Clinical and Hematologic Features Do Not Reliably Identify Children With Unsuspected Meningococcal Disease

Nathan Kuppermann, MD, MPH*; Richard Malley, MD‡§; Stanley H. Inkelis, MD¶; and Gary R. Fleisher, MD¶

ABSTRACT. Objective. To determine the frequency of unsuspected meningococcal disease (UMD) in young febrile children with meningococcal infections and evaluate whether clinical and laboratory parameters commonly used in the evaluation of fever can help identify children with UMD.

Methods. We reviewed the records of children with meningococcal disease from 1985 to 1996 at four referral centers. Children who were evaluated as outpatients and then discharged to home, from whom Neisseria meningitidis was isolated from blood or cerebrospinal fluid cultures obtained during these outpatient visits, were considered to have UMD. We compared clinical and laboratory parameters between children with UMD and 6414 febrile outpatients 3 to 36 months old with negative blood cultures enrolled in a separate study of occult bacteremia.

Results. We identified 381 children with meningococcal disease, of whom 45 (12%) had UMD. Of the 45 with UMD, 37 (82%) were 3 to 36 months old. Compared with the 6414 culture-negative patients, these 37 patients with UMD were significantly younger (8.9 ± 5.4 vs 14.2 ± 8.1 months) and had significantly higher band counts (14.3 ± 11.1 vs 7.3 ± 7.5%). There were no significant differences, however, in temperature, white blood cell counts, and absolute neutrophil counts. Multivariate analysis identified young age and the band count as independent predictors of UMD.

Conclusions. Children ultimately diagnosed with meningococcal disease have commonly been evaluated as outpatients and discharged to home before diagnosis. Of the hematologic parameters frequently used in the evaluation of fever, only the band count differs significantly between young febrile children with UMD and those with negative cultures. Because UMD is uncommon in young febrile pediatric outpatients, however, the predictive value of the band count is low. Thus, the complete blood count is not routinely helpful for the diagnosis of UMD. Pediatrics 1999;103(2). URL: http://www.pediatrics.org/cgi/content/full/103/2/620; Neisseria meningitidis, meningococcal infections, bacteremia, complete blood count, neutrophil.

ABBREVIATIONS. UMD, unsuspected meningococcal disease; CSF, cerebrospinal fluid; WBC, white blood cell count; ABC, absolute band count; ANC, absolute neutrophil count; ROC, receiver operating characteristic; CBC, complete blood count; OR, odds ratio; CI, confidence interval.

Meningococcal infections continue to cause serious morbidity and mortality in children.1–7 Approximately 2600 cases of meningococcal infection occur annually in the United States,9 with the highest attack rates occurring in young children.1,5,8

Most children with meningococcal disease have overt clinical signs of illness (ie, fever with toxic clinical appearance, irritability, lethargy, nuchal rigidity, and petechial and/or purpuric rashes).3,4,9,10 Some children infected with Neisseria meningitidis, however, initially develop fever without clinical toxicity. These children with unsuspected meningococcal disease (UMD) may inadvertently be discharged to home after outpatient evaluation4,11–17 and may deteriorate rapidly.11 The proportion of children infected with N meningitidis who initially present with clinically occult illness, however, is unknown.

The objectives of this study were to 1) determine the frequency of UMD among a large group of children with laboratory-documented meningococcal infections, and 2) identify clinical and hematologic predictors of UMD in febrile pediatric outpatients.

METHODS

Meningococcal Database

We reviewed the medical records of all patients younger than 20 years of age with blood or cerebrospinal fluid (CSF) cultures, or latex agglutination tests of the blood, CSF, or urine, positive for N meningitidis, from 1985 to 1996 at three pediatric referral centers and from 1990 to 1995 at one center. Subgroups of the population from this meningococcal database have been reported previously.3,5,8,17

Definitions

Children were considered to have UMD if they were evaluated and discharged as outpatients and had N meningitidis isolated from blood and/or CSF cultures (diagnostic cultures) obtained during these outpatient evaluations.

Patients hospitalized at the evaluation during which the diagnostic cultures were obtained were considered to have overt meningococcal disease. We documented possible clinical indications for admission in these patients including an abnormal general appearance (toxic, lethargic, or irritable), the presence of a petechial and/or purpuric rash, the presence of poor peripheral perfusion (cool, mottled skin or capillary refill time >2 seconds), the presence of CSF pleocytosis (>10 × 106 white blood cell count [WBC]/L), or being a febrile neonate (<1 month of age).

Finally, children in the overt group who had been evaluated for

From the *Department of Pediatrics and Division of Emergency Medicine, Department of Internal Medicine, University of California, Davis, School of Medicine, Davis, California; ‡Emergency Medicine and §Infectious Diseases, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts; and ¶Departments of Emergency Medicine and Pediatrics, Harbor-UCLA Medical Center, Torrance, California.

The results of this study were presented in part at the meeting of the Society for Pediatric Research, Washington, DC, May 4, 1997. Received for publication Dec 29, 1997; accepted Sep 24, 1998.

Address correspondence to Nathan Kuppermann, MD, MPH, Departments of Pediatrics and Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

PEDIATRICS (ISSN 0031-4005). Copyright © 1999 by the American Academy of Pediatrics.

http://www.pediatrics.org/cgi/content/full/103/2/620

PEDIATRICS Vol. 103 No. 2 February 1999
febrile illnesses as outpatients in the 48 hours before hospitalization, who did not have blood or CSF cultures obtained at these outpatient evaluations, were identified (but not included in the UMD group).

Data Collection

Demographic information, and clinical and laboratory findings at the time of initial evaluation, were recorded for all patients (ie, from the visit at which the diagnostic culture was obtained). Absolute band counts (ABCs) were calculated by multiplying the total WBC by the percentage bands. The absolute neutrophil counts (ANCs) were calculated by multiplying the total WBC by the sum of the percentage of mature neutrophils and percentage bands seen in the peripheral blood smear. If only an automated differential was performed, the ABC could not be calculated and the ANC was determined by multiplying the total WBC by the total neutrophil percentage.

Patients With Negative Blood Cultures From the Occult Bacteremia Database

We compared data from patients with UMD with data from a large cohort of young febrile children evaluated as outpatients with negative blood cultures. These patients were enrolled in a study of occult bacteremia at 10 medical centers from 1987 to 1991 (occult bacteremia database).13 In that study, 6649 nontoxic-nontoxic appearing children, 3 to 36 months old, with temperatures of 39°C or higher with no apparent bacterial focus of infection (other than otitis media) had blood cultures drawn and were discharged to home. Children with nonspecific signs of viral illnesses including diarrhea, vomiting and wheezing were not excluded; 614 from the 6649 children had negative blood cultures and comprised our comparison group. UMD patients from the meningococcal database who were 3 to 36 months of age were compared with these culture-negative patients with regard to demographic, clinical, and laboratory information at the time of initial evaluation.

Prevalence of UMD among nontoxic-nontoxic appearing febrile (temperature ≥39°C) outpatients 3 to 36 months of age was estimated based on the 2 of 6649 (0.03%) patients in the occult bacteremia database from whom N meningitidis was isolated from the blood.

Statistical Analysis

In the primary analysis, we compared patients 3 to 36 months old with UMD with the culture-negative patients (all of whom were 3–36 months old).

Univariate Analysis. We compared continuous variables between groups by using Student’s t test and categorical variables by using Fisher’s exact test. Receiver operating characteristic (ROC) curves were constructed from bivariate logistic regression models for each predictive variable with UMD as the outcome of interest. An ROC curve is a graphic representation of the sensitivity and specificity of a diagnostic test.20 To determine if variables should be entered into a multiple regression analysis in dichotomous or continuous form, we examined the individual ROC curves of each predictive variable for cutoff points at which a subsequent gain in sensitivity resulted in a large loss in specificity.20 Because no obvious cutoff points of this type existed, all predictive variables were represented in their continuous form for consideration into the multiple regression analysis, and not grouped into dichotomous categories.

Multivariate Analysis. Variables associated with UMD (P ≤ .05) in the univariate analysis were entered into a multiple logistic regression equation. Variables retaining a significant association were identified as independent predictors of UMD. In a subanalysis, we performed a second univariate and multivariate analysis comparing UMD patients of all ages with the culture-negative patients from the occult bacteremia database. All statistical analyses were performed using STATA statistical software, version 5.0.21 All tests were based on two-tailed alternatives. P values of .05 or less were considered significant and values between .05 and .10 were considered to represent a trend.

RESULTS

Patients With Meningococcal Disease

We identified 381 children with bacteriologically proven meningococcal disease (Table 1), 45 (12%) with UMD and 336 (88%) with overt infections. Of the 45 children with UMD, 2 (4.4%) died, compared with 34 (10.1%) of 336 patients with overt disease (P = .29).

Characteristics of Patients With UMD

Of the 45 patients with UMD, 10 were initially evaluated by the patient’s primary care provider, 3 were initially evaluated in clinics, and 32 were initially evaluated in hospital emergency departments. Initial diagnoses among patients with UMD included otitis media (13 patients), pneumonia (5 patients), viral syndrome (4 patients), gastroenteritis (2 patients), fever (2 patients), sinusitis (1 patient), pharyngitis (1 patient), febrile seizure (1 patient), bronchitis (1 patient), and unknown (ie, diagnosis not written in medical record, 15 patients). Only 1 of the 45 patients was described as possibly having a petechial rash (single nonblanching lesion) at first presentation. All 45 of the patients with UMD had blood cultures obtained at the outpatient evaluation and N meningitidis was isolated from 44 (98%). Seventeen (38%) of the patients with UMD had CSF cultures obtained at the outpatient evaluations, and 2 (12%) had growth of N meningitidis (including the 1 patient with a negative blood culture). No patient had CSF pleocytosis (>10 × 10⁶ WBC/L) or traumatic lumbar puncture (>10 000 × 10⁶ red blood cell count/L).

Twenty-four patients with UMD returned to the hospital after outpatient evaluations because of physician recall for positive cultures (median time, 2 days; range, 1–10 days), 14 for worsening conditions and/or the development of a rash (median time, 0.7 days; range, 0.3–3 days), 5 for scheduled follow-up examinations (median time, 1 day; range, 0.2–2 days), and 2 for persistent fevers (median time, 2 days). Seventeen patients (38%) were initially evaluated in hospital emergency departments, 33 (73%) were initially evaluated in clinics, and 32 were initially evaluated by the patient’s primary care provider. Twenty patients (44%) were initially evaluated within 24 hours of admission. Twenty-three patients (51%) were initially evaluated within 2 days of admission. Twenty-three patients (51%) were initially evaluated within 7 days of admission.

Children with nonspecific signs of viral illnesses including diarrhea, vomiting and wheezing were not excluded from the UMD group. UMD patients from the meningococcal database who were 3 to 36 months of age were compared with these culture-negative patients who had negative blood cultures and comprised our comparison group. UMD patients from the meningococcal database who were 3 to 36 months of age were compared with these culture-negative patients with regard to demographic, clinical, and laboratory information at the time of initial evaluation.

Prevalence of UMD among nontoxic-nontoxic appearing febrile (temperature ≥39°C) outpatients 3 to 36 months of age was estimated based on the 2 of 6649 (0.03%) patients in the occult bacteremia database from whom N meningitidis was isolated from the blood.

TABLE 1. Initial Clinical and Laboratory Findings in Patients With Meningococcal Disease From the Meningococcal Database*

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>UMD‡ (n = 45)</th>
<th>Overt Meningococcal Disease§ (n = 336)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in months</td>
<td>21 (± 40)</td>
<td>49 (± 57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age 3–36 months</td>
<td>37/45 (82%)</td>
<td>177/336 (53%)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>39.9 (± .8)</td>
<td>39.0 (± 1.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WBC (× 10⁹/L)</td>
<td>14.0 (± 5.6)</td>
<td>15.0 (± 9.7)</td>
<td>.36</td>
</tr>
<tr>
<td>WBC ≥15 × 10⁹/L</td>
<td>14/41 (34%)</td>
<td>145/335 (43%)</td>
<td>.32</td>
</tr>
<tr>
<td>WBC &lt;5 × 10⁹/L</td>
<td>1/41 (2%)</td>
<td>50/335 (15%)</td>
<td>.03</td>
</tr>
<tr>
<td>% Bands</td>
<td>16 (± 13)</td>
<td>21 (± 13)</td>
<td>.04</td>
</tr>
<tr>
<td>ABC (× 10⁹/L)</td>
<td>3.9 (± 1.2)</td>
<td>4.8 (± 1.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ANC (× 10⁹/L)</td>
<td>9.1 (± 4.9)</td>
<td>11.7 (± 9.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Platelets (× 10⁹/L)</td>
<td>390 (± 142)</td>
<td>258 (± 138)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: UMD, unsuspected meningococcal disease; CBC, complete blood count; WBC, white blood cell count; ABC, absolute band count; ANC, absolute neutrophil count.

* Values reported are those from the visit at which the positive culture was obtained. For UMD patients, this was at an outpatient visit, and for patients with overt disease, this was on the day of admission.
† Continuous variables reported as means (± standard deviation).
‡ Of patients with UMD, WBC recorded in 41, ANC recorded in 38, band count recorded in 35 and platelets recorded in 30.
§ Of patients with overt meningococcal disease, WBC recorded in 335, ANC recorded in 329, band count recorded in 300, and platelets recorded in 319.
Characteristics of Patients With Overt Meningococcal Disease

Of the 336 patients with overt disease, clinical indications for admission included petechial and/or purpuric rash in 232 (69%) and CSF pleocytosis in 203 (60%). Thirty-two (10%) patients classified as having overt disease had neither a petechial/purpuric rash nor CSF pleocytosis at presentation. All but 5 of these 32 patients, however, had either poor perfusion, an abnormal general appearance (toxic, lethargic, or irritable), or were younger than 1 month of age. Of the 5 patients with none of these clinical parameters, indications for admission were varied, and included pneumonia, a febrile sibling of a patient with meningococcal disease, acute abdomen, and ventriculoperitoneal shunt obstruction with fever.

Patients with UMD were younger, had higher temperatures, and were less likely to be leukopenic (WBC <5 × 10^9/L) than patients with overt meningococcal disease. In addition, children with UMD had significantly lower band counts, lower ANCs, and higher platelet counts than those with overt disease (see Table 1).

Patients Evaluated Without Cultures in the 48 Hours Before Hospitalization

In addition to the 45 patients with UMD, 58 (15%) of the 381 patients had been evaluated as outpatients for febrile illnesses in the 48 hours before hospitalization but did not have cultures obtained (median time, 1 day previous; range, 0.1–2 days). Initial diagnoses among these 58 patients included viral syndrome (12 patients), gastroenteritis (7 patients), otitis media (5 patients), pharyngitis (4 patients), conjunctivitis (4 patients), chicken pox (3 patients), upper respiratory infection (3 patients), pneumonia (2 patients), fever (2 patients), febrile seizure (1 patient), and unknown (21 patients). Eight (13.8%) of these 58 patients died. These patients were not included in the UMD group as diagnostic cultures were not obtained at the outpatient visits. Compared with the 45 patients with UMD, these 58 patients were older (39 ± 43 vs 21 ± 40 months; P = .04) and had lower temperatures (39.1 ± 1.2 vs 39.9 ± .8°C; P = .005) at the time of first evaluation. Nine of these 58 patients had complete blood counts (CBCs) at their first visits. There was no significant difference in WBCs (15.9 ± 4.8 vs 14.0 ± 5.6 × 10^9/L; P = .2) or band counts (14 ± 6.7 vs 16 ± 13%; P = .9) from the initial outpatient visits between these patients and those with UMD, respectively. All 8 patients who died among these 58 patients had outpatient evaluations in the 12 hours before hospitalization.

Comparison of Patients With Negative Blood Cultures From theOccult Bacteremia Database and Patients With UMD Ages 3 to 36 Months
Univariate Analysis

Of the 45 patients with UMD, 37 (82%) were 3 to 36 months old. The mean age of these 37 patients was significantly less than that of patients with negative blood cultures from the occult bacteremia database (Table 2). Height of fever, WBCs, and prevalence of leukocytosis and leukopenia were similar between the two groups. The band counts, however, whether expressed as percentage bands in the peripheral blood smear or ABCs, were significantly higher in patients with UMD. In addition, there was a trend toward higher ANCs in patients with UMD compared with culture-negative patients.

Despite the significant difference in mean band counts between patients with UMD and culture-negative patients, there was substantial overlap in band counts between these groups. Many culture-negative patients from the occult bacteremia database had elevated band counts (29% of the culture-negative patients had ≥10% bands in the peripheral blood smear, and 14% had band counts of ≥15%; see Table 2). The ROC curve for band count did not demonstrate a clear cutoff point above which patients with UMD could be clearly distinguished from culture-negative patients (Fig 1).

Multivariate Analysis

Age and band count were the only variables significantly associated (P ≤ .05) with UMD in the univariate analysis, and were therefore entered into the multivariate analysis. In the univariate analysis, band counts were represented and analyzed in two different continuous forms (percentage band count in the peripheral blood smear and the ABC), both of which differed significantly between patients with UMD and culture-negative patients. We selected the percentage band count for entry into the multivariate analysis, as this was the band variable that differed most significantly between patient groups (P = .003).

In the multivariate analysis, both age and the percentage band count retained statistical significance and thus were independently associated with UMD. The odds ratio (OR) for each 1 percentage point increase in the band count was 1.07 (95% confidence interval [CI], 1.05–1.10; P < .001). For a 10 percentage point increase in the band count, the OR was 2.0 (95% CI, 1.6–2.7; P < .001). The risk of UMD decreased with increasing age (OR for each 1-month increment, 0.86; 95% CI, 0.80–0.93; P < .001).

Subanalysis of Patients With UMD of All Ages

In a subanalysis, we compared patients with UMD of all ages to the culture-negative patients from the occult bacteremia database. In that univariate analysis, patients with UMD had significantly higher mean percentage band counts (16 ± 13 vs 7 ± 8%; P < .01) and ANCs (9.1 ± 4.9 vs 7.3 ± 4.9 × 10^9/L; P = .03) than culture-negative patients. There were no significant differences in mean temperature and WBC between groups in the univariate analysis (P > .05). When the significant variables from the univariate analysis were entered into a multiple logistic regression analysis, the percentage band count, but not the ANC, retained statistical significance. The OR and 95% CI for the band count remained identical to that of the primary analysis (ie, for UMD patients 3–36 months old).
Predictive Value of the Band Count

Despite the statistical association of band count with UMD, the positive predictive value of this variable is low because of the low prevalence of UMD among young febrile pediatric outpatients. Among the 6649 nontoxic-appearing children 3 to 36 months of age with temperatures of 39°C or higher evaluated as outpatients in the occult bacteremia database, only 2 (0.03%; 95% CI, 0.004–0.1%) had meningococcal bacteremia.13 The peripheral blood smears of those two children had 18% and 1% bands. In the same database, 1541 of the 5347 (29%) culture-negative patients who had peripheral blood smears performed had 10% or greater bands. Thus, using a band cutoff of 10% to identify meningococcal bacteria in the occult bacteremia database would have a positive predictive value of only 1 of 1542 (0.06%; 95% CI, 0.00–0.36%) and negative predictive value of 3806 of 3807 (99.97%; 95% CI, 99.85–99.99%). Use of a band cutoff of 20% would have allowed missing both patients with meningococcal bacteremia in the occult bacteremia database.

During a meningococcal outbreak, however, the attack rate may be 10 to 20 times higher than the endemic rate.5,22 In that setting, a band cutoff of 10% would have a greater positive predictive value for UMD. Of the 35 patients with UMD in the meningococcal database who had bands counts evaluated, 22 (63%; 95% CI, 45–79%) had band counts of 10% or more. By using these data along with the prevalence data for meningococcal disease in young febrile pediatric outpatients from the occult bacteremia database, one could extrapolate the positive predictive value of a band cutoff of >10% in the setting of an outbreak. Assuming a 15-fold higher disease rate in an outbreak, the prevalence of UMD among febrile pediatric outpatients 3 to 36 months old could be estimated to be 30 of 6677 (0.4%; 95% CI, 0.3–0.6%). The positive predictive value of a band cutoff of 10% could therefore be estimated as (.63 × 30)/1560 = 1.2% (95% CI, 0.7–1.9%).

DISCUSSION

In this study, we found that 45 (12%) of 381 children with invasive meningococcal disease had been evaluated as outpatients for febrile illnesses and discharged to home, and had blood (44 children) and/or CSF (2 children) cultures positive for N meningitidis at these outpatient visits. Two of these 45 patients with UMD died. In addition to the 45 patients with UMD, 58 (15%) of the 381 patients had been evaluated as outpatients for febrile illnesses and discharged to home in the 48 hours before hospitalization but did not have cultures obtained. Eight of

### Table 2. Comparison of Patients 3 to 36 Months of Age With UMD (From the Meningococcal Database) and Culture-negative Patients (From the Occult Bacteremia Database)

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>UMD† (n = 37)</th>
<th>Culture-negative‡ (n = 6414)</th>
<th>Difference Between Means for Continuous Variables (95% CI)</th>
<th>Odds Ratios for Categorical Variables (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in months</td>
<td>8.9 (± 5.4)</td>
<td>14.2 (± 8.1)</td>
<td>−5.3 (−3.5 to −7.1)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vital signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>40.0 (± 9)</td>
<td>39.8 (± 6.6)</td>
<td>0.2 (−0.1–0.5)</td>
<td></td>
<td>.25</td>
</tr>
<tr>
<td>CBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (× 10⁹/L)</td>
<td>13.8 (± 5.8)</td>
<td>12.9 (± 6.5)</td>
<td>0.9 (−1.1–−3.0)</td>
<td></td>
<td>.41</td>
</tr>
<tr>
<td>WBC ≥15 × 10⁹/L</td>
<td>$ 11/34 (32%)</td>
<td>1757/5695 (31%)</td>
<td>1.1 (1.5–2.2)</td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>WBC &lt; 5 × 10⁹/L</td>
<td>$ 1/34 (3%)</td>
<td>233/5695 (4%)</td>
<td>0.7 (0–4.1)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>% Bands</td>
<td>14.3 (± 11.1)</td>
<td>7.3 (± 7.3)</td>
<td>7.0 (2.8–11.2)</td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Bands ≥10%§</td>
<td>17/30 (57%)</td>
<td>1541/5347 (29%)</td>
<td>3.2 (1.6–6.6)</td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Bands ≥15%§</td>
<td>12/30 (40%)</td>
<td>752/5347 (14%)</td>
<td>4.1 (2.0–8.4)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bands ≥20%§</td>
<td>9/30 (30%)</td>
<td>380/5347 (7%)</td>
<td>5.6 (2.6–12.1)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ABC (× 10⁹/L)</td>
<td>2.0 (± 2.0)</td>
<td>1.0 (± 1.2)</td>
<td>1.0 (1.4–1.8)</td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ANC (× 10⁹/L)</td>
<td>8.8 (± 5.1)</td>
<td>7.3 (± 4.9)</td>
<td>1.5 (−0.2–3.3)</td>
<td></td>
<td>.08</td>
</tr>
</tbody>
</table>

UMD, unsuspected meningococcal disease; CI, confidence interval; CBC, complete blood count; WBC, white blood cell count; ABC, absolute band count; ANC, absolute neutrophil count.

* Continuous variables reported as means (± standard deviation).
† Of patients with UMD, WBC recorded in 34, band count recorded in 30, and ANC recorded in 32.
‡ Of culture-negative patients, WBC recorded in 5695, band count recorded in 5347, and ANC recorded in 5340.
§ Odds ratios denoting the increased odds of UMD are given for categorical variables (given as percentages and indented in the table); differences in mean values between patient groups are given for continuous variables.

![Fig 1. Receiver operating characteristic curve for the band count. The points on the curve represent the sensitivity/specificity profile in detecting unsuspected meningococcal disease for different band count cutoffs. The 45° line through the origin represents the receiver operating characteristic curve of a test of which the discriminatory ability is no better than chance.](image-url)
these 58 patients died. When we compared patients with UMD with a large cohort of young febrile pediatric outpatients with negative blood cultures and presumed viral illnesses, there was no significant difference in WBC, and only age and band count were independently associated with meningococcal disease. The positive predictive value of an elevated band count, however, is very low, because meningococcal disease is uncommon under normal circumstances in young febrile children treated as outpatients. Therefore, although identifying UMD would be a desirable clinical objective, screening all young febrile children for meningococcal bacteremia with CBCs is not clinically useful.

Several investigators have explored the utility of the CBC for identifying young febrile children with bacteremia. 23–41 Most cases of bacteremia in these studies, however, were due to Streptococcus pneumoniae, a Gram-positive organism, and Haemophilus influenzae, type b, a cause of bacteremia rarely observed in the United States since the introduction of a conjugated vaccine against this organism. 42 In these studies, the WBC and/or the ANC was the component of the CBC most frequently cited as distinguishing children with unsuspected bacteremia from culture-negative patients. 23–25,29,30,32,36–41 Similarly to the current study, however, some investigators have noted that the band count, but not the WBC, may be elevated in children with Gram-negative infections, including N meningitidis. 27,28,31 Furthermore, in a case series of children with unsuspected meningococcal meningitis, only 2 of 9 children had WBCs of 15 000/mm 3 or greater (band counts not reported). 11

Although unsuspected meningococcal bacteremia is uncommon, the morbidity and mortality of this disease is high. Despite the potential severity of UMD, the combination of low prevalence of UMD and poor ability of the CBC to discriminate UMD from viral infections makes routine screening for bands in the peripheral blood smears of otherwise healthy, nontoxic-appearing young febrile children impractical and of low clinical utility under normal circumstances. Screening the peripheral blood smears for bands in nontoxic febrile children, however, may be of use in selected clinical situations with higher prior probability of meningococcal disease such as in 1) patients with known contact with a case of meningococcal disease, 5,43 2) outbreaks of meningococcal disease, during which the attack rate may be 10 to 20 times higher than the endemic rate, 5,22 and 3) patients with fever associated with petechial rashes. 44,45

Several issues pertaining to our selected comparison groups are worthy of comment. The patients with UMD were identified from institutions that, with one exception, differed from those of the culture-negative control patients. We do not believe that this substantially affected our results, for several reasons. There was great overlap in the time periods of collection of both databases (1985–1996 vs 1987–1991), therefore time-dependent factors in the presentation of meningococcal disease would likely have been similar for all institutions. 6 Patients with otitis media or signs of viral illnesses (diarrhea/vomiting and wheezing) were included in both databases; therefore, differences in CBCs were unlikely to be related to these clinical conditions. Finally, when comparing patients from the two databases, we analyzed data only from children of similar age (3–36 months) to eliminate clinical and laboratory differences based on age.

The reliability and reproducibility of the band count has been questioned, 46,47 and this may further limit the utility of this test for the detection of UMD in any given patient. The questionable reproducibility of band counts, however, should not affect the validity of the association between band counts and UMD identified in the current study, because the status of the cultures of patients in both databases was not known at the time the band counts were read. Therefore, potential variability in band count readings would affect all patients equally.

There are several potential limitations to this study. As the study is retrospective in nature, we could not apply clinical scoring algorithms to patients with UMD. The assumption of nontoxic appearance was based on the fact that they were discharged to home after outpatient evaluation. Because we classified as UMD only those patients who had blood and/or CSF cultures obtained at initial outpatient evaluations that were positive for N meningitidis, it is likely that we underestimated the number of patients with UMD. In addition to the 12% of patients in our meningococcal database who were classified as having UMD, another 15% of the patients in our series had been evaluated as outpatients for febrile illnesses within 48 hours of diagnosis but did not have diagnostic cultures obtained. Therefore, the frequency of UMD among all patients with meningococcal disease may have been significantly higher than we reported. Furthermore, some outpatient visits to primary care physicians may not have been documented in the hospital records.

The implications of this study are several; 1) fever without clinical toxicity (ie, UMD) cannot be considered an uncommon initial presentation of invasive meningococcal disease, 2) children with this clinical presentation may progress to severe disease, and 3) routine laboratory screening of previously healthy, nontoxic-appearing young febrile children 3 to 36 months of age with CBCs is not likely to be clinically useful for detecting UMD under normal circumstances. The utility of screening may be greater in selected febrile pediatric outpatients with higher prior probability of meningococcal disease, but these data are currently unknown.

The current study has legal implications in addition to its clinical information. Lawsuits directed at physicians who have performed the initial evaluations of young febrile children with UMD (ie, before the development of overt signs of meningococcal disease) are well described. 48–50 Our data suggest that neither the clinical examination nor the CBC reliably distinguishes young febrile children with UMD from those with viral illnesses.
CONCLUSION
In summary, children with meningococcal disease are commonly evaluated and inadvertently discharged to home before diagnosis. Of the hematology parameters frequently used in the evaluation of fever, only the band count differs significantly between young febrile children with UMD and those with negative cultures. Because UMD is uncommon in young febrile pediatric outpatients, however, the predictive value of the band count is low. Thus, the CBC is not routinely helpful for the diagnosis of UMD.

ACKNOWLEDGMENTS
We thank Nicole Glaser, MD, and Luis Glaser, PhD, for their critical review of the manuscript, and Ian McCaslin, MD, for assistance with data gathering.

REFERENCES
Clinical and Hematologic Features Do Not Reliably Identify Children With Unsuspected Meningococcal Disease
Nathan Kuppermann, Richard Malley, Stanley H. Inkelis and Gary R. Fleisher
Pediatrics 1999;103;e20
DOI: 10.1542/peds.103.2.e20

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/103/2/e20

References
This article cites 49 articles, 11 of which you can access for free at:
http://pediatrics.aappublications.org/content/103/2/e20#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Hematology/Oncology
http://www.aappublications.org/cgi/collection/hematology:oncology_sub
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml
Clinical and Hematologic Features Do Not Reliably Identify Children With Unsuspected Meningococcal Disease

Nathan Kuppermann, Richard Malley, Stanley H. Inkelis and Gary R. Fleisher

*Pediatrics* 1999;103;e20
DOI: 10.1542/peds.103.2.e20

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/103/2/e20