Clinical Prediction Rule for Identifying Children With Cerebrospinal Fluid Pleocytosis at Very Low Risk of Bacterial Meningitis

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Context Children with cerebrospinal fluid (CSF) pleocytosis are routinely admitted to the hospital and treated with parenteral antibiotics, although few have bacterial meningitis. We previously developed a clinical prediction rule, the Bacterial Meningitis Score, that classifies patients at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF absolute neutrophil count (ANC) of at least 1000 cells/μL, CSF protein of at least 80 mg/dL, peripheral blood ANC of at least 10 000 cells/μL, and a history of seizure before or at the time of presentation.

Objective To validate the Bacterial Meningitis Score in the era of widespread pneumococcal conjugate vaccination.

Design, Setting, and Patients A multicenter, retrospective cohort study conducted in emergency departments of 20 US academic medical centers through the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. All children aged 29 days to 19 years who presented at participating emergency departments between January 1, 2001, and June 30, 2004, with CSF pleocytosis (CSF white blood cells ≥10 cells/μL) and who had not received antibiotic treatment before lumbar puncture.

Main Outcome Measure The sensitivity and negative predictive value of the Bacterial Meningitis Score.

Results Among 3295 patients with CSF pleocytosis, 121 (3.7%; 95% confidence interval [CI], 3.1%-4.4%) had bacterial meningitis and 3174 (96.3%; 95% CI, 95.5%-96.9%) had aseptic meningitis. Of the 1714 patients categorized as very low risk for bacterial meningitis by the Bacterial Meningitis Score, only 2 had bacterial meningitis (sensitivity, 98.3%; 95% CI, 94.2%-99.8%; negative predictive value, 99.9%; 95% CI, 99.6%-100%), and both were younger than 2 months old. A total of 2518 patients (80%) with aseptic meningitis were hospitalized.

Conclusions This large multicenter study validates the Bacterial Meningitis Score prediction rule in the era of conjugate pneumococcal vaccine as an accurate decision support tool. The risk of bacterial meningitis is very low (0.1%) in patients with none of the criteria. The Bacterial Meningitis Score may be helpful to guide clinical decision making for the management of children presenting to emergency departments with CSF pleocytosis.

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See also Patient Page.

ALTHOUGH BACTERIAL MENINgitis is the greatest concern when evaluating and treating children with cerebrospinal fluid (CSF) pleocytosis,[1] the majority of these children have aseptic rather than bacterial meningitis.[2,3] However, because exclusion of bacterial meningitis requires negative CSF (and blood) cultures after 2 to 3 days of incubation,[4,5] most children with CSF pleocytosis are admitted to the hospital to receive broad-spectrum antibiotics while awaiting culture test results. With the widespread introduction of highly effective bacterial conjugate vaccines against *Haemophilus influenzae* type b[6,7] and *Streptococcus pneumoniae*,[8-12] there has been a significant decrease in the incidence of bacterial meningitis in US children. This has further reduced the probability that a child with CSF pleocytosis will have bacterial meningitis. A

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highly accurate decision support tool that could identify which children with CSF pleocytosis had a near-zero risk of bacterial meningitis by using clinical and laboratory parameters readily available at the time of clinical presentation could guide decision making and limit unnecessary hospital admissions and prolonged antibiotic use.

We previously developed a clinical prediction rule, the Bacterial Meningitis Score,[1] which classifies patients at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF absolute neutrophil count (ANC) of at least 1000 cells/μL, CSF protein of at least 80 mg/dL, peripheral blood ANC of at least 10 000 cells/μL, and a history of seizure before or at the time of presentation (BOX). In the original study of 696 children hospitalized with CSF pleocytosis at a single institution, we derived the Bacterial Meningitis Score on a random two thirds of the children in the data set, and validated the score on the remaining one third of the children.[1,13] We found that of the 144 patients classified as very low risk in the validation set none had bacterial meningitis (negative predictive value, 100%; 95% confidence interval [CI], 97%-100%). In the validation set, the sensitivity of the Bacterial Meningitis Score for bacterial meningitis (ie, having ≥1 prediction rule risk factor) was 100% (37/37; 95% CI, 91%-100%).

For several reasons, clinical prediction rules are often less accurate when tested in a new clinical setting.[14] First, the assessment of either the predictor or outcome variables may not be reproducible with new patients and physicians.[15] Second, as in the case of bacterial meningitis since the advent of conjugate polysaccharide vaccines, the epidemiology of the disease or associated diagnostic testing studied may change over time and thus potentially affect the performance of any prediction rule. Finally, the observed relationships between predictors and outcome may depend on unique characteristics of the derivation population

and may differ if tested in a new patient population (model overfitting to the original data set).[16] Therefore, before implementation of a clinical prediction rule, the model should be validated externally using a different patient population and clinical setting from those on which the prediction rule was developed.[13,15-19] In practice, these methodological standards are seldom met.[18]

We desired to validate the Bacterial Meningitis Score in the era of widespread conjugate pneumococcal vaccination on a large population of children evaluated in emergency departments across the United States. To this end, we performed a validation study by using a network of 20 academic medical centers, as part of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. We planned to review the records of all children with meningitis evaluated in the emergency departments of these centers over a 4-year period. Thus, our study goal was to externally validate the Bacterial Meningitis Score, focusing primarily on the ability of the rule to identify patients at very low risk of bacterial meningitis. We also determined whether further refinement of the Bacterial Meningitis Score would simplify and improve the performance of this clinical prediction rule.

METHODS
Multicenter Collaborative Research Network

The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics reviewed, critiqued, and approved the study protocol. We identified coinvestigators from 20 emergency departments located across the United States, which routinely participate in this research network. Collectively, more than 1 million children per year are evaluated in emergency departments in these centers. Participating institutions were located in 16 different states, plus the District of Columbia, and included freestanding pediatric centers (n=17) and

> **Box. Components of the Bacterial Meningitis Score***
>
> **Variables in the Bacterial Meningitis Score**
>
> Positive cerebrospinal fluid Gram stain
>
> Cerebrospinal fluid absolute neutrophil count ≥1000 cells/μL
>
> Cerebrospinal fluid protein ≥80 mg/dL
>
> Peripheral blood absolute neutrophil count ≥10 000 cells/μL
>
> History of seizure before or at the time of presentation
>
> *Patients are classified as very low risk if none of these variables are present.

general emergency departments (n=3). Approval for the study and for data sharing with the coordinating institution was granted by the institutional review boards at each participating institution. Requirement for informed consent was waived by the institutional review boards of each participating institution.

Patient Identification

We reviewed the medical records of all patients aged 29 days to 19 years who received a diagnosis of meningitis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*], with the following codes: bacterial meningitis, 320.0-320.9; viral meningitis, 046.0-048.9; or unspecified meningitis, 321.0-322.9) at each of the participating emergency departments between January 1, 2001, and June 30, 2004. For consistency, only patients who had lumbar punctures performed in the emergency department of the study institutions were included (n=4369). We ensured complete capture of children with bacterial meningitis by cross-checking each institution's microbiology logs and by including all patients with CSF cultures growing bacterial pathogens (5 patients with bacterial meningitis were not identified by *ICD-9* codes). Cultures

that grew *Staphylococcus epidermidis*, *Streptococcus viridans*, or *Proprionobacterium acnes* were considered to represent contamination and were classified as being negative.

Inclusion Criteria

Children were classified as having meningitis and included in the study if either of the following criteria applied: CSF pleocytosis (CSF white blood cells ≥10 cells/μL, corrected for the presence of CSF red blood cells using a 1:500 ratio of leukocytes to erythrocytes usually found in peripheral blood[20,21]) or a positive CSF culture for a bacterial pathogen.

Exclusion Criteria

We excluded patients with CSF pleocytosis who would require hospital admission regardless of the risk of bacterial meningitis, including children with any of the following conditions or clinical findings: critical illness (defined as severely altered mental status, evidence of cerebral herniation, need for respiratory or blood pressure support), purpura, presence of ventricular shunt device, recent neurosurgery, immunosuppression, other bacterial infections necessitating inpatient antibiotic therapy (eg, urinary tract infections in infants <3 months, periorbital cellulitis, deep abscess, bone or joint infections, or known bacteremia), or active Lyme disease. Because antibiotic pretreatment can alter CSF profiles[22,23] and result in falsely negative blood cultures, CSF cultures, or both, we excluded patients who had received oral or parenteral antibiotics within 72 hours before their lumbar puncture.

Case Definitions

We defined a child as having bacterial meningitis if there was a positive CSF culture, CSF pleocytosis in association with a positive blood culture for a bacterial pathogen, or CSF pleocytosis in association with a positive CSF latex agglutination test for a bacterial pathogen. We defined a child as having aseptic meningitis if there was CSF pleocytosis with negative bacterial cultures of blood and CSF and a negative CSF latex agglutination test (if obtained).

Patients who did not have a CSF culture obtained were excluded (n=15); however, we did include patients who did not have blood cultures obtained provided that a CSF culture was obtained (n=342). Three of these patients had bacterial meningitis based on a positive CSF culture. The remaining 339 patients, all of whom had negative CSF cultures, had either Lyme meningitis (7 [2% of patients with aseptic meningitis and no blood culture]), enteroviral meningitis (79 [23%]), or unspecified aseptic meningitis (253 [75%]). Except for the patients with Lyme meningitis (who each received parenteral antibiotics for 21 days), none of these patients received a course of antibiotics for bacterial meningitis (defined by a course of antibiotics ≥7 days).

Data Collection

Each of the coinvestigators reviewed the computerized medical records, written medical records, or both for all study patients at their site. Patient information was entered by each investigator either onto a structured case report form (7 centers) or directly into a computerized database (identical in structure to the case report form) by using Microsoft Access database software[24] (13 centers).

Because we were also interested in refining the Bacterial Meningitis Score prediction rule in addition to validating the Bacterial Meningitis Score, we collected and recorded the following information: patient demographics (date of birth, date of presentation, sex), clinical data (coexisting medical conditions, antibiotic pretreatment, vaccination status, triage temperature and duration of fever at the time of presentation, occurrence and timing of seizures), physical examination findings (presence of rash, meningeal signs, and papilledema), laboratory test results (peripheral complete blood cell count and differential, peripheral glucose, CSF white blood cell count and differential, CSF red blood cell count, CSF glucose, CSF protein, CSF Gram stain, blood and CSF cultures), and other microbiology testing that was performed (herpes simplex virus, enteroviral or Lyme CSF polymerase chain reaction latex agglutination testing, *Borrelia burgdorferi* serology, and viral and/or mycobacterial culture). We also determined clinical outcome, final clinical diagnosis, length of hospital stay, and duration of parenteral antibiotics by medical record review. In case of discrepancies between clinicians in the medical record, only the attending physician's documentation was considered. When more than 1 CSF cell count was performed, the tube with the fewest red blood cells was always used regardless of its order in the sequence of collection.

Bacterial Meningitis Score Validation

In the main analysis, we evaluated the performance of the Bacterial Meningitis Score for predicting patients at very low risk of bacterial meningitis. Patients presenting with any predictors in the Bacterial Meningitis Score prediction rule were considered not to be at very low risk of bacterial meningitis. Patients missing data for any of the predictors were excluded from this analysis unless they had 1 or more positive predictors among those that could be evaluated, in which case they were considered not to be at very low risk for bacterial meningitis. We evaluated the performance of the rule with respect to sensitivity, specificity, negative predictive value, and positive and negative likelihood ratios for bacterial meningitis, and calculated 95% CIs where appropriate.

Bacterial Meningitis Score Refinement

To attempt to refine the Bacterial Meningitis Score, we performed in a subsequent analysis binary recursive partitioning using a classification tree algorithm. To approximate clinical decision making, we assigned in the analysis a relative cost of 100 for misclassifying a patient with bacterial meningitis as having aseptic meningitis. The recursive partitioning algorithm gener-

ated a decision tree classifying patients by risk of the outcome of interest using standard Gini splitting rules.[25] We then pruned the resulting tree for simplicity and plausibility. In the recursive partitioning analysis, we included 13 candidate predictors with biological plausibility and minimal missing data (<10%), including all of the predictors of the Bacterial Meningitis Score (Box). These variables were age, enteroviral season (June through October), seizure at or before presentation, duration of fever, triage temperature, meningismus, peripheral blood white blood cell count, peripheral blood ANC, CSF white blood cell count, CSF ANC, CSF glucose, CSF protein, and CSF Gram stain. Continuous variables were introduced into this analysis as continuous predictors, as the recursive partitioning algorithm identifies the cutoff point for continuous predictors, which maximizes the accuracy for distinguishing patients with and without the outcome of interest.[25] Patients with missing variables were included in the recursive partitioning analysis because the algorithm substitutes patient "surrogate" variables that most closely approximate the missing predictor with regard to partitioning the data. Continuous predictors that were identified by the algorithm as important for the final decision tree were then rounded slightly to make the resulting tree easier to use and interpret in the clinical setting. Finally, we used 10-fold cross-validation to internally validate the results of the recursive partitioning analysis.[25] This iterative process results in an accurate estimate of the misclassification rate of the decision tree on future cohorts of patients by using statistical resampling of the patients in the database.

We performed statistical analyses using SPSS.[26] Recursive partitioning analyses were performed using CART software.[27]

RESULTS

Patients

We identified 4369 children who met the inclusion criteria (**FIGURE**). We ex-

cluded 515 patients who would have required admission regardless of their risk of bacterial meningitis, 544 patients who had received antibiotic treatment before their lumbar puncture, and 15 patients who had no CSF culture obtained. Patients could be excluded for more than 1 reason. Among 3295 remaining patients with CSF pleocytosis, 121 (3.7%; 95% CI, 3.1%-4.4%) had bacterial meningitis and 3174 (96.3%; 95% CI, 95.5%-96.9%) had aseptic meningitis.

Characteristics of patients with bacterial and aseptic meningitis are shown

in **TABLE 1**. All patients (n=121) with bacterial meningitis and 2518 patients (80%) with aseptic meningitis were admitted to the hospital. The median length of parenteral antibiotic therapy was 14 days (interquartile range, 10-14 days) for patients with bacterial meningitis and 2 days (interquartile range, 1-2 days) for patients with aseptic meningitis. No deaths occurred among the patients with bacterial meningitis who met the study inclusion criteria (and thus did not present critically ill). Only 1 patient, a 17-year-old with aseptic meningoencephalitis, died.

Figure. Patient Flow Diagram, Including the Classification Performance of the Bacterial Meningitis Score
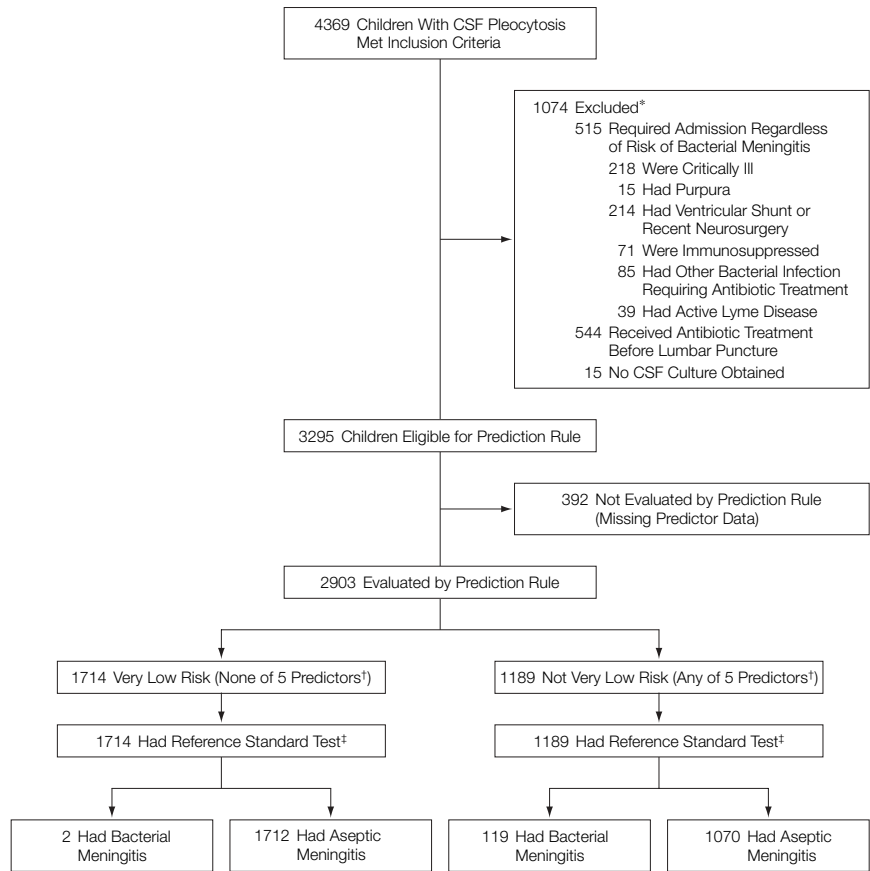
CSF indicates cerebrospinal fluid.
*Patients could be excluded for more than 1 reason.
†For list of predictors, see the Box.
‡Reference standard test was the determination of either bacterial meningitis or aseptic meningitis. We defined a child as having bacterial meningitis if there was a positive CSF culture, CSF pleocytosis in association with a positive blood culture for a bacterial pathogen, or CSF pleocytosis in association with a positive CSF latex agglutination test for a bacterial pathogen. We defined a child as having aseptic meningitis if there was CSF pleocytosis with negative bacterial cultures of blood and CSF and a negative CSF latex agglutination test (if obtained).

The etiology of bacterial meningitis was as follows: *S pneumoniae* (35 patients [29%]), *Neisseria meningitidis* (33 [27%]), group B Streptococcus (24 [20%]), *Escherichia coli* (9 [7%]), *H influenzae* (7 [6%, all nontypeable]), other gram-negative rods (7 [6%]), *Listeria monocytogenes* (3 [2.5%]), and group A Streptococcus (3 [2.5%]). The bacterial pathogen was identified by both CSF and blood culture in 65 patients (54%), CSF culture alone in 47 (39%), and blood culture alone in 9 (7%). No patient had a positive CSF latex agglutination test without either a positive CSF or blood culture.

Of the patients with aseptic meningitis, 1128 (36%) had enteroviral polymerase chain reaction testing performed, 391 (12%) herpes simplex virus polymerase chain reaction, 615 (19%) viral culture, and 231 (7%) *B burgdorferi* serology. Fifty-two percent of tested patients had a specific pathogen identified (enterovirus: n=839 [74% of all patients tested]; herpes simplex virus: n=6 [2%]; and *B burgdorferi*: n=24 [10%]).

Performance of the Bacterial Meningitis Score

The Bacterial Meningitis Score was calculated for 2903 (88%) of 3295 study patients and could not be calculated for 392 patients (12%) due to missing predictor data (none of the 392 had bacterial meningitis). Among the 2903 patients, the frequency of bacterial meningitis increased with greater numbers of additional Bacterial Meningitis Score risk factors (2 [0.1%] of 1714 patients with no risk factors; 24 [3%] of 924 with 1 risk factor; 37 [27%] of 133 patients with 2 risk factors; 40 [70%] of 57 patients with 3 risk factors; and 18 [95%] of 19 patients with ≥4 risk factors). **TABLE 2** demonstrates the risk of bacterial meningitis for patients with CSF pleocytosis with either 1, 2, or 3 or more Bacterial Meningitis Score predictors. In addition, **TABLE 3** demonstrates the odds of bacterial meningitis both for each Bacterial Meningitis Score predictor individually as well as after adjusting for all the other Bacterial Meningitis Score predictors. All variables remained significantly associated with bacterial meningitis; CSF Gram stain was the most highly associated.

Of 1714 patients categorized as very low risk by the Bacterial Meningitis Score, 2 had bacterial meningitis and 1712 had aseptic meningitis (negative predictive value, 99.9%; 95% CI, 99.6%-100%). Of the 1189 patients categorized as not very

Table 1. Characteristics of the 3295 Study Patients*

Characteristics	Bacterial Meningitis (n = 121)	Aseptic Meningitis (n = 3174)
Age, median (IQR), y	0.4 (0.2-2.6)	4.6 (0.2-9.8)
Male sex	83 (69)	1836 (58)
Presentation during enteroviral season†	34 (28)	2174 (69)
History of seizure before or at the time of presentation	7 (6)	80 (3)
Peripheral blood, median (IQR), cells/µL		
White blood cell count	14 400 (8600-22 000)	10 700 (8300-13 900)
Absolute neutrophil count	10 176 (3759-17 315)	5890 (3604-8786)
Cerebrospinal fluid, median (IQR)		
White blood cell count, cells/µL	1240 (274-3435)	120 (40-300)
Absolute neutrophil count, cells/µL	952 (155-2784)	29 (7-112)
Glucose, mg/dL	30 (12-53)	56 (49-64)
Protein, mg/dL	171 (85-251)	47 (32-69)
Positive cerebrospinal fluid Gram stain	74 (61)	6 (0.2)
Admitted to the hospital	121 (100)	2518 (80)
Duration of parenteral antibiotics, median (IQR), d	14 (10-14)	2 (1-2)

Abbreviation: IQR, interquartile range.
SI conversion: To convert glucose to mmol/L, multiply by 0.0555.
*Data are presented as number (percentage) unless otherwise specified.
†From June to October inclusive.

Table 2. Risk of Bacterial Meningitis for Patients With 1, 2, or 3 or More Bacterial Meningitis Score Predictors

Bacterial Meningitis Score Predictors Present	No. of Children With CSF Pleocytosis	No. (%) of Children With Bacterial Meningitis
1 Predictor		
Positive CSF Gram stain	12	7 (58)
CSF ANC ≥1000 cells/µL	11	1 (9)
CSF protein ≥80 mg/dL	445	8 (2)
Peripheral blood ANC ≥10 000 cells/µL	413	7 (2)
History of seizure before or at the time of presentation	43	1 (2)
2 Predictors		
Positive CSF Gram stain and CSF ANC ≥1000 cells/µL	1	1 (100)
Positive CSF Gram stain and CSF protein ≥80 mg/dL	14	14 (100)
Positive CSF Gram stain and peripheral blood ANC ≥10 000 cells/µL	5	4 (80)
Positive CSF Gram stain and seizure	0	NA
CSF ANC ≥1000 cells/µL and CSF protein ≥80 mg/dL	30	10 (33)
CSF ANC ≥1000 cells/µL and peripheral blood ANC ≥10 000 cells/µL	10	0
CSF ANC ≥1000 cells/µL and seizure	0	NA
CSF protein ≥80 mg/dL and peripheral blood ANC ≥10 000 cells/µL	46	7 (15)
CSF protein ≥80 mg/dL and seizure	12	1 (8)
Peripheral blood ANC ≥10 000 cells/µL and seizure	15	0
≥3 Predictors		
All combinations	76	58 (76)
Total patients with ≥1 predictor	1133	119 (10.5)

Abbreviations: ANC, absolute neutrophil count; CSF, cerebrospinal fluid; NA, not applicable.

low risk by the Bacterial Meningitis Score, 119 (10%) had bacterial meningitis and 1070 (90%) had aseptic meningitis. The sensitivity of the Bacterial Meningitis Score (ie, having ≥1 Bacterial Meningitis Score risk factor) for bacterial meningitis was 98.3% (119/121 patients with a Bacterial Meningitis Score calculated; 95% CI, 94.2%-99.8%) and the specificity was 61.5% (1712/2782; 95% CI, 59.7%-63.3%). The positive and negative likelihood ratios were 2.56 (95% CI, 2.43-2.69) and 0.03 (95% CI, 0.01-0.11), respectively.

Misclassified Patients

The Bacterial Meningitis Score misclassified 2 patients with bacterial meningitis as having aseptic meningitis. Both of these patients were infants between 1 and 2 months old with *E coli* meningitis and urinary tract infections, but with negative urinalyses at presentation (**TABLE 4**).

Bacterial Meningitis Score Refinement

We attempted to refine the prediction model using recursive partitioning analysis. The resulting decision tree identified the following predictors of bacterial meningitis in order of importance: CSF protein level of 80 mg/dL or higher, positive CSF Gram stain, and peripheral ANC of 10 000 cells/µL or more. Of 1786 patients with none of the 3 variables in the recursive partitioning model, 3 (0.2%) had bacterial meningitis (negative predictive value, 99.8%; 95% CI, 99.5%-100%). The recursive partitioning model misclassified the same 2 infants with *E coli* meningitis missed by the Bacterial Meningitis Score as well as an additional patient with nontypeable *H influenzae* meningitis. This patient was a 3½-month-old child who presented with a CSF ANC of 12 cells/µL, CSF protein of 51 mg/dL, negative Gram stain, peripheral blood ANC of 4500 cells/µL, and a seizure before presentation. This patient was correctly identified by the Bacterial Meningitis Score as having bacterial meningitis on the basis of a seizure before presentation to the emergency department.

Table 3. Bivariate and Multivariate Adjusted Odds Ratios of Bacterial Meningitis for Each of the Bacterial Meningitis Score Predictors

Predictor	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Positive cerebrospinal fluid Gram stain	866.1 (358.4-2093.2)	653.7 (216.6-1972.8)
Cerebrospinal fluid ANC ≥1000 cells/µL	47.2 (30.3-73.6)	8.0 (3.8-17.0)
Cerebrospinal fluid protein ≥80 mg/dL	17.9 (11.3-28.3)	12.2 (5.7-26.0)
Peripheral blood ANC ≥10 000 cells/µL	4.8 (3.3-6.9)	4.1 (2.2-8.0)
History of seizure before or at the time of presentation	2.4 (1.1-5.3)	3.7 (1.0-13.4)

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval.
*Adjusted for the other Bacterial Meningitis Score predictors.

Table 4. Characteristics of the 2 Patients With Bacterial Meningitis Misclassified by the Bacterial Meningitis Score

Characteristics	Patient 1	Patient 2
Patient age, mo	1.8	1.0
Peripheral blood, cells/µL		
White blood cell count	12 300	12 300
Absolute neutrophil count	8100	6600
Cerebrospinal fluid		
White blood cell count, cells/µL	23	540
Absolute neutrophil count, cells/µL	0	497
Glucose, mg/dL	53	52
Protein, mg/dL	31	65
Gram stain	Negative	Negative
History of seizure before or at the time of presentation	None	None
Bacterial pathogen isolated (both from cerebrospinal fluid and urine)	*Escherichia coli*	*Escherichia coli*

SI conversion: To convert glucose to mmol/L, multiply by 0.0555.

COMMENT

We have previously derived and validated the Bacterial Meningitis Score at a single institution to identify children with CSF pleocytosis who are at very low risk of bacterial meningitis.[1] In the current multicenter validation study in the era of widespread pneumococcal conjugate vaccination, the Bacterial Meningitis Score accurately identified patients at very low risk of bacterial meningitis, misclassifying only 0.1% of patients categorized as very low risk for bacterial meningitis. Our attempts to refine the model using recursive partitioning analysis led us to a somewhat simpler model that relied on 3 variables only; however, this predictive model misclassified an additional patient with bacterial meningitis compared with the Bacterial Meningitis Score. Furthermore, the refined model lacks any measure of CSF white blood cell count or CSF ANC, which may limit its acceptability to a clinician. The predictor variables of the Bacterial Men- ingitis Score, despite the greater number, retain intuitive appeal and are easily applied by the clinician. Therefore, we believe the Bacterial Meningitis Score is the more appropriate prediction rule for assisting the clinician with the identification of children with CSF pleocytosis at very low risk for bacterial meningitis.

Previously, other investigators have developed clinical prediction rules to distinguish aseptic from bacterial meningitis at the time of clinical presentation. These models have included the following parameters: age,[28-30] time of the year,[28] peripheral ANC,[29] CSF white blood cell count or ANC,[28-32] CSF-blood glucose ratio,[28,29,31,33] CSF protein,[29,30] and CSF Gram stain.[29] In our 20-center study, clinicians obtained peripheral glucose for only 50% of the study patients, making prediction rules that rely on CSF-blood glucose ratio less applicable. Furthermore, a prediction rule using a complicated fractional polynomial equation to calculate risk of bac-

terial meningitis would require automation to be applied in the clinical setting.[30,32] Previously published prediction rules were derived before the introduction of conjugate *H influenzae* type b[28] and *S pneumoniae* vaccines,[1,29-35] and were not internally[29,35] or externally validated.[12,28-35] In contrast, the Bacterial Meningitis Score provides a simple scoring system composed of easily collected data elements that could routinely be implemented by clinicians in the acute management of children with CSF pleocytosis. To our knowledge, this is the first bacterial meningitis prediction model to be both studied in the era of widespread conjugate pneumococcal vaccine use and externally validated.

Our validation study was conducted using strict methodological standards.[13,18,36] Our inclusion and exclusion criteria were such that only those patients with CSF pleocytosis who could be reasonably considered for outpatient management were included in the study (ie, we excluded patients with other reasons for hospital admission or with critical illness). Both the predictors and outcome measure were clearly and objectively defined. By careful standardized chart reviews, we had minimal missing data for the included clinical and laboratory predictors and were able to assign an appropriate outcome (aseptic vs bacterial meningitis) for all patients.

The Bacterial Meningitis Score has already been independently validated (prospectively and retrospectively) in 2 small pediatric studies in France and Belgium (166 and 277 study patients with meningitis, respectively), and shown to perform very well.[37,38] None of the patients classified by the Bacterial Meningitis Score in the very low risk category had bacterial meningitis (negative predictive value, 100% for both studies). Although a large prospective validation would be preferable to a retrospective validation, such a study would be difficult to accomplish given the very low incidence of bacterial meningitis. Four of the 5 predictors in the Bacterial Meningitis Score are objective laboratory measures and the fifth, a history of seizure, is a fairly objective clinical measure. Patients were classified as having a seizure for any abnormal neurological activity thought to possibly be a seizure to minimize the risk of variability in interpretation. Therefore, we think our study is nearly equivalent to a prospective validation. Thus, based on the 2 small studies and our validation study, our findings are likely to be widely generalizable and helpful in guiding clinical decision making, as the patient population encompasses a wide spectrum of ages, clinical settings, geographic regions, and seasons.

Our study has some limitations. First, our study was retrospective and therefore subject to potential information bias. However, the potential impact of this limitation is minimal because the Bacterial Meningitis Score includes only objective clinical characteristics and laboratory parameters. Furthermore, we used strict criteria to define the outcome variable (bacterial meningitis) to minimize misclassification bias. Cerebrospinal fluid cultures were available for all included patients and blood cultures were available for 90% of the study patients. Although it is conceivable that some of the patients with no blood culture obtained may have had bacterial meningitis, this seems unlikely given that CSF cultures were negative in all of these patients. In addition, none of the patients who did not have blood cultures drawn (except for those with Lyme meningitis) received a standard course of antibiotics for bacterial meningitis or a diagnosis of bacterial meningitis by the treating clinician. It is also possible that we may have missed potentially eligible study patients due to errors in emergency department diagnosis coding. However, we attempted to capture all cases of children with bacterial meningitis by cross-checking the institution's microbiology test results and by including all patients with CSF cultures growing bacterial pathogens.

Because our model was designed to identify patients at very low risk for bacterial meningitis, some patients with no predictors of bacterial meningitis may nevertheless have infections that require antimicrobial therapy, such as Lyme meningitis or herpes simplex virus encephalitis. Therefore, the Bacterial Meningitis Score should be used in concert with careful clinical assessment of the patient, which would include consideration of these other important treatable infections. In addition, the Bacterial Meningitis Score is designed to serve as an assistive clinical prediction rule to help guide clinical decision making, and not to serve as a directive decision rule that explicitly dictates clinical care.[15] We would particularly caution against the use of the Bacterial Meningitis Score for infants younger than 2 months for whom the Bacterial Meningitis Score may be less accurate, and who may not be appropriate candidates for outpatient management. In this subgroup of the 792 children younger than 2 months (of whom 26 had bacterial meningitis), the classification performance of the Bacterial Meningitis Score was sensitivity of 92.3% (95% CI, 74.9%-99.1%), specificity of 56.3% (95% CI, 52.7%-59.8%), and negative predictive value of 99.5% (95% CI, 98.3%-99.9%). Finally, the Bacterial Meningitis Score should also not be used to guide decision making for children pretreated with antibiotics in whom the diagnosis of aseptic meningitis is difficult and whose pretreatment may have affected CSF profiles.[22,23]

For patients with at least 1 Bacterial Meningitis Score risk factor or who are younger than 2 months, we suggest admission to the hospital and administration of parenteral antibiotics. For the 2111 patients older than 2 months in our study (of whom 95 had bacterial meningitis), the Bacterial Meningitis Score was highly accurate. The classification performance of the Bacterial Meningitis Score for identifying bacterial meningitis for these children was sensitivity of 100% (95% CI, 96.9%-100%), specificity of 63.5% (95% CI, 61.4%-65.6%), and negative predictive value of 100% (95% CI, 99.8%-100%). For patients older than 2 months with a Bacterial Meningitis

Score score of 0 and who are well appearing, physicians could consider 2 options: admission for observation or, in the proper clinical context and if adequate follow-up is available, outpatient management. Because the consequences of missing bacterial meningitis could be devastating, however, we would recommend serious consideration of administration of a long-acting parenteral antibiotic if the patient is to be discharged from the emergency department.

In the conjugate *H influenzae* type b and pneumococcal vaccines era, bacterial meningitis has become an uncommon disease in US children.[39] Therefore, the majority of children with CSF pleocytosis have aseptic rather than bacterial meningitis. Furthermore, our study confirms that most children with CSF pleocytosis are admitted to the hospital to receive parenteral antibiotics while awaiting bacterial culture test results. Using the Bacterial Meningitis Score prediction rule to assist with clinical decision making could substantially reduce unnecessary hospital admissions for children with CSF pleocytosis at very low risk of bacterial meningitis. Future investigations should study the clinical implementation of the Bacterial Meningitis Score as a guide to help care for children with CSF pleocytosis.

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