72%) | |
| >2 popliteal lymph nodes | 3 (33%) | 73 (84%) | |
| No. of diagnostic criteria present | | | |
| 0 | 1 (11%) | 1 (1%) | 10% |
| 1 | 3 (33%) | 0 (0%) | 35% |
| 2 | 3 (33%) | 7 (8%) | 71% |
| 3 | 2 (22%) | 24 (28%) | 92% |
| 4 | 0 (0%) | 30 (34%) | 98% |
| 5 | 0 (0%) | 22 (25%) | 100% |
| 6 | 0 (0%) | 3 (3%) | 100% |

*The values are given as the number of patients, with the percentage in parentheses.
with a joint effusion, 31% had LA and 11% had SA. In the study by Deanehan et al., 3% of patients had SA and 51% had LA. In the study by Baldwin et al., 74% of the patients had LA and 26% had SA, but no other diagnosis was excluded. We chose to focus on the affirmation of a diagnosis of LA because of the prevalence of Lyme disease in our geographical area of New England.

Utilizing a combination of clinical and MRI characteristics, our multivariate analysis found several independent predictive factors for LA including ability to bear weight, CRP of <3 mg/L, and the following 4 MRI criteria: (1) absence of subcutaneous edema, (2) myositis of >1 muscle, (3) myositis of the vastus lateralis, and (4) >2 popliteal lymph nodes (of any size). The probability of LA was 35% with 1 criterion, 92% with 3 criteria, and 100% with 5 criteria. Logistic regression analysis showed that 94% of our cases were correctly predicted with this model. There were 14 patients with LA who underwent a surgical procedure, and, if these criteria had been applied, all 14 of these patients may have avoided a surgical procedure. The AUC utilizing both clinical and MRI characteristics was 0.927, which is excellent.

This study had several limitations. First, as a retrospective review, it had the potential loss of data fidelity associated with these types of studies. We were unable to use some additional clinical variables, such as a short range-of-motion arc, that were utilized in the study by Baldwin et al. because the information in the charts was not sufficiently accurate. Additional data such as the presence of a bull’s-eye rash or known tick exposure were not elucidated. The addition of more clinical data might have yielded an improved model. Second, SA is much less common than LA in our geographic region and, thus, we had a comparatively small number of patients with SA who also underwent an MRI scan. A large cohort of patients with SA did not undergo MRI and so were unable to be analyzed in this study.

As a single-center study in a Lyme disease-endemic area, the results may not be applicable to all geographical areas, particularly those with a low prevalence of Lyme disease. Disease prediction models are all subject to the quality of the data and representation of the entire population, which is true of this study.

In conclusion, our study offers a useful prediction algorithm for LA that includes MRI for the evaluation of patients presenting with acute inflammation of the knee. Patients with lymphadenopathy, myositis, and CRP of <3 mg/L; without subcutaneous edema; and who are able to bear weight can be treated with oral antibiotics for LA while awaiting serologic results. Until serological testing is highly accurate and fast and does not require additional time-consuming validation, MRI is a useful adjunct tool to help to distinguish and identify LA.

References

1. Steere AC, Malawista SE, Snyder DR, Shope RE, Andiman WA, Ross MR, Steele FM. Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis & Rheumatism. 1977 Jan-Feb;20(1):7-17.
2. Petersen LR, Sweeney AH, Checco PJ, Magnarelli LA, Mishar PA, Gunn RA, Hadler JL. Epidemiological and clinical features of 1, 149 persons with Lyme disease identified by laboratory-based surveillance in Connecticut. Yale J Biol Med. 1989 May-Jun;62(3):253-62.
3. Schwartz AM, Hinckley AF, Mead PS, Hook SA, Kugeler KJ. Surveillance for Lyme disease - United States, 2008-2015. MMWR Surveill Summ. 2017 Nov 10;66(22):1-12.
4. Pulius YA, Kalish RA. Lyme arthritis: pathogenesis, clinical presentation, and management. Infectious Disease Clinics of North America. 2008 Jun;22(2):289-300, vi-vii.
5. Desforges JF, Baker DG, Schumacher HR. Acute monoarthritis. N Engl J Med. 1993 Sep 30;329(14):1013-20.
6. Kaandorp CJ, Kijnen P, Moens in HJ, Habbema JDF, van Schaardenburg D. The outcome of bacterial arthritis: a prospective community-based study. Arthritis & Rheumatism. 1997 May;40(5):884-92.
7. Steere AC, McHugh G, Danile N, Sikand VK. Prospective study of serologic tests for Lyme disease. Clin Infect Dis. 2008 Jul 15;47(2):188-95.
8. Thompson A, Mannik R, Bachur R. Acute pediatric monoarticular arthritis: distinguishing Lyme arthritis from other etiologies. Pediatrics. 2009 Mar;123(3):594-605.
9. Milewski MD, Cruz Al Jr, Miller CP, Peterson AT, Smith BG. Lyme arthritis in children presenting with joint effusions. Journal of Bone and Joint Surgery. 2011 Feb 2;93(2):252-60.
10. Baldwin KD, Brusalis CM, Nduaguba AM, Sankar WN. Predictive factors for differentiating between septic arthritis and Lyme disease of the knee in children. Journal of Bone and Joint Surgery. 2016 May 4;98(9):721-8.
11. Bancroft LW. MR imaging of infectious processes of the knee. Radiologic Clinics of North America. 2007 Nov;45(6):931-41v.
12. Ernst J, Riccio AI, Fitzpatrick K, Jo C, Wimberly RL. Osteomyelitis is commonly associated with septic arthritis of the shoulder in children. Journal of Pediatric Orthopaedics. 2017 Dec;37(8):S47-52.
13. Gibian JT, Daryoush JR, Wollenman CC, Johnson SR, Henry A, Koehler RJ, Moore-Lotridge SN, Schoenecker JL. The heterogeneity of pediatric knee infections: a retrospective analysis. Journal of Pediatric Orthopaedics. 2020 Jul;40(8):314-21.
14. Montgomery CO, Siegel E, Blasier RD, Suva LJ. Concurrent septic arthritis and osteomyelitis in children. Journal of Pediatric Orthopaedics. 2013 Jun;33(4):464-7.
15. Gottschalk HP, Moor MA, Muhamed AR, Wengringer D, Yasay B. Improving diagnostic efficiency: analysis of pelvic MRI versus emergency hip aspiration for suspected hip sepsis. Journal of Pediatric Orthopaedics. 2014 Apr-May;34(3):300-6.
16. Ecklund K, Vargas S, Zurakowski D, Sundel RP. MRI features of Lyme arthritis in children. American Journal of Roentgenology. 2005 Jun;184(6):1904-9.
17. Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. The Journal of Bone & Joint Surgery. 1999 Dec;81(12):1662-70.
18. Swets JA. Measuring the accuracy of diagnostic systems. Science. 1988 Jun 3;240(4857):1285-93.
19. Fleiss J. Statistical Methods for Rates and Proportion. New York: Wiley; 1981.
20. Cicchetti DV, Sparrow SA. Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. Am J Ment Defic. 1981 Sep;86(2):127-37.

21. Nigrovic LE, Bennett JE, Balamuth F, Levas MN, Neville D, Lyons TW, Branda JA, Maulden AB, Lewander D, Garro A; PEDI LYME NET. Diagnostic performance of C6 enzyme immunoassay for Lyme arthritis. Pediatrics. 2020 Jan;145(1):e20190593.

22. Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. The Journal of Bone and Joint Surgery-American Volume. 2004 Aug;86(8):1629-35.

23. Caird MS, Flynn JM, Leung YL, Millman JE, D'italia JG, Dormans JP. Factors distinguishing septic arthritis from transient synovitis of the hip in children. A prospective study. The Journal of Bone & Joint Surgery. 2006 Jun;88(6):1251-7.

24. Obey MR, Minaie A, Schipper JA, Hosseinzadeh P. Pediatric septic arthritis of the knee: predictors of septic hip do not apply. Journal of Pediatric Orthopaedics. 2019 Nov/Dec;39(10):e769-72.

25. Deanehan JK, Nigrovic PA, Milewski MD, Tan Tanny SP, Kimia AA, Smith BG, Nigrovic LE. Synovial fluid findings in children with knee monoarthritis in Lyme disease endemic areas. Pediatric Emergency Care. 2014 Jan;30(1):16-9.

26. Deanehan JK, Kimia AA, Tan Tanny SP, Milewski MD, Talusan PG, Smith BG, Nigrovic LE. Distinguishing Lyme from septic knee monoarthritis in Lyme disease-endemic areas. Pediatrics. 2013 Mar;131(3):e695-701.

27. Tang JS, Gold RH, Bassett LW, Seeger LL. Musculoskeletal infection of the extremities: evaluation with MR imaging. Radiology. 1988 Jan;166(1):205-9.

28. Tehranzadeh J, Wang F, Mesgarzadeh M. Magnetic resonance imaging of osteomyelitis. Crit Rev Diagn Imaging. 1992;33(6):495-534.

29. Horowitz DL, Katzap E, Horowitz S, Barilla-LaBarca ML. Approach to septic arthritis. Am Fam Physician. 2011 Sep 15;84(6):653-60.

30. Karchevsky M, Schweitzer ME, Morrison WB, Parellada JA. MRI findings of septic arthritis and associated osteomyelitis in adults. American Journal of Roentgenology. 2004 Jan;182(1):119-22.