Antibiotic Treatment of Children With Unsuspected Meningococcal Disease

Vincent J. Wang, MD; Richard Malley, MD; Gary R. Fleisher, MD; Stanley H. Inkelis, MD; Nathan Kuppermann, MD, MPH

Background: Data from an earlier study suggest that patients with unsuspected meningococcal disease (UMD) cannot be differentiated easily from febrile children with viral syndromes on the basis of physical examinations or peripheral blood counts. Some children with meningococcal disease therefore are treated inadvertently as outpatients.

Objective: To determine whether antibiotic therapy administered at the outpatient visit prevents complications, permanent sequelae, or death in children with UMD.

Methods: We reviewed the medical records of patients younger than 20 years with invasive meningococcal disease at 7 pediatric referral centers from January 1, 1981, through December 31, 1996. Patients were considered to have UMD if they underwent evaluation and discharge as outpatients and if blood and/or cerebrospinal fluid cultures obtained at evaluation yielded Neisseria meningitidis. We compared the frequency of development of complications (meningitis, sepsis, and pericarditis), permanent sequelae (limb amputation, skin grafting, and persistent neurologic disability) or death between patients who did and did not receive antibiotics at the outpatient visits.

Results: Of 58 children with UMD, 19 (33%) received antibiotics and 39 (67%) did not. Complications occurred significantly less frequently in the antibiotic-treated group (7/19 [37%] vs 27/39 [69%]; odds ratio [OR], 0.26; 95% confidence interval [CI], 0.08-0.81; P = .03). There was no significant difference in death or permanent sequelae between groups (0/19 vs 3/39 [8%]; OR, 0; 95% CI, 0-2.61; P = .54). There was insufficient power, however, to exclude the possibility of a clinically meaningful difference between the groups with regard to these latter outcomes.

Conclusions: Antibiotic administration to young patients with UMD at the time of the outpatient visit is associated with a reduction in complications from this disease. Although the routine use of antibiotics in febrile outpatients younger than 20 years cannot be advocated, empirical treatment should be considered in the setting of higher probability of meningococcal disease.


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PATIENTS AND METHODS

PATIENT POPULATION

We reviewed the medical records of patients with meningococcal disease younger than 20 years who underwent evaluation at 7 pediatric referral centers from January 1, 1981, through December 31, 1996 (Children's Hospital, New England Medical Center, Massachusetts General Hospital, and Boston Medical Center, Boston, Mass; Harbor–University of California–Los Angeles [UCLA] Medical Center, Torrance, Calif; University of California–Davis [UCD] Medical Center; and Children's Hospital and Health Center of San Diego, San Diego, Calif). All these centers provide a full range of pediatric subspecialty care, including critical care. Meningococcal disease was defined by a blood and/or cerebrospinal fluid (CSF) culture positive for Neisseria meningitidis and/or positive results of blood/CSF latex agglutination studies. Patients with meningococcal disease were identified by reviewing admission diagnosis log books, microbiology log books, and/or International Classification of Diseases, Ninth Revision,11 discharge codes from medical records at each institution. The medical records were reviewed in a structured format, with the use of a standardized data sheet. Subsets of this population of children have been described previously.10,12,13 The study was approved by the institutional review boards at each of these medical centers.

DEFINITIONS

Patients were considered to have overt meningococcal disease if they were hospitalized at the evaluation during which the diagnostic cultures and/or latex agglutination studies were obtained due to obvious signs of toxic effects (eg, purpura, hypotension, or nuchal rigidity). Children were considered to have UMD if they underwent evaluation and were discharged to home and had blood and/or CSF cultures positive for N meningitidis obtained during these outpatient evaluations. Patients undergoing outpatient evaluation without blood cultures and then discharged to home before hospitalization were not categorized as having UMD, because the presence of meningococcal infection at the time of the initial evaluation could not be definitively demonstrated.

Study outcomes were defined prospectively before the analysis of the data. Outcomes were divided into complications and permanent sequelae. Complications of UMD were defined as the occurrence of any of the following: meningitis, purpura, hypotension requiring pressor support (sepsis), respiratory failure, or pericarditis. Meningitis was defined as the presence of N meningitidis in the CSF culture, a positive result of CSF latex agglutination study, or a CSF white blood cell count of greater than 10 × 10^9/L in association with a positive blood culture. In addition to death, we defined permanent sequelae as limb amputation, skin loss requiring grafting for repair, or persistent neurologic abnormalities. We did not include hearing loss in our definition of permanent sequelae because audiologic data were often missing from the medical records.

DATA COLLECTION

Data were collected by 4 of us (V.J.W., R.M., S.H.I., and N.K.) by the use of structured data sheets. During several group meetings, the investigators discussed how data were to be collected. Data from most patients had been

Continued on next page
collected and entered onto a computerized database for a previous study.12 The current study hypothesis, however, was developed before the analysis of the data. One investigator (N.K.) reviewed the data collection and entry for all patients to ensure accuracy.

We collected the following data from each medical record of patients with UMD: demographic information, clinical and laboratory findings documented at each of the visits (including the outpatient visit during which the diagnostic cultures were obtained), treatments, complications, and permanent sequelae.

From each record, we identified whether the child received antibiotics at the outpatient visit (Abx group) or not (No Abx). The type and route of antibiotic administration (eg, oral or parenteral) were also recorded. Patients in the Abx group may have received antibiotics by the oral, intramuscular, or intravenous route at the time of the outpatient visit. Because our hypothesis was that antibiotic administration at the time of the outpatient visit would improve outcome of UMD, patients who did not receive a dose of antibiotics at the outpatient visit but who were given a prescription for antibiotics were classified in the No Abx group in the primary analysis. This classification was also justified in that, by only reviewing the medical record, we could not determine reliably whether patients who were given a prescription actually took the prescribed antibiotics. In addition, we could not determine how much time had elapsed between the outpatient visits, when the blood cultures were obtained, and the administration of antibiotics for this group of patients. In a subanalysis, however, patients receiving a dose of antibiotics or a prescription for antibiotics at the outpatient visit were included in the Abx group.

We compared the following 2 outcome variables between patients with UMD in the Abx and No Abx groups: development of complications and permanent sequelae.

STATISTICS

Sample Size Considerations

The database covered approximately 15 years at the 7 participating institutions, beyond which time medical record and microbiology data were limited at several of the institutions. We planned to address issues of sample size and power by evaluating the confidence intervals (CI) for the effect size.14,15 If the differences between groups were not found to be statistically significant, we planned to evaluate the 95% CI for the differences in outcomes between patient groups. Specifically, we sought to determine whether a clinically important difference between groups could be excluded before concluding that there were no differences between groups.

Data Analysis

We compared patient groups with regard to baseline clinical and laboratory findings and outcome variables. Continuous variables were analyzed using the t test, and categorical variables were compared using the Fisher exact test. A multiple logistic regression analysis was performed to assess the effect of antibiotic treatment after adjusting for known (absolute neutrophil count [ANC] and platelet count)12 and empirical (time to subsequent visit) risk factors for disease severity. All tests were performed based on 2-tailed alternatives. P < .05 was considered to be significant, and values from .05 to .10 to represent a trend. All statistical analyses were performed using STATA statistical software, version 5.0.16

In this study, we compared the outcomes of patients with unsuspected meningococcal disease who were treated with antibiotics at the time of the outpatient visit with patients who did not receive such treatment. Complications of UMD were significantly less likely to develop in patients who received antibiotics, even after adjustment for other factors known to be associated with adverse outcome in meningococcal disease. Given the infrequency of death or permanent sequelae in our study population, however, there were wide CIs for the effect of antibiotics on these particular outcomes. Therefore, we were not able to demonstrate a significant difference in the frequency of death or permanent sequelae between groups or to exclude the possibility of clinically important differences between groups with regard to these outcomes.

Table 1. Comparison of Initial Outpatient Diagnoses of Patients With Unsuspected Meningococcal Disease

<table>
<thead>
<tr>
<th></th>
<th>Abx Group (n = 19)</th>
<th>No Abx Group (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URI or viral syndrome</td>
<td>3 (16)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>10 (53)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (10)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Fever alone</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Other†</td>
<td>1 (5)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Not documented</td>
<td>3 (16)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

* Treatment groups are described in the “Data Collection” subsection of the “Patients and Methods” section. The No Abx group includes 17 patients who received a prescription for oral antibiotics but did not receive a dose of antibiotics administered at the time of the outpatient evaluation. URI indicates upper respiratory tract infection.
† Includes conjunctivitis (1 patient in each group), gastroenteritis, (2 patients), pharyngitis (1 patient), and febrile seizure (1 patient).
There have been several previous case series of patients with UMD. In one report, 3 patients with UMD were described, all of whom received antibiotics at the outpatient visit and recovered uneventfully. A second study also described 3 children with UMD treated as outpatients with oral antibiotics. These patients were later hospitalized, but complications of meningococcal disease did not develop. In a case series of 12 patients with UMD undergoing evaluation and treatment as outpatients, a trend suggesting improved survival in patients treated with antibiotics as outpatients was noted. No fatality occurred among the 8 patients who received antibiotic therapy; in contrast, 2 of 4 patients who were sent home without antibiotics died. Other studies of unsuspected bacteremia have reported the sporadic occurrence of UMD, but have not focused specifically on this type of bacteremia.

The major finding of our study is that complications are less likely to develop in patients who receive empirical outpatient antibiotic therapy for UMD than in patients who do not receive antibiotics. We were unable to demonstrate a significant reduction in the frequency of death or permanent sequelae, however, possibly because of the infrequency of these outcomes. To demonstrate statistical significance between a 7.7% frequency of death or permanent sequelae in patients not receiving antibiotics and less than a 0.1% frequency in treated patients (ie, the rates observed in this study), would require approximately 125 patients with UMD in each group (assuming a power of 80% and an α of .05). Because of the rarity of UMD, such a study would be difficult to conduct, even retrospec-

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### Table 2. Comparison of Initial Clinical Characteristics of Patients With Unsuspected Meningococcal Disease*

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Abx Group (n = 19)</th>
<th>No Abx Group (n = 39)</th>
<th>Difference Between Means or Percentages (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), mo</td>
<td>8.7 (5.5)</td>
<td>27.2 (49)</td>
<td>18.5 (2.3 to 34.5)</td>
</tr>
<tr>
<td>No. (%) aged &lt;24 mo</td>
<td>19 (100)</td>
<td>32 (82)</td>
<td>18.0 (6 to 32)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>16 (84)</td>
<td>23 (59)</td>
<td>25.0 (3 to 48)</td>
</tr>
<tr>
<td>Temperature, mean (SD), °C†</td>
<td>40.0 (0.9)</td>
<td>39.9 (0.9)</td>
<td>0.1 (−0.3 to 0.7)</td>
</tr>
<tr>
<td>WBC, mean (SD), ×10³/L</td>
<td>15.3 (7.1)</td>
<td>14.1 (4.9)</td>
<td>1.2 (−2.2 to 4.5)</td>
</tr>
<tr>
<td>No. (%) with WBC &lt;5.0 ×10³/L‡</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>3 (−9 to 15)</td>
</tr>
<tr>
<td>ANC, mean (SD), ×10³/L</td>
<td>10.8 (6.7)</td>
<td>9.2 (3.5)</td>
<td>1.6 (−2.0 to 5.1)</td>
</tr>
<tr>
<td>No. (%) with ANC &lt;3.0 ×10³/L§</td>
<td>1 (6)</td>
<td>0</td>
<td>6 (−5 to 16)</td>
</tr>
<tr>
<td>Platelet count, mean (SD), ×10³/L</td>
<td></td>
<td>381 (127)</td>
<td>389 (145)</td>
</tr>
<tr>
<td>No. (%) with platelets &lt;150.0 ×10³/L</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Treatment groups are described in the “Data Collection” subsection of the “Patients and Methods” section and Table 1. CI indicates confidence interval; WBC, white blood cell count; ANC, absolute neutrophil count; and ellipses, not applicable.
† Measured in 54 of 58 patients.
‡ Measured in 54 of 58 patients.
§ Measured in 49 of 58 patients.
|| Measured in 53 of 58 patients.

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### Table 3. Comparison of Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) of Patients</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>7 (37)</td>
<td>27 (69)</td>
<td>0.26 (0.08-0.81)</td>
<td>.03</td>
<td>0.16 (0.03-0.99)</td>
</tr>
<tr>
<td>Death or permanent sequelae</td>
<td>0</td>
<td>3 (8)</td>
<td>0 (0-2.61)</td>
<td>.54</td>
<td><strong>...</strong></td>
</tr>
</tbody>
</table>

* Treatment groups are described in the “Data Collection” subsection of the “Patients and Methods” section and Table 1. OR indicates odds ratio; ellipses, not applicable.
† Adjusted for absolute neutrophil count, platelet count, and time until subsequent visit in a multiple logistic regression analysis. We were unable to perform this analysis for death or permanent sequelae as the outcome, since no patient treated with antibiotics had these outcomes.

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*Graph: Frequency of complications in patients with unsuspected meningococcal disease who received (Abx group) and did not receive (No Abx group) antibiotics at the time of the outpatient visit.*

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tively. It is of interest to note that 5 of 22 patients who received no empirical antibiotic therapy and no prescription for antibiotics had spontaneous clearance of bacteremia and survived without development of any complications or permanent sequelae (data not shown). Spontaneous clearing of bacteremia in patients with UMD has been reported previously. 

There are other potential limitations to this study. As this was a retrospective study, we could not determine with certainty the clinical appearance of each patient at the time of the outpatient visit. All patients, however, were discharged home from their outpatient visits, and thus were unlikely to have a clinically toxic appearance at that time. In addition, we controlled for several known and potential markers of severity of meningococcal disease in the multivariate analysis, which did not change the results. A low ANC and platelet count have been shown to be associated with an increased risk of adverse outcome in meningococcal disease. We also controlled for time to subsequent visit, a possible marker for more severe illness. Other markers of severity (eg, blood pressure, coagulopathy) could not be addressed, as these measurements are obtained infrequently at the outpatient visit of a nontoxic-appearing febrile child. Other potential confounders, including type of antibiotic regimen, may exist but are difficult to determine.

We could not evaluate differences in outcomes of children receiving different antibiotic regimens because of the small number of patients in each treatment group. A difference in the efficacy of oral vs parenteral antibiotic therapy in children with UMD may in fact exist. It is also uncertain to what extent patients were compliant with outpatient oral antibiotic therapy and whether this could have affected our results. For this reason, in our primary analysis, we classified patients who only received a prescription for antibiotics in the No Abx group. This may have biased our study against an effect of empirical outpatient antibiotic therapy, as some patients in the No Abx group likely received some antibiotics before the follow-up visit. Our results, however, did not differ when we included patients who were given a prescription for antibiotics with the Abx group. The results of both analyses support the hypothesis that the administration of antibiotics for UMD is associated with fewer complications.

To our knowledge, this is the first study to describe an association between empirical antibiotic therapy in the outpatient setting and a decrease in complications due to UMD. Despite the fact that our data suggest this association, the practical implications of our study are somewhat limited. At present there are no reliable clinical or laboratory tests that allow for the rapid identification of UMD. In a previous study, we demonstrated that the complete peripheral blood cell count does not reliably distinguish patients with UMD from young febrile children with negative blood cultures, despite the fact that band counts are higher in patients with UMD. Because of the rarity of UMD, a strategy advocating the use of empirical antibiotic therapy in all febrile children is not warranted. Empirical outpatient antibiotics, however, can be considered in the settings of higher probability of UMD. These include selected outpatients during meningococcal epidemics, patients exposed to an index case with proven or suspected meningococcal disease, or nontoxic-appearing children with fever and petechial rashes treated as outpatients. In these limited settings, the use of empirical antibiotics to prevent complications from UMD is likely to be effective.

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