A Prospective Comparison of Malaria with Other Severe Diseases in African Children: Prognosis and Optimization of Management

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The burden of malaria in regions of high endemicity frequently overwhelms hospitals’ capacity to provide effective care. A rapid, simple method of identifying children who are at highest risk is vital to reduce mortality among hospitalized children. Multiple regression analysis identified prognostic variables predicting mortality in severely ill children admitted to a Ghanaian teaching hospital. These variables were compared in children with and without malaria. A total of 1492 (90.2%) of 1654 severely ill children referred for assessment had evaluable outcomes. Low Blantyre coma score (BCS), high blood lactate level, and high body mass index were independent predictors of mortality among children with malaria (area under the receiver operating characteristic curve [AUC/ROC], 0.84). In children without malaria, BCS and lactate level also predicted mortality, but the addition of respiratory distress and hematocrit improved the model (AUC/ROC, 0.77). Predictors of mortality in children with malaria differ from those for other severe illnesses and reflect differences in underlying pathophysiological processes.

Infection with Plasmodium falciparum afflicts ~400 million individuals and kills 1 million children annually [1]. In sub-Saharan Africa, more than one-half of the beds in pediatric wards may be occupied by children with severe malaria. This burden of ill children frequently overwhelms available diagnostic and treatment resources, which highlights the need for effective methods to triage disease severity in children.

Severe malaria has a case-fatality rate of 10%–20%. Most children who die of malaria do so ≤24 h after hospital admission [2]. Many recent studies have identified risk factors for death due to malaria. These prognostic variables include coma [3], hypoglycemia [4, 5], hyperlactatemia [6–8], metabolic acidosis [9], respiratory distress [10], repeated convulsions [11], hyperparasitemia (with anemia) [3], and malaria pigment in leukocytes [12]. Despite these improvements in understanding the pathophysiology of severe malaria, no interventional studies have succeeded in reducing the mortality rate. Indeed, several adjunctive interventions, including the use of steroids [13], anticonvulsants [14], anti-TNF monoclonal antibodies [15], and desferrioxamine [16], are all associated with increased morbidity or mortality. Furthermore, no class of antimalarial is

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clearly superior to another [17, 18], and established chloroquine resistance now significantly limits the choice of treatment for severe malaria in Africa [19].

In recent years, we have investigated dichloroacetate (DCA) treatment of lactic acidosis in malaria in phase 2 studies. Our objective here was to evaluate the prognostic importance of lactic acidosis in malaria and in other severe nonmalarial illness by comparison of prognostic variables, to identify potentially treatable pathophysiologi cal processes associated specifically with malaria.

**METHODS**

**Study site and team.** The institutional review boards of the University of Florida (Gainesville) and the University of Science and Technology (Kumasi, Ghana) approved this study, which was conducted at the Komfo-Anokye Teaching Hospital (KATH; Kumasi). KATH is the only government teaching hospital in Kumasi, a city of 1 million inhabitants. There are ~7600 pediatric admissions per year to KATH. Many of these children are extremely ill and travel long distances before hospital admission. From June 1997 through April 1999, all children admitted to the Department of Child Health were referred to the study team if the admitting physician diagnosed a severe febrile illness that was clinically suspected to be malaria. The following features were common: fever, coma, convulsions, prostration, and anemia. The team screening children comprised 1 full-time doctor, 6 part-time doctors, and 2 part-time laboratory technologists. A small number (n = 124) of children who were screened and were found to have malaria and hyperlactatemia (blood lactate level, ≥5 mmol/L) were referred for inclusion in a randomized, controlled trial evaluating DCA for the treatment of lactic acidosis [20].

**Clinical evaluation of severe disease.** The study team evaluated a sick child within 15 min after referral, and medical history and examination findings were recorded on a 1-page pro forma sheet. Respiratory distress was defined as the presence of any of the following conditions: alar flaring, chest recession (intercostal or subcostal), the use of the accessory muscles, or abnormally deep breathing [10]. Impaired consciousness was defined as a Blantyre coma score (BCS) of ≤4 at the time of assessment, and coma was defined as a BCS of ≤2 at the time of assessment. A CSF examination was performed for all children who had prolonged coma (≥30 min) or a convulsion, provided that there were no contraindications.

**Laboratory analyses.** We obtained 0.2 mL of whole capillary or venous blood, which was placed on ice and assayed within 15 min for detection of parasitemia and determination of hematocrit, lactate level, and glucose concentration. Malaria was defined as the presence of >2 asexual stages of *P. falciparum* on a thick blood film for a child for whom other diagnoses had been excluded by history, clinical examination, and simple laboratory investigations. Thick and thin blood films were prepared with Field’s stain. Peripheral parasitemia was expressed as the number of parasites per cubic millimeter and was normalized to 200 WBCs or 1000 erythrocytes for thick and thin films, respectively, as described elsewhere [5]. Hematocrit was measured using a microhematocrit centrifuge (Hawksley). Blood and CSF glucose and lactate values were measured with a YSI 2300 analyzer (YSI). Venous blood gas measurements were performed on an AVL blood gas analyzer (AVL) for a small proportion of the children who were admitted to a sub-study of lactic acidosis.

**Treatment of patients.** Outcomes (death or discharge) were monitored by the study team. Admitting physicians were responsible for treating most children according to local standards of care on general pediatric wards. There were 3 pediatric wards, with ~40 children in each. Each ward was staffed by a team of up to 5 doctors and 4 nurses during the day. At night, 1 resident physician would attend all 3 wards, each of which was staffed by 1 nurse. There were no facilities for mechanically assisted ventilatory support for children. This study did not include standardized care for all children who were screened. In general, meningitis was treated with intravenous chloramphenicol and benzylpenicillin, and pneumonia was treated with intravenous ampicillin.

Children with severe malaria were treated with quinine dihydrochloride (20 mg/kg im single loading dose, followed by 10 mg/kg im b.i.d.), as described elsewhere. Complications of malaria were managed in a standard manner [21].

**Statistical analyses.** Descriptive statistics are given as the mean ± SD and range or the proportion of responses. The major variables examined are shown in table 1. Univariate and multivariate logistic regression was used to generate predictive models of survival as a function of the clinical variables noted at the time of screening. Logistic regression modeling was stratified by the results of slides (positive vs. negative).

The area under the receiver operator characteristics curve (AUC/ROC) was used as a summary measure of the predictive value of each variable individually, as well as for the multivariate models. The values for AUC/ROC range from 0.5 (connoting no predictive value) to 1 (connoting perfect diagnostic accuracy). In general, a value for AUC/ROC of 0.8–0.9 indicates moderate diagnostic accuracy, whereas a value for AUC/ROC of 0.9–1.0 implies very good diagnostic accuracy. First, univariate analyses were performed to determine which individual variables generated the highest AUC/ROC value. Variables were then added to the model in a forward selection type procedure, starting with those with the largest AUC/ROC value. Successive variables were then added to the model if they increased the
Table 1. Baseline characteristics of children admitted to a study of the prognosis and optimization of management of malaria.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 1654)</th>
<th>Slide-positive patients (n = 854)</th>
<th>Slide-negative patients (n = 800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, months</td>
<td>37.7 ± 28.4</td>
<td>38.0 ± 26.0</td>
<td>37.4 ± 30.1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>12.1 ± 4.9</td>
<td>12.3 ± 4.7</td>
<td>12.0 ± 5.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>90.5 ± 17.2</td>
<td>91.1 ± 16.4</td>
<td>89.9 ± 18.0</td>
</tr>
<tr>
<td>BMI</td>
<td>14.6 ± 3.1</td>
<td>14.6 ± 2.6</td>
<td>14.7 ± 3.6</td>
</tr>
<tr>
<td>Female sex, % of patients</td>
<td>44</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.8 ± 1.2</td>
<td>37.9 ± 1.1</td>
<td>37.8 ± 1.2</td>
</tr>
<tr>
<td>Pulse, beats/min</td>
<td>141 ± 26</td>
<td>144 ± 25</td>
<td>137 ± 27</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>66.7 ± 12.8</td>
<td>65.8 ± 12.7</td>
<td>65.5 ± 12.8</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>44 ± 14</td>
<td>45 ± 14</td>
<td>43 ± 14</td>
</tr>
<tr>
<td>BCS of ≤2, % of patients</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Respiratory distress, % of patients</td>
<td>28</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>25.6 ± 8.7</td>
<td>24.6 ± 7.9</td>
<td>26.6 ± 9.4</td>
</tr>
<tr>
<td>Glucose level, mmol/L</td>
<td>6.2 ± 3.7</td>
<td>6.1 ± 3.5</td>
<td>6.3 ± 4.0</td>
</tr>
<tr>
<td>Hypoglycemia, % of patients</td>
<td>4.3</td>
<td>4.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Lactate level, mmol/L</td>
<td>3.4 ± 3.1</td>
<td>3.7 ± 3.0</td>
<td>3.1 ± 3.1</td>
</tr>
<tr>
<td>CSF lactate level, mmol/L</td>
<td>3.09 ± 3.1</td>
<td>3.6 ± 2.0</td>
<td>4.2 ± 4.1</td>
</tr>
<tr>
<td>Geometric mean parasite level, parasites/μL (IQR)</td>
<td>NA</td>
<td>24,700 (6300–201,000)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE. Data are mean ± SD, unless otherwise indicated. BCS, Blantyre coma score; BMI, body mass index; IQR, interquartile range; NA, not available.

a Blood glucose level, <2.2 mmol/L.
b Data are for 182 patients.
c Data are for 105 patients.
d Data are for 77 patients.

AUC/ROC value by ≥5%. Similar modeling techniques were used to examine predictors for slide-positive versus slide-negative individuals, as well as for the complications of hyperlactatemia and respiratory distress. ORs were calculated from the various logistic models to quantify the effect of each clinical indicator.

RESULTS

From June 1997 through April 1999, 14,668 children were admitted to 3 pediatric wards. There were 903 deaths (6.16%) in this population, which included patients with severe and immediately recognized medical conditions, such as diarrheal diseases and measles. The admitting physicians suspected that 1654 (11.3%) of these children had malaria and referred them to the study team (figure 1).

Outcome. Table 1 summarizes the admission characteristics of 854 children (51.6%) who had malaria and 800 children (48.4%) who did not. Information on outcome (survival or death) was available for 1492 patients (90.2%). The case-fatality rate for all-cause hospital mortality was 8.5% (127 of 1492 patients); it was 6.0% (48 of 794 patients) for the *P. falciparum* slide–positive patients and 11.3% (79 of 698 patients) for the slide-negative patients. The most common clinical diagnoses for children who had negative blood film results were bacterial meningitis, pneumonia, and sickle cell disease.

Clinical and prognostic features. To determine the prognostic significance of clinical and laboratory indices, we performed a univariate analysis of all variables listed in table 1. Data were modeled using logistic regression for the outcome variable of survival. The analysis was performed separately for slide-positive and slide-negative patients (table 2). The regression model predicted mortality in children who were slide positive (AUC/ROC, 0.84) and in those who were slide negative (AUC/ROC, 0.77). Variables predicting mortality in slide-positive children were BCS, hyperlactatemia, and, less importantly, body mass index. In slide-negative children, the variables were BCS, respiratory distress, hematocrit, and hyperlactatemia.
Malaria: Prognostic Indicators

Figure 1. Profile of subjects in a study of prognosis and optimization of management of malaria.

When only hyperlactatemia and impaired consciousness (BCS, ≤4) were used to predict outcome in children with malaria, the combined sensitivity was 91% and the specificity was 52%. Figure 2A illustrates the association of impaired consciousness and hyperlactatemia with mortality in evaluable slide-positive subjects. Hyperlactatemia and respiratory distress were associated in univariate analysis (OR, 3.8; 95% CI, 2.7–5.3).

Figure 2B shows the associations between mortality and hyperlactatemia, respiratory distress, and impaired consciousness for slide-negative children. The combined sensitivity and specificity of those variables were 82% and 53%, respectively.

Comparison of slide-positive and slide-negative patients. To examine differences in presentation of malaria and other severe illnesses, we modelled clinical and laboratory variables to determine which ones were independently associated with positive slide results. The most strongly associated variable was the whole capillary or venous blood lactate level measured at the time of screening (AUC/ROC, 0.610). Mean blood lactate levels were higher in patients who had malaria (3.7 ± 3 mmol/L) than in those who did not (3.1 ± 3.1 mmol/L), even though the case-fatality rate was higher among slide-negative individuals. Furthermore, there was a much stronger relationship between the CSF and blood lactate levels in children with malaria (n = 105; r = 0.66; P = .0001) than in those without malaria (n = 77; r = 0.24; P = .038) (figure 3). The CSF lactate level predicted mortality in both patient groups; the OR for each 1-mmol/L increase in the CSF lactate level was 5.71 (P = .025) for children who had malaria and 13.0 (P = .0003) for children who did not.

Blood lactate findings. Because hyperlactatemia was an important independent prognostic variable, we examined models to identify factors associated with hyperlactatemia. The findings were similar for slide-positive and slide-negative patients. In both categories, BCS and hematocrit predicted hyperlactatemia, although predictability was greater in slide-negative patients (AUC/ROC, 0.81 vs. 0.72).

Respiratory distress. Twenty-eight percent of patients with malaria and a similar proportion without malaria had respiratory distress, a clinical variable previously identified as predictive of mortality [10]. Age, pulse, BCS, and severe anemia were all associated with respiratory distress in both slide-positive and slide-negative patients. Using these variables, the logistic regression models we constructed were equally good at predicting respiratory distress in both patient groups (for slide-positive patients, the AUC/ROC was 0.80; for slide-negative patients, the AUC/ROC was 0.79).

Acid-base status. Venous blood gases were measured in 83 children, all of whom had hyperlactatemia. The mean venous blood partial pressure of oxygen, partial pressure of carbon dioxide, and pH of this group were 8.3 ± 4.0 kPa, 3.8 ± 1.0 kPa, and 7.29 ± 0.13, respectively. A blood lactate measurement was repeated at the time that venous blood gases were measured (usually 30–60 min after the initial blood screening), and the mean blood lactate level was 7.2 ± 3.2 mmol/L. There was a borderline association between severe acidemia (pH, <7.3) and hyperlactatemia (n = 83; P = .052).

Table 2. Model of outcome for both slide-negative and slide-positive patients.

<table>
<thead>
<tr>
<th>Patient group, variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slide-positive patients</strong></td>
<td></td>
</tr>
<tr>
<td>Blantyre coma score</td>
<td>0.56 (0.46–0.68)</td>
</tr>
<tr>
<td>Hyperlactatemia</td>
<td>3.97 (2.06–7.65)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.003 (1.001–1.005)</td>
</tr>
<tr>
<td><strong>Slide-negative patients</strong></td>
<td></td>
</tr>
<tr>
<td>Blantyre coma score</td>
<td>0.75 (0.65–0.87)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>0.32 (0.18–0.58)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>1.06 (1.03–1.10)</td>
</tr>
<tr>
<td>Hyperlactatemia</td>
<td>3.40 (1.76–6.57)</td>
</tr>
</tbody>
</table>

a Area under the receiver operator characteristic curve for model overall, 0.843.

b Lactate level, ≥5 mmol/L.

c Area under the receiver operating characteristic curve for model overall, 0.772.
Figure 2.  A, Venn diagram showing numbers of and mortality rates among 742 slide-positive children. The variables hyperlactatemia and impaired consciousness are included. B, Venn diagram showing numbers of and mortality rates among 658 slide-negative children. The variables hyperlactatemia, impaired consciousness, and respiratory distress are included. Case-fatality rates are shown in parentheses.
DISCUSSION

In Africa, most deaths due to severe childhood illness occur in areas where appropriate health care is poorly resourced [1]. The number of severely ill children admitted to hospitals often overwhelms personnel working in wards with low ratios of staff to children, which makes it impossible to monitor all patients carefully [1]. Therefore, simple and quick triage of children is vital.

Expert panels have emphasized the importance of triage in the integrated treatment of hospitalized African children [22, 23]. These have been formalized into expert guidelines that rely only on clinical assessment, such as the emergency triage assessment and treatment protocol [24]. Methods for rapid diagnosis of malaria are underused and can easily be incorporated into management algorithms for sick children [25]. Recent advances in “near-patient” tests allow confirmation of malaria diagnosis and assessment of the metabolic status of patients and of severity of anemia within 15 min after patient referral [25]. These technologies may be particularly valuable when used in conjunction with standardized protocols for patient management. A recent study of patients with sepsis syndrome confirmed that mortality can be reduced significantly (by ~30%) by rapid triage and diagnostic maneuvers (including measurement of mixed venous saturation) and management with standardized protocols [26], although these findings do not necessarily apply directly to children with malaria.

We prospectively compared variables prognostic for mortality in children with and without malaria. These variables, and presumably their underlying pathophysiological bases, differ between slide-positive and slide-negative patients. This highlights the usefulness of a malaria film in the assessment of children with severe illness in Africa.

An important finding of this study is that only 2 variables, hyperlactatemia and the depth of coma, are needed to predict mortality in childhood malaria, (AUC/ROC, >0.8; sensitivity, 91%; specificity, 52%). Furthermore, only hyperlactatemia is an objective marker of death. We did not find respiratory distress to be an independent risk factor in this population, although, in the absence of an assay for determination of blood lactate levels, it may still be a useful clinical indicator of severity of malaria. Respiratory distress, impaired consciousness, and severe anemia (hematocrit, <15%) were previously identified as predictors of mortality (with sensitivity of 84%) in Kenyan children with malaria [10]. In our study, the combined sensitivity and specificity of these 3 variables are 85% and 54%, respectively, in children with malaria; this confirms the utility of these measurements for children living in areas with different transmission rates of malaria. If the absence of hyperlactatemia and impaired consciousness are used to identify less severely ill children so that staff time can be concentrated on more severely ill children with malaria, then 1 of every 100 children in the “low risk” category would die (given a negative predictive

![Figure 3. Relationship between CSF and blood lactate levels. Slide-positive patients are indicated by circles and slide-negative patients by squares. Deaths are indicated by filled symbols.](image-url)
value of 99% and assuming a case-fatality rate of 6%). In contrast, if the absence of respiratory distress, impaired consciousness, and severe anemia were used to identify children as being at “low risk” for death, 2 of every 100 children would be wrongly identified as being at low risk (given a negative predictive value of 98%). Some definitions of coma suggest that assessment of a child should take place at least half an hour after a convolution occurs or after receipt of anticonvulsants [27]. We have adopted a simpler procedure and determine a child’s consciousness level at the time of screening for malaria. In these circumstances, the BCS is a better predictor of outcome than are attempts to differentiate between children who have impaired consciousness (BCS, ≤4) or unrousable coma (BCS, ≤2) from those who do not.

To our knowledge, this study is the most powerful one to have shown that hyperlactatemia and coma are the most useful prognostic indicators in severe malaria in African children [6–8]. It goes further than other studies and identifies additional prognostic markers in non–slide-positive patients. Different underlying processes are clearly contributing, either quantitatively or qualitatively, to clinical and biochemical markers of disease severity in patients with malaria, compared with other diseases. Lactate level at hospital admission are significantly higher in slide-positive patients, and hyperlactatemia is strongly associated with the clinical marker of respiratory distress. In contrast, respiratory distress, in addition to hyperlactatemia, identifies severely ill children with slide-negative cases, perhaps because children with primary pneumonic processes are included in this category.

There is a striking difference between slide-positive and slide-negative individuals in the relationship between plasma and CSF lactate levels. In children with cerebral malaria, lactate turnover is positively correlated with time to recovery from coma and with plasma lactate level [28]. Our results are consistent with the hypothesis that microvascular hypoxia, because of sequestration of infected erythrocytes, underlies the 2 prognostically useful variables of impaired consciousness and lactic acidosis [2].

Hyperlactatemia is a well-recognized prognostic variable in many conditions and influences management decisions in some, such as liver failure [29]. We suggest that assessment of blood lactate levels is one of the most useful maneuvers for stratifying the risk of fatality objectively in sick children.

A major public health challenge for the next few years is to reduce mortality associated with severe childhood infections, of which malaria is among the most common. This goal is more likely to be achieved by implementing straightforward screening and triage methods. The triage paradigm reported here is robust and is adaptable to hospital settings found commonly in sub-Saharan Africa.

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References


