Predictors of Bacterial Meningitis in the Era After Haemophilus influenzae

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Objective: To determine if, in the era after Haemophilus influenzae type b, the cerebrospinal fluid (CSF) white blood cell (WBC) count can be safely used to stratify children suspected of having bacterial meningitis into low- and high-risk groups.

Design: Retrospective analysis of CSF samples.


Patients: All CSF samples collected on children aged 2 months to 17 years were included. The final database consisted of 1617 atraumatic samples from children without prior neurologic or immunologic disease who underwent a lumbar puncture to assess the possibility of community-acquired bacterial meningitis.

Main Outcome Measures: The predictive values of CSF WBC count, differential, protein, and glucose.

Results: There were 44 cases of bacterial meningitis. Five had 3 CSF WBCs per microliter or less, and 6 had 4 to 30 CSF WBCs per microliter. The negative predictive value of CSF specimens with 30 WBCs per microliter or less for bacterial meningitis was 99.3%. Cerebrospinal fluid samples with greater than 30 WBCs per microliter had a likelihood ratio for bacterial meningitis of 10.3 (95% confidence interval, 8.0-13.1) and a positive predictive value of 22.3%. Other significant predictors of bacterial meningitis included age, CSF glucose, protein, gram stain, CSF-serum glucose ratio, and peripheral blood band count.

Conclusions: Given the occurrence of bacterial meningitis in children in the absence of CSF pleocytosis, other factors should be considered when managing children with suspected bacterial meningitis. Children older than 6 months with 30 CSF WBCs per microliter or less are at low risk for bacterial meningitis. If clinically stable and without other laboratory markers of bacterial meningitis, hospital admission and empiric antibiotic therapy may be unwarranted.


Since the introduction of a conjugate vaccine against Haemophilus influenzae type b (Hib) disease, the incidence of bacterial meningitis has decreased dramatically.1 In Canada, the most recent advance occurred in 1992, with the introduction of a potent vaccine. The result was a 95% reduction in the number of cases of invasive Hib infections during 1991-1994 compared with 1985-1990.2 Similar successes have been documented in other countries.3,4 Unfortunately, meningitis still occurs and, if not treated promptly, brings with it severe morbidity and mortality.5

As antimicrobial resistance among pathogenic bacteria6 continues to emerge, physicians are attempting to avoid unnecessary use of broad-spectrum antibiotics.7 The declining incidence of bacterial meningitis may lead to lower rates of culture-positive cerebrospinal fluid (CSF) samples and more incidences of culture-negative CSF pleocytosis. This may, in turn, result in an increase in the proportion of children treated expectantly whose culture results ultimately are negative.

Previous studies8-10 have devised formulas to predict a patient’s risk for bacterial meningitis, but the formulas are complex and based on data from the era before the Hib conjugate vaccine. It has been shown that the mean CSF white blood cell (WBC) count is significantly different between patients with Hib meningitis and those with pneumococcal meningitis.11 However, no studies have assessed the yield of lumbar punctures and diagnostic characteristics of CSF indexes with the current pathogens. The foremost textbooks of pediatrics12-14 indicate that a CSF WBC count greater than 5 or 6/µL is abnormal. Little information is available on positive or negative predictive values (PPVs or NPVs),
**SUBJECTS AND METHODS**

**STUDY DESIGN**

The study was a retrospective cohort review of the diagnostic accuracy and yield of CSF specimens obtained for the evaluation of community-acquired bacterial meningitis.

**STUDY POPULATION**

The study population included children aged 2 months to 17 years who underwent a lumbar puncture in the emergency department, intensive care unit, or infectious disease or general pediatric wards of The Hospital for Sick Children, Toronto, Ontario, a tertiary care pediatric hospital, to diagnose or rule out community-acquired bacterial meningitis between January 1, 1992, and October 1, 1996. Exclusion criteria included (1) clotted samples, (2) CSF red blood cell count greater than 10,000/µL, (3) identified ventriculoperitoneal shunt sample, (4) second lumbar puncture within 14 days, or (5) any underlying medical condition that predisposed the child to bacterial meningitis or altered CSF findings, including preexisting conditions such as malignant neoplasms, immunodeficiency, trauma, prior neurosurgical procedure, or metabolic diseases. Clinical features of the acute illness did not affect inclusion or exclusion.

**DATA EXTRACTION**

Primary Predictors

Data were obtained from the bacteriology database (Excel 5.1; Microsoft, Redmond, Wash), which contained information on all samples submitted for culture. Cross-referencing with additional data sources (list of all CSF latex agglutination results, health records discharge abstracts database, and separate microbiology database containing data on all patients diagnosed as having bacterial meningitis) was used to ensure accurate sampling. A microfilm database (Oracle Microimage Terminal; Kodak, Rochester, NY) was used to extract additional data.

Selected medical charts were reviewed to extract additional information to ensure that the diagnosis of bacterial meningitis was correct and to verify that inclusion and exclusion criteria were met. Selection criteria for medical chart review were (1) positive CSF culture, (2) diagnosis of bacterial meningitis, (3) incomplete information in bacteriology or microfilm databases, (4) ambiguous timing of shunt with respect to lumbar puncture, (5) greater than 300 WBCs per microliter in the CSF, or (6) more than 1 lumbar puncture performed on a patient.

Secondary Predictors

A computer-generated random subset of patients who did not have bacterial meningitis was also selected for medical chart review and data abstraction. This group served as a control group for analysis of variables not available from the bacteriology computer database. This medical chart review contributed (1) serum glucose data, (2) complete blood cell count (CBC) and differential, and (3) clinical variables, such as reason for lumbar puncture, hypotension, inotropic support, fluid boluses, seizures, focal deficits, intensive care unit admission, lumbar puncture deferral, and determination of duration of antibiotic treatment.

**OUTCOME MEASURES**

To analyze the yield and diagnostic accuracy of CSF findings, the specimens were grouped into 3 clinically relevant outcome categories. Definite bacterial meningitis consisted of patients whose CSF was positive for a common central nervous system pathogen on CSF culture, or on CSF latex agglutination in individuals who had received antibiotics before the lumbar puncture. Presumed bacterial meningitis consisted of children for whom the diagnosis of bacterial meningitis was not definitively proven with culture, likelihood ratios (LRs), or specific treatment guidelines for given CSF WBC counts.

Our primary objective was to evaluate the predictive values and LR of the CSF WBC count, differential, protein, and glucose, with respect to CSF culture probability in an era of widespread Hib immunization.

**RESULTS**

The microbiology database contained records for 11,454 CSF samples from January 1, 1992, to October 1, 1996. Of these, 9847 did not conform to the inclusion or exclusion criteria (Table 1). Therefore, 1617 CSF samples were included in our final database.

Antibiotics were administered to 636 (39.3%) patients before the lumbar puncture was performed. Of those who received antibiotics, 73 (11.5%) had a CSF latex agglutination performed, 7 (9.6%) with positive findings. Of the 30 patients who had a latex agglutination performed but did not receive antibiotics before the lumbar puncture, none had a positive result.

**MENINGITIS**

There were 29 cases of definite bacterial meningitis, for a yield of 1.79% (95% CI, 1.20-2.56). The addition of 15 cases of presumed bacterial meningitis (total of 44) resulted in a yield of definite or presumed bacterial meningitis of 2.72% (95% CI, 1.93-3.56). These 2 groups were compared with respect to age, CSF red blood cell and WBC counts, and gram stain results. There were no statistically significant differences. Therefore, the case definition of definite or presumed bacterial meningitis was used.

Only 5 (11.4%) diagnoses of bacterial meningitis were based on positive CSF latex agglutination findings. The CSF samples that were culture-negative but latex agglutination-positive had in excess of 250 CSF WBCs per microliter, except for a patient whose latex agglutination was positive for *Neisseria meningitidis*. He received antibiotics before the lumbar puncture was performed and had 2 CSF WBCs per microliter.

Children aged 2 to 6 months accounted for 32% of the cases of bacterial meningitis. The median CSF WBC...
but the clinical situation warranted diagnosis and treatment as bacterial meningitis (ie, with a third-generation cephalosporin for a minimum of 1 week). Inclusion criteria were (1) positive CSF cultures for uncommon central nervous system pathogens, such as *Staphylococcus aureus*, *Enterococcus*, and *Pseudomonas aeruginosa*, (2) partially treated bacterial meningitis diagnosed on clinical grounds, including children with CSF pleocytosis who received antibiotics before the lumbar puncture and did not have a CSF latex agglutination performed, and (3) clinical diagnosis of bacterial meningitis, based on bacteremia involving a common central nervous system pathogen, and CSF pleocytosis. The last category was not bacterial meningitis, which included all other CSF specimens. All analyses, unless otherwise indicated, were performed using the reference diagnosis of definite or presumed bacterial meningitis.

In this study, positive findings on CSF latex agglutination were considered diagnostic of bacterial meningitis based on evidence of its high degree of sensitivity and specificity. Cerebrospinal fluid latex agglutination is performed at our institution by request on CSF samples that meet the following criteria: antibiotics administered before lumbar puncture, negative gram stain and CSF culture, and CSF WBCs in excess of 50/µL. This strategy is in keeping with guidelines suggested by Maxson et al. 

### DATA ANALYSIS

All calculations and discussions pertaining to bacterial meningitis are based on a reference diagnosis of bacterial meningitis for CSF samples that met the definitions of either definite or presumed bacterial meningitis. Confidence intervals (CIs) were calculated using the binomial distribution. Sensitivity, specificity, PPV, NPV, and LR were determined for intervals of each predictive variable. Confidence intervals for LRs were calculated using the Simel formula. The primary focus of our analysis was the NPV and LR of the CSF WBC count. The NPV describes the posttest probability that the child does not have bacterial meningitis and is a valuable indicator of how well the test rules out bacterial meningitis. The LR is the likelihood that a given test result is expected in a patient with the target disorder (bacterial meningitis) compared with the likelihood that the same result would be expected in a patient without the target disorder. Its main advantage over PPV and NPV and specificity is that it is less likely to change with the prevalence of the disorder. Likelihood ratios can be calculated for several levels of the test, and they can be used to calculate posttest probability for a target disorder.

Multivariate logistic regression analysis was used to confirm the independent predictive value of the CSF WBC count and age, as demonstrated by odds ratios. Wilcoxon rank sum and Fisher exact tests were used for testing for statistically significant differences between the groups of definite and presumed bacterial meningitis. Statistical analysis was performed using commercially available software (SAS version 7.00; SAS Institute, Cary, NC).

### CSF CELL COUNTS

Cutoffs chosen a priori for assessing the accuracy of the CSF WBC count were based on previous literature about normal and significant CSF counts and on logarithmic properties. The resulting groups, 0 to 3, 4 to 30, 31 to 300, and greater than 300 WBCs per microliter, are part of the series \( \log_{10}(\text{count}/3) \).

### OTHER PREDICTORS

A computer-generated random subset of patients was used to calculate the sensitivities, specificities, and LRs for bacterial meningitis of CSF protein, glucose, CSF–serum glucose ratio, peripheral WBC, and polymorphonuclear (PMN) band counts. Intervals were specified a priori and included cutoff values as previously defined in the literature. Cutoffs chosen a priori for assessing the accuracy of the CSF WBC count were based on previous literature about normal and significant CSF counts and on logarithmic properties. The resulting groups, 0 to 3, 4 to 30, 31 to 300, and greater than 300 WBCs per microliter, are part of the series \( \log_{10}(\text{count}/3) \).

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reveal any significant differences between the observed distribution of bacterial meningitis probabilities and those predicted by the model ($P = .77$).

**OTHER PREDICTORS**

Table 4 illustrates the sensitivity and LRs for several variables that can aid in determining an individual's likelihood of having bacterial meningitis. As independent mark-

<table>
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<tr>
<th>Pathogen</th>
<th>Culture-Positive</th>
<th>Latex Agglutination-Positive</th>
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<tbody>
<tr>
<td>Streptococcus pneumonia</td>
<td>16 (49)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>3 (9)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Haemophilus influenza type b</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>2 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>2 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Group B Streptococcus</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (85)</td>
<td>5 (15)</td>
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*LP indicates lumbar puncture.

Physicians often are concerned by any degree of CSF pleocytosis in children older than 2 months who are being assessed for bacterial meningitis. These children, when no other abnormal clinical or biochemical factors consistent with bacterial meningitis are identified, often are hospitalized and treated empirically with antibiotics. This study confirms that bacterial meningitis can occur with mild or no CSF pleocytosis. On the other hand, when the CSF WBC count is 30/µL or less, the NPV is high.

**EXCEPTIONAL CASES**

There were 5 patients with bacterial meningitis in whom the CSF samples contained 3 WBCs per microliter or less. Two children had N meningitidis, 2 had Enterococcus, and 1 had Escherichia coli. The 2 children with enterococcus were younger than 3 months. The first had a CSF protein of 0.45 g/L, CSF–serum glucose ratio of 44%, and CBC WBC count of 19.5 × 10³/µL. The second child with enterococcus appeared septic, with a CBC WBC count of 69.6 × 10³/µL and peripheral PMN count of 64.0 × 10³/µL. The child with E coli meningitis was aged 3½ months. The CSF had less than 3 red blood cells and WBCs per microliter, with a normal CBC, differential, and chemistry. The CSF sample of a child aged 2 months isolated N meningitidis, despite a CSF WBC count of 2/µL. He had an erythrocyte sedimentation rate of 92 mm/hr, a CBC PMN count of 0.87 × 10³/µL, and a band count of 0.53 × 10³/µL. A child aged 3 years presented with lethargy, arthralgia, photophobia, headache, and a petechial rash. He received antibiotics before his lumbar puncture, and his CSF culture was negative. His CSF latex agglutination was positive for N meningitidis. His CBC had a WBC count of 28.8 × 10³/µL, with a PMN count of 21.0 × 10³/µL and a band count of 3.5 × 10³/µL.
(99.3%) and the posttest likelihood of bacterial meningitis is similar to that of children with a WBC count of 3/µL or less. Those with higher cell counts have likelihoods of bacterial meningitis that are significantly elevated. In children with low CSF WBC counts, attention to other laboratory results can help minimize the risk of missing a case of bacterial meningitis.

In this study, 11.4% of the cases of bacterial meningitis occurred in CSF samples with 3 WBCs per microliter or less. All of these children had at least one factor (younger than 1 year, decreased CSF glucose, increased CSF protein, or increased CBC band count) that independently indicated that the child was at an increased risk for bacterial meningitis. The finding of bacterial meningitis in the absence of CSF pleocytosis is not new. A review of 55 cases of meningococcal meningitis, from 1985 to 1988, found that 11% lacked CSF pleocytosis, hypoglycorrhachia, or organisms on gram stain. A similar study, from 1980 to 1985, of 261 cases of pediatric bacterial meningitis found that 3% had a normal CSF analysis, including WBC count, differential, glucose, protein, and gram stain.

Because a CSF WBC count of 3/µL or less does not demonstrate 100% sensitivity, consideration of other predictors of bacterial meningitis, such as age, CSF glucose and serum glucose ratio, protein, and Gram stain, may help clinicians optimize their decision making with respect to hospital admission and antibiotic administration.

Based on the high NPV of a CSF WBC count of 30/µL or less, the use of antibiotics and hospitalization for all cases of “abnormal” (ie, >5 to 6 WBCs per microliter) lumbar punctures might not be necessary. Less aggressive treatment of some patients might be a more appropriate strategy. Based on our data, it is proposed that hospitalization and expectant antibiotic treatment be reserved for patients with any of the following high-risk characteristics: (1) CSF WBC count of greater than 30/µL; (2) younger than 6 months; or (3) an abnormality in one of the other factors that was significantly predictive of bacterial meningitis (abnormal CSF glucose, serum–CSF glucose ratio, protein, gram stain, or peripheral band count). Applying these criteria to our population would result in the treatment and hospital admission of all cases of bacterial meningitis in our study population, including all cases with 30 CSF WBCs per microliter or less. This approach in our study had a sensitivity of 100.0%, a specificity of 47.7%, a PPV of 5.10%, an NPV of 100.0%, and an LR of 1.91 (95% CI, 1.82-2.00).

The most obvious limitation of this study is the fact that it was a retrospective analysis. Because the gold standard for diagnosing bacterial meningitis is not as clear-cut as it might at first appear, we dealt with problems such as “partially treated meningitis” by creating a more clinically relevant group termed presumed bacterial meningitis.

![Figure 1. Likelihood ratios for bacterial meningitis based on cerebrospinal fluid (CSF) white blood cell (WBC) count on a log10 scale.](image1)

![Figure 2. Cerebrospinal fluid (CSF) white blood cell (WBC) count (per microliter) distribution for children with definite and presumed bacterial meningitis.](image2)

<table>
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<tr>
<th>Table 4. Diagnostic Characteristics for Predicting Bacterial Meningitis, With the Prevalence of Bacterial Meningitis at 2.72%*</th>
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<tbody>
<tr>
<td><strong>Sensitivity, %</strong></td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Multiple factors†</td>
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<tr>
<td>CSF WBC &gt;3/µL</td>
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<tr>
<td>CSF WBC &gt;30/µL</td>
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<tr>
<td>CSF protein &gt;45 mg/dL</td>
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<tr>
<td>CSF-serum glucose ratio &lt;40%</td>
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<tr>
<td>CSF glucose &lt;40 mg/dL</td>
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<tr>
<td>CBC band count &gt;0.5 × 10³/µL</td>
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<tr>
<td>Positive gram stain</td>
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<tr>
<td>CBC polymorphonuclear &gt;10 × 10³/µL</td>
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<tr>
<td>CBC WBC &gt;15 × 10³/µL</td>
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*Ellipses indicate indeterminate because of specificity of 100% (numerator = 0).
†Combination of any one cerebrospinal fluid (CSF) white blood cell (WBC) count greater than 30/µL; age younger than 6 months; or abnormal CSF glucose, CSF serum–glucose ratio, CSF protein, CSF gram stain, or peripheral band count, or positive CSF gram stain.
Although one might assume that this group will bias the results toward inclusion of children with significant CSF pleocytoses, in fact, they constituted a much larger percentage of cases with CSF WBC counts of 30/µL or less. The data analysis ultimately did not reveal any significantly different results between the groups of definite and presumed bacterial meningitis.

Our institution provides tertiary care; hence, our incidence of bacterial meningitis may be greater than that seen at most nonreferral centers. In addition, because not all institutions use the same criteria for the performance of lumbar punctures on children older than 2 months, extrapolation to other institutions requires some caution.

The CSF WBC count should not be used alone to rule out bacterial meningitis in children aged 2 months to 17 years. When it is combined with other factors—such as age, CSF glucose, protein, Gram stain, CSF–serum glucose ratio, and peripheral band count—improved decision making in children with suspected bacterial meningitis may occur. In the absence of other risk factors, children older than 6 months with 30 CSF WBCs per microliter or less are at low risk for bacterial meningitis. Strategies for the outpatient management and follow-up of these children appear justified if the children are clinically well and do not possess specific laboratory markers (positive CSF gram stain, abnormal glucose, protein, CSF–serum glucose ratio, or CBC band count) that are indicative of bacterial meningitis.

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The results and conclusions are those of the authors; no official endorsement by the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

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REFERENCES


What This Study Adds

It is well known that the introduction of conjugate vaccine against Hib disease has decreased the incidence of bacterial meningitis dramatically. The declining incidence of bacterial meningitis has led to lower rates of culture-positive CSF and greater incidences of culture-negative pleocytosis. This study assessed the yield of lumbar punctures on children older than 6 months, a low-risk population is identified that may be more appropriately managed as outpatients.