ABSTRACT. **Objective.** Acute bacterial meningitis remains an important cause of death and neurologic sequelae in African children. The clinical features of meningitis are often nonspecific and in this setting may overlap with those of malaria. Early diagnosis and appropriate antibiotic treatment are perhaps the most important steps in management, but published data suggest that fewer than half of the cases of childhood meningitis are identified at first assessment in hospitals in this region. The objective of this study was to identify clinical indicators of acute bacterial meningitis by examining components of the World Health Organization Integrated Management of Childhood Illness (IMCI) referral criteria for meningitis (lethargy, unconsciousness, inability to feed, stiff neck, or seizures) and other symptoms and signs.

**Methods.** Kilifi District Hospital, serving ~200,000 people in a rural, malaria-endemic area of the Kenyan coast, was studied. A Kenya Medical Research Institute research center is located at the hospital. All pediatric admissions aged ≥60 days between June 2001 and July 2002 were eligible.

**Results.** A total of 91 (2.0%) of 4582 admissions had meningitis, including 77 (4.0%) of 1929 of those who met the IMCI referral criteria for meningitis at admission (sensitivity: 85%; specificity: 59%). Independent indicators of the presence of meningitis were a bulging fontanel, neck stiffness, cyanosis, impaired consciousness, partial seizures, and seizures outside the febrile convulsions age range. One or more of these indicators was present in 895 (19%) of admissions, 72 (8.0%) of whom had meningitis (sensitivity: 79%; specificity: 80%). Independent indicators of the absence of meningitis were the absence of a history of fever, a history of diarrhea, and a positive malaria slide. The area under the receiver operating characteristic curve for a set of simple screening rules based on the positive indicators identified was 0.88 (95% confidence interval: 0.85–0.92).

**Conclusions.** The presence of ≥1 of a bulging fontanel, neck stiffness, cyanosis, impaired consciousness, partial seizures, and seizures outside the febrile convulsions age range is a clear indication for lumbar puncture and/or presumptive treatment. However, careful observation and reassessment may be the only practical way to identify one fifth of meningitis cases in this setting.

**METHODS**

**Location**

The study was conducted at Kilifi District Hospital, which serves a rural population of ~200,000 in a malaria-endemic area on the Kenyan coast. A Kenya Medical Research Institute research center is located at the hospital. All pediatric admissions aged ≥60 days were eligible.

**ABBRVIEATIONS.** IMCI, Integrated Management of Childhood Illness; LP, lumbar puncture; CSF, cerebrospinal fluid; PLR, positive likelihood ratio; NLR, negative likelihood ratio; ALR, adjusted likelihood ratio; ROC, receiver operating characteristic.
Clinical Methods

A standard set of clinical and laboratory data were collected on admission for all pediatric admissions from June 2001 to July 2002 and have been previously described.1,2 Clinical officers and pediatric resident physicians made the initial clinical assessment, supervised by a consultant pediatrician. Specific training was given in the recognition of standardized clinical signs. Clinical definitions used are given in Table 1.

Lumbar puncture (LP) was initially guided by the findings on admission according to a unit policy (not by the IMCI referral criteria); any signs of meningitis, impaired consciousness (delayed until neurologically stable), and/or febrile seizures (other than those regarded as a simple febrile seizures with full recovery within 1 hour). Admissions were reviewed at least daily, and an LP was subsequently performed when meningitis was then suspected. The first-line treatment for children with suspected meningitis was benzyl penicillin with chloramphenicol.10 Antibiotic treatment was subsequently guided by laboratory findings and clinical response. All treatments were given according to current World Health Organization recommendations.11

Laboratory Methods

The cerebrospinal fluid (CSF) leukocyte count was determined manually with a modified Neubauer counting chamber. A Gram-stain, latex agglutination antigen test for Haemophilus influenzae type b and Streptococcus pneumoniae (Murex Diagnostics, Dartford, United Kingdom) were performed when the CSF leukocyte count was >10 cells per μL. Glucose was assayed in CSF and a concurrent blood sample (Analox Ltd, London, United Kingdom). CSF and blood were cultured using standard techniques.12 H influenzae were not typed during this study. Meningitis was defined as a positive CSF culture or a positive CSF latex agglutination test, or bacteria seen on Gram-stain, or a CSF total leukocyte count ≥50 cells per μL. Possible meningitis was defined, in children without proven meningitis, as a CSF total leukocyte count >10 and ≤50 cells per μL.12 For malaria diagnosis, a thick and thin blood smear was stained with Giemsa and examined at ×1000 magnification.

Analysis

Those in whom an LP was not performed were classified as not having meningitis. Admissions with possible meningitis were excluded from analysis. The diagnostic value of individual clinical features was investigated by examining their positive and negative likelihood ratios (PLR and NLR) for meningitis. Variables found to have crude likelihood ratios of ≥1.5 or ≤0.67 were adjusted for the potential confounding effects of related variables in a multivariate analysis according to the method of Speigelhalter and Knill-Jones.8,13,14 Variables with adjusted likelihood ratios (ALRs) of ≥1.5 or ≤0.67 were regarded as potentially useful, independent clinical indicators. Practical screening rules incorporating the indicators identified were evaluated by calculating the area under the receiver operating characteristic (ROC) curve and identifying the point of maximum discriminatory value. Analysis was performed using STATA 8.0 (Stata Corp, College Station, TX).

RESULTS

There were 4616 admissions aged ≥60 days during the study, 999 (22%) of which had an LP. Ninety-one (2.0%) admissions had meningitis (Table 2), and 34 (0.7%) had possible meningitis. Data from admissions with possible meningitis were excluded from additional analysis, leaving 4582 admissions with a median age of 22 months (interquartile range: 11-40 months). A bacterial pathogen was cultured from CSF in 58 (64%) meningitis cases (Table 2): S pneumoniae (n = 31), H influenzae (n = 24), nontyphoid Salmonella (n = 2), and Pseudomonas aeruginosa (n = 1). There were 29 (32%) deaths in meningitis cases, representing 10% of the 281 inpatient deaths aged ≥60 days during the study.

One or more items of the simplified IMCI referral criteria for meningitis (lethargy, unconsciousness, seizures, neck stiffness) were present in 1929 (42%) of 4582 admissions, including 77 of 91 cases of meningitis (sensitivity: 85%; specificity: 59%; PLR: 2.05; NLR: 0.26). Thus, 14 (0.5%) of 2653 admissions that did not meet the IMCI referral criteria had meningitis.

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Neck stiffness or a bulging fontanel were present in 71 (1.5%) and 30 (0.6%) of admissions, respectively (Table 3), and 37 (41%) of 91 cases of meningitis had 1 of these signs. Crude likelihood ratios and ALRs suggested that these signs were independently and strongly predictive of meningitis. An abnormal conscious state (including lethargy or agitation) was found in 1312 (29%) admissions, and the crude likelihood ratios suggested potential predictive value. However, only the ALR for impaired consciousness exceeded 1.5. The ALR for a normal conscious state (0.74) did not suggest that this finding was likely to be valuable in excluding meningitis. Seizures before admission were reported in 1210 (26%) admissions. The majority of these were in children within the age range for febrile convulsions. The ALRs for seizures within the febrile convulsions age range, generalized seizures, and multiple seizures suggested that these were not likely to be useful, independent predictors of meningitis (all ALRs <1.5). There was no evidence that the absence of seizures reliably indicated the absence of meningitis. Seizures outside the febrile convulsions age range (6 months to 6 years) occurred in 147 (3.2%) admissions, 29 (20%) of whom had meningitis. In 333 (28%) of admissions with seizures, the seizures were partial, 31 (10%) of whom had meningitis. The ALRs for a history of seizures out-
side the febrile convulsions age range and partial seizures indicated that these were likely to be use-
fully predictive of meningitis.

A history of fever was given for 3902 (85%) admis-
sions (Table 4), and meningitis seemed less likely in
the absence of a history of fever. Among respiratory
symptoms and signs, only cyanosis was indepen-
dently predictive of meningitis, and no signs seemed
to predict the absence of meningitis. For signs of
poor peripheral perfusion (capillary refill, palpable
temperature gradient, pulse volume) or hypothermia
(<36°C), crude likelihood ratios were close to 1.5, but
none had an ALR ≥1.5. _Plasmodium falciparum_ malaria parasitemia was found in 2072 (45%) admis-
sions, including 16 (18%) of 91 meningitis cases. The
ALRs for a positive malaria slide and for history of
diabetes suggested that the presence of these was
associated with a lower likelihood of meningitis.

The performance of a set of practical screening
rules on the basis of the indicators identified is
shown in Table 5. The area under the ROC curve (Fig
1) for the set of rules was 0.88 (95% confidence in-
terval: 0.85–0.92). The greatest discriminatory value
was for ≥1 of a bulging fontanel, neck stiffness,
cyanosis, seizures outside the febrile convulsions age
range, partial seizures, and impaired consciousness
(sensitivity: 79%; specificity: 80%; PLR: 4.31; NLR:
0.26). The positive predictive value of this rule was
8.0%, indicating that 12 children would need to have
an LP or be presumptively treated for each case of
meningitis identified (Table 5).

**DISCUSSION**

Our aim in this study was to identify simple indi-
cators of meningitis that would be useful as a screen-
ing tool in practice rather than to produce a complex
predictive model. This was a comprehensive study of
a large number of pediatric hospital admissions. Our
findings confirm the difficulties of early recognition
of meningitis among hospital admissions in a malar-
ia-endemic area. Only 1 in 24 admissions that met the
simplified set of IMCI criteria for referral actually

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**TABLE 2.** Diagnostic Criteria for Meningitis and Bacterial Species Detected

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Age &lt;1 y</th>
<th>Age 1–4 y</th>
<th>Age ≥5 y</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>9</td>
<td>10</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Nontyphoidal salmonella</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Latex antigen test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Gram-stain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CSF pleocytosis or CSF/blood glucose ratio</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>21*</td>
</tr>
</tbody>
</table>

* Four (19%) of 21 had a positive blood culture: _S. pneumoniae_ (n = 2), _Escherichia coli_ (n = 1), nontyphoidal salmonella (n = 1).

**TABLE 3.** Likelihood Ratios for Meningitis of Neurologic Symptoms and Signs

<table>
<thead>
<tr>
<th>No Meningitis</th>
<th>Meningitis</th>
<th>Crude Likelihood Ratio</th>
<th>ALR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck stiffness</td>
<td>Absent</td>
<td>4446</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Bulging fontanelle</td>
<td>Absent</td>
<td>4472</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Conscious level</td>
<td>Normal</td>
<td>3245</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Lethargic</td>
<td>603</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Agitated</td>
<td>145</td>
<td>6</td>
</tr>
<tr>
<td>Impaired conciousness</td>
<td></td>
<td>498</td>
<td>48</td>
</tr>
<tr>
<td>Inability to feed</td>
<td>Absent</td>
<td>3998</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>493</td>
<td>46</td>
</tr>
<tr>
<td>History of seizures</td>
<td>None</td>
<td>3338</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Seizures within febrile convulsions age range</td>
<td>1035</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Seizures outside febrile convulsions age range</td>
<td>118</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>No seizures</td>
<td>3338</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>≥3 seizures in 24 h</td>
<td>842</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>311</td>
<td>20</td>
<td>3.17</td>
</tr>
<tr>
<td></td>
<td>No seizures</td>
<td>3338</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Generalized seizures</td>
<td>851</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Partial seizures</td>
<td>302</td>
<td>31</td>
</tr>
</tbody>
</table>

— indicates that the sign was not potentially clinically useful (ALR >0.67 and <1.5).
had meningitis. The low specificity of these criteria makes them impractical for screening for meningitis at the secondary level in our setting. The “gap” between the performance of clinicians in practice (30–42% sensitivity) at the secondary level in practice and the 98% reported sensitivity of the simplified IMCI referral criteria in the Gambian study initially seems surprising. However, we found that 96% of children

<table>
<thead>
<tr>
<th>Screening Criteria</th>
<th>No. With Criteria</th>
<th>No. With Meningitis</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>NNLP/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Bulging fontanel or neck stiffness</td>
<td>90</td>
<td>37</td>
<td>41</td>
<td>98</td>
<td>41</td>
<td>99</td>
<td>2</td>
</tr>
<tr>
<td>B. Cyanosis or any of the above</td>
<td>120</td>
<td>39</td>
<td>43</td>
<td>97</td>
<td>33</td>
<td>99</td>
<td>3</td>
</tr>
<tr>
<td>C. Seizures outside 6 mo to 6 y or any of the above</td>
<td>248</td>
<td>54</td>
<td>59</td>
<td>94</td>
<td>22</td>
<td>99</td>
<td>5</td>
</tr>
<tr>
<td>D. Partial seizures or any of the above</td>
<td>524</td>
<td>65</td>
<td>71</td>
<td>88</td>
<td>12</td>
<td>99</td>
<td>8</td>
</tr>
<tr>
<td>E. Impaired consciousness or any of the above</td>
<td>895</td>
<td>72</td>
<td>79</td>
<td>80</td>
<td>8.0</td>
<td>98</td>
<td>12</td>
</tr>
<tr>
<td>F. Fever without malaria parasitemia or any of the above</td>
<td>2520</td>
<td>88</td>
<td>97</td>
<td>44</td>
<td>3.5</td>
<td>98</td>
<td>29</td>
</tr>
<tr>
<td>G. IMCI referral criteria: neck stiffness, lethargy, impaired consciousness, or seizures</td>
<td>1852</td>
<td>77</td>
<td>85</td>
<td>59</td>
<td>4.2</td>
<td>98</td>
<td>24</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value; NNLP/T, number needed to LP or treat to identify 1 meningitis case.
Our findings now need prospective external validation. Sensitivity (eg, up to 97%) is possible but only at the expense of an unacceptable loss of specificity. ROC curve illustrates that additional improvements could be identified at the first assessment without performing an excessive number of LPs (specificity: 80%). Although this is considerably better than the 30% to 42% of cases currently identified at the first assessment at hospitals, these simple indicators still fail to identify 1 in 5 cases at first assessment. The ROC curve illustrates that additional improvements in sensitivity (eg, up to 97%) are possible but only at the expense of an unacceptable loss of specificity. Our findings now need prospective external validation, ideally in both malaria-endemic and nonendemic areas.

There are 2 main potential weaknesses inherent in this and other, similar studies. Both concern the difficulty in defining a “gold standard” for the diagnosis of bacterial meningitis. First, CSF culture is highly specific but lacks sensitivity, especially when antimicrobials have been given. When culture is negative, “possible” or “probable” cases are typically defined by CSF leukocyte count and/or CSF/blood glucose ratio. However, pleocytosis may be caused by aseptic meningitis, viral meningitis, or possibly even prolonged convulsions. Furthermore, proven bacterial meningitis may present with clear CSF and a low CSF leukocyte count. One approach is to analyze only CSF culture–positive meningitis cases versus no meningitis. However, we delayed LP when there was impaired consciousness or other contraindications to immediate LP and when meningitis was suspected later during the admission. Because antibiotics may render the CSF culture negative in these cases, the analysis would clearly be biased were only culture-positive cases included. We chose to use cutoffs for the CSF leukocyte count and CSF/blood glucose ratio that we had previously determined to be strongly associated with culture-proven bacterial meningitis. However, the diagnosis in culture-negative cases and “possible” cases is not absolutely clearcut. The set of predictive signs identified would not have been substantially different were all “possible” cases included in the analysis or if we had chosen a higher threshold for CSF pleocytosis, such as 200 cells per μL, for example.

The second weakness is the assumption that children who die without receiving an LP do not have meningitis. If cases were missed in this way, then there would be the potential for circularity: the final model might simply reflect the policy or perceived indications for LP, and sensitivity would be overestimated. We performed an LP in 22% of pediatric admissions during this study. We had previously developed a clinical policy with a low threshold for performing an LP because of our increasing concern about the difficulty of recognizing meningitis. The introduction of this policy was associated with an increase in the proportion of admissions who had an LP and an increase in the number of cases of bacterial meningitis detected. We think that our LP policy considerably reduced the chances that cases of meningitis were missed during the study. However, 183 (65%) of 281 children who died did not receive an LP. In the Gambian study of IMCI signs, 15% of children who presented with suspected invasive bacterial infection had an LP, and similarly 66% of those who died did not have an LP done. At our hospital, as elsewhere in sub-Saharan Africa, postmortem examination or LP is not usually done because of cultural considerations. However, these data are needed for a comprehensive picture of meningitis in the region.

Our results are likely to reflect the local etiology of bacterial meningitis and our location in a malaria-endemic area. The most common causes of bacterial meningitis were *S pneumoniae* and *H influenzae*. These principal bacterial causes are in keeping with reports of endemic meningitis in much of sub-Saharan Africa. Disease caused by *Neisseria meningitidis* is rare at our hospital, and a nonblanching rash was not seen during this study. In areas where meningococcal disease is prevalent, a nonblanching rash will almost certainly be of diagnostic value. *H influenzae* type b conjugate vaccine was started in the district during the study. With adequate coverage, a fall in invasive disease caused by *H influenzae* is expected, and this may alter the pattern of predictive clinical signs. However, currently, the vast majority of African children are not immunized against the principal bacterial causes of meningitis.

We were reassured that the predictive clinical
signs that emerged from our analysis are those that might be expected. Signs such as a bulging fontanel are clearly age dependent, but the NLRs suggested that absence of this sign was as unhelpful in excluding meningitis in infants <1 year old as it was in older children for anatomic reasons. We did not find evidence that generalized seizures in children without major indicators were more strongly predictive of meningitis in children aged between 6 months and 1 year than in children >1 year old. We therefore did not construct models on the basis of subgroup analysis by age. We found no evidence that signs compatible with lower respiratory tract infection influenced the chances of meningitis, as has been reported elsewhere. In a study of Nigerian infants who were <6 months old, 41% of meningitis cases were reported to have a coexisting lower respiratory tract infection. In our cohort, we found that 20% of admissions with seizures outside the febrile convulsions age range were associated with 3 (0.5%) of 570 cases of meningitis (2 cases were 14 months old and 1 was 16 months old). Despite a much higher incidence of childhood bacterial meningitis in sub-Saharan Africa,1,2,7 this proportion seems remarkably similar to that reported in recent European reviews.9,20 Our data therefore suggest a similar conclusion to those reviews: that routine LP or empirical treatment for meningitis after an apparently uncomplicated febrile convulsion alone, without the presence of other indicators, is unjustified. A lack of independent association between meningitis and seizures per se within the age range for febrile convulsions in hospitalized children has also been reported from children in Papua New Guinea.15 Notably, we found that 20% of admissions with seizures outside the age range for febrile convulsions and 10% of children with partial seizures had meningitis.

The aim of early diagnosis of acute bacterial meningitis is a reduction in death and neurologic sequelae by timely administration of appropriate antibiotic therapy and appropriate supportive care. The first-line treatment of acute bacterial meningitis in most of the developing world is intravenous penicillin with chloramphenicol because of their low cost. However, increasing antimicrobial resistance of H influenzae and S pneumoniae challenges the first-line use of penicillin with chloramphenicol in this setting.7,20 If third-generation cephalosporins become the standard of care for empirical treatment of meningitis in the developing world, then improvements in early diagnosis at the secondary level would be needed to be able to reap the benefits. Because the majority of admissions with signs compatible with meningitis in this setting do not actually have meningitis, early diagnosis would reduce the use of a costly treatment in these children. There is no consensus on what constitutes a sufficient risk of having meningitis to justify LP or presumptive treatment, but we would regard a risk of 1 in 12 as sufficient given the consequences of delayed or missed diagnosis in this setting.

The clinical features of malaria include fever, impaired consciousness, partial seizures, subtle seizures, and opisthotonus, which can mimic meningism.9 Reliable clinical differentiation from meningitis therefore is impossible. Our approach is initially to treat all cases with clinical signs compatible with severe malaria with parenteral antimalarials, stopping when either the first 3 malaria slides are found to be negative or when full treatment is complete. Similarly, when clinical criteria for meningitis are met but LP is delayed, full meningitis treatment is given until results of LP are available. Thus, children are commonly initially treated for both conditions until each has independently been ruled out or fully treated.

In many secondary health facilities in sub-Saharan Africa, severely ill children are initially assessed and treated by resident physicians or clinical assistants without adequate clinical or laboratory support and often with little postbasic pediatric training. Straightforward guidelines therefore are essential. We think that applying a set of minimum criteria for LP at admission would lead to reductions in diagnostic delay, missed cases of meningitis, and unnecessary treatment. Questions remain regarding the safety of LP in children with impaired consciousness without cranial computed tomography, and additional studies are needed in this respect. Our data suggest that a bulging fontanel, neck stiffness, cyanosis, seizures outside the febrile convulsions age range, partial seizures, and impaired consciousness should be absolute indications for LP and/or presumptive treatment for meningitis at admission. However, careful clinical observation and a low threshold for subsequent LP may be the only practical way to identify one fifth of cases of acute bacterial meningitis in this setting.

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J.A.B. designed the study, participated in patient care, and did the statistical analysis. A.C.V. participated in study design and analysis. I.M. participated in study design and patient care. B.S.L. was responsible for laboratory analysis and study design. C.R.J.C.N. participated in study design, supervised clinical care, and guided the analysis and is guarantor. J.A.B. and C.R.J.C.N. wrote the initial manuscript, and all authors contributed to the final version. All members of the Kenya Medical Research Institute medical, nursing, laboratory, and computing team participated in patient care, data collection, and data storage.

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