PEDIATRIC EMERGENCY MEDICINE CRITICAL ARTICLE REVIEW (PEMCAR)	
QUESTION	In children with knee monoarthritis in Lyme disease endemic areas, does an absolute neutrophil count (ANC) of ≥ 10,000 cells/mm³ or an erythrocyte sedimentation rate (ESR) of ≥ 40 mm/hour, accurately identify children with and without septic arthritis?
TYPE	Diagnosis: Clinical Decision Rule: Validation
TOPIC	Orthopedics: Septic Arthritis
DATE	January 2022
REVIEWER	Jennifer Grad, MD, Rebecca Burton, MD
CITATION	Grant DS, Neville DN, Levas M, Balamuth F, Garro AC, Bennett JE, Thompson AD, Kharbanda AB, Lyons TW, Nigrovic LE; for Pedi Lyme Net. Validation of Septic Knee Monoarthritis Prediction Rule in a Lyme Disease Endemic Area. Pediatr Emerg Care. 2021 May 13., PubMed ID: 34160185.

STUDY DEFINITIONS	
POPULATION	Inclusion: 1-21 years of age Knee monoarthritis Treating physician chose to evaluate for Lyme disease Exclusion: None specified Setting: 8 Emergency Departments in Lyme disease endemic areas that participate in Pedi Lyme Net (Northeast and Midwest). 6/2015-3/2021 (enrollment dates varied by center).
RULE PARAMETERS	Previously derived 2-factor septic knee arthritis clinical prediction rule. ANC ≥ 10,000 cells/mm³ ESR ≥ 40 mm/hour The presence of either result was classified as “not low risk” for septic arthritis. The absence of both results was classified as “low risk” for septic arthritis
REFERENCE STANDARD	Septic Arthritis: Growth of pathogenic bacteria from synovial fluid culture or blood culture with synovial fluid WBC count > 50,000 cells/uL. Lyme Arthritis: Positive 2-tier Lyme disease test in patients without septic arthritis*. If an equivocal or positive first-tier test (C6 EIA) was obtained, a supplemental immunoblot was performed. A positive immunoblot was defined as (+) IgG or (+) IgM within 30 days of symptoms. Lyme testing occurred at a single reference laboratory. *No patients met criteria for both septic arthritis and Lyme arthritis Inflammatory Arthritis: Not meeting above criteria for septic or Lyme arthritis
OUTCOME	Rule Characteristics
DESIGN	Observational: Prospective Cohort

CRITICAL REVIEW FORM: CLINICAL DECISION RULE: VALIDATION

HOW SERIOUS WAS THE RISK OF BIAS?	
Were the patients chosen in an unbiased fashion and do they	Unclear. Patients were chosen based on availability of study staff (convenience sample) and therefore eligible

represent a wide spectrum of severity of disease?	cases may have been missed. In addition, inclusion criteria included “treating physician chose to evaluate for Lyme disease. The patients represented a wide spectrum knee monoarthritis diseases (septic arthritis (2.4%), Lyme arthritis (43.1%), or inflammatory arthritis (54.5%)), but disease severity was not discussed. 27.3% of patients were excluded due to absence of ANC, ESR or both.
Was there a blinded assessment of the criterion standard for all patients?	Unclear. Reference standards that defined the type of arthritis were objective laboratory tests and thus unlikely to be influenced by knowledge of the ANC and ESR. This could be an issue if providers decided to obtain the reference standard (e.g. arthrocentesis) based on knowledge of the ANC and ESR (verification bias). Only 27.1% of patients had an arthrocentesis.
Was there an explicit and accurate interpretation of the predictor variables and the actual rule without knowledge of the outcome?	Yes. Data was collected prospectively prior to the results of synovial fluid cultures, blood cultures or Lyme serology. The predictors are two objective laboratory tests. It is unclear if clinicians used the two tests in the form prescribed by the rule.
Was there 100% follow up of those enrolled?	Unclear. There was clinical follow-up, including telephone calls to families to confirm treatment received and outcome, as well as medical record review one month after study enrollment. However, it is unclear what percentage were available for follow-up.

WHAT ARE THE RESULTS?

DEMOGRAPHIC CHARACTERISTICS

n=543 (research sample collected)
Median Age: 7 years, IQR (4-11 years)
Male: 65.9% (358/543)
Antibiotic Pretreatment: 7.0% (38/543)
Fever: 15.6% (139/543)
Type of Arthritis
Septic: 2.4% (13/543)(Staph aureus (8), Kingella kingae (3), Strep pyogenes (1), Pasteurella (1))
Lyme: 43.1% (234/543)(56.8% with both (+) IgG and IgM, 38.9% (+) IgG alone, 4.3% (+) IgM alone
Inflammatory: 54.5% (296/543)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITH THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SENSITIVITY AND PREDICTIVE VALUE OF A NEGATIVE RULE WITH 95% CONFIDENCE INTERVALS)

HOW WELL DID THE RULE CORRECTLY IDENTIFY PATIENTS WITHOUT THE PRIMARY OUTCOME? HOW PRECISE WAS THIS MEASUREMENT? (SPECIFICITY AND PREDICTIVE VALUE OF A POSITIVE RULE WITH 95% CONFIDENCE INTERVALS)

RULE CHARACTERISTICS: BROAD VALIDATION COHORT

	Septic Arthritis		
	YES	NO	
RULE (+): ANC ≥ 10,000 OR ESR ≥ 40	12	142	154
RULE (-): ANC <10,000 AND ESR < 40	0	303	303
	12	445	457
Prevalence	12/457		2.6% (1.5, 4.4%)

Sensitivity	12/12	100% (75.8, 100%)
Specificity	303/445	68.1% (63.6, 72.3%)
Predictive Value (+) Rule	12/154	7.8% (4.5, 13.1%)
Predictive Value (-) Rule	303/303	100% (98.8, 100%)
Likelihood Ratio (+) Rule	(12/12)/(142/445)	3.1 (2.7, 3.6)
Likelihood Ratio (-) Rule	(0/12)/(303/445)	(0 in calculation)
Rule applied to 82.7% (457/543), 86 patients missing ANC (6) or ESR (21) or both (59) The 2x2 table was generated from the data presented in Table 2. Septic Arthritis No = Lyme arthritis and inflammatory arthritis combined Rule characteristics are nearly identical to the derivation cohort (See Appendix)		

The rule stratified a population with a 2.6% risk of septic arthritis into a group with a 7.8% risk (3-fold increase) of septic arthritis if the rule was positive and 0% risk of septic arthritis (2.6-fold decrease) if the rule was negative.

HOW WOULD USE OF THE RULE IMPACT RESOURCE UTILIZATION?

The rule has the potential to decrease the rate of arthrocentesis, operative joint washout and admission and decrease the rate of unnecessary/inappropriate antibiotics in patients at low risk for septic arthritis. In this validation cohort, 66.3% (303/457) of patients had a negative rule and would be classified as low risk. In low risk patients, use of the rule would decrease the rate of arthrocentesis by 17.2%, operative joint washout by 5.3% and admission by 17.8%.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
At what level of development is this rule? How can it be applied? (see Appendix)	☐ I: Impact ■ II: Validated: Broadly ☐ III: Validated: Narrow ☐ IV: Derived This is a level II clinical decision rule. It has been validated broadly at 8 study centers. An impact analysis has not been performed. Level II rules can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve. The rule is likely generalizable to patients meeting the inclusion criteria in Lyme endemic areas. In non-Lyme endemic areas, the prevalence of Lyme disease will be lower and the prevalence of septic arthritis relatively higher. Thus, the post-test probability of septic arthritis will be higher with both a positive and negative rule. The rule should not be applied to patients with non-knee monoarthritis or polyarthritis.
Does the rule make clinical sense?	Yes and No. The 2 predictors included in the rule are clinically associated with a risk of septic arthritis. However, they can also be associated with other pathology and are not specific primarily to septic arthritis. Use of the rule should be limited to those presenting with a knee monoarthritis in Lyme endemic areas.
Will the reproducibility of the rule and its interpretation be satisfactory in my clinical setting?	The rule consists of 2 objective laboratory tests (ANC and ESR). There should be no issues with interpretation if it is clearly stated that the rule is positive if either test meets criteria and negative if both tests are below threshold.

Is the rule applicable to the patients in my practice?	Potentially. Would be helpful to have more demographic data. New York State is considered a Lyme endemic by the CDC. Ticks have been found throughout New York City parks. Lyme disease carrying ticks have been identified in the Bronx and Staten Island (accessible by deer).
Will the rule results change my management strategy?	Unclear. The answer to this question is dependent on the current strategy for diagnosing and managing patients with an isolated knee monoarthritis. Any change is strategy must be made in conjunction with our orthopedic and infectious disease colleagues.
What are the benefits of applying the rule to my patients?	The primary benefit of the rule is rule is reducing the rate of arthrocentesis, operative joint washout, admission and the use of unnecessary/incorrect antibiotics. It is unclear if the rule would reduce the rate of orthopedic consultation.
What are the risks of applying the rule to my patients?	The primary risk of using the rule is in missing septic arthritis. The lower limited of the 95% confidence interval for the sensitivity of the rule was 75.8%, indicating that 24.2% (1 in 4) of patients with septic arthritis could be misidentified as low risk. The lower limited of the 95% confidence interval for the predictive value of a negative rule was 98.8%, indicating that 1.2% (1 in 83) of patients with a negative rule could have septic arthritis.

CLINICAL BOTTOM LINE

BACKGROUND: Children with knee monoarthritis from Lyme disease and septic arthritis can have similar presentations. The early disseminated stage of Lyme disease, when knee monoarthritis would present typically, occurs 3-5 weeks post tick bite and a history of tick bite may not be present. In addition, synovial fluid cell counts do not distinguish between septic and Lyme arthritis and bacterial cultures and Lyme disease serology may take several days to result. Despite the similarities in presentation, the treatment of septic arthritis and Lyme arthritis is different. Lyme arthritis can be safely treated with oral antibiotics, while septic arthritis requires operative joint washout and initial parenteral antibiotics.

A retrospective cohort of children with knee monoarthritis were evaluated at 2 pediatric centers, both located in Lyme disease-endemic areas, with the goal of deriving and internally validating a clinical prediction rule to identify children at low risk for septic arthritis who may not require invasive diagnostic techniques, such as arthrocentesis and operative joint washout (Deanehan, *Pediatrics*, 2013, PubMed ID: 23420916). The author's concluded that "children with ANC $\geq 10 \times 10^3$ cells per mm^3 and ESR $\geq$ 40 mm/hour are at low risk for septic arthritis…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." However, the authors did acknowledge that large validation studies are needed before widespread implementation of this model.

CLINICAL QUESTION: In children with knee monoarthritis in Lyme disease endemic areas, does an absolute neutrophil count (ANC) of $\geq$ 10,000 cells/mm^3 or an erythrocyte sedimentation rate (ESR) of $\geq$ 40 mm/hour, accurately identify children with and without septic arthritis?

DESIGN/RISK OF BIAS: The study is a multicenter (n=8), prospective validation of the previously derived 2-factor, septic knee arthritis clinical decision rule. All children presented with a knee monoarthritis to the Emergency Department in Lyme endemic areas. No exclusion criteria were described. The rule included an ANC of ≥ 10,000 cells/mm^3 or an ESR of ≥ 40 mm/hour. The presence of either result was classified as "not low risk" for septic arthritis. The absence of both results was classified as "low risk" for septic arthritis. Septic arthritis was defined as growth of pathogenic bacteria from synovial fluid culture or blood culture with a synovial fluid WBC count of 50,000 cells/uL or greater. Lyme arthritis was defined as a positive 2-tier Lyme disease test conducted in a single reference laboratory in patients without septic arthritis. Inflammatory arthritis was defined as not meeting above criteria for septic or Lyme arthritis.

As noted by the authors in their discussion, this study design had several limitations including:
1. Not enrolling all eligible children due to study staff availability (convenience sample)
2. 27.3% of enrolled patients did not have both an ANC and ESR obtained
3. Small sample size of patients with septic arthritis (n=13)
4. Septic arthritis may have been underdiagnosed since not all children had synovial fluid cultures (27.1%), though no patients were subsequently diagnosed with septic arthritis at follow-up
5. Pretreatment with antibiotics (7.0%) before arthrocentesis may have caused false negatives
6. Children with Lyme arthritis may have been misclassified as per a positive C6 EIA or IgM immunoblot alone.
7. Did not include newer acute phase reactants such as CRP and procalcitonin.

In addition, the proportion of patients receiving unnecessary or incorrect antibiotics after enrollment was not presented in order to determine the potential impact of the rule on these outcomes

PRIMARY RESULTS: 543 patients had a research sample collected. The rule was applied to 82.7% (457/543) with both and ANC and ESR obtained. The median age was 7 years, IQR (4-11 years) and 65.9% (358/543) were male.

Septic arthritis occurred in 2.4% (13/543) Synovial culture yielded: Staph aureus (n=8), Kingella kingae (n=3), Strep pyogenes (n=1), Pasteurella (n=1)). Lyme arthritis occurred in 43.1% (234/543)(56.8% with both (+) IgG and (+) IgM, 38.9% with (+) IgG alone, 4.3% with (+) IgM alone). Inflammatory arthritis occurred in the remaining 54.5% (296/543).

457 children had all available laboratory predictors and were included in calculation of the rule characteristics. No patients with septic arthritis were misidentified by the rule. The rule stratified a population with a 2.6% risk of septic arthritis into a group with a 7.8% risk (3-fold increase) of septic arthritis if the rule was positive and 0% risk of septic arthritis (2.6-fold decrease) if the rule was negative. Rule characteristics were nearly identical to those in the derivation cohort. Both the external validation cohort and derivation cohort had a higher specificity than the Kocher rule. It should be noted that the Kocher rule was derived in patients with a concern for hip septic arthritis.

RULE CHARACTERISTICS: COMPARISON						
	Validation[1]		Derivation[2]		Kocher[2]	
	Septic Arthritis		Septic Arthritis		Septic Arthritis	
	Yes	No	Yes	No	Yes	No
Rule (+)[3]	12	142	13	151	13	286

Rule (-)[3]	0	303	0	251	0	103
Prevalence	2.6% (1.5, 4.4%)		3.1% (1.8, 5.3%)		3.2% (1.9, 5.5)	
Sensitivity	100% (75.8, 100%)		100% (77.2, 100%)		100% (77.2, 100%)	
Specificity	68.1% (63.6, 72.3%)		62.4% (57.6, 67.0%)		26.5% (22.3, 31.1%)	
Predictive Value (+) Rule	7.8% (4.5, 13.1%)		7.9% (4.7, 13.1%)		4.3% (2.6, 7.3%)	
Predictive Value (-) Rule	100% (98.8, 100%)		100% (98.5, 100%)		100% (96.4, 100%)	
Likelihood Ratio (+) Rule	3.1 (2.7, 3.6)		2.7 (2.3, 3.0)		1.4 (1.3, 1.4)	
Likelihood Ratio (-) Rule	(0 in calculation)		(0 in calculation)		(0 in calculation)	
% Negative Rule	66.3% (61.8, 70.5%)		60.5% (55.7, 65.1%)		25.6% (21.6, 30.1%)	

1. Grant, Pediatr Emerg Care. 2021 May 13., PubMed ID: 34160185
2. Deanehan, Pediatrics, 2013., PubMed ID: 23420916
3. Rule (+) = ANC ≥ 10,000 OR ESR ≥ 40, Rule (-) = ANC < 10,000 and ESR < 40

The rule has the potential to decrease the rate of arthrocentesis, operative joint washout and admission and decrease the rate of unnecessary/inappropriate antibiotics in patients at low risk for septic arthritis. In this validation cohort, 66.3% (303/457) of patients had a negative rule and would be classified as low risk. In low risk patients, use of the rule would decrease the rate of arthrocentesis by 17.2%, operative joint washout by 5.3% and admission by 17.8%.

APPLICABILITY: The rule is likely generalizable to patients meeting the inclusion criteria in Lyme endemic areas. In non-Lyme endemic areas, the prevalence of Lyme disease will be lower and the prevalence of septic arthritis relatively higher. Thus, the post-test probability of septic arthritis will be higher with both a positive and negative rule. The rule should not be applied to patients with non-knee monoarthritis or polyarthritis.

This is a level II clinical decision rule. It has been validated broadly at 8 study centers. An impact analysis has not been performed. Level II rules can be used in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve.

AUTHOR'S CONCLUSION: "We performed an external validation of the 2-factor septic knee arthritis clinical prediction rule in a multicenter prospective cohort of children undergoing evaluation for Lyme disease. This rule accurately identified children at low risk of septic arthritis. In Lyme disease–endemic areas, clinicians can use this tool to guide initial management for a child with knee monoarthritis to avoid potentially unnecessary and invasive procedures for low- risk children without missing a case of septic arthritis. Future studies are needed to evaluate the ability of newer biomarkers and novel diagnostics to more accurately identify children at the lowest risk for septic arthritis."

POTENTIAL IMPACT: Clinical application of this 2-factor septic knee arthritis clinical prediction rule may decrease potentially unnecessary invasive diagnostic procedures in children, including arthrocentesis and operative joint washout, who are low risk for septic arthritis in Lyme endemic areas. Any change in management strategy should be discussed with our orthopedic and infectious disease colleagues. A rapid turnaround, highly-specificity serum Lyme disease test could facilitate diagnostic decision making.

APPENDIX: CLINICAL DECISION RULE STAGES

LEVEL	CRITERIA	APPLICABILITY
I	• ≥ 1 prospective validation in population separate from derivation set • Impact analysis with change in clinician behavior and benefit	Use rule in wide variety of settings with confidence
II	• Validated in 1 large prospective study including a broad spectrum of patients or in several smaller settings that differ from each other. • No impact analysis	Use rule in wide variety of settings with confidence in the accuracy of the rule but no certainty that patient outcomes will improve
III	• Validated in 1 narrow prospective sample	Consider use with caution and only in patients similar to the study population
IV	• Rule has been derived only or validated only in split samples, large retrospective databases or by statistical methods	Requires further validation before it can be applied clinically

APPENDIX: RULE CHARACTERISTIC COMPARISON

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