Randomized Trial of Volume Expansion with Albumin or Saline in Children with Severe Malaria: Preliminary Evidence of Albumin Benefit

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Background. Metabolic acidosis is the best predictor of death in children with severe falciparum malaria; however, its treatment presents a therapeutic dilemma, because acidosis and hypovolemia may coexist with coma, which can be associated with elevated intracranial pressure. We postulated that volume resuscitation with albumin might correct acidosis and hypovolemia with a lower risk of precipitating cerebral edema than crystalloid. In an open-label, randomized, controlled trial, we compared the safety of resuscitation with albumin to saline in Kenyan children with severe malaria.

Methods. We randomly assigned children with severe malaria and metabolic acidosis (base deficit, >8 mmol/L) to receive fluid resuscitation with either 4.5% albumin or normal saline. A control (maintenance only) group was only included for patients with a base deficit of <15 mmol/L. The primary outcome measure was the percentage reduction in base deficit at 8 h. Secondary end points included death, the requirement for rescue therapies, and neurological sequelae in survivors.

Results. Of 150 children recruited for the trial, 61 received saline, 56 received albumin, and 33 served as control subjects. There was no significant difference in the resolution of acidosis between the groups; however, the mortality rate was significantly lower among patients who received albumin (3.6% [2 of 56 patients]) than among those who received saline (18% [11 of 61]; relative risk, 5.5; 95% confidence interval, 1.2–24.8; \( P = .013 \)).

Conclusions. In high-risk children with severe malaria and acidosis, fluid resuscitation with albumin may reduce mortality. Our study design did not enable us to determine whether saline administration is preferable to fluid restriction or whether saline administration is actually hazardous. Further studies are needed to confirm our findings before definitive treatment recommendations can be made.

More than 1 million children die of falciparum malaria each year in sub-Saharan Africa [1]. Although general reductions in this death toll might be expected to follow improvements in both prevention and access to effective treatment [2], case-fatality rates for children who develop severe malaria remain in excess of 20% [3]. Most of these deaths occur soon after admission to the hospital, before patients can receive the full therapeutic benefits of antimalarial drugs [4]. Reductions in mortality are therefore likely to depend on supportive therapies targeted at correcting the underlying pathophysiology.

For many decades, it was commonly believed that the main cause of death in children with severe malaria was cerebral malaria, which is clinically defined by impaired consciousness [5]. More recently, however, there has been increasing recognition that acidosis is a better predictor of death in African children than is coma or neurological impairment alone [6–9]. For example, in our hospital, case-fatality rates for children with both cerebral malaria and acidosis are 32%–41%, compared with only 12% for children with cerebral malaria alone [8, 10]. These rates are comparable with rates reported for similar case series from other health care centers [6, 7]. Management strategies targeted at the cause of acidosis in such children might therefore improve outcome. A number of therapies have been investigated.
with this aim, including use of sodium bicarbonate [3], dichloroacetate (an inducer of pyruvate dehydrogenase) [11], and N-acetylcystine [12]. Many have lead to resolution of acidosis but not to reductions in the mortality rate. In critically ill children, the most common cause of metabolic acidosis worldwide is shock caused by hypovolemia [13, 14]. The rapid correction of shock by volume expansion is central to the management of virtually all other causes of childhood acidosis in modern intensive care settings [14] and would be the logical treatment for children with severe malaria if hypovolemia were etiologically important.

We have recently shown that hypovolemia is common in critically ill children with malaria-related acidosis [15]; how it should be treated, however, presents a therapeutic dilemma. If elevated intracranial pressure is the major cause of death in children with cerebral malaria [16, 17], then rapid volume expansion (which would be the usual treatment for acidosis due to volume depletion) may aggravate intracranial hypertension, precipitate cerebral edema, and increase the risk of cerebral herniation. This concern has led to the development of treatment protocols in some health care centers that include relative fluid restriction. Conversely, if impaired organ perfusion (including perfusion of the brain) is an important factor in the etiology of both acidosis and neurological dysfunction, then volume expansion would both correct acidosis and improve brain function. We reasoned that, because of its particular biological properties [18], human albumin solution might be a more suitable resuscitation fluid than normal saline for these children. By simultaneously increasing colloidal osmotic pressure and expanding intravascular volume, albumin therapy might reduce the risk of both cerebral and pulmonary edema. In the case of cerebral malaria, for which loss of endothelial integrity has been demonstrated [19, 20], albumin may also act as a neuroprotective therapy through its beneficial role in reducing microvascular permeability. To test this hypothesis, we conducted a randomized, controlled trial comparing volume expansion with use of either normal saline or 4.5% human albumin solution in critically ill children with severe malaria associated with acidosis.

**PATIENTS, MATERIALS, AND METHODS**

**Study design and treatment protocol.** The study was conducted at the pediatric high-dependency unit at the Kenya Medical Research Institute, Kilifi District Hospital, Kenya. Malaria is endemic in Kilifi District, where falciparum parasitemia is present in >30% of children in the community and complicates 46% of hospital admissions. Children were eligible for inclusion in the study if they presented with all of the following entry criteria: a clinical feature of severe malaria (i.e., prostration, coma, or respiratory distress), *Plasmodium falciparum* parasitemia, metabolic acidosis with a base deficit of >8 mmol/L, and a hemoglobin concentration of >50 g/L. Children with any of the following characteristics were excluded: pulmonary edema (defined below), edematous malnutrition, papilledema, or parental refusal of consent. Patients who presented with clinical features of severe malaria and who required immediate resuscitation were randomized to receive treatments, after parental consent was provided, without waiting for laboratory results; however, such patients were subsequently withdrawn from the study if the clinical diagnosis was not subsequently confirmed. The study was approved by the Kenya national ethical review committee and the research ethics committee of Imperial College (St. Mary’s Hospital, London, UK) and was conducted from May 2002 through August 2003.

Eligible patients were randomly assigned to receive 20 mL/kg of either 4.5% human albumin solution (Bio Products Laboratory) or 0.9% saline or to be a control subject if the base deficit at presentation was 8–15 mmol/L (i.e., moderate acidosis), or they were assigned to receive 40 mL/kg of either 4.5% albumin or 0.9% saline if the base deficit was >15 mmol/L (i.e., severe acidosis). On the basis of the results of a pilot study [15], both the trial committee and external reviewers felt that withholding resuscitation fluids would be unacceptable for children with severe acidosis. Random allocation was assigned by the use of sealed cards, and study interventions were not masked. The interventions were received as single boluses infused over the first hour. Additional boluses were prescribed after the first hour for children who fulfilled the criteria for rescue therapy. Study children were otherwise treated in accordance with our standard treatment protocol, which includes intravenous quinine, maintenance fluid (4% dextrose/0.18% saline at a rate of 4 mL/kg/h), face mask oxygen (if oxygen saturation decreased to <95%), rectal acetaminophen to control fever, and potassium supplements (if the plasma potassium level was <3.5 mmol/L) [21]. Hypoglycemia and seizures were treated per protocol [22].

On the basis of previous observations at our unit, the expected mortality rate for children entering the study was in the range of 15% [23] to 41% [8, 10]. As a result, we anticipated that close monitoring would identify a number of children who would develop life-threatening complications, for whom it would be unethical to withhold appropriate interventions. Development of the following conditions in some children with cerebral malaria was agreed a priori as an indication for the use of “rescue therapies”: (1) hypotension (systolic blood pressure of <70 mm Hg or of <80 mm Hg in children >1 year of age), (2) sustained oliguria (urine output of <1 mL/kg/h), (3) worsening metabolic acidosis (development of severe acidosis [base deficit, >15 mmol/L] in the moderate acidosis group or worsening [increase of ≥20%] or refractory acidosis in the severe acidosis group), (4) pulmonary edema, or (5) acute neurological deterioration suggestive of elevated intracranial pressure. Pulmonary edema was clinically defined as bilateral fine crepitations in association with sus-
tained hypoxia (oxygen saturation, <95%), and elevated intracranial pressure was defined as either a systolic blood pressure in the >90th percentile for age in association with a decreasing heart rate, papilledema, or brain stem features of coning [16]. Children who developed hypotension, oliguria, or worsening acidosis received boluses of 20 mL/kg of normal saline until perfusion was restored. Children in whom acidemia (pH, <7.2) was refractory to volume expansion received partial correction with an infusion of sodium bicarbonate. Clinical features suggestive of pulmonary edema or of elevated intracranial pressure were treated with furosemide or mannitol, respectively.

**Monitoring and event identification.** Children were continuously monitored for blood pressure, electrocardiography findings, respiratory rate, oxygen saturation, and core temperature using a Siemens SC 7000 multichannel recorder. In addition, study children were regularly monitored for conscious level (using the Blantyre Coma Score [BCS] [24]), pupillary size and reactivity, and the presence of focal neurological signs, seizures, and abnormal posturing. Blood gas levels, plasma biochemistry findings, and hematologic findings were assessed at 4, 8, 12, 24, and 48 h after study admission. Blood and urine samples were cultured at the time of study admission for all children, and a delayed lumbar puncture was performed as clinically indicated [25].

**Outcome measures.** The trial was primarily designed as a phase II safety study; however, we also aimed to determine the relative benefits of study interventions. We used the percentage reduction in base deficit at 8 h as a surrogate marker of improved perfusion, as our primary outcome measure. Prospectively defined secondary outcome measures included mortality and neurological sequelae in survivors. In addition, we reasoned that the tolerability of each intervention would also be reflected by the proportion of children who attained a clinical end point that necessitated rescue therapy. Mortality was not identified as a primary end point because we did not expect that the trial would be large enough to demonstrate an effect on death, and a study designed to address that aim specifically could not be justified without preliminary safety data.

**Statistical analysis.** The trial was powered to compare the percentage reduction in base deficit at 8 h by assigned intervention, assuming a 2-sided error rate of 5% and a power of 90%. For the moderate acidosis group, we required 33 participants per treatment arm to show a difference between a 40% reduction in mean (±SD) base deficit (e.g., 13 to 7.8 ± 4 mmol/L) in the saline or albumin arms, compared with a 15% reduction (e.g., 13 to 11 ± 4 mmol/L) in the control arm. In the severe acidosis group, we required 22 participants per treatment arm to show a difference between a 40% reduction in base deficit (e.g., 20 to 12 ± 3 mmol/L) in the superior treatment group versus a 25% reduction (e.g., 20 to 15 ± 3 mmol/L) in the inferior treatment group [26].

All analyses were performed on an intention-to-treat basis. Proportions for baseline and outcome variables were compared using χ² and Fisher’s exact tests, and continuous data were compared by analysis of variance F statistic. In both the moderate acidosis and severe acidosis groups, we compared the primary and secondary outcome measures between allocated treatments. The relative safety and efficacy of saline and albumin were compared across the whole trial. We determined the OR for death in children randomized to receive saline, compared those randomized to receive albumin, with use of a Mantel-Haenszel test adjusted for baseline factors. The results
of the trial were reviewed by an independent trial-monitoring committee that oversaw the conduct of the trial and examined the case records for all deaths.

**RESULTS**

Of the 159 children randomly assigned to receive a study treatment, 61 children were allocated to receive saline, 56 to receive albumin, and 33 to receive control therapy (maintenance only). Nine children were randomized to a study treatment as emergencies but were later excluded (figure 1). The median age of the trial participants was 2.8 years (interquartile range, 1.8–3.5 years) and was similar across the treatment groups. Baseline clinical and laboratory features of the trial participants are shown in table 1. In each study group (i.e., the moderate acidosis and severe acidosis groups), there were no significant clinical differences at the time of hospital admission, although among children in the severe acidosis group, hypotension, seizures, and hypoglycemia were all slightly more common among children assigned to receive saline than among those assigned to receive albumin. In 3 children, severe malaria was complicated by bacteremia at hospital admission. Cases in 2 children randomized to receive albumin were complicated by bacteremia; in 1 child, culture grew a non-typhoidal salmonellae, and in the other, it yielded *Staphylococcus aureus*. Culture for 1 child assigned to receive saline grew a group A *Streptococcus* species. All 3 children survived. No microbiological evidence was found for either a urinary tract infection or meningitis in any study participant. Salicylate ingestion was suspected in 87 subjects, of which 73 had an un-

<table>
<thead>
<tr>
<th>Laboratory variable</th>
<th>Albumin recipients (n = 26)</th>
<th>Saline recipients (n = 25)</th>
<th>Control arm (n = 33)</th>
<th>Albumin recipients (n = 33)</th>
<th>Saline recipients (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasite count, ×10⁶ parasites/μL</td>
<td>1.5 (0.6–3.6)</td>
<td>1.6 (0.8–3.4)</td>
<td>0.6 (0.3–1.4)</td>
<td>0.3 (0.1–0.6)</td>
<td>0.7 (0.3–1.5)</td>
</tr>
<tr>
<td>Hemoglobin level, g/L</td>
<td>84 ± 4</td>
<td>72 ± 3</td>
<td>83 ± 3</td>
<td>73 ± 4</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>pH</td>
<td>7.14 ± 0.03</td>
<td>7.17 ± 0.03</td>
<td>7.27 ± 0.02</td>
<td>7.27 ± 0.02</td>
<td>7.29 ± 0.02</td>
</tr>
<tr>
<td>Base deficit, mmol/L</td>
<td>20 ± 0.8</td>
<td>20 ± 0.8</td>
<td>12.6 ± 0.5</td>
<td>13.7 ± 0.9</td>
<td>12.6 ± 0.6</td>
</tr>
<tr>
<td>Venous Pco₂, kPa</td>
<td>3.1 ± 0.3</td>
<td>3.1 ± 0.3</td>
<td>4.4 ± 0.4</td>
<td>3.6 ± 0.2</td>
<td>3.8 ± 0.2</td>
</tr>
<tr>
<td>Lactate level, mmol/L</td>
<td>6.4 ± 1.0</td>
<td>5.0 ± 0.8</td>
<td>3.9 ± 0.5</td>
<td>3.7 ± 0.4</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Sodium level, mmol/L</td>
<td>133 ± 1</td>
<td>134 ± 1</td>
<td>133 ± 2</td>
<td>135 ± 2</td>
<td>134 ± 2</td>
</tr>
<tr>
<td>Creatinine level, μmol/L</td>
<td>90 ± 7</td>
<td>99 ± 9</td>
<td>66 ± 4</td>
<td>66 ± 5</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>Potassium level, mmol/L</td>
<td>4.7 ± 1</td>
<td>4.6 ± 1</td>
<td>4.4 ± 0.2</td>
<td>4.3 ± 0.1</td>
<td>4.2 ± 0.1</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects or mean ± SEM, unless otherwise indicated. There were no significant differences for any of the variables between the interventions groups in both moderate acidosis and severe acidosis groups. AMP, abnormal motor posturing; Pco₂, partial pressure of carbon dioxide.

a Heart rate, >180 beats/min.

b Respiratory rate, >60 breaths/min.

c Oxygen saturation of <90% determined by pulse oximetry.

d Systolic blood pressure of <70 mm Hg for children aged <1 year or <80 mm Hg for those aged >1 year.

e Classified as decorticate, decerebrate, or opisthotonic posturing.

f Geometric mean parasite count (95% reference range).
recordable salicylate level; of the rest, only 4 (4.6%) had salicylate ingestion of any potential clinical significance (>10 mg/dL). Two patients had definite features of toxicity.

**Major outcome.** In the severe acidosis group, the percentage reduction in the base deficit was similar in the albumin and saline arms (F = .01; P = .93), and in the moderate acidosis group, it was similar between the albumin, saline, and control arms (F = 1.0; df = 2; P = .37) (table 2). The volumes administered as bolus and the total volume received (bolus plus maintenance) in the first 8 h were similar in the 2 intervention groups (table 2). No further fluid boluses were prescribed after 8 h, and most children continued to receive intravenous maintenance fluid (supplemented with potassium) at 4 mL/kg/h until they were able to drink.

**Tolerability of allocated treatment.** In the moderate acidosis group, the proportion of children who required rescue therapy was significantly greater in the control arm than in either the saline or albumin arms (χ² = 10.9; P = .004) (table 2). Before 8 h (the primary end point), 5 children in the control arm developed hypotension or sustained oliguria and required volume resuscitation with normal saline. In the severe acidosis group, 3 children assigned to receive saline and 4 children assigned to receive albumin required rescue therapy (P = .45) (figure 1).

**Safety.** Two children developed pulmonary edema, both of whom had been randomized to receive saline (2 [3%] of 60 children). The first child developed pulmonary edema following a whole blood transfusion 34 h after hospital admission, having been clinically stable previously. Salicylate toxicity, a known cause of pulmonary edema, was identified in the second child. The frequency of pulmonary edema secondary to intravenous fluid resuscitation was therefore 0.9% (1 of 115 children). Eight children developed signs suggestive of elevated intracranial pressure [16]; all died within 48 h after hospital admission. Seven of these children had been randomized to receive saline (4 in the severe acidosis group and 3 in the moderate acidosis group; 7 [11%] of 61 children), and 1 child (in the severe acidosis group) had been randomized to receive albumin (1 [2%] of 56; Fisher’s exact test, 5.3; df = 1; P = .02). The putative cause of death was brain swelling, but this finding remains unsubstantiated, because we did not monitor intracranial pressure or provide autopsy evidence.

**Mortality.** Mortality was significantly more common among children assigned to receive saline (11 [18%] of 61 children) than among children assigned to receive albumin (2 [3.6%] of 56; relative risk, 5.1; 95% CI, 1.2–22.8; P = .013). Most deaths occurred among children with severe acidosis (8 [31%] of 25 saline recipients vs. 2 [9%] of 23 albumin recipients; P = .06). After adjustment for baseline factors (hypotension, presence of coma, hypoglycemia, and seizures), the OR for death among children

<table>
<thead>
<tr>
<th>Outcome, group</th>
<th>Albumin recipients</th>
<th>Saline recipients</th>
<th>Control subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Status at 8 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Base deficit reduction, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with MA</td>
<td>22 (8–37)</td>
<td>24 (10–39)</td>
<td>33 (23–43)</td>
<td>.37</td>
</tr>
<tr>
<td>Patients with SA</td>
<td>35 (25–45)</td>
<td>28 (19–36)</td>
<td>...</td>
<td>.93</td>
</tr>
<tr>
<td>Rescue therapy received,* n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with MA</td>
<td>0/33</td>
<td>0/35</td>
<td>5/33 (15)</td>
<td>.004</td>
</tr>
<tr>
<td>Patients with SA</td>
<td>4/23 (17)</td>
<td>3/25 (12)</td>
<td>...</td>
<td>.45</td>
</tr>
<tr>
<td><strong>Volume received, mL/kg (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>As boluses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with MA</td>
<td>21 (18–24)</td>
<td>22 (18–26)</td>
<td>3 (0–7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients with SA</td>
<td>38 (31–45)</td>
<td>46 (39–53)</td>
<td>...</td>
<td>.06</td>
</tr>
<tr>
<td>Total volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with MA</td>
<td>45 (39–51)</td>
<td>48 (44–52)</td>
<td>35 (31–39)</td>
<td>.14</td>
</tr>
<tr>
<td>Patients with SA</td>
<td>63 (55–70)]</td>
<td>69 (62–78)</td>
<td>...</td>
<td>.19</td>
</tr>
<tr>
<td><strong>Final status, n/N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal outcome</td>
<td>2/56 (3.6)</td>
<td>11/61 (18)</td>
<td>2/33 (6)</td>
<td>.02</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>2/61 (3)</td>
<td>0</td>
<td>.35</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>1/56 (1.8)</td>
<td>9/61 (15)</td>
<td>0/33</td>
<td>.02</td>
</tr>
<tr>
<td>Neurological sequelae</td>
<td>6/54 (11)</td>
<td>3/50 (6)</td>
<td>0/31</td>
<td>.09</td>
</tr>
</tbody>
</table>

**NOTE.** There were no significant differences between the groups for the primary outcome. Statistical differences for rescue therapies and mortality are reported in the text. Control subjects included only children with moderate acidosis (MA). SA, severe acidosis.

* See “Study design and treatment protocol” in Patients, Materials, and Methods.
allocated to receive saline, compared with those allocated to receive albumin, was 8.3 (95% CI, 1.3–51.6; \( P = .007 \)). The subgroup of children who presented with coma was of particular interest, because one of our rationales for the use of albumin was that it might prevent the development of cerebral edema in children who presented with coma. Among children presenting with coma, 11 (46%) of 24 in the saline arm died, compared with only 1 (5%) of 21 in the albumin arm (relative risk, 9.6; 95% CI, 1.4–68; \( P = .002 \)). Mortality in the subgroup of children who were not comatose at hospital admission was very low in both the saline arm (0 of 37 children) and albumin arm (1 [3%] of 35) (\( P = .7 \)).

**DISCUSSION**

Before the start of this trial, the mortality rate at our hospital for children admitted with severe malarial acidosis was 24% [8], increasing to 42% [10] for cases complicated by coma. The main finding in the present study was that, for children with severe malaria complicated by either moderate or severe metabolic acidosis, rapid volume expansion with albumin appeared to be safe and resulted in a significantly lower mortality (4%) than did use of normal saline (18%). This was seen even in the absence of a superior effect of albumin on improving perfusion or reducing acidosis. Although the present study had limited power to show differences in mortality, we observed important differences in the subgroup of children with coma (a group for whom we justified the use of albumin), among whom only 1 (5%) of 21 children randomized to receive albumin died, compared with 11 (46%) of 24 children who received saline, with the latter mortality rate being similar to those in previously published studies (table 3). Among non-comatose children receiving either saline or albumin, death was rare (1 [1%] of 70), lending support for the safety of volume expansion in this group. Our previous observations of clinical features associated with hypovolemia [10, 15] in children with severe malaria and the widely held belief that acidosis in cases of critical illness reflects poor perfusion secondary to hypovolemia precluded a position of equipoise over the inclusion of a maintenance-only control group for children with severe acidosis (base deficit, >15 mmol/L) at the design stage of this study. We were therefore not able to resolve the question of whether volume expansion confers any benefit when compared to administration of maintenance fluids alone.

There are a number of scientific and practical limitations of this study. First, any trial that attempts to resolve a therapeutic dilemma resulting from 2 diametrically opposed approaches to treatment is likely to raise major ethical questions. Therefore, it was not surprising that a major difficulty in the design of the study was how to reconcile the conflicting views on what constituted an ethically acceptable and safe trial design. This resulted in a trial design that could only address the question of whether colloid was preferable to saline for volume expansion in the severely acidic patients, but the trial could not resolve the debate about whether volume expansion is preferable to fluid restriction in this group. Second, how reliable and objective is resolution of base deficit as a proxy measure of outcome? Base deficit is widely used in intensive care units to guide treatment when its resolution is used as a marker of the restoration of tissue perfusion [27, 28]. However, opinion remains divided with regard to its validity in defining recovery, because volume resuscitation with chloride-rich solutions, such as normal saline and albumin, can also potentiate base deficit.
Despite improving both perfusion and prognosis [29, 30]. Third, even though we used strict case definition to enroll persons in the studies, the results may not be generally applicable, especially because impairment of consciousness or respiratory distress may encompass a wide range of pathologies with incidental parasitemia [31]. Other considerations that had to be taken into account included the prohibitive cost of colloid solutions in African health care centers and the lack of evidence for the superiority of albumin as a resuscitation fluid. Albumin has recently been reported as clinically equivalent to saline in the intravascular volume resuscitation of a large, heterogeneous population of adult patients admitted to intensive care units [32]. Nevertheless, limited evidence was provided for a difference in mortality in 2 major subgroups: patients admitted to the hospital after trauma, in whom an increased risk of death was seen in the albumin group, and patients with sepsis, in whom albumin was associated with a reduced risk of death [32]. Consequently, albumin therapy may still prove to be beneficial in studies designed to target specific disease etiologies—for example, those that result in endothelial activation, such as sepsis or severe malaria. By generating colloid osmotic pressure and preserving microvascular integrity [33, 34], use of albumin might have superior efficacy over use of other intravenous fluids when hypovolemia coexists with increased permeability of the blood-brain barrier. In common with meningitis, recent studies involving both Vietnamese adults and Malawian children have shown that the blood–brain barrier is impaired in severe malaria, albeit mildly so [20, 35]. In this study, we have provided preliminary evidence to support the hypothesis that albumin may act as a neuroprotective therapy in children with clinically defined cerebral malaria, and it may be preferable to saline when used for resuscitation of acidic children with malaria complicated by coma. However, any inference about data for particular subgroups should be treated with caution until the results are confirmed in adequately powered studies.

This study indicates that a relatively simple targeted intervention with volume replacement may reduce the rate of mortality associated with severe malaria from >20% to <5%. If widely applicable, such an intervention could save thousands of lives each year. Because albumin is expensive and is currently unavailable in Africa, these initial results, if confirmed, would present a dilemma for doctors who treat children with severe malaria. One approach would be to recommend the use of a cheaper, licensed colloid or whole-blood transfusion, because many children are also anemic. However, the beneficial effect of albumin may result from its peculiar physiological properties, and safety concerns exist for all of the synthetic colloids that are currently available. These issues, as well as the question of whether volume expansion is preferable to the provision of maintenance fluids alone, need to be addressed definitively in large, adequately powered, multicenter studies before treatment recommendations can be made.

Acknowledgments

We are indebted to the medical, nursing, and other staff of the pediatric high-dependency unit at the Kenyatta Medical Research Institute for their dedication and hard work. We would like to thank Prof. Timothy Peto and Dr. Simon Nadel for reviewing trial conduct and for performing an independent assessment of critical and fatal events. We would like to thank the Hospital Superintendent and all the staff of Kilifi District Hospital for their participation and cooperation. This paper is published with the permission of the Director of the Kenya Medical Research Institute.

Financial support. The Wellcome Trust (grant 045194, career development fellowship 050563 [to M.E.], and senior fellowships 070114 [to C.N.] and 061702 [to K.K.]).

Potential conflicts of interest. All authors: no conflicts.

References