Immature Neutrophils in the Blood Smears of Young Febrile Children

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Objective: To determine whether the immature neutrophil (band) count in the peripheral blood smear helps to distinguish young febrile children with bacterial or respiratory viral infections.

Design and Setting: A prospective cohort study in 3 pediatric emergency departments.

Patients: A convenience sample of 100 febrile children aged 2 years or younger with either laboratory-documented bacterial infections (n = 31; 24 with urinary tract infections, 7 with bacteremia) or laboratory-documented respiratory viral infections (n = 69). Each patient received a clinical appearance score using the Yale Observation Scale prior to laboratory evaluation. A complete blood cell count was obtained from all patients and manual differential count of the peripheral blood smear was performed by 1 senior technician masked to clinical information.

Main Outcome Measure: Band counts, represented as a percentage of white blood cells in the peripheral blood smear, the absolute band count, and band-neutrophil ratio. Logistic regression analysis was performed to determine whether the band count helps to distinguish bacterial infections from viral infections after adjusting for age, temperature, Yale Observation Scale score, and absolute neutrophil count.

Results: Patients with bacterial infections had a higher mean absolute neutrophil count (11.3 vs 5.9 × 10⁹/L; P < .01) than patients with respiratory viral infections. There was no difference, however, in percentage band count (13.5% vs 13.3%; P = .90), absolute band count (2.2 vs 1.9 × 10⁹/L; P = .31), or band-neutrophil ratio (0.24 vs 0.33; P = .08, bacterial vs viral, respectively); the band count did not help to distinguish bacterial and viral infections after adjusting for age, temperature, Yale Observation Scale score, and absolute neutrophil count in the regression analysis.

Conclusion: The band count in the peripheral blood smear does not routinely help to distinguish bacterial infections from respiratory viral infections in young febrile children.

as opposed to the determination of the total neutrophil count, which only requires the use of an automated cell counter. It would therefore be important to ascertain whether band counts differ between young febrile children with documented viral and bacterial infections. If differences in the band count between children with these infections did exist, it would also be important to determine whether the band count adds additional information for distinguishing bacterial and viral infections after adjusting for clinical information, as well as information available from an automated CBC (ie, ANC).

The objectives of this study were (1) to determine whether the percentage band count, the absolute band count (ABC), or the band-neutrophil ratio (BNR) in the peripheral blood smear differs between young febrile children with documented bacterial or respiratory viral infections, and (2) to determine whether the band count helps to distinguish young febrile children with bacterial infections from those with respiratory viral infections after adjusting for readily available clinical information (age, temperature, clinical appearance) and hematologic information available from an automated CBC (ie, ANC).

PATIENTS AND METHODS

PATIENT POPULATION

The data were derived from a cohort of young febrile children enrolled in a study of unsuspected bacterial infections. In that study, we prospectively enrolled a convenience sample of febrile children younger than 2 years seen in the emergency departments of 3 pediatric referral hospitals between November 1994 and April 1995, and between November 1995 and February 1996. Patients were included in the study if they had fevers determined rectally in the emergency department, or at home within 4 hours of presentation, of temperature of 38°C or higher for patients younger than 3 months and temperature of 39°C or higher for patients 3 to 24 months old. Patients were excluded from the study if they (1) were immunized or had received antibiotics within 48 hours of presentation to the emergency department, (2) had a clearly identifiable infection apparent on physical examination (ie, varicella, croup, gingivostomatitis, cellulitis, or septic arthritis), (3) had a chronic illness or known immunodeficiency, (4) were currently taking immunosuppressive medication, or (5) if a parent or legal guardian was unable or refused to give written informed consent. The study was approved by the institutional review boards of each participating institution.

Patients with clearly evident viral syndromes known to be associated with high fevers (ie, croup, gingivostomatitis, and varicella) were excluded because ethical considerations precluded obtaining laboratory tests on these patients. Patients with less specific signs of viral illness (ie, diarrhea or wheezing), however, were included. Otitis media was not considered an exclusion criterion because febrile infants with and without otitis media have a similar risk of bacteremia.

CLINICAL AND LABORATORY EVALUATION

An attending physician obtained a history and performed a physical examination on each patient. Prior to laboratory investigation, a study investigator evaluated the general appearance of each patient using the Yale Observation Scale (YOS), with a score of 10 or less representing well appearance. A CBC, manual differential count, and blood culture were then obtained from all patients. Total WBC was determined using an electronic cell counter, and 100 cells of the Wright-stained peripheral blood smear were evaluated by 1 senior technician unaware of clinical and laboratory information. Catheterized urine cultures were obtained from girls of all ages and from boys younger than 6 months, according to the guidelines by Baraff et al. Lumbar punctures were performed on patients younger than 2 months and on any other patient for whom it was believed to be clinically indicated by the responsible physician. Nasopharyngeal specimens were obtained for detection of RSV, adenovirus, influenza, and parainfluenza viruses by immunofluorescence from all patients whose guardians consented to this procedure (parents were also given the option to participate in the original study without having nasopharyngeal specimens obtained). Specimens were obtained by scraping the nasopharynx using a plastic spoon-tipped curette (RhinoProbe; Arlington Scientific, Inc, Arlington, Tex). The results of these tests were not immediately available to the physician caring for the patient. In cases where the responsible physician required immediate results of the nasopharyngeal specimen analysis for diagnostic or therapeutic purposes, an enzyme-linked immunosorbent assay was performed. These results were also included in the data analysis.

Chest radiographs were obtained for patients with signs of lower respiratory tract illness (wheezes, rales, crackles), and all radiographs were interpreted by a single pediatric radiologist masked to patient and laboratory information. Patients with lobar infiltrates were excluded from the present

STUDY POPULATION

A total of 432 patients were prospectively evaluated and enrolled in the study. Nasopharyngeal specimens were obtained for viral analysis from 226 patients (52%), 75 of whom had documented respiratory viral infections (64 with RSV, 6 with parainfluenza, 3 with influenza, and 2 with adenovirus infections; 37 of these patients had clinical bronchiolitis). Of the 432 enrolled patients, 31 had documented bacterial infections (24 with UTI, 7 with bacteremia) (Table 1). No patient had bacterial meningitis.

Chest radiographs revealed lobar pneumonias in 15 of the 432 patients, who were subsequently excluded from analysis. One RSV-positive patient had a UTI and was also excluded from the analysis. The remaining 69 patients with laboratory-documented viral infections were compared with the 31 patients with documented bacterial infections (Table 1). Fourteen (45%) of the 31 patients with bacterial infections and 28 (41%) of the 69 patients with viral infections were girls (P = .67). Of the 100 patients with laboratory-documented infections, 14 were Afri-
analysis owing to the inability to distinguish viral from bacterial etiology. Patients with documented simultaneous viral and bacterial infections were also excluded.

DEFINITIONS AND OUTCOME VARIABLES

Respiratory viral infection was defined as the detection of any of the previously mentioned respiratory viruses on either immunofluorescence or enzyme-linked immunosorbent assay. A bacterial infection was defined as growth of a known bacterial pathogen from the blood (bacteremia) or pure growth of at least 10^4 colony-forming units per milliliter of a bacterial pathogen from a catheterized or suprapubic specimen of urine. Hematogenous isolates considered pathogens included Haemophilus influenzae type b, Streptococcus pneumoniae, Neisseria meningitidis, Salmonella species, Strepctococcus pyogenes, Streptococcus agalactiae (group B streptococcus), Moraxella catarrhalis, Escherichia coli, or Staphylococcus aureus.

STATISTICAL ANALYSIS

Univariable Analysis

We compared patients with respiratory viral infections with those with bacterial infections with regard to age, temperature, YOS score, WBC, ANC, ABC, percentage band count, and BNR. The ANC was calculated by multiplying the total WBC by the sum of the percentage mature neutrophils and percentage band forms seen on the peripheral blood smear. The ABC was calculated by multiplying the total WBC by the percentage band forms; the BNR was calculated by dividing the percentage band count by the percentage total neutrophil count. Continuous variables were compared between patients with viral and bacterial infections using the Student t test, except in subanalyses in which there were fewer than 20 patients in each group, in which continuous variables were compared using the Wilcoxon rank sum test. Categorical variables were compared using the Fisher exact test, and YOS scores were compared using the Wilcoxon rank sum test. All tests were based on 2-tailed alternatives. P ≤ .05 was considered significant.

Multivariable Analysis

A logistic regression analysis was performed with bacterial infection as the dependent variable and the following independent variables: age (grouped in categories of ≤ 3 or >3 months), YOS score (grouped as well-appearing [YOS score ≤10] or ill-appearing [YOS score >10]), temperature, ANC, and band count. The purpose of this analysis was to determine whether the band count (represented as the percentage band count, the ABC, or BNR) added significant information after adjusting for important clinical variables (ie, age, temperature, clinical appearance) and hematologic information available from an automated CBC (ie, ANC).

In addition, we performed 3 abbreviated subanalyses. In the first subanalysis, we assumed all patients with negative blood and urine cultures had viral infections. The intent of this subanalysis was to determine whether our findings for patients with documented respiratory viral infections could be generalized to all culture-negative patients with presumed viral infections. In an additional subanalysis, we excluded patients with positive urine cultures who had fewer than 5 WBC per high-powered field on urinalysis, because these results could be interpreted as asymptomatic bacteriuria. In the last subanalysis, we compared patients with RSV infections with those with UTIs (with pyuria ≥5 WBC per high-powered field), as these represented the most common infections in the viral and bacterial groups, respectively.

The statistical analyses were performed using Stata statistical software, version 5.0.
In the first subanalysis, we compared patients with bacterial illness (bacteremia or UTI) with all patients with negative blood and urine cultures, regardless of whether nasopharyngeal specimens had been obtained for respiratory viral identification. Mean band counts were 13.5% in the bacterial group and 10.9% in the culture-negative group (difference, 2.6 percentage points; 95% confidence interval [CI], 0.3% to 4.9%; P = .01). The percentage band count (adjusted OR = 0.97 for each increase of 1 percentage point in band count; 95% CI, 0.92 to 1.03; P = .37), ABC (adjusted OR = 0.74 for every 10^9/L increase in ABC; 95% CI, 0.48 to 1.15; P = .19), and BNR (adjusted OR = 0.99 for each increase of 1 percentage point in BNR; 95% CI, 0.91 to 1.04; P = .49) did not add significant predictive information after adjusting for the age, temperature, YOS score, and ANC.

In the second subanalysis, we excluded the 5 patients with positive urine cultures who had less than 5 WBC per high-power field on urinalysis, because we could not exclude the possibility that they had asymptomatic bacteriuria. Mean band counts were 14.8% in the bacterial group and 13.3% in the respiratory viral group (difference, 1.5 percentage points; 95% CI, −3.1% to 6.1%; P = .52). The results of the multivariable analysis were unchanged from the primary analysis.

In the last subanalysis, we compared patients with RSV infections with those with UTIs (with pyuria ≥5 WBC per high-power field), as these represented the most common infections in the viral and bacterial groups, respectively. Mean band counts were 15.2% in the UTI group and 13.4% in the RSV group (difference, 1.8 percentage points; 95% CI, −3.4% to 7.0%; P = .49). The percentage band count (adjusted OR = 0.97 for each increase of 1 percentage point in band count; 95% CI, 0.91 to 1.04; P = .43), ABC (adjusted OR = 0.74 for every 10^9/L increase in ABC; 95% CI, 0.48 to 1.15; P = .19), and BNR (adjusted OR = 0.99 for each increase of 1 percentage point in BNR; 95% CI, 0.91 to 1.02; P = .41) did not add significant predictive information after adjusting for the age, temperature, YOS score, and ANC.

**Table 1. Univariable Comparisons of Patients With Bacterial and Respiratory Viral Infections***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bacterial Infection (n = 31)†</th>
<th>Respiratory Viral Infection (n = 69)‡</th>
<th>Difference Between Means or Percentages (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (± SD), mo</td>
<td>6.2 (5.4)</td>
<td>4.1 (4.4)</td>
<td>2.1 (0.1 to 4.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Aged &lt;3 mo, No. (%)</td>
<td>11 (35)</td>
<td>39 (57)</td>
<td>−22 (−43 to 0)</td>
<td>.08</td>
</tr>
<tr>
<td>Median YOS score (range)</td>
<td>10 (6-18)</td>
<td>8 (6-18)</td>
<td>Not applicable</td>
<td>.67</td>
</tr>
<tr>
<td>YOS score &gt;10, No. (%)</td>
<td>5/31 (16)</td>
<td>11/69 (16)</td>
<td>0 (−16 to 16)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Temperature, mean (± SD), °C</td>
<td>39.7 (0.9)</td>
<td>39.9 (0.7)</td>
<td>0.7 (0.4 to 1.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>WBC, mean (± SD), x10^9/L</td>
<td>18.0 (5.8)</td>
<td>13.3 (5.5)</td>
<td>4.7 (2.3 to 7.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>WBC &gt;15 x10^9/L, No. (%)</td>
<td>21/31 (68)</td>
<td>18/68 (26)</td>
<td>42 (21 to 63)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ANC, mean (± SD), x10^9/L</td>
<td>11.3 (5.1)</td>
<td>5.9 (4.2)</td>
<td>5.4 (3.5 to 7.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ANC ≥10 x10^9/L, No. (%)</td>
<td>19/31 (61)</td>
<td>10/68 (15)</td>
<td>46 (27 to 65)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ABC, mean (± SD), x10^9/L</td>
<td>2.2 (1.5)</td>
<td>1.9 (1.7)</td>
<td>0.3 (−0.3 to 1.1)</td>
<td>.31</td>
</tr>
<tr>
<td>ABC &gt;0.5 x10^9/L, No. (%)</td>
<td>27/31 (87)</td>
<td>52/68 (76)</td>
<td>11 (−6 to 28)</td>
<td>.29</td>
</tr>
<tr>
<td>Percentage band count, mean (± SD)</td>
<td>13.5 (9.6)</td>
<td>13.3 (10.3)</td>
<td>0.2 (−4.1 to 4.6)</td>
<td>.90</td>
</tr>
<tr>
<td>Band-neutrophil ratio, mean (± SD)</td>
<td>0.24 (0.19)</td>
<td>0.33 (0.24)</td>
<td>−0.09 (−0.18 to 0.01)</td>
<td>.08</td>
</tr>
<tr>
<td>Band-neutrophil ratio ≥0.20, No. (%)</td>
<td>16/31 (52)</td>
<td>46/68 (68)</td>
<td>−16 (−37 to 20)</td>
<td>.18</td>
</tr>
</tbody>
</table>

**Subanalyses**

In this study of young febrile children with laboratory-documented bacterial or respiratory viral infections, several variables were significantly associated with bacterial infection, including age, temperature, WBC, and ANC. The band count, however, whether represented as the percentage band count, the ABC, or the BNR, was similar between children with bacterial and respiratory viral infections. In the univariable analysis, the point estimate of the difference in percentage band count between groups was 0.20%. Not only is this value clinically unimportant, but the extremes of the 95% CI for this estimate (4.1% favoring viral infection or 4.6% favoring bacterial infection), are likely clinically unimportant as well. More important, the band count did not help distinguish bacterial infections from respiratory viral infections in the multivariable analysis after adjusting for readily available clinical information (age, temperature, clinical appearance) and hematologic information available from

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an automated CBC (ie, ANC). The results did not significantly differ in our subanalyses in which we assumed all culture-negative patients had viral infections, when we limited our definition of UTI to culture-positive urine and pyuria, or when we compared only patients with RSV infections with those with UTIs.

Some investigators have previously studied the role of the CBC and its different components in identifying febrile children with occult bacterial infections. The band count has been used and/or evaluated as one of several criteria to assess the risk of bacterial illness in young febrile children. Studies of the predictive value of the CBC, however, vary in many ways, including the age group examined, the presence of overt focal infections, and the statistical methods used.

It is well known that an increased number of bands is commonly seen in the peripheral blood smears of children with bacterial illnesses. Several studies have used and/or supported the use of band counts to identify febrile infants younger than 3 months with bacterial infections. Only one of these studies, however, evaluated the marginal contribution of the band count for the prediction of bacterial illness in a multivariable analysis. In that study, a band count of 0.5 × 10⁹/L or higher was correlated with bacterial infection by stepwise discriminant analysis. Other investigators have not found the band count to be useful in identifying bacterial infections in these young infants. In pediatric patients 3 months and older, there is also disagreement regarding the utility of bands counts for the evaluation of fever.

Our study differs from these previous studies in some important ways. All of the peripheral blood smears in our study were evaluated by one senior technologist, thus eliminating the issue of interobserver differences in interpreting band counts. In addition, previous studies have uncommonly used multivariable statistical methods, and thus lack adjustment for the presence of other important associated and confounding variables. In the present study we used multivariable statistical methods to determine whether the band count offered any significant additional information regarding the prediction of bacterial illness after adjusting for important clinical information (age, temperature, clinical appearance) and hematologic information available from an automated CBC with total neutrophil count (ie, ANC). With these methods, we found that the band count did not add additional information in distinguishing bacterial and viral infections.

Several previous investigators have noted elevated band counts in patients with viral infections as observed in many of the patients in the present study. One study reported that leukocytosis and elevated band counts were seen in patients with severe viral lower respiratory tract infections compared with those with asymptomatic infections with the same viruses. Additional studies have reported elevated band counts in children with influenza infections as well as in hypoxic children with RSV infections. Elevated band counts in viral disease do not appear to be limited to patients with lower respiratory tract infections. One group of investigators found that many patients with proven entovirus and rotavirus infections, as well as patients with influenza and RSV infections, had elevation of their band counts and would have been considered to be at high risk for bacterial illness based on band criteria advocated by some.

There are some limitations to this study. The study was conducted during the winter months and the majority of the patients with laboratory-documented viral illness had RSV infections. We excluded patients with clearly evident viral syndromes known to be associated with high fevers (ie, croup, gingivostomatitis, and varicella), because ethical considerations precluded obtaining laboratory tests on these patients. We therefore cannot necessarily generalize our findings to all viral pathogens. Presumably, many of the patients with both negative bacterial cultures and negative respiratory viral antigen studies (as well as patients who did not have nasopharyngeal specimens obtained) also had viral illnesses. These other viruses might have been detected if sites other than the nasopharynx had been sampled for viral detection. Because these patients did not have a proven viral or bacterial diagnosis, we excluded them from our primary analysis. In the subanalysis in which we assumed all patients with negative blood and urine cultures had viral infections, however, the results were unchanged, as the band count did not contribute significant predictive information.

Although it is possible that some of the culture-negative patients may have actually had clinically occult bacterial infections, this is unlikely for several reasons. All of these patients had negative blood cultures and all of those with signs of lower respiratory tract infections had chest radiographs with no evidence of lobar pneumonias. Finally, urine samples were obtained from more than 90% of girls in this study, as well as more than 90% of boys younger than 6 months of age as recommended by guidelines for the evaluation of young febrile children. Most of the patients with bacterial infections in our study had UTIs rather than bacteremia. The results of this study, however, reflect the typical prevalence of UTIs and bacteremia in young febrile children evaluated as outpatients. The results of this study did not appreciably change in the subanalysis in which we included only patients with UTIs in the bacterial infection group. The data in this study concur with those of a large study of occult pneumococcal bacteremia, in which the band count did not add significant predictive information after adjusting for age, temperature, and ANC. Although there were no patients with meningococcal infections in this study, clinically unsuspected meningococcal infections in young febrile pediatric outpatients are very uncommon. Therefore, despite the fact that band counts are frequently elevated in children with meningococcal infections, the utility of routinely using the band count as a screen for clinically unsuspected meningococcal disease is low.

The number of patients with documented bacterial and respiratory viral infections was insufficient to stratify the analysis for patients younger and older than 3 months. Although we did not find significant differences in band counts between patients with bacterial and viral infections in the younger age group, there was insufficient statistical power to detect differences of small magnitude because...
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