Development and Validation of a Multivariable Predictive Model to Distinguish Bacterial From Aseptic Meningitis in Children in the Post-Haemophilus influenzae Era

Lise E. Nigrovic, MD*; Nathan Kuppermann, MD, MPH§; and Richard Malley, MD¶

ABSTRACT. Context. Children with meningitis are routinely admitted to the hospital and administered broad-spectrum antibiotics pending culture results because distinguishing bacterial meningitis from aseptic meningitis is often difficult.

Objective. To develop and validate a simple multivariable model to distinguish bacterial meningitis from aseptic meningitis in children using objective parameters available at the time of patient presentation.

Design. Retrospective cohort study of all children with meningitis admitted to 1 urban children's hospital from July 1992 through June 2000, randomly divided into derivation (66%) and validation sets (34%).

Patients. Six hundred ninety-six previously healthy children aged 29 days to 19 years, of whom 125 (18%) had bacterial meningitis and 571 (82%) had aseptic meningitis.

Intervention. Multivariable logistic regression and recursive partitioning analyses identified the following predictors of bacterial meningitis from the derivation set: Gram stain of cerebrospinal fluid (CSF) showing bacteria, CSF protein ≥80 mg/dL, peripheral absolute neutrophil count ≥10 000 cells/mm3, seizure before or at time of presentation, and CSF absolute neutrophil count ≥1000 cells/mm3. A Bacterial Meningitis Score (BMS) was developed on the derivation set by attributing 2 points for a positive Gram stain and 1 point for each of the other variables.

Main Outcome Measure. The accuracy of the BMS when applied to the validation set.

Results. A BMS of 0 accurately identified patients with aseptic meningitis without misclassifying any child with bacterial meningitis in the validation set. The negative predictive value of a score of 0 for bacterial meningitis was 100% (95% confidence interval: 97%–100%). A BMS ≥2 predicted bacterial meningitis with a sensitivity of 87% (95% confidence interval: 72%–96%).

Conclusions. The BMS accurately identifies children at low (BMS = 0) or high (BMS ≥2) risk of bacterial meningitis. Outpatient management may be considered for children in the low-risk group. Pediatrics 2002;110:712–719; prediction model, bacterial meningitis, aseptic meningitis.

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ABBREVIATIONS. CSF, cerebrospinal fluid; WBC, white blood cell count; Hib, Haemophilus influenzae type b; ANC, absolute neutrophil count; RBC, red blood cells; ROC, receiver operating characteristic; BMS, Bacterial Meningitis Score; NPV, negative predictive value; CI, confidence interval; PPV, positive predictive value.

Bacterial meningitis remains an important cause of morbidity and mortality in children despite the advent of highly effective bacterial conjugate vaccines. In the United States each year, there are close to 6000 new cases of bacterial meningitis, of which approximately half occur in children younger than 18 years of age.1 Streptococcus pneumoniae and Neisseria meningitidis are the major bacterial pathogens in children beyond the immediate neonatal period1 and have associated overall mortality rates of 6% to 12%2–4 and 3% to 5%,1,5 respectively. Despite antimicrobial therapy, up to 25% of survivors of bacterial meningitis have significant sequelae, such as neurologic deficits or hearing loss.6

Because discrimination between bacterial meningitis and aseptic meningitis at the time of presentation is often difficult, children with cerebrospinal fluid (CSF) pleocytosis are routinely admitted to the hospital to receive broad-spectrum antibiotics pending bacterial culture results. Previously, investigators have evaluated means to distinguish bacterial from aseptic meningitis before the results of blood and/or CSF cultures are available. When evaluated on patients not previously treated with antibiotics, the CSF Gram stain has been reported to have a sensitivity between 60% and 92%.7,8 Other rapidly available parameters, such as the peripheral white blood cell count (WBC) and the CSF WBC with differential, have wide zones of overlap in patients with bacterial and aseptic meningitis.9–14 Measurements of CSF leukocyte aggregation, CSF lactate, and serum procalcitonin lack either sensitivity or specificity and are not routinely available.15–22 The serum concentration of C-reactive protein has been evaluated as well, but has limited value as it may be low early in bacterial disease or elevated in patients with viral infections.23,24 Endogenous inflammatory mediators such as CSF tumor necrosis factor-α, interleukin-1β, or interleukin-6 have good predictive power but are not routinely available in the clinical setting.25,26

Two multivariable models have previously been developed to distinguish bacterial versus aseptic meningitis. The first study—which was derived from
an all-ages population and before the widespread introduction of Haemophilus influenzae type b (Hib) conjugate vaccine, and which used CSF absolute neutrophil count (ANC), CSF-blood glucose ratio, age, and time of year—demonstrated excellent sensitivity and specificity for the prediction of bacterial versus aseptic meningitis.27 A second, more recent study was based on a pediatric population in the era of universal Hib vaccination and used the following dichotomous predictors: CSF WBC >30 cells/mm3, CSF-blood glucose ratio <40%, CSF glucose <40 mg/dL, CSF protein >45 mg/dL, positive Gram stain, peripheral band count >500 cells/mm3, and age <6 months.13 This model also had excellent predictive ability; however, the authors did not attempt to validate their findings, which makes it difficult to assess the robustness and generalizability of their model.

Because most children admitted to the hospital for meningitis have viral rather than bacterial infections, we wished to develop and validate a simple model to predict bacterial versus aseptic meningitis in a pediatric population in the era of Hib vaccination. We also sought to identify a low-risk group of patients who may be candidates for outpatient management.

METHODS

Patient Population

We reviewed the charts of all patients aged 29 days to 19 years who were admitted to Children’s Hospital, Boston, between July 1, 1992, and June 30, 2000, with a final diagnosis of meningitis. A computerized search tool was used to identify patients with the following International Classification of Disease diagnosis codes: bacterial meningitis (320.0–320.9), viral meningitis (046.0–048.9), tuberculous meningitis (013.0), and unspecified meningitis (321.0–322.9).

Definitions

Patients were defined as having bacterial meningitis if either of the following 2 criteria were met: 1) the CSF culture was positive for a bacterial pathogen; or 2) the presence of CSF pleocytosis (>7 WBC per mm3) and either a positive blood culture or CSF latex agglutination test positive for S pneumoniae, N meningitidis, H influenzae, or Streptococcus agalactiae (group B Streptococcus). Patients in whom CSF culture revealed an organism usually associated with contamination (such as Staphylococcus epidermidis or Propionibacterium acnes in previously healthy patients) were excluded.

We then performed 2 multivariable statistical analyses on the derivation set to identify significant predictors of bacterial meningitis. Only those patients with complete information on all candidate variables were considered in the multivariable analyses. First, we entered the candidate variables as described above, then used a forward stepwise multivariable logistic regression analysis. Variables independently associated (P < .05) with bacterial meningitis in this analysis were then ranked according to the magnitude of the β-coefficient.

Statistical Methods

Univariate and multivariate analyses were conducted using the Statistical Program for the Social Sciences.30 Confidence intervals for proportions were calculated using Stata statistical software.31 Answer Tree statistical software was used to perform recursive partitioning of the data.32 The database was randomly divided into a derivation set comprising two thirds of the patients and a validation set comprising the remaining patients. The Student t test was used to compare means between the derivation and validation sets and to identify variables in the derivation set that were significantly associated (P < .05) with bacterial meningitis. To limit the number of variables considered, only those that were objective, biologically plausible, readily available at the time of hospital presentation, and correlated with bacterial meningitis in previous studies were chosen. Because of the colinearity of some of these variables, we selected peripheral ANC over WBC and CSF ANC over CSF WBC based on inspection of the receiver operating characteristic (ROC) curves of these variables against bacterial meningitis. To obtain a simple and practical model, continuous predictors were dichotomized using rounded whole number values that allowed effective discrimination between bacterial meningitis and aseptic meningitis. We selected these cutoffs by identifying predictor variable values associated with a point of the ROC curve with the best sensitivity-specificity trade off. These optimal cutoff points typically occur where the ROC curve “turns the corner,” at which point an incremental gain in sensitivity results in a substantial loss of specificity. We then rounded off these values for numerical and clinical simplicity.

For ease of use in the clinical setting, we then created a Bacterial Meningitis Score (BMS), using the predictor variables identified by months with urinary tract infections (n = 7), as well as children with brain abscesses (n = 2) or periorbital cellulitis (n = 1).
both of these multivariable statistical methods. The relative weighting of each component variable of the BMS score was based on its β value in the logistic regression analysis. The performance of the BMS was then evaluated on patients in the validation set.

We also conducted 2 subset analyses of the data. To estimate the performance of the model in the era of routine pneumococcal conjugate vaccination, we performed a subgroup analysis excluding cases of *S pneumoniae* meningitis. Patients with missing values were excluded in the multivariable analyses. We also analyzed the subset of patients between 29 and 60 days of age to determine how well the prediction model identified children with bacterial meningitis among this younger, high-risk group.

Approval for review of the medical records was granted by the institutional review board of Children’s Hospital, Boston.

RESULTS

**Patient Characteristics**

We identified 696 children, including 125 (18%) with bacterial meningitis and 571 (82%) with aseptic meningitis. Cases of bacterial meningitis were caused by the following pathogens: *S pneumoniae* (79, 63%), *N meningitidis* (21, 17%), group B Streptococcus (13, 10%), *H influenzae* (6, 5%, all nontypeable), *Listeria monocytogenes* (3, 2%), enteric Gram-negative rods (2, 2%), and other streptococci (1, 1%). No cases of tuberculous meningitis were identified.

The bacterial pathogen was identified in both CSF and blood culture in 60 patients (48%), CSF culture alone in 35 (28%), blood culture alone in 28 (22%), and by latex agglutination alone in 2 (2%). Of the pretreated patients with bacterial meningitis, the pathogen was identified in both CSF and blood culture in 18 patients (35%), CSF culture alone in 12 (23%), blood culture alone in 22 (42%) and by CSF latex agglutination alone in 0. Of patients with bacterial meningitis, 42% had antibiotics administered within 72 hours before lumbar puncture (42% oral and 58% parenteral antibiotics). Latex agglutination tests were performed in 61 patients. Four patients died, all with bacterial meningitis (3% of total patients with bacterial meningitis).

**Comparison of the Derivation and Validations Sets**

Patients were randomly divided into 2 sets: the derivation set (*n* = 456, 66% of patients) and the validation set (*n* = 240, 34% of patients). Patients in the derivation set were, on average, older at presentation and more likely to be male (Table 1). There were no other statistically significant differences between the derivation and validation sets.

**Univariate Analysis of the Derivation Set**

Patients with bacterial meningitis were significantly more likely to be admitted in the nonenteroviral season and to have had seizures at or before presentation than patients with aseptic meningitis. Other variables commonly associated with bacterial infection were also significantly different in patients with bacterial compared with aseptic meningitis, including the peripheral ANC, CSF ANC, CSF glucose, CSF protein, and positive Gram stain (Table 2).

Optimum cut offs for continuous variables were then selected by analyzing the ROC curve for each variable, as previously described (Fig 1). The following dichotomous variables were thus selected for consideration in the multivariate analyses: admission during nonenteroviral season, seizure at or before presentation, peripheral ANC ≥10,000 cells/mm³, CSF ANC ≥1000 cells/mm³, CSF glucose ≤35 mg/dL, CSF protein ≤80 mg/dL, and positive Gram stain.

**Multivariate Analyses**

*Logistic Regression*  

The variables listed above were entered into a forward stepwise logistic regression analysis, to identify independent predictors of bacterial meningitis (Table 3). The presence of a positive Gram stain was the most significant predictor of bacterial meningitis (β = 5.6). The other variables independently associated with bacterial meningitis in this analysis were CSF protein ≥80 mg/dL, peripheral ANC ≥10,000 cells/mm³, seizure at or before presentation, and CSF ANC ≥1000 cell/mm³. Only 4% of patients were excluded from this analysis because of missing values.

**Recursive Partitioning**

Recursive partitioning was used to identify important predictors in the derivation set (Fig 2). The same

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**TABLE 1.** Characteristics of Patients in the Derivation Set and Validation Set*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derivation Set (± Standard Deviation)</th>
<th>Validation Set (± Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>n</em> = 456</td>
<td><em>n</em> = 240</td>
</tr>
<tr>
<td>Median age in mo (interquartile range)†</td>
<td>5.0 (2.0–7.20)</td>
<td>3.0 (1.7–39.6)</td>
</tr>
<tr>
<td>Male gender, n (%)†</td>
<td>281 (62%)</td>
<td>126 (33%)</td>
</tr>
<tr>
<td>Peak fever (°C)</td>
<td>39.0 ± 1.0</td>
<td>39.0 ± 0.8</td>
</tr>
<tr>
<td>Duration of fever (d)</td>
<td>2.1 ± 1.7</td>
<td>2.0 ± 1.8</td>
</tr>
<tr>
<td>Antibiotic pretreatment, n (%)</td>
<td>36 (8%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Enteroviral season, n (%)</td>
<td>291 (64%)</td>
<td>154 (64%)</td>
</tr>
<tr>
<td>Seizure at or before presentation, n (%)</td>
<td>35 (7%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>4 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peripheral WBC (&gt;10³ cells/mm³)</td>
<td>13.5 ± 6.8</td>
<td>13.6 ± 9.6</td>
</tr>
<tr>
<td>CSF WBC (cells/mm³)</td>
<td>844 ± 2759</td>
<td>611 ± 1501</td>
</tr>
<tr>
<td>CSF glucose (mg/dL)</td>
<td>53 ± 19</td>
<td>55 ± 19</td>
</tr>
<tr>
<td>CSF protein (mg/dL)</td>
<td>89 ± 137</td>
<td>75 ± 74</td>
</tr>
<tr>
<td>Positive Gram stain, n (%)</td>
<td>64 (14%)</td>
<td>31 (33%)</td>
</tr>
<tr>
<td>Bacterial meningitis, n (%)</td>
<td>86 (19%)</td>
<td>39 (16%)</td>
</tr>
</tbody>
</table>

* Means and their standard deviations are given for all continuous variables (with the exception of age, which is presented as a median because of substantial skewness).
† *P* < .05.
variables identified as independent predictors in the logistic regression analysis were identified as important predictors in the recursive partitioning analysis. The most important variable, identified at the top of the resultant decision tree, was the Gram stain result. For the patients with negative CSF Gram stains, the other predictors in the decision tree accurately discriminated bacterial from aseptic meningitis. At each step of the decision tree, the risk of bacterial meningitis can be estimated for any particular combination of predictor variables.

Prediction Model

Based on the results of both the logistic regression and the recursive partitioning analyses, we developed the BMS. Because the presence of a positive Gram stain was the strongest independent predictor of bacterial meningitis using both analytical methods, with the relative magnitude of the $\beta$-coefficient roughly twice that of the other variables, 2 points were attributed to a positive Gram stain and 1 point for each of the remaining variables. The range of the resulting BMS was thus 0 to 6 points (Table 4).
The performance of the BMS was then tested on the validation set (Fig 3). A BMS of 0 accurately identified patients with aseptic meningitis without misclassifying any child with bacterial meningitis as having aseptic meningitis. The negative predictive value (NPV) of a score of 0 for bacterial meningitis was 100% (144/144, 95% confidence interval [CI]: 97%–100%), and the specificity was 73% (144/196, 95% CI: 91%–100%). A BMS ≥ 2 predicted bacterial meningitis with a sensitivity of 87% (33/38, 95% CI: 72%–96%), and a positive predictive value of 87% (33/38, 95% CI: 72%–96%).

When applied to the entire data set, the BMS misclassified only 3.3% of the patients. Of all patients with a BMS = 0 in the derivation and validation data sets (predicted to have a low likelihood of bacterial meningitis), 2 of 404 patients (0.5%; 95% CI: 0.06%–1.8%) actually had bacterial meningitis. The 2 patients thus misclassified were both in the derivation set. One was a 7-month-old child with pneumococcal meningitis who had a CSF WBC of 11 cells/mm³ and peripheral ANC of 4.5 × 10^3 cells/mm³. This patient had been pretreated with parenteral antibiotics before the lumbar puncture. The second patient was a 6-month-old child with meningococcal meningitis with CSF WBC of 10 cells/mm³ and peripheral ANC of 8.0 × 10^3 cells/mm³.

### Subset Analyses

We performed 2 subset analyses. In the first subset analysis, we evaluated the performance of the model after exclusion of patients infected with *S. pneumoniae*. In our study, 63% of the children with bacterial meningitis cases were infected with *S. pneumoniae*. Because the conjugate pneumococcal vaccine reduces the incidence of invasive pneumococcal infections attributable to vaccine-type strains, the prediction rule was reexamined after exclusion of
children with pneumococcal meningitis. When applied to the validation set, a BMS of 0 predicted aseptic meningitis with 73% sensitivity (144/196, 95% CI: 67%–80%), 100% specificity (11/11, 95% CI: 72%–100%), and positive predictive value of 100% (144/144, 95% CI: 97%–100%). A BMS ≥2 predicted bacterial meningitis with 100% sensitivity (11/11, 95% CI: 72%–100%), 97% specificity (191/196, 95% CI: 94%–99%), and 69% positive predictive value (11/16, 95% CI: 41%–89%).

We performed a second subanalysis to evaluate the performance of the prediction rule on patients younger than 2 months old, because these children are typically difficult to evaluate clinically and likely have different risk of bacterial meningitis than older patients. Of the 77 patients between 29 to 60 days of age in the validation set, the prediction model accurately identified the 3 patients with bacterial meningitis.

**DISCUSSION**

Because accurately distinguishing bacterial meningitis from aseptic meningitis at the time of presentation is difficult, children with CSF pleocytosis are routinely admitted to the hospital for treatment with broad-spectrum antibiotics while awaiting results of bacterial cultures. We have developed a scoring system based on multivariate logistic regression and recursive partitioning analyses of data obtained from hospitalized children with bacterial and aseptic meningitis. This prediction rule is based solely on data that are objective and readily available at the time of presentation. As shown by the performance of the BMS on the validation set, this score accurately identifies patients both at high and very low risk of bacterial meningitis.

Several findings of the current study are consistent with prior investigations. We found Gram stain, seizure at or before presentation, peripheral ANC, CSF ANC, and CSF protein to be significant univariate predictors of bacterial meningitis, as shown in previous analyses.7–11,13,14 The considerable overlap of these variables between the patients with aseptic and bacterial meningitis, however, limits their discriminative ability when applied as univariate predictors.

Our study differs from previous studies in being the first validated multivariate model derived from a pediatric population in the postconjugate Hib vaccine era. As compared with the multivariate model developed by Spanos and colleagues,27 our study population comprises only children from an era in which meningitis attributable to Hib has become exceedingly rare because of widespread vaccination (and indeed, no cases of Hib meningitis were found in our population). In the model by Spanos, age was a highly predictive variable, whereas the age of the patient was not a significant predictor in our study. This difference may reflect the fact that their study included patients of all ages (≥1 month), whereas our study included only pediatric patients (29 days–18 years of age). Finally, although aseptic meningitis is more likely to occur in the enteroviral season, we did not find that time of the year provided significant independent discriminative power with respect to the prediction of bacterial versus aseptic meningitis. The predictive model by Freedman and colleagues13 was developed on a pediatric population in the era of widespread Hib vaccination, but the absence of validation makes it difficult to ascertain the generalizability of their findings.

The use of the BMS score could have important implications for clinicians caring for children with meningitis. First, it is simple to use, as it is based on variables that are readily available at the time of initial patient evaluation. Second, it allows for rapid and accurate discrimination of patients at either high or very low risk of bacterial meningitis. The determination that a patient has a high risk of bacterial meningitis would allow for prompt recognition of the severity of illness and immediate antibiotic administration and hospitalization, with transfer to a tertiary pediatric facility, if necessary. Conversely, patients with a BMS score of 0 can be considered to be at very low risk of bacterial meningitis. Hospitalization may not necessarily be warranted for some of these patients. Four hundred four (60%) admitted patients in our study had a BMS of 0 and thus could have been considered to be at very low risk of bacterial meningitis (with a misclassification rate of 0.5%). A subset of these patients—including those who were very well appearing, well hydrated, and without any signs of neurologic or hemodynamic compromise—could conceivably have been followed as outpatients, perhaps after the administration of a long-acting parenteral antibiotic.36,37

Potential limitations of our study should be considered. Ideally, a prediction rule should be derived, and then be validated prospectively on a separate population.38 However, because the incidence of bacterial meningitis is relatively low, our study was based on a retrospective analysis of data from hospitalized children over an 8-year period. We confirmed the validity and robustness of this model by evaluating the performance of the BMS on a separate, randomly selected, subset of patients. Although evaluation of the general appearance of the patients and prospective validation of the model would be ideal, the fact that all the variables used in the BMS are objective historical and laboratory parameters gathered at the time of initial presentation makes it unlikely that the results would greatly change had the study been conducted prospectively using the same predictor variables. We also had high rate of complete data collection; 96% of the patients in the database had no missing data for the analyzed variables. Because patients with aseptic meningitis who were pretreated were excluded from the analysis, this model should not be applied to patients who have received systemic antibiotics within 72 hours of lumbar puncture.

The incidence of bacterial meningitis in our study was 18%, considerably higher than reported population estimates. This likely reflects referral bias, as patients with bacterial meningitis were transferred from other hospitals for admission more often than those with aseptic meningitis (52% vs 6%). Because this bias affects the prevalence of bacterial meningitis in our patient population, the PPVs and NPVs of the
BMS must be interpreted with this in mind. In contrast, however, the sensitivity and specificity of our scoring system are not affected by this potential bias. Finally, several of the lumbar puncture results may have been confounded by the presence of a high CSF RBC (≥10 000 cells/mm³). From the outset of the study, we chose not to attempt to apply any correction factor in these cases, as there is no routinely accepted method to adjust for CSF WBC or protein in the presence of elevated CSF RBC. We believe that this decision did not adversely affect our results, however, because the number of children in which the CSF RBC was elevated was relatively low (n = 23, 3% of all patients), but similar to other centers, and all of these patients had aseptic meningitis. This would tend to bias against our model because of the corresponding increase in CSF WBC and protein in these children with aseptic meningitis who had elevated CSF RBC.

The epidemiology of bacterial meningitis in the United States has been substantially transformed over the past decade with the advent of universal Hib immunization. The incidence of bacterial meningitis in children is likely to be reduced further over the next few years as a consequence of pneumococcal conjugate immunization. Nevertheless, because of the multiple pathogens responsible for pediatric meningitis,1 the possibility of pneumococcal serotype replacement11–13 and the realities of underimmunization14 and vaccine failures,15,16 a prediction rule such as the BMS that identifies patients at very low risk of bacterial meningitis and who may be considered for outpatient therapy may be beneficial to patients and result in important cost savings.

ACKNOWLEDGMENTS

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REFERENCES


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**Florida Is Poised to Recognize Their Role**

“... In Florida ... the State Legislature unanimously passed a bill last week that extends to people who have seizure disorders the right to be accompanied in public places by a trained service dog. ... Florida may be the first state to pass such a measure. ... A study of patients and their seizure-alert dogs by the University of Florida’s Epilepsy Clinic in 1998 determined that some dogs do detect seizures, but the scientists did not have the money to investigate whether early detection was a spontaneous reaction or trainable behavior. ... One nonprofit agency that trains the dogs, Canine Assistants, Inc. of Alpharetta, Georgia, says it has placed 17 Golden and Labrador Retrievers with epileptic owners in 7 years, expects to place 10 this year alone and has a waiting list for 60 dogs.”


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