Utility of the Peripheral Blood White Blood Cell Count for Identifying Sick Young Infants Who Need Lumbar Puncture

Study objective: We assess the utility of the peripheral blood WBC count as a screen for lumbar puncture among young infants evaluated for serious bacterial infections.

Methods: We performed logistic regression modeling and receiver operating characteristic curve analysis of peripheral blood WBC count and cerebrospinal fluid WBC count for results obtained from 3- to 89-day-old infants undergoing a full sepsis evaluation.

Results: Twenty-two of 5,353 (4.1 per 1,000) infants had acute bacterial meningitis. For diagnosing acute bacterial meningitis, the peripheral blood WBC count was poorly discriminating and significantly inferior to the cerebrospinal fluid WBC count. This was true both when the odds of meningitis were modeled to vary linearly and as a U-shaped function of the peripheral blood WBC count. When relying on single and interval-based high-risk thresholds of peripheral blood WBC counts alone, the majority of infants with acute bacterial meningitis would have been missed.

Conclusion: Decisions to perform or withhold lumbar puncture should not be based on prevailing interpretations of the total peripheral blood WBC counts to maximize detection of bacterial meningitis in young infants.

INTRODUCTION

Although rare, acute bacterial meningitis is a serious infection that continues to be a public health problem among children.\(^1\)\(^2\) Clinical diagnosis is particularly difficult in young infants, so that preliminary analysis and routine culture of cerebrospinal fluid are recommended if such children present with a fever, hypothermia, or worrisome history or are ill appearing.\(^3\)

Because parents often perceive the lumbar puncture to be more invasive than other routinely performed procedures, such as venipuncture and bladder catheterization, they might be reluctant to give consent for the test. Also, clinicians might not always be able to perform this procedure in their offices. As a result, parents often inquire about and clinicians might be inclined to use simple screening tests to determine the need to perform a lumbar puncture. It has been our impression that the peripheral blood WBC count, because of its role in detecting other serious bacterial infections and its widespread availability, is sometimes used in this manner. In this respect, clinicians might interpret the risk of meningitis to be a linear or U-shaped function of the peripheral blood WBC count.

Unfortunately, no analysis directed specifically at the overall utility of the peripheral blood WBC count for such purposes has been performed, and the likelihood of diagnosing bacterial meningitis after obtaining results within particular peripheral blood WBC count intervals has not been fully specified. In this study, we formally evaluate the validity of decisionmaking that relies on the peripheral blood WBC count alone to perform lumbar puncture and compare the discriminatory capability of this test with that of the cerebrospinal fluid WBC count among young infants evaluated for infection.

METHODS

We analyzed the results of a computerized database in which were entered the laboratory results of consecutive infants 3 to 89 days of age evaluated for serious bacterial infection in the emergency department at Children's Hospital Boston between January 1992 and July 1999. Data were entered prospectively into a computerized database at the time of evaluation in the ED. At our institution, all infants presenting with a temperature of 38°C (100.4°F) or greater (physician referred or self-referred by reliable caretakers) or who are noted to have a temperature at triage of 38°C (100.4°F) or greater routinely undergo a sepsis evaluation. This evaluation includes cerebrospinal fluid WBC count, cell differential, Gram stain, chemistry, and bacterial culture; peripheral blood WBC count and bacterial culture; and urine for urinalysis and bacterial culture. The peripheral blood WBC count is not used as a screen for spinal tap at our institution. Thus, we avoided workup bias when evaluating the comparative utility of cerebrospinal fluid WBC and peripheral blood WBC counts for diagnosis.

The study ED is located within an academic children’s hospital, sees an average of 50,000 visits a year, and serves a varied socioeconomic population, of whom 70% have private insurance. All care is supervised by board-certified pediatric emergency attending physicians.

Medical records were reviewed from a computerized database that included age, cerebrospinal fluid culture, peripheral blood WBC count, and cerebrospinal fluid WBC count. For the purposes of our study, bacterial meningitis was considered present if standard bacterial culture of cerebrospinal fluid isolated \textit{Streptococcus pneumoniae}, \textit{Neisseria meningitidis}, group B streptococci, \textit{Haemophilus influenzae} type b, \textit{Listeria monocytogenes}, \textit{Salmonella} species, or \textit{Escherichia coli}. In addition, bacterial meningitis was also considered to be present if other potential pathogens, such as \textit{Acinetobacter}, \textit{Citrobacter}, and \textit{Klebsiella} species (gram-negative rods) were isolated from the cerebrospinal fluid of an infant who was less than 1 month of age at the time of diagnosis. All cerebrospinal fluid samples that were blood contaminated, as defined by an RBC count of 10,000 cells/mm\(^3\) or greater, or that were obtained from infants given a diagnosis of leukemia were excluded.

The medians for the distribution of peripheral blood WBC counts for children with versus those of children without bacterial meningitis were compared by using the Wilcoxon rank sum test. Similarly, the medians for the
distribution of the cerebrospinal fluid WBC counts for children with versus those of children without bacterial meningitis were also compared by using the same test.

Receiver operating characteristic (ROC) curves, which plot sensitivity versus 1–specificity (likelihood ratio), were constructed for each test cut-off point of peripheral blood WBC and cerebrospinal fluid WBC counts, and the areas under these curves were calculated non-parametrically and compared. The area under the ROC curve (AUC) determines the diagnostic performance or accuracy of a test over its full range of values. An AUC value of 0.5 indicates that a test has no discriminatory ability, whereas an AUC value of 1.0 indicates that a test has perfect discriminatory ability. Some investigators have suggested that an AUC of 0.7 is a reasonable lower threshold for concluding that a test has sufficient discriminatory value to be useful in practice. We have adopted this convention to classify the diagnostic value of the peripheral blood WBC and cerebrospinal fluid WBC counts. The null hypothesis was rejected if the difference between the areas under the ROC curves for peripheral blood WBC and cerebrospinal fluid WBC counts was statistically significant (P<.05).

To capture and compare the discriminatory value of these tests as they are commonly used in clinical practice, we performed our analyses in 2 different ways. Our primary models were based on the assumption that the odds of bacterial meningitis vary directly with the untransformed values of the peripheral blood WBC and cerebrospinal fluid WBC counts. This is consistent with the way most clinicians interpret the cerebrospinal fluid WBC count and the way some interpret the peripheral blood WBC count (ie, risk is assumed to vary monotonically with these tests). Alternatively, some have interpreted the odds of serious bacterial infections to be not linearly related to the peripheral blood WBC count but instead to be a U-shaped function of the peripheral blood WBC count. To permit this U-shaped relationship to be specified and evaluated, we also created a nonlinear logistic model of the peripheral blood WBC count known as a piecewise polynomial or natural cubic spline function (details provided on request). We refer to this model as the U-shaped model. Finally, in a related but separate analysis, we determined whether the peripheral blood WBC count provided information that was incremental to that provided by the cerebrospinal fluid WBC count alone. This was achieved by comparing the AUCs of 2 regression models: one that included the cerebrospinal fluid WBC count alone and another that combined the cerebrospinal fluid WBC count with the peripheral blood WBC count.

Interval likelihood ratios were calculated for the following peripheral blood WBC count intervals (1,000/mm³): less than 2, 2 to 2.99, 3 to 3.99, 4 to 4.99, 5 to 9.99, 10 to 14.99, 15 to 19.99, 20 to 24.99, 25 to 29.99, and greater than 30. Interval likelihood ratios were also calculated for the following cerebrospinal fluid WBC intervals: 9 or less, 10 to 99, 100 to 999, and 1,000 or greater cells/mm³. In interpreting these ratios, some suggest that values of less than 0.5 or greater than 2.0 associated with a test result suggest that the test is associated with a clinically important change in the odds of the disease.

We calculated the sensitivity, specificity, positive predictive value, and negative predictive value at various thresholds of both tests. We also calculated the miss-to-diagnosis ratio for both tests. The miss-to-diagnosis ratio was defined as the ratio of false-negative results to true-positive results among patients with bacterial meningitis. It is represented by the following equation:

\[(1/\text{Sensitivity}) - 1\]

The miss-to-diagnosis ratio only has value when it is used to compare the relative number of cases missed by 2 or more tests in the same patients and at test thresholds previously established to be optimal for a particular disease.

For parts of the analyses, the data were stratified by a peripheral blood WBC count of 5,000 cells/mm³ because decrements of less than this threshold, like increments greater than this threshold, are considered by some to increase the risk of serious bacterial infections. All data were analyzed with the Stata statistical package (version 6.0, Stata Corporation, College Station, TX).
The institutional review board of Children's Hospital Boston approved this study.

RESULTS

For the period of study, our laboratory received 5,353 consecutive cerebrospinal fluid samples for bacterial culture from children aged 3 to 89 days. Twenty-two infants met the criteria for bacterial meningitis, giving an overall prevalence of 4.1 cases per 1,000 (95% confidence interval [CI] 2.6 to 6.2). Organisms isolated included *E coli* (n=11), group B streptococci (n=9), *S pneumoniae* (n=1), and *Citrobacter koseri* (n=1). Only one child with meningitis, caused by *E coli*, was discharged after the initial encounter. This child was 49 days old, had a peripheral blood WBC count of 13,500 cells/mm³, a peripheral band (1%) to total neutrophils ratio of 0.05, a cerebrospinal fluid WBC count of 5 cells/mm³, and a sterile blood culture result.

The rate of bacterial meningitis among children 3 to 28 days of age was 0.7 per 1,000 (11/1,617; 95% CI 0.3 to 1.2). The rate among children aged 29 to 56 days was 0.3 per 1,000 (7/2,054; 95% CI 0.1 to 0.7). For children 57 to 89 days of age, the rate was 0.2 per 1,000 (4/1,682; 95% CI 0.1 to 0.6). When stratified by a peripheral blood WBC count of 5,000 cells/mm³, the rate of bacterial meningitis was 31.7 per 1,000 (7/221; 95% CI 12.8 to 64.2) for children with peripheral blood WBC counts of less than 5,000 cells/mm³ versus 2.9 per 1,000 (15/5,132; 95% CI 1.6 to 4.8) for children with peripheral blood WBC counts of 5,000/mm³ or greater (odds ratio 11.2; 95% CI 4.6 to 26.9).

We modeled the odds of bacterial meningitis as a linear function of the peripheral blood WBC count. Because of concerns with nonlinearity, we also modeled the peripheral blood WBC count by using spline functions. This nonlinear (U-shaped) model did not add appreciable predictive power but added considerable complexity and risked overfitting and instability, and therefore, all subsequent analyses used only linear terms. The AUCs for the linear model and for the U-shaped model did not reach statistical or clinical significance. For the linear model of the peripheral blood WBC count, the AUC was 0.43 (95% CI 0.28 to 0.58) when the curve was ordered at incremental thresholds of the test (Figure) and 0.57 (95% CI 0.42 to 0.72) when ordered at decreasing thresholds. For the U-shaped model, the AUC was 0.55 (95% CI 0.39 to 0.70). These models were not statistically different (P=.4).

AUC values for the peripheral blood WBC counts were significantly less than AUC values for the cerebrospinal fluid WBC count, which was 0.82 (95% CI 0.71 to 0.94). Thus, prevailing conceptions of the risk of acute bacterial meningitis that are based on the peripheral blood WBC count are less accurate than those based on the cerebrospinal fluid WBC count and do not allow discrimination between infants with and those without acute bacterial meningitis to a degree greater than would be expected by chance. Furthermore, the ability of the cerebrospinal fluid WBC count alone to discriminate between infants with and without acute bacterial meningitis (AUC 0.82) is not improved by incorporating the peripheral blood WBC count into the logistic model (AUC 0.64). Thus, the peripheral...
blood WBC count does not provide incremental information for discrimination in addition to that provided by the cerebrospinal fluid WBC count alone.

For the peripheral blood WBC count, the median value for children with bacterial meningitis was 10,200 cells/mm³, with an interquartile range (IQR) from 4,000 to 15,200 cells/mm³. The median peripheral blood WBC count for children without bacterial meningitis was 11,200 cells/mm³, with an IQR of 8,500 to 14,600 cells/mm³ (P = .26). Two hundred twenty-two (8%) of 5,353 infants had peripheral blood WBC values of less than 5,000 cells/mm³. At peripheral blood WBC values of less than 5,000 cells/mm³, the median peripheral blood WBC count for infants with bacterial meningitis of 3,200 cells/mm³ (IQR 2,300 to 4,000) was statistically different from that for children without bacterial meningitis (4,200 cells/mm³; IQR 3,700 to 4,600; P = .005). When limiting the analysis to children with peripheral blood WBC values of 5,000 cells/mm³ or greater, there was no statistically significant difference between the median peripheral blood WBC count for infants with (13,300 cells/mm³; IQR 9,900 to 17,100) versus those without (11,400 cells/mm³; IQR 8,800 to 14,800) bacterial meningitis (P = .13).

For the cerebrospinal fluid WBC count, the median value for all patients was 3 cells/mm³ (IQR 2 to 7). The median cerebrospinal fluid WBC count for children with bacterial meningitis was 79 cells/mm³ (IQR 8 to 1,315 cells/mm³) versus 3 cells/mm³ (IQR 2 to 6 cells/mm³) for those without bacterial meningitis (P < .0001).

Likelihood ratios at incremental cut-off points of peripheral blood WBC counts are presented in Table 1. No cases of bacterial meningitis occurred in the peripheral blood WBC count interval range of greater than 25,000 cells/mm³. The odds of bacterial meningitis among infants with a peripheral blood WBC count of between 5 and 25,000 cells/mm³ did not change significantly or to a clinically important degree. By contrast, the odds of bacterial meningitis among children with a peripheral blood WBC count of less than 5,000 cells/mm³ increased between 3- and 35-fold (Table 1). The sensitivity, specificity, positive predictive value, and negative predictive value of the peripheral blood WBC counts at prespecified test cut-off points are presented in Table 2.

Forty-one percent and 64% of infants with bacterial meningitis would be falsely excluded if intervals of the peripheral blood WBC counts of between 5 and 15,000 cells/mm³ and 5 and 20,000 cells/mm³ were accepted as low risk. This is equivalent to a miss-to-diagnosis ratio

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**Table 1.**

Likelihood ratios for bacterial meningitis at various intervals of peripheral blood WBC counts among infants younger than 90 days.

<table>
<thead>
<tr>
<th>Peripheral Blood WBC Interval*</th>
<th>LR</th>
<th>95% CI</th>
<th>Cases/Total (Rate per 1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1.99</td>
<td>34.6</td>
<td>4.4–270.0</td>
<td>1/8 (125)</td>
</tr>
<tr>
<td>2–2.99</td>
<td>30.3</td>
<td>7.4–124.0</td>
<td>2/18 (111)</td>
</tr>
<tr>
<td>4–4.99</td>
<td>3.7</td>
<td>1–14.0</td>
<td>2/133 (15)</td>
</tr>
<tr>
<td>5–9.99</td>
<td>0.5</td>
<td>0.2–1.2</td>
<td>4/1,839 (2)</td>
</tr>
<tr>
<td>10–14.99</td>
<td>0.6</td>
<td>0.3–1.3</td>
<td>5/2,084 (3)</td>
</tr>
<tr>
<td>15–19.99</td>
<td>1.4</td>
<td>0.6–3.1</td>
<td>5/855 (5)</td>
</tr>
<tr>
<td>20–24.99</td>
<td>0.9</td>
<td>0.1–6.3</td>
<td>1/268 (3)</td>
</tr>
<tr>
<td>≥30</td>
<td></td>
<td></td>
<td>0/79 (0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>22/5,353 (4.1)</td>
</tr>
</tbody>
</table>

LR, Interval likelihood ratio.

*Units are 1,000 cells/mm³.

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**Table 2.**

Test sensitivity, specificity, positive predictive value, negative predictive value, and miss-to-diagnosis ratio for bacterial meningitis at various thresholds of the peripheral blood WBC count among infants younger than 90 days.

<table>
<thead>
<tr>
<th>Test Cut-off Point</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>MDR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>31.9</td>
<td>96.0</td>
<td>1.0</td>
<td>99.7</td>
<td>2.1</td>
</tr>
<tr>
<td>≥10</td>
<td>50.0</td>
<td>38.4</td>
<td>0.3</td>
<td>99.5</td>
<td>1.0</td>
</tr>
<tr>
<td>≥15</td>
<td>27.2</td>
<td>77.1</td>
<td>0.5</td>
<td>99.6</td>
<td>2.7</td>
</tr>
<tr>
<td>≥20</td>
<td>4.5</td>
<td>93.0</td>
<td>0.3</td>
<td>99.6</td>
<td>21.2</td>
</tr>
<tr>
<td>≥25</td>
<td>0.0</td>
<td>97.9</td>
<td>0.0</td>
<td>99.6</td>
<td>∞</td>
</tr>
<tr>
<td>≤5 or &gt;15</td>
<td>59.1</td>
<td>73.1</td>
<td>0.9</td>
<td>99.8</td>
<td>0.7</td>
</tr>
<tr>
<td>≤5 or &gt;20</td>
<td>36.4</td>
<td>89.9</td>
<td>1.3</td>
<td>99.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

PPV, Positive predictive value; NPV, negative predictive value; MDR, miss-to-diagnosis ratio.

*Units are 1,000 cells/mm³.

†False-negative to true-positive rate or (1/Sensitivity) – 1.
of 0.7 and 1.8, respectively. Similarly, single high-risk criterion values of greater than 15,000 and 20,000 cells/mm$^3$ for the peripheral blood WBC count would fail to identify 73% and 95% of infants with bacterial meningitis or have a miss-to-diagnosis ratio of 2.7 and 21.2, respectively (Table 2). By contrast, the miss-to-diagnosis ratios were lower for generally accepted thresholds of cerebrospinal fluid WBC counts: 0.4 for a cut-off point of 10 cells/mm$^3$ or greater and 0.3 for a cut-off point of 8 cells/mm$^3$ or greater. Likelihood ratios for predefined cerebrospinal fluid WBC counts were generally significant and are presented in Table 3. Sensitivities, specificities, positive predictive values, and negative predictive values at various cut-off points of the cerebrospinal fluid WBC count are presented in Table 4.

**Table 3.**
Likelihood ratios for bacterial meningitis at various intervals of the cerebrospinal fluid WBC count among infants younger than 90 days.

<table>
<thead>
<tr>
<th>Cerebrospinal Fluid WBC Interval*</th>
<th>LR</th>
<th>95% CI</th>
<th>Cases/Total (Rate per 1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>0.3</td>
<td>0.2–0.6</td>
<td>6/4,456 (1.3)</td>
</tr>
<tr>
<td>10–99</td>
<td>4.4</td>
<td>3.4–5.7</td>
<td>7/686 (10.2)</td>
</tr>
<tr>
<td>100–999</td>
<td>10.8</td>
<td>6.4–18.2</td>
<td>3/168 (17.9)</td>
</tr>
<tr>
<td>≥1,000</td>
<td>39.3</td>
<td>18.4–83.5</td>
<td>6/43 (139.5)</td>
</tr>
<tr>
<td>Total</td>
<td>22/5,353 (4.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*Units are cells/mm$^3$.

**Table 4.**
Test sensitivity, specificity, positive predictive value, negative predictive value, and miss-to-diagnosis ratio for bacterial meningitis at various thresholds of the cerebrospinal fluid WBC count among infants younger than 90 days.

<table>
<thead>
<tr>
<th>Test Cut-off Point*</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>MDR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8</td>
<td>77.2</td>
<td>78.8</td>
<td>1.5</td>
<td>99.9</td>
<td>0.3</td>
</tr>
<tr>
<td>≥10</td>
<td>72.7</td>
<td>83.5</td>
<td>1.8</td>
<td>99.9</td>
<td>0.4</td>
</tr>
<tr>
<td>≥100</td>
<td>40.9</td>
<td>96.2</td>
<td>4.2</td>
<td>99.8</td>
<td>1.4</td>
</tr>
<tr>
<td>≥1,000</td>
<td>22.7</td>
<td>99.3</td>
<td>13.9</td>
<td>99.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>
*Units are cells/mm$^3$.
†False-negative to true-positive rate or (1/Sensitivity) – 1.

**Discussion**

Our results indicate that the peripheral blood WBC count, as it is commonly interpreted, is not an accurate test for predicting bacterial meningitis in infants and performs significantly worse than the cerebrospinal fluid WBC count. Specifically, diagnosis is inaccurate both when the risk of meningitis is interpreted to vary linearly with or to have a U-shaped relationship with the peripheral blood WBC count. In addition, a strategy that combines the peripheral blood WBC count with the cerebrospinal fluid WBC count performs no better than a strategy that uses the latter alone.

The limited ability of the peripheral blood WBC count to identify children who have bacterial meningitis is supported by the shallow slope of its ROC curves. This means that no interval or cut-off point of the peripheral blood WBC count is very accurate for diagnosis. Consequently, when intervals of the peripheral blood WBC count of between 5 and 15,000 cells/mm$^3$ and 5 and 20,000 cells/mm$^3$ are accepted as low risk,$^9,10$ 41% and 64% of infants with bacterial meningitis will be falsely excluded. Even worse, single high-risk criterion values of greater than 15,000 and 20,000 cells/mm$^3$ will fail to identify 73% and 96% of infants with meningitis, respectively.$^7,8$

The cerebrospinal fluid WBC count, by contrast, performs well over its full range of values (AUC 0.82), an observation that makes it more useful for screening and treatment. The steeper slope of the ROC curve means that this test is better at differentiating acute bacterial meningitis from competing diagnoses. Unfortunately, even spinal fluid testing will fail to identify 23% and 27% of young infants with bacterial meningitis at the thresholds that are recommended in the medical literature (ie, 8 and 10 cells/mm$^3$ in cerebrospinal fluid, respectively).$^7,8$ Furthermore, because the peripheral blood WBC count performs so poorly, combining it with the cerebrospinal fluid WBC count does not improve the ability of the cerebrospinal fluid WBC count to detect meningitis. An example of this was observed in an infant seen at our ED for bacterial meningitis who had a normal WBC count of cerebrospinal fluid and...
Identifying Young Infants Who Need Lumbar Puncture

Bonsu & Harper

In our study population and using commonly used cutoff points, the effect of substituting the peripheral blood WBC count becomes more evident. For example, on the basis of test performance alone, for every case diagnosed correctly, there are 2.7 versus 0.4 (sevenfold greater number) missed cases of bacterial meningitis at a peripheral blood WBC threshold of 15,000 cells/mm³ compared with a cerebrospinal fluid WBC threshold of 10 cells/mm³, respectively. When a peripheral blood WBC count of 20,000/mm³ is substituted for a cerebrospinal fluid WBC count of 10 cells/mm³, there is a 53-fold (21 versus 0.4) increase in the relative number of cases missed for every case correctly identified.

Peripheral blood WBC count ranges of 5 to 15,000 cells/mm³ or 5 to 20,000 cells/mm³, when considered low risk, result in fewer missed cases for each case of bacterial meningitis correctly diagnosed. Unfortunately, these criteria are still associated with miss-to-diagnosis ratios that are 2 to 4 times greater than those associated with a cerebrospinal fluid WBC count of less than 10 cells/mm³.

These examples indicate that attempts directed at the diagnosis or exclusion of bacterial meningitis that depend heavily on the peripheral blood WBC count will miss a substantial proportion of cases. We recommend, in the absence of validated alternatives and concordant with published guidelines, that cerebrospinal fluid be obtained from all young infants undergoing a sepsis evaluation unless the diagnosis of bacterial meningitis can be excluded clinically. Such a general approach will maximize the early detection of bacterial meningitis and guide empiric antibiotic treatment. Clinicians should not rely on the total WBC count of blood alone to determine whether a child needs a lumbar puncture.

Other investigators have assessed the utility of the peripheral blood WBC count for predicting bacterial illnesses, such as urinary tract infections, bacteremia, sepsis, and bacterial meningitis. Generally, these investigators have not relied on the peripheral blood WBC count alone but have used it in conjunction with clinical examination and other tests, such as formal urinalysis and cerebrospinal fluid WBC counts, as part of a full sepsis evaluation. The unique value of the individual tests for diagnosis of specific diseases is obscured because these investigators have usually grouped these infections under the collective title of serious bacterial infection. A high negative predictive value when using such strategies might overestimate test performance because of the rarity of diseases such as bacterial meningitis (0.4% in our study). In fact, for bacterial meningitis, our results indicate that simply assuming that no infant had the diagnosis (performing no tests) would result in a negative predictive value of 99%. For this reason, we believe that a better way to gauge the effect of substituting the peripheral blood WBC count for the cerebrospinal fluid WBC count is to compare the respective miss-to-diagnosis ratios for bacterial meningitis when using both tests at commonly accepted thresholds in the same infants.

When comparing the miss-to-diagnosis ratios of the peripheral blood and cerebrospinal fluid WBC counts in our study population and using commonly used cutoff points, the effect of substituting the peripheral blood WBC count becomes more evident. For example, on the basis of test performance alone, for every case diagnosed correctly, there are 2.7 versus 0.4 (sevenfold greater number) missed cases of bacterial meningitis at a peripheral blood WBC threshold of 15,000 cells/mm³ compared with a cerebrospinal fluid WBC threshold of 10 cells/mm³, respectively. When a peripheral blood WBC count of 20,000/mm³ is substituted for a cerebrospinal fluid WBC count of 10 cells/mm³, there is a 53-fold (21 versus 0.4) increase in the relative number of cases missed for every case correctly identified.

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Our study differs methodologically and conceptually from work done by other investigators reporting on the diagnostic utility of screening tests among febrile young infants. Primarily, we do not assume equal utility of each test for diagnosing all serious bacterial infections but systematically evaluate their specific value when used to screen for bacterial meningitis in a wide but identical spectrum of infants. No direct attempts were made to exclude infants pretreated with antibiotics or

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Our study differs methodologically and conceptually from work done by other investigators reporting on the diagnostic utility of screening tests among febrile young infants. Primarily, we do not assume equal utility of each test for diagnosing all serious bacterial infections but systematically evaluate their specific value when used to screen for bacterial meningitis in a wide but identical spectrum of infants. No direct attempts were made to exclude infants pretreated with antibiotics or
to characterize them on the basis of their clinical appearance because it was not logistically feasible to accomplish this reliably in our data set. This is a minor limitation because prior antibiotic treatment in this age group is unlikely and has been associated with only a modest decrease in the ability to recover organisms from the cerebrospinal fluid. More importantly, applying these laboratory tests to the same infants cancels out any differences caused by prior treatment or case mix.

Our study had other potential limitations. One was the fact that although it was eventually rejected, the number of parameters estimated when creating the piecewise polynomial model (spline function) of the peripheral blood WBC count was relatively large. This posed no problems because this model was not intended to be used for prediction but instead for the more restricted goal of ordering the performance of the peripheral blood and cerebrospinal fluid WBC tests: bias reduction through overfitting, within reasonable limits, is suitable and often desirable for estimation and hypothesis testing problems. Still, the smaller number of cases did mean that we could not reliably characterize novel or more complex alternative models of the risk of meningitis that are based on the peripheral blood WBC count. Such models might exist, and we are currently collecting data to evaluate this possibility. Finally, it should be noted that we have not reported the screening properties of other indices of peripheral blood, such as the absolute band count, the immature-to-total neutrophil ratio, and the bands percentage, which are based on the manual cell differential. These tests are not performed routinely at our institution and have been reported to be unreliable.

In summary, among young infants evaluated for serious bacterial infections, the total WBC count of peripheral blood, as it is commonly interpreted, has limited utility when screening for bacterial meningitis and cannot act as a proxy for the total WBC count of spinal fluid. Generally, decisions to perform lumbar puncture that are based solely on current conceptions of the total peripheral blood WBC count should be abandoned because they will lead to a significant increase in the relative number of cases of bacterial meningitis that are missed.

Author contributions: This study was conceived and designed by BKB and MBH. MBH abstracted the data. BKB analyzed the data in close consultation with MBH. BKB drafted the manuscript, but both authors contributed substantially to the revision of the manuscript. MBH supervised all stages of this work from its conception and design to completion of the manuscript. BKB takes responsibility for the paper as a whole.

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Address for reprints: Bema K. Bonsu, MBChB, Division of Emergency Medicine, Children’s Hospital, 700 Children’s Drive, Columbus OH 43216; 614-722-4385; E-mail bonsub@pediatrics.ohio-state.edu.

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