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# Prospective Validation of a Clinical Prediction Model for Lyme Meningitis in Children

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## What's Known on This Subject

A clinical prediction model was developed to distinguish LM from other forms of AM on the basis of the percentage of CSF mononuclear cells, duration of headache, and presence of cranial neuropathy.

## What This Study Adds

This study validates the clinical decision model and presents LRs for LM on the basis of low (<10%), medium (10%–50%), and high (>50%) calculated probability of LM.

## ABSTRACT

**OBJECTIVE.** Lyme meningitis is difficult to differentiate from other causes of aseptic meningitis in Lyme disease–endemic regions. Parenteral antibiotics are indicated for Lyme meningitis but not viral causes of aseptic meningitis. A clinical prediction model was developed to distinguish Lyme meningitis from other causes of aseptic meningitis. Our objective was to prospectively validate this model.

**METHODS.** Children between 2 and 18 years of age presenting to Hasbro Children's Hospital from April through October of 2006 and 2007 were enrolled if a lumbar puncture for meningitis showed a cerebrospinal fluid white blood cell count of >8 cells per  $\mu\text{L}$ . Cerebrospinal fluid was sent for Lyme antibody testing. The probability of Lyme meningitis was calculated by using the percentage of cerebrospinal fluid mononuclear cells, duration of headache, and presence of cranial neuropathy by using the prediction model. Definite Lyme meningitis cases were defined as cerebrospinal fluid pleocytosis with (1) positive Lyme serology confirmed by immunoblot or (2) erythema migrans rash. Possible Lyme meningitis cases were defined as cerebrospinal fluid pleocytosis with positive cerebrospinal fluid Lyme antibody. Sensitivity, specificity, and likelihood ratios for definite and possible Lyme meningitis were determined by using 10% increments of calculated probability of Lyme meningitis.

**RESULTS.** Fifty children were enrolled, including 14 children with definite Lyme meningitis, 6 with possible Lyme meningitis, and 30 with aseptic meningitis. A calculated probability of <10% for Lyme meningitis had a negative likelihood ratio of 0.006 for definite and possible Lyme meningitis cases. A calculated probability of >50% for Lyme meningitis had a positive likelihood ratio of 100 using these definitions.

**CONCLUSIONS.** A clinical prediction model using the percentage of cerebrospinal fluid mononuclear cells, headache duration, and presence of cranial neuropathy can differentiate children with Lyme meningitis from children with aseptic meningitis. Our findings suggest categories of low (<10%), indeterminate (10%–50%), and high (>50%) probability of Lyme meningitis. *Pediatrics* 2009;123:e829–e834

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### Key Words

Lyme disease, Lyme neuroborreliosis, aseptic meningitis, decision making

### Abbreviations

AM—aseptic meningitis  
 CDC—Centers for Disease Control and Prevention  
 CI—confidence interval  
 CSF—cerebrospinal fluid  
 ELISA—enzyme-linked immunosorbent assay  
 EM—erythema migrans  
 LD—Lyme disease  
 LM—Lyme meningitis  
 LR<sup>+</sup>—positive likelihood ratio  
 LR<sup>−</sup>—negative likelihood ratio  
 PCR—polymerase chain reaction

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**A**SEPTIC MENINGITIS (AM) is a common infection of the central nervous system affecting children. AM is caused by enteroviruses in the majority of cases,<sup>1</sup> but can be caused by other organisms including *Borrelia burgdorferi*, the causative agent of Lyme disease (LD). Meningitis occurs in 2% to 12% of children with LD.<sup>2–4</sup> In addition, both enteroviral infections and LD peak during the summer and early fall. Although treatment of viral meningitis is supportive, treatment of Lyme meningitis (LM) with parenteral antibiotics has been shown to significantly decrease both acute and long-term symptoms.<sup>5,6</sup> Lyme serology and cerebrospinal fluid (CSF) studies take several days to report results, leaving the clinician to decide whether to initiate treatment of possible LM with intravenous antibiotics while results are pending.

Several retrospective studies have compared demographic, clinical, and laboratory characteristics of LM and other

causes of AM in children. These studies have demonstrated that children with LM have a longer duration of headache at the time of diagnosis, predominance of CSF mononuclear cells (lymphocytes and monocytes), and presence of cranial neuritis when compared with children with viral meningitis.<sup>7-9</sup> Using retrospective data comparing children with LM and those with other forms of AM for these 3 independent variables, Avery et al<sup>9</sup> developed a clinical prediction model to help practitioners calculate the probability of a child with meningitis having LM. We designed the current study to prospectively evaluate this clinical prediction model in a cohort of children presenting with meningitis to a tertiary-care children's hospital in a Lyme disease–endemic region.

## METHODS

Rhode Island is identified as 1 of 10 Lyme disease–endemic states in the United States, and the majority of children in this state are in the catchment area of Hasbro Children's Hospital, a tertiary care pediatric center.<sup>10</sup> Children between 2 and 18 years of age presenting to Hasbro Children's Hospital from April through October of 2006 and 2007 were enrolled if a lumbar puncture performed to evaluate for meningitis had a CSF white blood cell count of >8 per  $\mu\text{L}$ . Exclusion criteria were antibiotic use within the preceding 2 weeks, a positive CSF Gram-stain, chronic neurologic abnormality, or an indwelling ventricular shunt.

Informed consent was obtained and historical and physical examination data were collected by using a standardized instrument. The data collected included age, gender, race/ethnicity, presence and duration of headache, presence of cranial nerve palsy, and presence of erythema migrans (EM) rash. CSF testing for all enrolled patients included cell count, protein, glucose, Gram-stain, and culture. Cyto-centrifuged Gram-stain, a test that has 100% sensitivity for detecting bacteria compared with culture,<sup>11,12</sup> was used on all CSF samples.

CSF samples from all enrolled patients were sent for Lyme antibody testing by enzyme-linked immunosorbent assay (ELISA) at 1 reference laboratory (Quest Diagnostics, Chantilly, VA). This reference laboratory uses ELISA (*Borrelia* Immunowell [Gen-Bio, San Diego, CA]) for antibody testing, with an index value cutoff of <0.6 considered negative. Although test characteristics for CSF samples have not been reported, serum samples have shown sensitivity of 88% for stage 1 disease, and 100% for stage 3 and unknown stage disease.<sup>13</sup> Sensitivity for stage 2 disease was not reported because of low numbers of patients reported in this stage. Specificity for LD-negative patients was 96% to 100%.<sup>13</sup> At the reference laboratory, Western blot is used discriminately, mainly as a supplement for equivocal ELISA results.

If Lyme serology was sent by the treating clinician, these results were recorded. Lyme serology was performed at the study institution by using *B burgdorferi* ELISA II (Wampole Laboratories, Inc, Princeton, NJ) with an index value cutoff of <0.91 considered negative. This test has a concordance of 94% to 96% when compared with reference immunofluorescent antibody procedures, and all antibody-positive and equivocal serum

results are routinely supplemented by Western blot. Laboratory personnel were not aware of study hypotheses or predictor variables.

Each patient was assigned a probability of having LM on the basis of the clinical prediction model derived by Avery et al.<sup>9</sup> This model incorporates the number of CSF mononuclear cells, duration of headache, and presence of cranial neuritis as follows:

$$\begin{aligned} \text{Predicted probability of LM} = & \\ & (1)/(1 + e^{-2.063 + 0.026 \times \% \text{CSF mononuclear cells}} \\ & + 0.128 \times \text{duration of headache} \\ & + [-2.833 \times (1 - \text{cranial neuritis})]) \end{aligned}$$

Participants were considered to have definite LM if they met Centers for Disease Control and Prevention (CDC) criteria<sup>4</sup> by having CSF pleocytosis as defined above in conjunction with EM rash or positive Lyme serology by ELISA confirmed by immunoblot. Possible LM cases were defined as CSF pleocytosis with positive CSF Lyme antibody. Participants who did not meet either of these criteria were classified as having AM.

On the basis of the calculated probability of LM, we determined sensitivity, specificity, positive likelihood ratio (LR<sup>+</sup>), and negative likelihood ratio (LR<sup>-</sup>) for successive 10% increments of probability of LM on the basis of the clinical prediction model. For categories in which the sensitivity or specificity was 100%, a value of 99.5% was substituted to allow for likelihood ratio calculations. Calculations were made separately for definite LM cases and combined LM cases (definite and possible).

In a published editorial about the clinical prediction model, Porwancher<sup>14</sup> noted that individuals with EM rash and CSF pleocytosis already meet the CDC criteria for a diagnosis of LM. Therefore, use of a clinical prediction model for LM would be unnecessary in these patients. To address this concern, we performed a secondary analysis in which we calculated sensitivity, specificity, LR<sup>+</sup>, and LR<sup>-</sup> of the clinical prediction model for only those patients who did not have a EM rash or previous positive Lyme serology with confirmatory immunoblot.

All data were analyzed by using Stata9.0 (Stata Corp, College Station, TX). The study was approved by the institutional review board of the participating hospital.

## RESULTS

There were 84 children eligible for enrollment between April and October over 2 consecutive years (2006–2007). Of these, 15 patients were missed, 15 were excluded for previous antibiotic use, 1 refused study participation, and 3 had insufficient CSF obtained to perform testing for *B burgdorferi* and no serum Lyme disease studies performed. Fifty patients were successfully enrolled. All enrolled patients presented between early June and mid October. The mean age of enrolled patients was 10.4 years (SD: 3.9), 60% were boys, and 78% were white. No patient had a CSF Gram-stain positive for bacteria.

Using our algorithm, 14 patients had definite LM, 6 had possible LM, and 30 had AM. A comparison of the

**TABLE 1 Comparison of Participant Characteristics and Components of the Clinical Prediction Model for Children With LM and AM**

	LM (n = 20) <sup>a</sup>	AM (n = 30)	P
Age, mean (SD), y	11.3 (3.7)	9.8 (4.0)	.21 <sup>b</sup>
Gender, male	75%	45%	<.001 <sup>c</sup>
Race, white	100%	62%	<.001 <sup>c</sup>
Median (range) duration of headache, d	14 (0–60)	3 (1–17)	<.001 <sup>b</sup>
Median (range) percentage of mononuclear cells per $\mu$ L	96 (72–100)	58.5 (4–100)	<.001 <sup>b</sup>
Cranial neuritis, n	6	0	.002 <sup>d</sup>

<sup>a</sup> Combined definite and possible LM cases.

<sup>b</sup> Student's *t* test.

<sup>c</sup>  $\chi^2$  test.

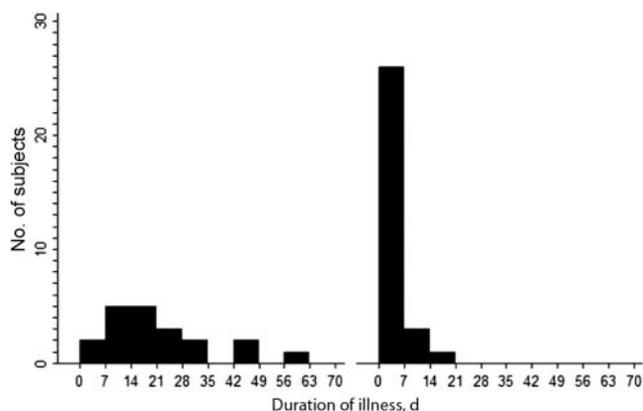
<sup>d</sup> Fisher's exact test.

demographics and components of the clinical prediction model for children with LM and AM is presented in Table 1. The duration of the acute illness for each of the groups (using combined LM data) is depicted in Fig 1.

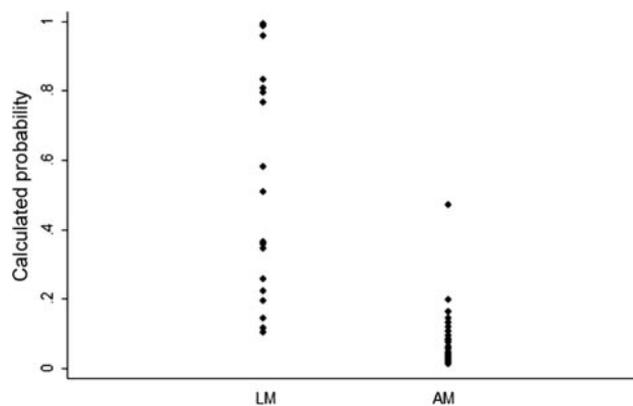
A scatter plot of the diagnosis of LM and AM compared with calculated probability of LM using the clinical prediction model is shown in Fig 2.

Results based on calculated probability at 10% intervals for LM are presented in Table 2. True-positives occurred if a child with LM had a predicted probability of LM higher than the interval value, with false-negatives occurring if a child with LM had a predicted probability of LM lower than the interval value. True-negatives occurred if a child with AM had a predicted probability of LM lower than the interval value, with false-positives occurring if a child with AM had a predicted probability of LM higher than the interval value.

In our sample, negative predictive value of the clinical prediction model was 100% (95% confidence interval [CI]: 82%–100%) at an optimal cutoff of <10% for calculated LM probability. The positive predictive value was 100% (95% CI: 66%–100%) at an optimal cutoff of >50% for calculated LM probability. When considering definite LM cases only, using a cutoff of <10% probability of LM resulted in a LR<sup>-</sup> of 0.006 (95% CI: 0–0.35).



**FIGURE 1** Duration of acute illness according to type of meningitis: left, LM; right, AM.



**FIGURE 2** Scatter plot of calculated probabilities of LM.

Using a cutoff of >50% probability of LM resulted in a LR<sup>+</sup> of 100 (95% CI: 2.0–144). The predictive values and likelihood ratios at these cutoffs remained unchanged when considering combined definite and possible LM cases (see Table 3).

A secondary analysis excluding children with EM rash or previously positive Lyme serology (confirmed by immunoblot) was conducted. On the basis of the findings of optimal LR<sup>-</sup> at 10% probability and optimal LR<sup>+</sup> at 50% probability, these probabilities were used in this subanalysis. Of the 50 patients in the study, 6 presented with EM rash and 3 had known positive Lyme serology. The sensitivity, specificity, and likelihood ratios for the remaining 41 patients using the 10% and 50% low and high probability of LM categories is presented in Table 4. In the subanalysis, despite exclusion of patients already meeting CDC diagnostic criteria for LM, the LR<sup>-</sup> remained unchanged and the LR<sup>+</sup> increased to 128 (95% CI: 2.3–176) at the optimal cut points of 10% and 50%, respectively, of LM probability as calculated by the clinical prediction model.

Of note, CSF enterovirus polymerase chain reaction (PCR) was performed for 20 (66%) of the patients with AM with 8 positive results and 12 negative results. CSF enterovirus PCR was performed for 10 (50%) of the patients with LM. None of the children classified as having LM had a positive CSF enterovirus PCR result.

**TABLE 2 Results of Calculated LM Probability for Definite LM, Possible LM, and AM Cases**

Cutoff for Probability of LM, %	n < Cutoff	Definite LM < Cutoff	Possible LM < Cutoff	AM < Cutoff
10	23	0	0	23
20	34	3	2	29
30	36	4	3	29
40	39	7	3	29
50	40	7	3	30
60	42	8	4	30
70	42	8	4	30
80	45	10	5	30
90	47	11	6	30

**TABLE 3 Sensitivity, Specificity, LR<sup>+</sup>, and LR<sup>-</sup> of the Clinical Prediction Model for Combined Definite and Possible LM Cases vs Definite LM Cases**

Cutoff for Probability of LM	LM Cases	Sensitivity (95% CI)	Specificity (95% CI)	LR <sup>+</sup> (95% CI)	LR <sup>-</sup> (95% CI)
10%	Combined	1.0 (0.80–1)	0.77 (0.57–0.89)	4.3 (1.9–9)	0.006 (0–0.35)
	Definite	1.0 (0.73–1)	0.77 (0.57–0.89)	4.3 (1.7–9)	0.006 (0–0.47)
50%	Combined	0.50 (0.28–0.72)	1.0 (0.86–1.0)	100 (2.0–144)	0.01 (0–0.84)
	Definite	0.50 (0.24–0.76)	1.0 (0.86–1.0)	100 (1.7–152)	0.01 (0–0.88)

**TABLE 4 Test Characteristics in Subjects Without EM Rash or Known Serum Positivity for LD at Presentation**

% Probability of LM	n	LM <sup>a</sup>	AM	Sensitivity (95% CI)	Specificity (95% CI)	LR <sup>+</sup> (95% CI)	LR <sup>-</sup> (95% CI)
>10	18	11	7	1.0 (0.68–1.0)	0.77 (0.57–0.89)	4.3 (1.6–9)	0.006 (0–0.56)
<10	23	0	23				
>50	7	7	0	0.64 (0.32–0.88)	1.0 (0.86–1.0)	128 (2.3–176)	0.36 (0–0.79)
<50	34	4	30				

<sup>a</sup> Combined definite and possible LM cases.

## DISCUSSION

This is the first study of North American children residing in a Lyme disease–endemic region evaluated prospectively for LM using the clinical prediction model developed by Avery et al.<sup>9</sup> We found that the clinical prediction model could be applied to distinguish patients most likely to have LM from patients with other types of AM in a Lyme disease–endemic region. Our study validated that longer duration of headache, the presence of cranial nerve palsy, and CSF mononuclear cell predominance were associated with LM in this cohort.

Another finding of our study is that defined percentages for the clinical prediction model can be used to categorize patients as having a “low risk,” “intermediate risk,” and “high risk” of LM. Calculated probabilities of <10% resulted in 100% negative predictive value for LM in our sample, and a LR<sup>-</sup> for LM of 0.006 (95% CI: 0–0.35 for combined LM). Calculated probabilities between 10% and 50% put patients into an indeterminate risk group. Calculated probabilities of >50% resulted in a 100% positive predictive value for LM in our sample, and a LR<sup>+</sup> for LM of 100 (95% CI: 2.0–144 for combined LM). These cutoffs may be useful in the design of future studies that use the clinical prediction model.

LM is a diagnosis based on both laboratory evidence and clinical factors.<sup>4</sup> Clinical findings may suggest a diagnosis of LM, but the laboratory findings consistent with LD, including positive Lyme serology and CSF antibodies, may take a number of days to become available and may have variable sensitivity for acute neuroborreliosis.<sup>15–21</sup> In the interim, the clinician must decide whether to initiate intravenous antibiotic therapy, as is the standard of care for LM,<sup>22</sup> or manage the patient supportively as is the norm for AM.

The initiation of intravenous antibiotics in pediatric patients typically requires an inpatient hospital stay, and the complete 14- to 28-day course often necessitates the placement of a long-term intravenous catheter. These

requirements create significant patient discomfort, possible complications, and medical expenditures, which might be reduced if patients determined to be at low probability of LM are not managed with antibiotics empirically. Conversely, earlier initiation of antibiotic therapy may improve long-term outcomes associated with LM. More evidence that earlier administration of antibiotics results in improved outcomes needs to be obtained before initiation of antibiotics based on preliminary clinical and laboratory data can be considered a standard of care. Alternative therapies may also prove effective, for example, initiating oral antibiotics while awaiting Lyme disease study results. Nevertheless, the predictive value of the clinical prediction model may be useful when CSF samples are of insufficient volume to perform Lyme disease testing, or test results are equivocal. Identification of a high-risk group for LM in these scenarios may allow for initiation of antibiotics in those patients most likely to have LM.

Our data underscores that in areas where LD is prevalent, cranial neuropathy with prolonged headache may warrant evaluation for possible LM. In children with proven CSF pleocytosis in a Lyme disease–endemic region, this combination is highly predictive of LM. Although most cranial neuropathies in the setting of LD will resolve without parenteral antibiotics,<sup>23</sup> in cases associated with LM, parenteral antibiotics are indicated.<sup>5,6</sup> Additional studies are needed to delineate when lumbar puncture in the setting of cranial neuropathy is indicated to evaluate for LM.

Our findings occurred in an area and season in which LD is endemic. We included likelihood ratios for the clinical prediction model cutoffs to allow for interpretation based on different pretest probabilities of LM in less endemic areas. Examples of clinical prediction model interpretations for 2 extremes of prevalence are presented in Table 5.

An acknowledged limitation of the clinical prediction model is that in its current form, it can be cumbersome

**TABLE 5** Examples of Predictive Value of the Clinical Prediction Model Based on Prevalence of LM in All Children Presenting With Aseptic Meningitis

Clinical Prediction Model Calculated Probability of LM, %	Endemic Areas and Season: Prevalence 40% (95% CI)	Not Endemic: Prevalence 1% (95% CI)
<10	Posttest probability of LM is 0.4% (0%–20%)	Posttest probability of LM is 0.01% (0%–0.35%)
>50	Posttest probability of LM is 98.5% (57%–100%)	Posttest probability of LM is 50.3% (2%–100%)

to use. Dr Avery<sup>9</sup> has made an Excel file with the formula for the model available via the Internet. Unless clinicians have the foresight to install this file in a readily available computer in the area where they practice, the model is unlikely to be used. To determine if there was an easy combination of the 3 component variables of the model that could be remembered by clinicians, we examined all combinations of the variables that would produce calculated probabilities of 10% or 50%. Although there was no readily apparent pattern for a 50% cutoff, a combination did emerge that consistently provides a calculated probability of <10%. If a subject had <7 days of headache, <70% mononuclear cells, and no cranial nerve 7 palsy (or other cranial neuropathy), the calculated probability of LM was always <10%. We propose this “Rule of 7’s” as an easily remembered set of criteria that clinicians may be able to use to identify patients at low risk of LM. Future studies should evaluate this rule before it can be adopted into clinical practice.

Our study is limited by our relatively small sample size and this is reflected in the wide-ranging CIs for our likelihood ratios. The relative insensitivity of intrathecal antibody production for *B burgdorferi* is also a limitation of these data. We attempted to minimize this limitation by collecting all CSF samples for testing at the time of enrollment, having all CSF antibody results performed by the same commercial reference laboratory, and differentiating between definite LM cases and possible LM cases. A second limitation is that 2-tier serum Lyme disease testing was not required for study entry, allowing for possible misclassification of cases. Classifying LM cases as possible or definite addressed possible misclassification in the LM cases and did not affect the predictive value of the clinical prediction model. In the 30 patients with AM, it is noteworthy that 8 patients had a positive enterovirus PCR result and 9 others had negative Lyme serology results.

## CONCLUSIONS

We present the first prospective study to evaluate the clinical prediction model for LM proposed by Avery et al.<sup>9</sup> Our data suggest that the model can be applied discriminatively if the pretest probability of LM at presentation can be estimated. The major utility of the clinical prediction model is to limit unnecessary use of parenteral antibiotics in patients presenting with men-

ingitis during peak enteroviral and LD seasons. Additional data from a larger, multicenter, prospective study in areas endemic for LD would provide additional validation for the use of this model in clinical practice.

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