

FACTORS DISTINGUISHING SEPTIC ARTHRITIS FROM TRANSIENT SYNOVITIS OF THE HIP IN CHILDREN

A PROSPECTIVE STUDY

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Background: Distinguishing septic arthritis from transient synovitis of the hip in children can be challenging. Authors of recent retrospective studies have used presenting factors to establish algorithms for predicting septic arthritis of the hip in children. This study differs from previous work in three ways: data were collected prospectively, C-reactive protein levels were recorded, and the focus was on children in whom the findings were so suspicious for septic arthritis that hip aspiration was performed.

Methods: Over four years, we prospectively collected data on every child (a total of fifty-three) who underwent hip aspiration because of a suspicion of septic arthritis at our institution. Diagnoses of confirmed septic arthritis, presumed septic arthritis, and transient synovitis were determined on the basis of the results of Gram staining, culture, and a cell count of the hip aspirate. Presenting factors and laboratory values were recorded. To evaluate the strength of predictors, we performed univariate and multivariate analysis on data from forty-eight patients who met the inclusion criteria.

Results: Univariate analysis showed that fever, the C-reactive protein level, and the erythrocyte sedimentation rate were strongly associated with the final diagnosis ($p < 0.05$). On multivariate analysis, the C-reactive protein level and erythrocyte sedimentation rate were found to be significant predictors. However, the erythrocyte sedimentation rate was not independent of the C-reactive protein level on backward elimination, and the C-reactive protein level was the only risk factor that was strongly associated with the outcome at a 5% significance level. Patients with five predictive factors had a 98% chance of having septic arthritis, those with four factors had a 93% chance, and those with three factors had an 83% chance.

Conclusions: This prospective study of children who presented with findings that were highly suspicious for septic arthritis of the hip builds on the work of previous authors. We found fever (an oral temperature $>38.5^{\circ}\text{C}$) was the best predictor of septic arthritis followed by an elevated C-reactive protein level, an elevated erythrocyte sedimentation rate, refusal to bear weight, and an elevated serum white blood-cell count. In our study group, a C-reactive protein level of >2.0 mg/dL (>20 mg/L) was a strong independent risk factor and a valuable tool for assessing and diagnosing children suspected of having septic arthritis of the hip.

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

Several recent studies have focused on the difficult problem of differentiating septic arthritis from transient synovitis of the hip in children¹⁻³. Whereas transient synovitis is a self-limited disorder that is managed nonoperatively, septic arthritis requires early intervention including intravenous antibiotics and operative irrigation and débridement to best avoid an

unfavorable outcome^{4,5}. Delayed treatment of septic arthritis of the hip can result in damage to the physis or articular cartilage, osteonecrosis of the proximal part of the femur, femoral osteomyelitis, and sepsis^{6,7}. In the absence of a single, easily performed test that clearly distinguishes between septic arthritis and transient synovitis of the hip, clinical prediction algorithms that combine a number of presenting variables have been proposed^{1-3,8,9}.

A recent retrospective study by Kocher et al.¹ identified four presenting factors that, when combined, were highly pre-



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dictive of septic arthritis in children. These included the refusal to bear weight, a history of fever (an oral temperature of $>38.5^{\circ}\text{C}$), a serum white blood-cell count of $>12,000/\text{mm}^3$ ($>12.0 \times 10^9/\text{L}$), and an erythrocyte sedimentation rate of >40 mm/hr. The authors found that, overall, the clinical prediction algorithm had an excellent diagnostic performance. It was later validated at their institution in a prospective study¹⁰.

Measurement of the C-reactive protein level, a laboratory study that previously was not readily available in many hospitals, is now an important part of the diagnostic evaluation of pediatric musculoskeletal infection. C-reactive protein is an acute-phase reactant that is elevated in the presence of infection and tissue injury. It is produced in the liver, and its levels in the blood rise within six to eight hours after the onset of an inflammatory process, an injury, or an infection¹¹. Kallio et al.¹² determined that the C-reactive protein level also rises within six hours after the onset of septic arthritis of the hip and peaks at two days. The test has been shown to be very useful for diagnosing a septic hip and for monitoring its treatment^{8,13}. The C-reactive protein level rises more quickly and returns to normal more rapidly than does the erythrocyte sedimentation rate. Levine et al.¹⁴ examined the test characteristics of the C-reactive protein level for the diagnosis of septic arthritis in children and found it to be a better independent predictor of infection than the erythrocyte sedimentation rate.

To validate the predictive factors proposed by Kocher et al.¹ and to determine the usefulness of adding the C-reactive protein level to this statistical algorithm, we initiated the prospective collection of data on patients with a clinical presentation that was suspicious for a septic hip.

Materials and Methods

Beginning on January 1, 2000, data were prospectively collected on all children under eighteen years of age who underwent ultrasound-guided hip aspiration at our tertiary-care children's hospital because of a concern that they had septic arthritis. The institutional review board approved this study.

Children who presented to our orthopaedic clinic or children's emergency department with a history that was suspicious for septic hip arthritis were evaluated by the pediatric orthopaedic service, which recorded a comprehensive history and performed a physical examination for each child. Ultrasound evaluation and aspiration were performed only

on those children whose presentation was the most suspicious for septic arthritis of the hip, and only patients with hip aspiration were included in this study. All hip aspirations were performed by the orthopaedic service using ultrasound guidance with the patient sedated.

Over the four-year study period, fifty-three patients underwent hip aspiration. Four were excluded from the study because they had an underlying immunosuppressive disease or had been previously diagnosed with inflammatory arthritis. Another patient was excluded when laboratory studies done prior to treatment established a diagnosis of active Lyme arthritis. Thus, forty-eight children were included in the study, and all were followed until the diagnosis was established. No child with transient synovitis revisited the emergency department because of recurrent hip pain or a refusal to bear weight, and no child with presumed septic arthritis or transient synovitis had further problems suggestive of osteomyelitis.

Demographic data, the medical history, and laboratory values were recorded at presentation for all study patients. Demographic data included patient age and gender. The medical history included underlying immunosuppression or inflammatory disorders as well as a history of fever, chills, or previous antibiotic use. The patient's temperature at the time of presentation to the emergency department was documented, with an oral temperature of $>38.5^{\circ}\text{C}$ considered a fever. Whether the patient had a limp or frankly refused to bear weight on the affected lower limb was documented by the examiner. Patients who limped or walked with an abnormal gait were considered "weight-bearing" for the purposes of the study. Serum laboratory values included a serum white blood-cell count (cells/mm³ [cells $\times 10^9/\text{L}$]), an erythrocyte sedimentation rate (mm/hr), a C-reactive protein level (mg/dL [mg/L]), blood culture, and Lyme disease titers. Laboratory tests of the hip aspirate included a Gram stain and a white blood-cell count (cells/mm³ [cells $\times 10^9/\text{L}$]) with the percentage of polymorphonuclear leukocytes. We noted the appearance of the aspirate (clear, cloudy, purulent, or other), and the organisms that grew on culture.

Laboratory values were used to make a diagnosis of confirmed septic arthritis, presumed septic arthritis, or transient synovitis for each patient, according to the criteria designated by Kocher et al.¹ (Table I). The group with confirmed septic arthritis and the group with presumed septic arthritis were com-

TABLE I Diagnostic Groups

	Diagnostic Criteria			
	Culture of Hip Aspirate (Not Contaminants)	Bacteria on Gram Staining of Hip Aspirate	Blood Culture	White Blood-Cell Count in Hip Aspirate ($\times 10^9/\text{L}$)
Confirmed septic arthritis	+	Any	Any	Any
	-	+	Any	Any
	-	-	+	>50.0
Presumed septic arthritis	-	-	-	>50.0
Transient synovitis	-	-	-	<50.0

TABLE II Summary of Contingency Tables Used for Univariate Analysis

Clinical Predictors	Positive in Patients with Septic Arthritis (no. [%])	Negative in Patients with Transient Synovitis (no. [%])	Positive in Patients with Transient Synovitis (no. [%])	Negative in Patients with Septic Arthritis (no. [%])	P Value
Temperature >38.5°C	15 (44)	14 (100)	0 (0)	19 (56)	0.0020
White blood-cell count in serum >12.0 × 10 ⁹ /L	17 (50)	10 (71)	4 (29)	17 (50)	0.2135
Erythrocyte sedimentation rate >40 mm/hr	19 (56)	12 (86)	2 (14)	15 (44)	0.0108
Refusal to bear weight	31 (91)	4 (29)	10 (71)	3 (9)	0.1711
C-reactive protein level >20.0 mg/L	29 (85)	10 (71)	4 (29)	5 (15)	0.00027

bined for statistical analysis. A white blood-cell count in the hip aspirate of >50,000/mm³ (>50.0 × 10⁹/L) was used as a diagnostic threshold for septic arthritis^{1,15}. The group with confirmed septic arthritis had, in addition to a white blood-cell count of >50,000 cells/mm³ in the hip aspirate, bacterial growth on culture of the hip aspirate, demonstration of bacteria by Gram staining of the hip aspirate, or bacterial growth on blood culture. The group with presumed septic arthritis had a synovial fluid cell count of >50,000 cells/mm³, but no evidence of bacteria on Gram staining of the hip aspirate, no bacterial growth on culture of the hip aspirate, and no bacterial growth on blood culture. The group with transient synovitis had no evidence of bacteria on Gram staining or on culture and had a cell count of <50,000 cells/mm³ in the hip aspirate.

Each diagnostic factor established in the study by Kocher et al.¹ was classified as either positive or negative for each patient. Positive findings included an oral temperature of >38.5°C, a serum white blood-cell count of >12,000/mm³ (>12.0 × 10⁹ cells/L), an erythrocyte sedimentation rate of >40 mm/hr, and strict refusal to bear weight on the affected limb as assessed by the orthopaedic examiner. A C-reactive protein level of >2.0 mg/dL (>20 mg/L) was considered positive as well^{12,16}.

Statistical Methods

Univariate analysis was performed with the Fisher exact test to determine whether there was a significant association between each of the five variables and the outcome. Multivariate analysis was conducted to assess the adjusted effect of each variable. Stepwise logistic regression was completed to select the best-fit model. A p value of <0.05 was considered to be significant. The influence of each predictor on the model was examined with use of Akaike's information criterion. Statistical analysis was performed with SAS software (SAS Institute, Cary, North Carolina).

Results

Forty-eight patients were included in the analysis. Twenty-three were male and twenty-five were female. They ranged in age from seven months to sixteen years, with an average age of 5.5 years. Eight children were under the age of two years. Fourteen patients were diagnosed with transient synovitis of the hip, and

thirty-four patients were diagnosed with septic arthritis of the hip. Half of the diagnoses of septic arthritis were confirmed, and half were presumed. The average age was 6.9 years for the patients with presumed septic arthritis, 4.9 years for those with confirmed septic arthritis, and 4.7 years for those with transient synovitis. Organisms that grew on culture of specimens from the group with confirmed septic arthritis included *Staphylococcus aureus* in ten patients, *Streptococcus pneumoniae* and *Staphylococcus epidermidis* in two patients each, and *Micrococcus*, *Corynebacteria*, and *Abiotrophia* in one patient each.

No patient with a culture-negative hip aspirate had positive blood cultures. Four patients who were included in the group with confirmed or presumed septic arthritis had a cell count of <50,000/mm³ (<50.0 × 10⁹/L) in the hip aspirate. One of these patients had evidence of bacteria on Gram staining, and the remaining three had bacterial growth on culture of hip aspirate.

Information on previous antibiotic use was available from the parent or from the outpatient charts. Twelve children had received antibiotics before arthrocentesis, twenty-eight had not received antibiotics, and the history regarding previous antibiotic administration was unclear for eight patients. Information regarding previous antibiotic use was available for all seventeen patients who had presumed septic arthritis, and six of them had received antibiotics. Such information was available for fourteen of the seventeen patients who had confirmed septic arthritis, and four of those children had received antibiotics. Finally, the antibiotic status was known for ten of the fourteen patients with transient synovitis, and two of them had received antibiotics.

Three patients with atypical findings were included in the septic arthritis group. Two of these patients met the diagnostic criteria for septic arthritis with a cell count in the hip aspirate of 54,000/mm³ (54.0 × 10⁹/L) for each. Both of these borderline patients were admitted to the hospital, treated with intravenous antibiotics, and discharged home without an arthrotomy. Both patients had improvement without additional therapy, and the cultures remained negative. A third patient with presumed septic arthritis had positive Lyme titers. The Lyme profiles did not indicate recurrence or reinfection but

TABLE III Results of Multivariate Analysis of Predictors of Septic Arthritis

Multivariate Predictor	Regression Coefficient	Adjusted Odds Ratio	95% Confidence Interval
White blood-cell count in synovial fluid $>12.0 \times 10^9/L$	0.5899	1.804	0.414-8.59
Erythrocyte sedimentation rate >40 mm/hr	1.9518	7.041	1.52-51.84
Refusal to bear weight	1.1674	3.214	0.52-23.2
C-reactive protein level >20.0 mg/L	—	14.496	3.240-64.862

TABLE IV Predicted Probability of Septic Arthritis

No. of Factors	Septic Arthritis (N = 34) (no. [%])	Transient Synovitis (N = 14) (no. [%])	Predicted Probability of Septic Arthritis (%)	
			Current Study	Study by Kocher et al. ¹
0	1 (3)	3 (21)	16.9	0.2
1	3 (9)	6 (43)	36.7	3
2	3 (9)	2 (14)	62.4	40
3	9 (26)	2 (14)	82.6	93.1
4	15 (44)	1 (7)	93.1	99.6
5	3 (9)	0	97.5	

were consistent with a resolved, previously documented Lyme infection¹⁷⁻¹⁹. This patient had been diagnosed with Lyme arthritis four years earlier on the basis of positive IgG (immunoglobulin G) titers (present in association with acute infection), and he had had a full course of antibiotic treatment. He had resumed full activities with no sequelae. He was entered into the study when he presented with refusal to bear weight, an elevated serum white blood-cell count, an elevated erythrocyte sedimentation rate, an elevated C-reactive protein level, and a white blood-cell count of $135,000/mm^3$ ($135.0 \times 10^9/L$) in the hip aspirate. Serum profiles for Lyme arthritis revealed positive IgM titers (lasting immunity from previous infection) with no acute elevation of those titers. The patient was treated with surgical irrigation and débridement of the hip and intravenous antibiotics. He did not meet our exclusion criteria and therefore was included in the study. Cultures remained negative, and he responded well to the treatment up to the final follow-up evaluation.

Univariate analysis was carried out with the Fisher exact test and use of the previously defined cutoff thresholds for a history of fever, an elevated white blood-cell count, an elevated erythrocyte sedimentation rate, non-weight-bearing, and an elevated C-reactive protein level. The patients with septic arthritis differed significantly from those with transient synovitis group with regard to fever, the erythrocyte sedimentation rate, and the C-reactive protein level ($p < 0.05$). These results are summarized in Table II.

Multivariate logistic regression analysis was then performed. No patient with transient synovitis had a fever (a temperature of $>38.5^\circ C$) at any time during their hospital stay.

Because of this, the inclusion of fever left the analysis without a mathematical solution; thus, fever was excluded as a factor. The strength of the association of each of the other factors with the septic arthritis outcome was measured, and the findings are summarized in Table III. The adjusted odds ratios suggest that non-weight-bearing, an elevated erythrocyte sedimentation rate, an elevated white blood-cell count, and an elevated C-reactive protein level were all related to the outcome. However, patients with septic arthritis differed significantly from those with transient synovitis with regard to the erythrocyte sedimentation rate and the C-reactive protein level as indicated by the 95% confidence interval excluding 1.0.

The probability of a patient having septic arthritis was calculated as a function of the number of positive presenting factors. As demonstrated in Table IV, the likelihood of a patient having septic arthritis increased with the number of positive factors.

TABLE V Relative Strength of Predictors

Excluded Predictor	Akaike's Information Criterion
Temperature	49.00
C-reactive protein level	47.32
Erythrocyte sedimentation rate	46.39
Refusal to bear weight	45.50
White blood-cell count in synovial fluid	42.41

The influence of each of the presenting factors on the algorithm was examined. Each factor was sequentially excluded from the model, and Akaike's information criterion was calculated. In this analysis, the best model has the smallest Akaike's information criterion. Results are summarized in Table V, which shows that the worst model excludes temperature as a predictor and the best model excludes the serum white blood-cell count.

After univariate and multivariate analysis of the factors, backward elimination was performed to find the best model fitting the data. The factors used were a high erythrocyte sedimentation rate (>40 mm/hr), a high serum white blood-cell count ($>12,000/\text{mm}^3$ [$>12.0 \times 10^9/\text{L}$]), non-weight-bearing, and a high C-reactive protein level (>2.0 mg/dL [>20.0 mg/L]). Again, because no child with transient synovitis had a fever, inclusion of fever left the analysis without a mathematical solution, and fever was excluded as a factor. The C-reactive protein level was the only risk factor that was strongly associated with the outcome at a 5% significance level. The results are summarized in Table VI.

Discussion

Discriminating between septic arthritis and transient synovitis of the hip in children is at times difficult, but it is always important. These two pathologic processes differ with regard to both the necessary treatment and possible complications in the growing hip. There is no simple, highly sensitive and specific, easily administered test to distinguish between these entities. Rather, when making a diagnosis, the physician considers multiple clinical factors determined from the history, physical examination, and laboratory studies. If clinical suspicion warrants it, an ultrasound evaluation of the hip and arthrocentesis of any documented effusion with the patient under conscious sedation or under anesthesia are performed. The analysis of the hip aspirate, including Gram staining and a white blood-cell count with differential, suggests the final diagnosis and helps to guide treatment. Final results of cultures of hip aspirate are not usually available for twenty-four hours or more, and in most cases a treatment course must be selected before then.

Kocher et al.¹ recently used retrospective data to develop a clinical prediction algorithm to distinguish septic arthritis from transient synovitis. The algorithm combines four independent multivariate predictive factors that, when con-

sidered together, had excellent diagnostic performance in identifying septic arthritis in the examined patient population. Children with no predictors had a 0.2% chance of having septic arthritis, whereas those with all four factors had a 99.6% chance. The authors verified the findings in a prospective manner¹⁰ but recognized the need for further evaluation of their algorithm in other clinical settings prior to its application in other populations.

Luhmann et al.⁹ retrospectively applied the Kocher algorithm to determine its predictive value in their study of children. They did not find it to be valid for differentiating between septic arthritis and transient synovitis of the hip; indeed, the predicted probability of septic arthritis was only 59% when all four factors were present. The authors did not include a C-reactive protein level in their analysis, but they noted a much higher frequency of transient synovitis in their study (117 of 163 patients), which might have been due to a lower threshold for performing hip arthrocentesis.

The current study advances the previous work involving clinical prediction algorithms for septic arthritis of the hip in three ways: (1) data were collected prospectively, which allowed our orthopaedic examiners to clearly document factors such as a child's absolute refusal to bear weight on the affected limb; (2) C-reactive protein levels, which have become a common part of the diagnostic evaluation of infections in children, were measured; and (3) we focused on children with more hip signs and symptoms, which prompted aspiration and pose a genuine diagnostic challenge in everyday practice.

Clinicians can identify most cases of transient synovitis of the hip on the basis of the history and physical examination. An afebrile, non-toxic-appearing child playing in the examining room and walking with a slight limp of recent onset is promptly recognized as having transient synovitis and is treated with close monitoring, without the need for invasive studies. In contrast to these mild cases, we studied children whose clinical presentation was most suspicious for septic arthritis, prompting ultrasound-guided aspiration of the hip. This may explain why the percentage of children with transient synovitis in our study (29%) was much lower than that in either the study by Kocher et al.¹ or that by Luhmann et al.⁹ (51% and 72%, respectively).

In our study, statistical analysis showed a C-reactive protein level of >2.0 mg/dL (>20.0 mg/L) to be an independent risk

TABLE VI Summary of Backward Elimination

Step	Effect Removed	Wald Chi Square	Pr > Chi Square*
1	Elevated erythrocyte sedimentation rate	0.1782	0.6729
2	Elevated white blood-cell count in synovial fluid	0.3811	0.5370
3	Refusal to bear weight	0.9765	0.3231
	Elevated C-reactive protein level	12.2337	0.0005

*Pr > chi square means probability that the effect is greater than the chi-square or critical value. Pr = probability.

factor strongly associated with septic hip arthritis. Assessment of the C-reactive protein level was not readily available during the entire time-period over which the retrospective studies by Kocher et al.¹ and Luhmann et al.⁹ were conducted. Our findings were consistent with those of other studies that demonstrated the utility of measurement of the C-reactive protein level for diagnosing infections in children^{8,13,14}.

An interesting finding in our patient group was the relationship between the erythrocyte sedimentation rate and the C-reactive protein level. An elevated C-reactive protein level was the only predictive factor strongly associated with the outcome on backward elimination. This suggests that an elevated erythrocyte sedimentation rate, the only other risk factor that was significantly associated with outcome in the univariate and multivariate analyses, was not significant when its effect was adjusted for an elevated C-reactive protein level.

The predicted probability of septic hip arthritis increased with the number of predictors present. As demonstrated in Table IV, the predicted probability of septic hip arthritis was 98% when our five predictors were present, which shows a trend similar to the findings reported by Kocher et al.¹. It is important to note that only a fever of $>38.5^{\circ}\text{C}$, an elevated erythrocyte sedimentation rate, and an elevated C-reactive protein level reached significance in the univariate analysis. Still, as shown by the adjusted odds ratios for refusal to bear weight and a high serum white blood-cell count, the point estimations of the associations suggest that they were related to the outcome. Our prospective study suggests that the clinical prediction algorithm developed by Kocher et al. for the diagnosis of septic hip arthritis is applicable to other patient populations. Most notably, our findings highlight the importance of the inclusion of the C-reactive protein level in any predictive algorithm for septic arthritis of the hip in children.

Akaike's information criterion calculations were used to measure the best model of the data. On the basis of these calculations, we ranked the predictors in the order of their influence on the predicted probability of septic arthritis. Fever of $>38.5^{\circ}\text{C}$ was the most influential predictor; in fact, although some children with transient synovitis had a low-grade fever, no child with transient synovitis had a fever of $>38.5^{\circ}\text{C}$. A C-reactive protein level of $>2.0\text{ mg/dL}$ ($>20.0\text{ mg/L}$) was the next strongest predictor, followed by an erythrocyte sedimentation rate of $>40\text{ mm/hr}$, refusal to bear weight, and a serum white blood-cell count of $>12,000/\text{mm}^3$ ($12.0 \times 10^9/\text{L}$).

It is important to note that, although the predictors performed well, there were false-negative findings in the study. Table II shows that although a fever of $>38.5^{\circ}\text{C}$ and a C-reactive protein level of $>2.0\text{ mg/dL}$ ($>20.0\text{ mg/L}$) were strong predictors of septic arthritis, they were still negative for 56% and 15% of children with septic arthritis, respectively. Furthermore, as demonstrated in Table IV, which lists the predicted probability of septic arthritis based on the number of predictors, 12% of the patients with septic arthritis had one or no positive factors. The predictors cannot be considered alone, and ultimately clinical judgment must

be exercised to ensure that cases of septic arthritis are not missed.

A limitation of our study was that there were small numbers of patients in both the transient synovitis and the septic arthritis group, and the study may have lacked the power to detect significant differences in weight-bearing status and serum white blood-cell count between those groups. In addition, the confirmed and presumed septic arthritis groups were not large enough for us to examine differences between them. We did note that children with presumed septic arthritis received antibiotics prior to arthrocentesis more often than did the other groups.

Other challenges were presented by the patients in our study who had an atypical course—i.e., a borderline clinical presentation or previous Lyme arthritis. The child with a history of Lyme arthritis had been adequately treated previously, and the serum profiles indicated no current Lyme infection. He was included in the study because the presentation was consistent with current presumed septic arthritis. These cases highlight the difficulties in diagnosing and treating children with hip pain and possible infection.

This work builds on previous studies in which clinical algorithms for identifying septic arthritis of the hip in children have been proposed. Our data indicate that, even in children with the most suspicious presentation, a C-reactive protein level of $>2.0\text{ mg/dL}$ ($>20.0\text{ mg/L}$) is a strong independent risk factor for septic arthritis of the hip and the C-reactive protein level is a valuable tool with which to assess the presence of septic arthritis. As other authors have stressed^{1,3,7-9}, clinical judgment must always be used along with clinical predictors. ■

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