Point-of-Care Measurement of Blood Lactate in Children Admitted With Febrile Illness to an African District Hospital

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Background. Lactic acidosis is a consistent predictor of mortality owing to severe infectious disease, but its detection in low-income settings is limited to the clinical sign of "deep breathing" because of the lack of accessible technology for its measurement. We evaluated the use of a point-of-care (POC) diagnostic device for blood lactate measurement to assess the severity of illness in children admitted to a district hospital in Tanzania.

Methods. Children between the ages of 2 months and 13 years with a history of fever were enrolled in the study during a period of 1 year. A full clinical history and examination were undertaken, and blood was collected for culture, microscopy, complete blood cell count, and POC measurement of blood lactate and glucose.

Results. The study included 3248 children, of whom 164 (5.0%) died; 45 (27.4%) of these had raised levels of blood lactate (>5 mmol/L) but no deep breathing. Compared with mortality in children with lactate levels of ≤3 mmol/L, the unadjusted odds of dying were 1.6 (95% confidence interval [CI], 0.8–3.0), 3.4 (95% CI, 1.5–7.5), and 8.9 (95% CI, 4.7–16.8) in children with blood lactate levels of 3.1–5.0, 5.1–8.0, or >8.0 mmol/L, respectively. The prevalence of raised lactate levels (>5 mmol/L) was greater in children with malaria than in children with nonmalarial febrile illness (P < .001) although the associated mortality was greater in slide-negative children.

Conclusions. POC lactate measurement can contribute to the assessment of children admitted to hospital with febrile illness and can also create an opportunity for more hospitals in resource-poor settings to participate in clinical trials of interventions to reduce mortality associated with hyperlactatemia.

Metabolic acidosis, predominantly associated with hyperlactatemia, is a common manifestation of severe infection. This is particularly pronounced in malaria; up to a third of all childhood deaths caused by malaria occur in association with metabolic acidosis [1–3]. The 2006 World Health Organization (WHO) definition of severe malaria includes “malaria with respiratory distress,” and this was updated in 2010 to include “deep breathing, respiratory distress (acidotic breathing) or hyperlactataemia (>5.0 mmol/L) or metabolic acidosis (plasma bicarbonate <15 mmol/L)” [4, 5].

The detailed pathogenesis of acidosis associated with infection is not well understood and may differ between malaria and bacterial disease [6]. Metabolic acidosis in children with malaria has been found in association with severe anemia, hypoglycemia, altered consciousness, and fluid and electrolyte disturbance [7–10]. In addition Day et al found evidence that renal and hepatic dysfunction may be contributory causes in adults with severe malaria [11].

Identifying acidosis in hospitalized children in Africa is important to assess the risk of a fatal outcome and may contribute to clinical decisions on the use of oxygen, antibiotics, blood, and possibly other fluids. However, laboratory measures of acidosis are rarely available in resource-poor settings owing to the cost of a blood gas analyzer or other laboratory equipment [12].
The clinical sign of “abnormally deep breathing” has been shown in a specialist unit to reliably detect severe metabolic acidosis (defined as a base deficit of $>12$ mmol/L) [13], but the sign is based on subjective judgment, and high levels of interobserver variation have been documented among nonphysician clinicians assessing children admitted to African district hospitals [14, 15]. In addition, the high mortality associated with malaria complicated by respiratory distress suggests that children with deep breathing may represent the tip of an “acidosis iceberg,” and a more sensitive test might detect lesser degrees of acidosis that may still be associated with substantial mortality.

Hand-held point-of-care (POC) lactate meters to monitor athletic fitness have been in use for a number of years, and a study in Uganda found that a POC measure of lactate in predominantly human immunodeficiency virus (HIV)–infected adults effectively identified patients at risk of dying [16]. Although POC lactate meters have been used in a few African hospitals to assess children with severe malaria, as far as we are aware only one study has so far reported on the results [3], and no study has yet reported on their use in nonmalarial febrile illness in hospitalized children.

In this study we have analyzed data from a 1-year study of children admitted to a district hospital in an area of intense transmission of *Plasmodium falciparum* in northeastern Tanzania, where a POC device to measure blood lactate (Lactate-Pro) was used for all children admitted with a febrile illness. We used the results to assess the association between hyperlactatemia and mortality in children with and without malaria and suggest how POC lactate results could contribute to clinical decision making.

**METHODS**

**Study Site and Data Collection**

The study was conducted in a district hospital in northeastern Tanzania serving a predominantly rural population with childhood mortality that is typical for Tanzania (165 deaths/1000 person-years for children <5 years of age) [17]. The area is highly endemic for *P. falciparum* malaria.

Data were collected as part of a study of the cause of febrile illness in children admitted to the pediatric ward, and further details are published elsewhere [18]. Over the course of 1 year, all daytime pediatric admissions were screened for inclusion, and children were eligible if aged 2 months to 13 years with a history of fever within the previous 48 hours or axillary temperature $\geq 37.5^\circ C$. Children with chronic illness (except HIV infection or malnutrition) and those admitted with trauma or for a surgical condition were excluded.

After consent procedures, a standard clinical history and examination were recorded by a study clinician using WHO guidelines [19]. Pulse oximetry was used on a finger or toe, and height and weight were measured. Venous blood was obtained for POC tests of hemoglobin concentration, blood glucose (Hemocue; Anglholm), blood lactate (Lactate-Pro; Arkray). In addition, an i-STAT (Abbott Laboratories) hand-held biochemical analyzer with EC8+ cartridges was used to measure serum electrolytes and bicarbonate in a subset of children with severe malaria enrolled toward the end of the study. Blood was sent to the laboratory for full blood cell count (Act/Dif; Beckman-Coulter), and aerobic blood culture (BactAlert; Biomerieux) was undertaken with identification of organisms by standard means, as described elsewhere [18]. All POC measures were performed according to manufacturers’ manuals of operation. Blood slides were stained with Giemsa and independently double read, with discordant results resolved by a third reader. Lactate-Pro was purchased on the open market in 2005; the meter cost €315, and test strips €1.90 each.

**Data Management and Analysis**

Data were scanned using Teleforms (Verity software) into MS-Access software (Microsoft) and analyzed using Stata-10 software (Stata Version 10). Severe malaria was defined as the presence of *P. falciparum* asexual parasitemia and any of the following: hemoglobin level $<5g/dL$, Blantyre coma scale score $<4$, blood glucose level $<2.5$ mmol/L, deep “acidotic” breathing, blood lactate level $>5.0$ mmol/L, jaundice, $\geq 2$ convulsions in the previous 24 hours, or prostration (inability to sit up or, if $<8$ months of age, inability to drink) [5].

Raised lactate levels were defined as levels $>5.0$ mmol/L, and metabolic acidosis as plasma bicarbonate levels $<15$ mmol/L. We assessed the sensitivity and specificity of other clinical signs and symptoms for raised lactate levels. We showed the correlation between lactate (Lactate-Pro) and plasma bicarbonate (i-STAT) measurements in a subset of children with simultaneous measures of both. Logistic regression models were used to show crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between raised lactate levels and clinical features on admission.

Logistic regression was used to explore factors that predict mortality by showing crude and adjusted ORs and 95% CIs for associations between admission characteristics of children and subsequent death. We used the receiver operating characteristics from the logistic regression to plot the sensitivity and specificity for mortality of blood lactate measurements by themselves and as part of a model of factors significantly associated with mortality.

**Ethics**

The study was approved by the Ethics Committees of the National Institute for Medical Research, Tanzania (NIMR/HQ/...
RESULTS

During the 1-year study, 3639 children were enrolled, 3248 (89.3%) of whom had a record of lactate measurement and were included in this analysis; 2299 (70.8%) were 12 months old, and 1749 (53.8%) were male.

Clinical and Laboratory Features Associated With Raised Blood Lactate Levels

Overall, there were 164 (5.0%) deaths among the 3248 children in the study, and the risk of mortality increased with increasing levels of lactate (Figure 1); 429 children (13.2%) had serum lactate levels >5 mmol/L, and 92 (21.4%) of them died, compared with a mortality of 72 of 2819 (2.6%) among the children with lactate levels ≤5 mmol/L. Thus, 92 of 164 deaths (56.1%) in the study occurred in the 429 children with serum lactate levels >5 mmol/L. Raised lactate levels were more common in children who had positive blood slide results for *P. falciparum* infection (OR, 2.9; *P* < .001), whereas in those with raised levels, the associated mortality was higher in children with nonmalarial illness (OR, 3.08; *P* < .001); raised lactate levels were found in 338 of 1921 slide-positive children (17.6%), 57 (16.9%) of whom died, compared with 91 of 1327 slide-negative children (6.9%), 35 (38.5%) of whom died.

Of the 92 children with raised lactate levels who died, 47 (51.1%) had the clinical sign of “deep breathing,” compared with only 17 (24%) of the 72 children without raised lactate levels who died; using a raised lactate level (>5 mmol/L) as a reference standard for acidosis, the presence of deep breathing had a sensitivity of 28.2% (95% CI, 26.7%–29.8%), a specificity of 96.5% (95% CI, 95.9%–97.1%), a positive predictive value of 55.0% (95% CI, 53.3%–56.7%), and a negative predictive value of 89.8% (95% CI, 88.8%–90.9%). The correlation coefficient for 115 simultaneous lactate (Lactate-Pro) and bicarbonate (i-STAT) readings was −0.62. Using a reference standard of acidosis, defined as a plasma bicarbonate level <15 mmol/L, raised lactate levels (>5.0 mmol/L) had a sensitivity of 73.6% (95% CI,
Table 1. Logistic Regression Model of Clinical and Laboratory Factors Associated With Blood Lactate Levels >5.0 mmol/L in 3211 Children

<table>
<thead>
<tr>
<th>Factor</th>
<th>Children, no.</th>
<th>Unadjusted odds</th>
<th>Adjusted oddsa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>With lactate &gt;5 mmol/L (%)</td>
<td>OR (95% CI) P</td>
</tr>
<tr>
<td>Age, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–11 (baseline group)</td>
<td>936</td>
<td>147 (16)</td>
<td>1</td>
</tr>
<tr>
<td>12–59</td>
<td>1999</td>
<td>255 (13)</td>
<td>0.78 (0.63–0.98) 0.048</td>
</tr>
<tr>
<td>≥60</td>
<td>276</td>
<td>16 (6)</td>
<td>0.33 (0.19–0.56) &lt;.001</td>
</tr>
<tr>
<td>P. falciparum, no./μL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None seen (baseline)</td>
<td>1317</td>
<td>89 (7)</td>
<td>1</td>
</tr>
<tr>
<td>1–4999</td>
<td>359</td>
<td>39 (11)</td>
<td>1.68 (1.13–2.50) 0.015</td>
</tr>
<tr>
<td>5000–50 000</td>
<td>786</td>
<td>102 (13)</td>
<td>2.06 (1.53–2.78) &lt;.001</td>
</tr>
<tr>
<td>&gt;50 000</td>
<td>749</td>
<td>188 (25)</td>
<td>4.62 (3.53–6.06) &lt;.001</td>
</tr>
<tr>
<td>Invasive bacterial diseaseb</td>
<td>316</td>
<td>55 (17)</td>
<td>1.47 (1.08–2.01) 0.01</td>
</tr>
<tr>
<td>Hemoglobin &lt;5 g/dL</td>
<td>483</td>
<td>198 (41)</td>
<td>7.92 (6.31–9.95) &lt;.001</td>
</tr>
<tr>
<td>Oxygen saturation &lt;90%</td>
<td>70</td>
<td>25 (36)</td>
<td>3.88 (2.36–6.41) &lt;.001</td>
</tr>
<tr>
<td>Blood glucose &lt;2.5 mmol/L</td>
<td>103</td>
<td>53 (52)</td>
<td>7.97 (5.33–11.90) &lt;.001</td>
</tr>
<tr>
<td>Severe malnutritionc</td>
<td>99</td>
<td>15 (15)</td>
<td>1.20 (0.69–2.10) .562</td>
</tr>
<tr>
<td>Shockd</td>
<td>835</td>
<td>182 (22)</td>
<td>2.53 (2.04–3.13) &lt;.001</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>213</td>
<td>115 (54)</td>
<td>10.44 (7.78–14.0) &lt;.001</td>
</tr>
</tbody>
</table>

**NOTE.**Thirty-seven children were excluded from this analysis owing to missing data on oxygen saturation (n = 34) or deep breathing (n = 3). CI, confidence interval; OR, odds ratio; P. falciparum, Plasmodium falciparum.

a Adjusted for age, P. falciparum density, invasive bacterial disease, hemoglobin level, oxygen saturation, blood glucose level, severe malnutrition, shock, and deep breathing.

b Bacterial pathogen isolated from blood or cerebrospinal fluid.

c Weight-for-height Z score ≤3 or visible severe wasting.

d Limb-core palpable temperature gradient, capillary refill >3 seconds, or heart rate >180 beats/min.

65.5–81.6) and a specificity of 71.0% (95% CI, 62.7–79.3) for detecting decreased plasma bicarbonate.

Detailed clinical and laboratory factors associated with raised lactate levels are shown in Table 1. Raised lactate levels were associated with clinical indicators of poor perfusion (“shock”), reduced tissue oxygenation (hypoxia or severe anemia), and lack of peripheral glucose (malnutrition or hypoglycemia) (Table 1).

The association between raised lactate levels and mortality differed for children aged <12 months and those aged ≥12 months (Tables 2 and 3), with an interaction between the 2 age groups (P = .04). Although higher lactate measurements were still significantly associated with death in younger children, a stronger association was seen in older children. For both older and younger children, after adjustment for other predictors of mortality, raised lactate levels remained a better predictor than shock or severe anemia.

**Determining the Appropriate Cutoff for Raised Lactate Levels**

The sensitivity and specificity of lactate levels >5.0 mmol/L for predicting mortality in children aged ≥12 months were 64% and 90%, respectively (Figure 2). Figure 2 shows the predicted probability of mortality from a logistic regression model including age, P. falciparum infection, invasive bacterial disease, severe anemia, altered consciousness, severe malnutrition (weight-for-height Z score, ≤3), hypoglycemia, lactate and deep breathing, which improved the sensitivity to 86% while keeping the specificity for mortality at 90% (Figure 2). The best performance in the prediction of mortality is seen when both the sensitivity and specificity are ~86% (when the predicted probability of death in these children was 2.8%). In the absence of other factors in the model, a lactate level of 6 mmol/L would predict 86% of deaths with 86% specificity, but if we do not know whether a child has or does not have any other risk factor for mortality, then a lactate level of 2.8 mmol/L would predict 86% of deaths but with a specificity of 65%.

**Potential for POC Lactate Measure to Guide Treatment and/or Nursing Care**

At least 1 of the WHO criteria for severe malaria was present at admission in 78 of 83 children (93.1%) who died of malaria and 57 (73.1%) of these children had a raised lactate level. The most common qualifying criteria for severe malaria were hemoglobin levels <5 g/dL (344/724 [47.5%]), followed by blood lactate levels >5.0 mmol/L (338/724 [46.7%]) and “prostration” (270/724 [37.3%]). Ninety-one of 724 children (12.5%) had the common qualifying criteria for severe malaria were hemoglobin levels <5 g/dL (344/724 [47.5%]), followed by blood lactate levels >5.0 mmol/L (338/724 [46.7%]) and “prostration” (270/724 [37.3%]). Ninety-one of 724 children (12.5%) had the
To illustrate the contribution of lactate results to predicting mortality among children with nonmalarial illness, we assessed the association between raised lactate levels and severity of pneumonia. Children with a cough or breathing difficulty and raised respiratory rate for age meet WHO criteria for nonsevere pneumonia, and the addition of “low chest wall indrawing” defines the criteria for severe pneumonia. Among children with nonsevere pneumonia, 9 of 335 (2.7%) had raised lactate levels, and these included 2 of 8 (25.0%) of the children with nonsevere pneumonia who died. By contrast, in children with severe pneumonia, 50 of 323 (15.5%) had raised lactate levels, as did 27 of 51 (52.9%) of the children who died of severe pneumonia.

Table 3. Logistic Regression Model of Clinical and Laboratory Factors Associated With Mortality Among 2299 Children Aged ≥12 Months

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of children (n = 2299)</th>
<th>No. (%) of deaths (n = 69)</th>
<th>Unadjusted odds</th>
<th>Adjusted odds*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12–59 (baseline)</td>
<td>2022</td>
<td>82 (4.1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥60</td>
<td>277</td>
<td>13 (4.7)</td>
<td>1.17 (0.64–2.12)</td>
<td>.6</td>
</tr>
<tr>
<td>P. falciparum positive</td>
<td>1494</td>
<td>60 (4.0)</td>
<td>0.92 (0.60–1.41)</td>
<td>.6</td>
</tr>
<tr>
<td>Invasive bacterial disease</td>
<td>208</td>
<td>30 (14.4)</td>
<td>5.25 (3.32–8.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>351</td>
<td>26 (7.4)</td>
<td>2.18 (1.37–3.47)</td>
<td>.001</td>
</tr>
<tr>
<td>Shock</td>
<td>516</td>
<td>41 (8.0)</td>
<td>2.76 (1.82–4.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>215</td>
<td>62 (28.8)</td>
<td>25.19 (16.01–39.62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe malnutrition</td>
<td>76</td>
<td>11 (14.5)</td>
<td>4.31 (2.19–8.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>91</td>
<td>35 (38.5)</td>
<td>22.38 (13.65–36.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3.0 (baseline)</td>
<td>1517</td>
<td>17 (1.1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3.1–5.0</td>
<td>482</td>
<td>17 (3.5)</td>
<td>3.23 (1.63–6.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5.1–8.0</td>
<td>173</td>
<td>20 (11.6)</td>
<td>11.53 (5.92–22.49)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥8.1</td>
<td>127</td>
<td>41 (32.3)</td>
<td>42.07 (22.95–77.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Deep breathingb</td>
<td>140</td>
<td>38 (27.1)</td>
<td>13.73 (8.70–21.66)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; OR, odds ratio; P. falciparum, Plasmodium falciparum.

* Adjusted for density of P. falciparum parasites, severe anemia, shock, altered consciousness, severe malnutrition, hypoglycemia, deep breathing, and lactate measurements.

b Two values were missing for deep breathing.

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DISCUSSION

The results demonstrate that a POC measure of blood lactate (Lactate-Pro) was strongly predictive of mortality in children with severe febrile illness. In children with WHO criteria of severe malaria, almost three-quarters of those with fatal cases had a raised lactate level on admission, although 90 of 100 of these had other features of severe malaria. In children with nonmalarial illness, standard criteria defining severity do not include raised lactate levels, but more than half of the deaths associated with severe pneumonia did occur in children with this finding.

Our findings, similarly to those of Newton et al, suggest that the large majority of malaria fatalities can be identified on admission by a high standard of clinical assessment as is available in research centers [3]. Unfortunately, this standard is rarely reached in routine practice [20, 21], and, although the use of POC devices should not be used as an alternative to clinical examination, they can encourage and complement routine clinical assessments. In addition, the feasibility of lactate measurement in these settings is greatly enhanced by the availability of a low-cost POC device. A similar case can be made for the use of other POC devices for measurement of hemoglobin, oxygen saturation, acute-phase proteins, and blood glucose, although rigorous assessment of their contribution to care requires some level of randomization, a requirement that raises complex ethical and logistic challenges.

Although it was not possible to validate Lactate-Pro or i-STAT results against a laboratory-based reference standard, the 2 measures were reasonably well correlated with each other, and this is consistent with findings of another study that compared 4 POC lactate meters [22]. More importantly, blood lactate values at admission strongly predicted mortality, which is also consistent with findings of other studies [1, 7]. Use of the clinical sign of deep breathing identified a group of children at high risk of death, but almost half of the children who died with a raised lactate level were judged not to have abnormally deep breathing at admission. Conversely, a smaller number of children were judged to be positive for deep breathing but with a normal blood lactate level, a finding that could be due to nonlactic acidosis, poor specificity of the sign, or interobserver variability in the detection of deep breathing, which has been described elsewhere [14, 15].

The study explored the use of a POC measure of lactate in children admitted for both malaria and nonmalarial febrile illness. Raised blood lactate levels were more strongly associated with malaria than invasive bacterial disease, and this may relate to the pathophysiology of malaria, which includes a number of processes known to result in tissue hypoxia (eg, parasite sequestration) or hypoglycemia, resulting in altered cellular metabolism [8]. The results of multiple logistic regression suggested that the association between malaria and lactic acidosis persisted after allowance for the contribution of the other clinical and laboratory measures included in the model. This suggests additional factors causing raised lactate levels for which this study had no direct measure. Parasite sequestration in small blood vessels could be one such factor, and this interpretation is consistent with the finding that increasing blood lactate values were associated with increasing *P. falciparum* parasite densities. For nonmalarial illness, the clinical and laboratory factors included in the model fully explained the association between bacterial infection and raised lactate levels. Studies with more detailed measures of acidosis and tissue respiration are better suited to explore these associations.

The study identified increased odds of death for children with blood lactate levels at the higher end of the “normal” range (by WHO standards), compared with those with levels at the low
end of that range. The analysis of sensitivity and specificity identified the most efficient cutoff defining raised lactate levels (ie the cutoff that resulted in the optimum combination of sensitivity and specificity) to be below the 5.0 mmol/L currently recommended by WHO. Given lack of evidence on the cost and efficacy of treatment, however, the current cutoff seems appropriate [8, 23, 24].

Limitations of this study include the lack of comparison with laboratory measures of blood lactate and the inclusion of only one POC lactate test on admission to the ward. In addition, a comparison of clinical outcomes under conditions in which POC lactate results were and were not available is required to fully assess their contribution to care.

In conclusion, the findings of this study demonstrate that the use of lactate meters creates possibilities for improved clinical assessment of severely ill children. In addition, POC measurement of lactate provides an opportunity for pragmatic clinical trials for the treatment of acidosis. In particular, the indications for the use of blood, fluids, and antibiotics could all be modified by the availability of POC lactate measurement, resulting in improved use of these basic interventions to reduce mortality in severely ill children.

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References