Perturbations in Electrolyte Levels in Kenyan Children with Severe Malaria Complicated by Acidosis

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Background. To date, information about the frequency of electrolyte disturbances among children with severe falciparum malaria is limited.

Methods. We describe changes in potassium, calcium, magnesium, and phosphate levels in 56 Kenyan children (42 who survived and 14 who died) admitted to the hospital with clinical features of severe malaria (impaired consciousness or deep breathing) complicated by acidosis (base deficit, >8 mmol/L).

Results. Mild-to-moderate hypercalcemia was common at admission, particularly among children with severe anemia. Severe hyperkalemia complicated falciparum malaria in 9 children (16%), of whom 7 (78%) died, generally soon after admission. Hypokalemia, hypomagnesemia, and hypophosphatemia were uncommon (<7% of children) at admission but developed in >30% of children within 24 h. Hypocalcemia was infrequent (<5% of children) at any time point. Apart from administration of potassium, electrolyte deficiencies were not corrected and were not associated with an adverse outcome.

Conclusions. At admission to the hospital, hyperkalemia may complicate cases of acidosis due to severe malaria and is associated with high, early mortality. After admission, mild asymptomatic deficiencies in magnesium and phosphate levels were common but were not associated with any deleterious effect. Thus, routine correction when serial measurement of electrolyte levels cannot be performed is unwarranted. Asymptomatic potassium deficiency developed despite provision of this electrolyte at maintenance doses. Further studies are justified but are unlikely to be a major research priority because, as these data suggest, the impact on mortality would at most be limited.

Correction of fluid and electrolyte imbalance forms a major component of the treatment of critically ill patients in modern intensive care settings [1, 2]. Disturbances in potassium [3], calcium [4], magnesium, and phosphate [5] levels are frequently observed in such patients, most commonly in those with sepsis syndrome [6]. Despite universal recognition of the importance of fluid and electrolyte administration to critically ill patients, recommendations for the management of fluid and electrolyte levels for patients with severe falciparum malaria are at present undefined.

The clinical spectrum of severe malaria in African children encompasses a wide range of pathophysiological derangements that affect multiple organ systems and are comparable to those seen in patients severe bacterial sepsis [7]. Acidosis is a common complication of severe malaria and has been identified as the single most important prognostic feature of this disease [8–11]. We have recently provided clear evidence of hypovolemia in children with severe malaria and acidosis and have demonstrated that hypovolemia corrected with rapid volume expansion [12]. Because severe malaria shares many features with sepsis syndrome, we postulated that the electrolyte derangements commonly associated with sepsis might also complicate severe malaria. Indeed, we have reported that hypokalemia is a

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common complication of severe malaria but does not generally become apparent until hypovolemia and acidosis are corrected [13]. Although hypophosphatemia and hypocalcemia have been reported in adults with severe malaria [14], the frequency of disturbances in a broader range of electrolyte levels, clinical associations, and consequences among African children with severe falciparum malaria have not yet been described. Blood samples obtained during the course of a recent randomized controlled trial of volume resuscitation in children with severe malaria complicated by acidosis enabled us to describe the derangements of potassium, magnesium, calcium, and phosphate levels in children with severe malarial acidosis during the 48-h period after admission to the hospital.

PATIENTS, MATERIALS, AND METHODS

Study site and patients. The study involved patients treated at the high-dependency unit at Kilifi District Hospital (Kilifi, Kenya) between May 2002 and June 2003. Children >2 months of age with a clinical feature of severe malaria (prostration, coma, or respiratory distress), parasitemia due to *Plasmodium falciparum,* and metabolic acidosis with a base deficit of >8 mmol/L were eligible for this study. Parental consent was obtained for all subjects. Children were excluded on the basis of the following criteria: pulmonary edema, severe malnutrition, severe anemia secondary to another obvious cause (e.g., trauma or surgery), or refusal of consent. The Kenya Medical Research Institute (Nairobi, Kenya) national ethics committee approved the study.

Monitoring and treatment. Baseline clinical parameters were measured by use of a Siemens multichannel recorder. Children were randomized to receive treatment for acidosis. Children with base deficits of 8–15 mmol/L received 20 mL/kg 0.9% saline, 4.5% human albumin solution, or maintenance-only treatment, whereas those with base deficits of >15 mmol/L (severe acidosis) received up to 40 mL/kg of either 0.9% saline or 4.5% human albumin solution. Children with severe anemia (hemoglobin concentration, <5 g/dL) were given a whole-blood transfusion (20–30 mL/kg) without diuretics. Our standard management includes intravenous quinine and maintenance fluids (containing 4% dextrose and 0.18% saline and administered at a rate of 4 mL/kg/h) and, if oxygen saturation is <95%, administered of oxygen by means of a face mask [15]. Hypoglycemia and seizures were treated according to standard protocols [16]. Potassium supplements were prescribed if the plasma potassium level decreased to <3.5 mmol/L [13]. Children in whom hyperkalemia was identified received nebulized salbutamol, a 2-mL/kg bolus injection of solution containing 25% glucose, and 1 mmol/kg calcium. Measurements of calcium, magnesium, and phosphate levels were not available until after the trial. Thus, administration of intravenous or oral solutions containing these electrolytes were not routinely administered.

Study procedures. At admission to the hospital (and before treatment), the following investigations were routinely performed: complete blood cell count (MDII; Beckman Coulter) and measurement of venous blood gas (IL1620; Instrumentation Laboratory), lactate, and glucose (GM7; Anolox Instruments) levels. Blood and urine specimens were obtained for culture from all children at admission; lumbar puncture and further investigations were done as clinically indicated [15, 17]. Additional sampling occurred at a mean of 8 h (range, 6–9 h), a mean of 24 h (range, 20–26 h), and a mean of 48 h after admission. Samples for electrolyte analysis were collected into tubes containing lithium heparin. The main laboratory is adjacent to the high-dependency unit, and thus plasma was immediately separated by centrifugation. Sodium and potassium levels were assayed immediately (614 analyzer; Bayer), whereas plasma for measurement of magnesium, calcium, phosphate, and albumin levels was stored at −20°C until assayed in June 2003 (Vitalab Selectra E analyzer; Vital Scientific). The quality of all of our laboratory assays are monitored through participation in the UK National External Quality Assessment Schemes for clinical chemistry and hematological analysis. The total calcium level was adjusted for serum albumin content by use of the following formula: [total calcium level − (albumin level /40)] + 1, where the total calcium the albumin levels are specified in mmol/L and g/dL, respectively. All reported results are for adjusted calcium levels. Ionized calcium levels were not available.

Statistical analysis. Dichotomous values were derived for abnormally "high" and "low" electrolyte levels, based on common recommended treatment thresholds. The following definitions were used: hypoglycemia, blood glucose level of <2.5 mmol/L; hypokalemia and hyperkalemia, potassium levels of <3.5 mmol/L and >5.5 mmol/L, respectively; hypocalcemia and hypercalcemia, adjusted total calcium levels of <2.0 mmol/L and >2.62 mmol/L, respectively; hypomagnesemia, total plasma magnesium level of <0.75 mmol/L; and hypophosphatemia, plasma phosphate level of <0.7 mmol/L [18]. A modified shock score was used to define overall malaria severity, as described elsewhere [19].

Between-group differences were compared by χ^2 test, χ^2 test for linear trend, or Fisher's exact test. Numerical data are reported as mean values ± SEM, and differences in group means were compared by 1-way analysis of variance. Multivariate analysis was used to compare the mean change in each electrolyte level between baseline and 24 h after admission with simultaneous mean changes in the other electrolyte levels, the albumin level, and the base deficit. The degree of association was measured between the biochemical and hematological variables at admission by use of the Spearman rank corre-

Table 1. Admission clinical and laboratory characteristics of Kenyan children with severe malaria complicated by acidosis who survived or died.

Characteristic	Patients who survived (n = 42)	Patients who died (n = 14)	All patients (n = 56)	Test statistic	P
Clinical					
Age, median years ± SD	2.5 ± 1.9	2.1 ± 1.7	2.3 ± 1.7	0.24[a]	.6
Prostration	26 (62)	5 (36)	31 (55)	2.9[a]	.09
Coma	11 (26)	8 (57)	19 (34)	4.5[a]	.03
Fitting/posturing	18 (43)	9 (64)	27 (48)	1.9[a]	.14
Respiratory distress	39 (93)	13 (93)	52 (93)	0[a]	1
Hypoxia (<95% saturation)	7 (17)	8 (57)	15 (27)	8.8[a]	.003
Systolic blood pressure <80 mm Hg	2 (5)	1 (7)	3 (5)	0.1[a]	1
Shock score	2 ± 1	3 ± 1	2 ± 1	10.2[a]	.002
Severe anemia	14 (33)	4 (29)	18 (32)	2.5[a]	.27
Hypoglycemia	5 (12)	8 (57)	13 (23)	12.0[a]	.001
Laboratory					
Parasitemia level, geometric mean parasites $\times 10^4/\mu$L (95% reference range)	7.0 (3.7–13.6)	4.2 (1.4–12.5)	6.2 (3.6–10.8)	2.1[b]	.15
pH	7.29 ± 0.02	7.18 ± 0.04	7.26 ± 0.02	7.9[b]	.007
Base deficit, mmol/L	15 ± 0.7	19 ± 1.0	16 ± 0.7	7.1[b]	.01
Lactate level, mmol/L	5.0 ± 0.6	5.0 ± 1.1	5.0 ± 0.5	0.1[b]	.97
PCO_2, kPa	3.2 ± 0.2	3.3 ± 0.6	3.2 ± 0.2	0.8[b]	.79
Sodium level, mmol/L	134 ± 1	141 ± 1	135 ± 1	16.7[b]	<.001
Potassium level, mmol/L	4.3 ± 0.1	5.8 ± 0.5	4.7 ± 0.2	21.0[b]	<.001
Magnesium level, mmol/L	1.0 ± 0.3	1.1 ± 0.1	1.0 ± 0.1	1.8[b]	.2
Phosphate level, mmol/L	1.5 ± 0.8	1.7 ± 0.2	1.6 ± 0.1	1.7[b]	.2
Calcium level, mmol/L	2.5 ± 0.1	2.4 ± 0.1	2.4 ± 0.3	0.5[b]	.8
Creatinine level, μmol/L	76 ± 4	108 ± 16	84 ± 5	7.5[b]	.01
Albumin level, g/L	37 ± 1	34 ± 2	36 ± 1	2.5[b]	.15
Hemoglobin level, g/dL	6.6 ± 0.4	7.1 ± 0.8	6.7 ± 0.3	1.6[b]	.2
WBC count, $\times 10^9$ cells/L	19 ± 2	35 ± 6	23 ± 17	11[b]	.002
Platelet count, $\times 10^9$ platelets/L	152 ± 21	210 ± 44	161 ± 19	1.6[b]	.2

NOTE. Data are no. (%) of patients or mean value ± SEM, unless otherwise indicated. Normal ranges of the base deficit and electrolyte levels are as follows: base deficit, −2 to +2 mmol/L; sodium, 135–145 mmol/L; potassium, 3.5–5.5 mmol/L; adjusted calcium, 2.2–2.62 mmol/L; phosphate, 1.2–1.8 mmol/L; magnesium, 0.78–1.03 mmol/L; and albumin, 34–42 g/L. PCO_2, partial pressure of CO_2.

[a] By χ^2 analysis or Fisher's exact test.

[b] By 1-way analysis of variance.

lations coefficient. Multiple analysis of variance was used to examine the association between the simultaneous changes in multiple electrolyte levels between baseline and various time points by fluid and outcome. The baseline predictors of a fatal outcome were explored by multivariable analysis. Analysis was conducted with SPSS, version 11.5 (SPSS) and Stata, version 8 (Timberlake).

RESULTS

During the study, 346 children were admitted to the hospital with clinical features of severe malaria: 121 (35%) had base deficits of <8 mmol/L, and 245 (71%) had base deficits of >8 mmol/L. Serial measurements of electrolyte levels were done for 56 children with acidosis, 42 of whom survived and 14 of whom died. Twenty children (36%) received albumin, 21 (38%) received 0.9% saline, and 15 (27%) received maintenance fluid only. Clinical and laboratory characteristics at admission for patients who survived and patients who died are compared in table 1. All patients had features of severe malaria: 50 (89%) had impaired consciousness (prostration or coma), 52 (93%) had deep "acidotic" breathing, and 18 (32%) had symptomatic severe anemia (hemoglobin level, <5 g/dL). Patients with fatal cases were significantly more frequently unconscious, had a higher median shock score and WBC count, and had worse metabolic derangements (acidosis, hypoglycemia, hyperkalemia, and increased creatinine levels) than did survivors. No

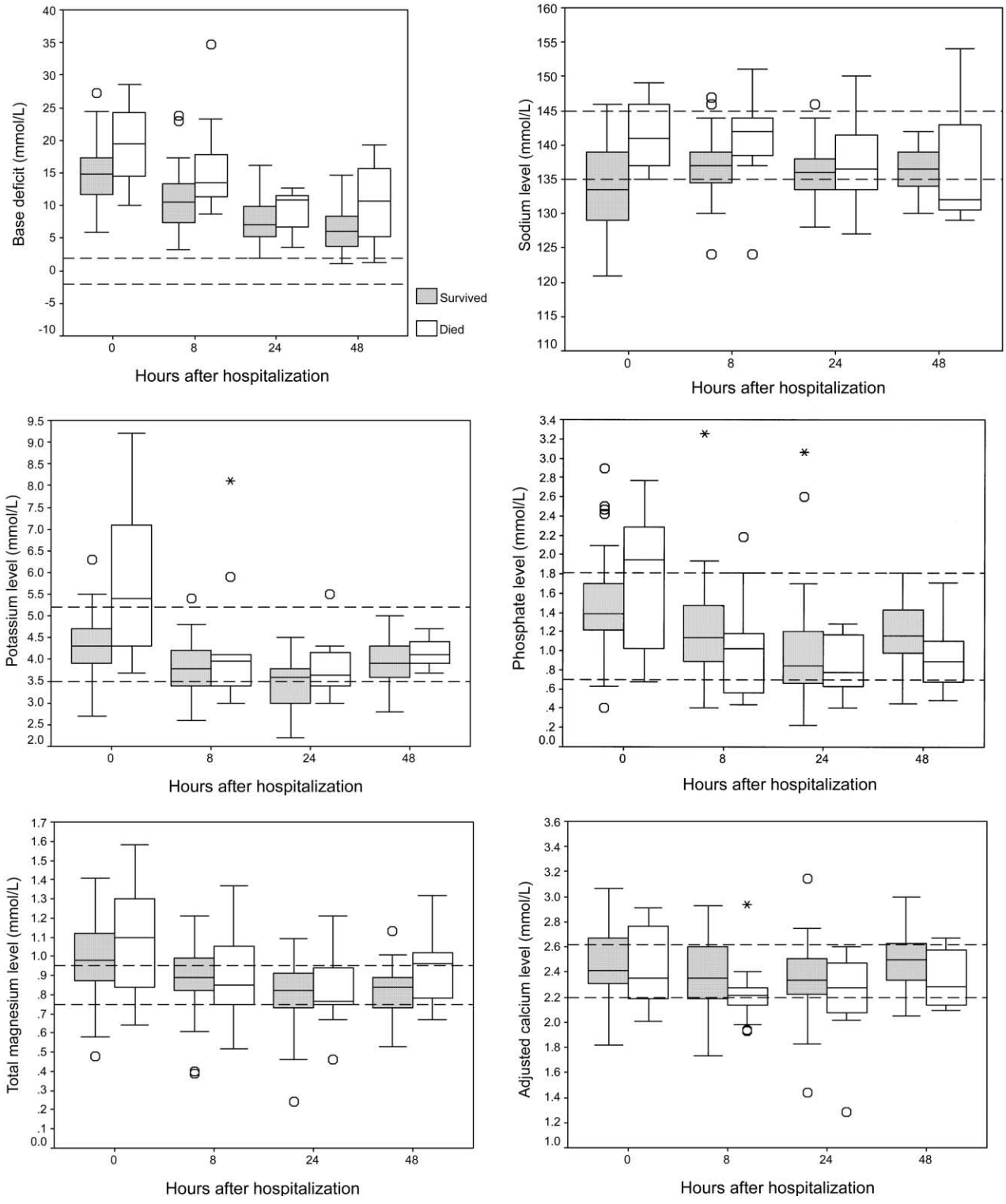

Figure 1. Changes in base deficits and electrolyte levels during the 48-h period after admission to the hospital. At 0 h (admission), data represent 42 children who survived and 14 who died; 8 h, 42 who survived and 13 who died; 24 h, 40 who survived and 10 who died; and 48 h, 35 who survived and 6 who died. *Boxes,* interquartile ranges and median values *(horizontal lines); bars,* 95% CIs; *lower dashed lines,* levels at which replacement therapy would normally be considered; *upper dashed lines,* upper limits of normal; *circles,* outliers (values 1.5–3 box lengths from the upper or lower edge of the IQR box); *asterisks,* extreme values (values >3 box lengths from the upper or lower edge of the IQR box).

Table 2. Mean electrolyte levels over time for Kenyan children with severe malaria complicated by acidosis.

Parameter	Baseline (n = 55)	8 h (n = 54)	24 h (n = 50)	48 h (n = 40)	F	P
pH	7.26 ± 0.02	7.35 ± 0.02	7.39 ± 0.06	7.41 ± 0.01	22.2	<.001
Base deficit, mmol/L	16.3 ± 0.7	11.9 ± 0.8	8.1 ± 0.5	6.8 ± 0.7	36.7	<.001
Sodium level, mmol/L	136 ± 0.9	138 ± 0.8	136 ± 0.7	136 ± 0.8	1.2	.31
Potassium level, mmol/L	4.69 ± 0.16	3.92 ± 0.13	3.50 ± 0.09	3.97 ± 0.09	6.3	<.001
Adjusted calcium level, mmol/L	2.45 ± 0.04	2.35 ± 0.03	2.32 ± 0.04	2.48 ± 0.04	3.5	.02
Magnesium level, mmol/L	1.02 ± 0.03	0.90 ± 0.03	0.81 ± 0.02	0.84 ± 0.02	12.3	<.001
Phosphate level, mmol/L	1.56 ± 0.08	1.16 ± 0.07	0.97 ± 0.07	1.16 ± 0.06	12.7	<.001
Creatinine level, μmol/L	84 ± 5	70 ± 5	51 ± 3	50 ± 3	13.1	<.001
Hemoglobin level, g/dL	6.7 ± 0.3	6.5± 0.3	6.4 ± 0.2	6.5 ± 0.3	0.2	.88
Albumin level, g/L	36 ± 0.9	33 ± 0.9	32 ± 1	34 ± 1	3.8	.01

NOTE. Data are mean values ± 2 SEMs. Differences in groups means were compared by 1-way analysis of variance (F statistic, 3 df).

microbiological evidence was found for septicemia, urinary tract infection, or meningitis in any study participant. The trends in plasma electrolyte and acid-base balance are shown in figure 1 and summarized in table 2. The frequencies of abnormal values over time are shown in table 3.

Admission

Hypocalcemia, hypomagnesemia, and hypophosphatemia. At admission and before acidosis was corrected, electrolyte levels were generally within the normal range. Hypocalcemia, hypomagnesemia, and hypophosphatemia were uncommon at admission (≤7% of patients), but hyponatremia (sodium level, <130 mmol/L) was present in 14 children (25%) (table 2). Mild-to-moderate hypercalcemia was present in >30% of patients at admission and was significantly more frequent among those with severe anemia (10 [56%] of 18 children) than among those with an equally severe acidosis (1 [7%] of 15 children) ($\chi^2 = 8.8$; $df = 2$; $P = .003$). The presence of any of these derangements at admission was not associated with the severity of acidosis, the clinical complications at presentation, or the prognosis.

Hyperkalemia. Hyperkalemia was present in 9 (16%) of 56 children; 7 (78%) of the 9 patients died, compared with 7 (15%) of 47 children without hyperkalemia ($\chi^2 = 15.9$; $df = 1$; $P = .001$). Six of the fatalities occurred <2 h after admission. Cardiac arrhythmias (i.e., generally marked widening of the QRS complex, followed by the development of ventricular fibrillation) were common among these patients and were usually refractory to intervention. Compared with patients in the normokalemic group, those in the hyperkalemic group displayed a greater degree of biochemical derangement: the latter were more frequently hypoglycemic (7 [78%] of 9 vs. 6 [13%] of 47 patients; $\chi^2 = 18$; $P < .001$), hypoxic (6 [67%] of 9 vs. 9 [19%] of 47 patients; $\chi^2 = 8.7$; $P = .003$), and acidotic (base deficit, >20 mmol/L) (6 [86%] of 7 vs. 8 [17%] of 47 patients; $\chi^2 = 15.5$; $P < .001$). Potassium levels were not associated with the severity of parasitemia, serum creatinine levels, or lactate levels.

Table 3. Frequencies of specific electrolyte abnormalities over time among Kenyan children with severe malaria complicated by acidosis.

Abnormality	Baseline (n = 55)	8 h (n = 54)	24 h (n = 50)	48 h (n = 40)	χ^2	P
Hyponatremia, <130 mmol/L	14 (25)	3 (6)	5 (10)	4 (10)	3.4	.33
Hypernatremia, >145 mmol/L	6 (11)	4 (7)	2 (4)	1 (3)	10.7	.014
Hypokalemia, <3.5 mmol/L	4 (7)	16 (30)	18 (36)	7 (18)	15.3	.002
Hyperkalemia, >5.5 mmol/L	9 (16)	2 (4)	1 (2)	0	13.3	.004
Hypocalcemia, <2.62 mmol/L	5 (9)	3 (6)	4 (8)	0	3.8	.28
Hypercalcemia, >5.5 mmol/L	17 (31)	8 (15)	6 (12)	10 (25)	7.4	.06
Hypomagnesemia, <0.75 mmol/L	4 (7)	9 (17)	15 (30)	10 (25)	9.9	.02
Hypophosphatemia, <0.7 mmol/L	3 (5)	6 (11)	15 (30)	6 (15)	13.3	.004

NOTE. Data are no. (%) of patients with the abnormal finding. Group proportions were compared by the χ^2 test for linear trend (1 df).

A number of children with hyperkalemia had the complication of hypernatremia (sodium level, >145 mmol/dL). In this group, plasma creatinine concentrations were significantly higher (117 ± 13 μmol/L) than those in the group with sodium levels ≤145 mmol/dL (71 ± 4 μmol/L; $F = 18.3$; $P < .0001$), suggesting that dehydration may have contributed to hyperkalemia.

After Admission

Most of the abnormal homeostasis of electrolytes that developed after admission was due to plasma levels that decreased below the normal range. Hypocalcemia was an uncommon complication, and its development was not associated with receipt of a whole-blood transfusion. Twelve-lead electrocardiography was not routinely available; therefore, the frequency of abnormal electrocardiographic findings associated with electrolyte disorders was unknown. The simultaneous decrease in potassium, magnesium, and phosphate levels 0–8 h after admission was not associated with the type or volume of fluids (intervention or maintenance) received ($F = 1.2$, by multiple analysis of variance; $P = .3$). Similarly, the type or volume of fluid did not account for the differences in electrolyte levels 24 h after admission ($F = 0.51$, by multiple analysis of variance; $P = .8$).

Magnesium level. Hypomagnesemia became more prevalent during hospitalization, affecting 30% of children 24 h after admission. Death was not more prevalent among children who developed hypomagnesemia. Among children with hypomagnesemia 24 h after admission, 4 (27%) of 15 had a subsequent seizure. All episodes were self-limiting partial seizures that did not require treatment. Between baseline and 24 h after admission, the magnesium level was linearly associated with the plasma albumin level ($r = .56$; $P < .0001$) and adjusted calcium levels ($r = .56$; $P < .001$). Albumin concentrations were lower in children with hypomagnesemia (28 ± 2 g/L), compared with children with normal magnesium levels (35 ± 1 g/L) ($F = 7.6$; $P = .008$). Regression analysis identified significant associations between mean changes in the adjusted calcium level ($\beta = 0.32$; 95% CI, 0.18–0.46; $P < .0001$) and albumin level ($\beta = 0.13$; 95% CI, 0.05–0.22; $P = .003$) and the mean change in the magnesium level between baseline and 24 h after admission.

Phosphate level. The frequency of hypophosphatemia (phosphate level <0.7 mmol/L) increased from 6% (3 of 50 patients) at admission to 30% (15 of 50 patients) by the end of the first hospital day. In general, plasma albumin levels were lower among children with hypophosphatemia (28 ± 2 g/L), compared with children with a phosphate concentration of >0.7 mmol/L (34 ± 1 g/L) ($P = .012$). Of the 199 measurements of phosphate levels, severe hypophosphatemia (phosphate level <0.32 mmol/L) was recorded on only 1 occasion. There was a significant association between the mean changes in the magnesium level ($\beta = 1.4$; 95% CI, 0.8–1.98; $P < .0001$) and base deficit ($\beta = 0.04$; 95% CI, 0.01–0.07; $P = .006$) and the mean change in the phosphate level between baseline and 24 h after admission.

Potassium level. There was a similar increase in the frequency of hypokalemia, which was present in 36% of children (18 of 50) 24 h after admission. Over this period, there was a negative correlation between plasma potassium levels and glucose levels ($r^2 = -.51$; $P = .001$). Regression analysis identified significant changes between the mean changes in the glucose level ($\beta = -0.12$; 95% CI, −0.04 to −0.20; $P = .006$) and base deficit ($\beta = 0.08$; 95% CI, 0.01–0.13; $P = .016$) and the mean change in the potassium level between baseline and 24 h after admission. The development of hypokalemia was not associated with the intervention received or the outcome. Because the correction of potassium deficits is often refractory in children with concomitant magnesium deficiency, we examined the data to see whether the timing of these disorders was coincident. At both 8 h and 24 h after admission, there were no significant associations between these deficiencies; only 20%–27% of children with hypokalemia (<3.5 mmol/L) at these times had concomitant hypomagnesemia (<0.75 mmol/L).

Fatal Outcome

Multivariable analysis identified 3 factors at admission that were independently associated with a fatal outcome: plasma potassium level of ≥5.5 mmol/L (OR, 21; 95% CI, 2.5–163); $P = .009$), coma (OR, 9.8; 95% CI, 1.4–70; $P = .02$), and increased WBC count (OR, 1.1; 95% CI, 1.0–1.12; $P = .05$). The area under the receiver-operating curve predicted by these 3 variables was 0.88. Perturbations in other electrolyte levels during the sampling period were not associated with fatal outcome.

DISCUSSION

In emergency and intensive care medicine, correction of fluid volume and electrolyte deficits is the standard of care for any critically ill patient because acidemia, hypokalemia, hypophosphatemia, hypocalcemia, and hypomagnesemia exacerbates myocardial dysfunction and increases the risk of arrhythmias [6, 20]. The advent of whole-blood analysis has facilitated bedside biochemical "critical care profiling" within minutes after blood sampling and has led to rapid correction of electrolyte abnormalities when adequate amenities are present [21]. In Africa, where malaria is endemic, few health care facilities have the ability to perform routine biochemical analysis. Even fewer can provide an extended critical care profile. Information about electrolyte perturbations complicating severe malaria—a very frequent cause of pediatric admissions in sub-Saharan Africa—will be informative for developing future recommendations for fluid and electrolyte management.

We have shown that, among Kenyan children with severe falciparum malaria complicated by acidosis, disorders involving the major intra- and extracellular electrolytes were common. Most disorders, however, developed after admission and were due to plasma levels that decreased below normal limits; hypomagnesemia, hypophosphatemia, and hypokalemia were common (>30%) on the day after admission. Hypocalcemia, which was defined on the basis of the adjusted total blood calcium level, was an infrequent complication at any juncture. All of these disorders were apparently asymptomatic, because routine correction was not part of the standard protocol (except for the provision of potassium). Indeed, we were unable to detect any relationship between adverse events or outcome and the presence of these abnormalities. On the other hand, hyperkalemia, which was present in 16% of children in this study at admission to hospital, was associated with a case fatality rate of 78%.

To date, the only information about changes in levels of electrolytes other than sodium [22] in cases of falciparum malaria comes from a study involving Thai adults [14]. Hypocalcemia, hypophosphatemia, and hypomagnesemia were common at admission to the hospital, appearing in 30%, 70%, and 40% of patients, respectively. Severe hypophosphatemia (phosphate level <0.30 mmol/L) was relatively common, particularly among adults with complicated malaria, and Davis et al. [14] recommended that phosphate replacement therapy should be considered. In contrast, we demonstrated mild, asymptomatic depletion of potassium, magnesium, and phosphate levels, which became evident only with the correction of hypovolemia and hypoglycemia and the partial correction of metabolic acidosis. Our results suggest that the findings at admission were consistent with transcellular shift and that these findings reflect the reverse shift that followed the correction of acidosis, hypoglycemia, and the hemodynamic features of shock. Two clinical subgroups of patients with severe malaria that were not considered in this study were children with impaired consciousness but without metabolic acidosis and children with severe malaria-associated anemia but without respiratory distress. Further studies describing the common electrolyte abnormalities may be warranted in the subgroup with impaired consciousness but would be unnecessary in the latter subgroup, because inpatient mortality is ~1% [23].

The finding that hypocalcemia was uncommon at any juncture contrasts with data series' for critically ill children [24, 25] and adults [26]. Hypocalcemia is a common complication in sepsis and critical illness and has recently been shown to correlate with disease severity score and mortality risk among patients admitted to the intensive care unit [4]. In our study, we found that increased serum calcium levels were common at admission (31% of patients) and that hypocalcemia was unexpectedly rare. The accuracy of both of these observations would have been improved if the extracellular ionized calcium level was known. Measurement of the total calcium level may have masked the true frequency of decreased ionized calcium levels, but increases in total calcium levels are likely to involve increases in free ionized calcium levels. Intraerythrocytic calcium levels are substantially increased in parasitized RBCs [27], and we suggest that the increase in calcium levels resulted from the intracellular release of calcium secondary to the predictable erythrocyte lysis due to falciparum malaria. This is supported by the association between hypercalcemia and severe malarial anemia, the inverse linear relationship between plasma calcium and hemoglobin levels ($r = -0.46$; $P < .01$), and a previous report of this association in Thai adults with severe malaria [14]. RBC lysis—an inevitable consequence of falciparum malaria—may also provide some explanation for the infrequency of hypocalcemia in this series.

We have recently reported that urinary potassium wasting and hypokalemia are common complications of severe malaria and that potassium depletion becomes apparent only with correction of acidosis [13]. In the current study, hypokalemia remained a significant complication despite the provision of potassium at standard maintenance doses. Higher replacement doses of potassium may be justified and should be examined prospectively. Nevertheless, the routine provision of potassium supplementation should be withheld during the first 8 h after admission to the hospital, because of the frequency of hyperkalemia and its association with a high early mortality. Furthermore, the prevalence of hyperkalemia and hypercalcemia among children with severe malaria complicated by acidosis may have implications for the choice of resuscitation fluids. In many areas of Africa where malaria is endemic, Ringer's lactate, which contains both calcium and potassium in physiological doses, is more widely available than normal saline. The results of the current study suggest that Ringer's lactate may be potentially harmful and should not be used in the resuscitation of children with severe malaria.

We have demonstrated that electrolyte derangements are common among children with severe malaria complicated by acidosis. At admission to the hospital, hypercalcemia and severe hyperkalemia were present in 31% and 16% of children, respectively, and severe hyperkalemia was associated with high, early mortality (78%). Taken together, these data suggest that the use of Ringer's lactate, which contains both calcium and potassium in physiological doses, may be unsafe if used as a resuscitation fluid in this patient group. After admission, mild, asymptomatic deficiencies in magnesium, phosphate, and potassium developed, but these were not associated with an adverse outcome. Unlike sepsis, hypocalcemia was an infrequent complication at any juncture. These findings suggest that routine measurement and provision of magnesium, phosphate, or calcium for children with severe malaria acidosis are not major

treatment priorities. Potassium supplementation should be prescribed only after correction of volume deficits (>8 h after admission) but should be considered for most children ⩽24 h after admission. Additional studies are warranted but are unlikely to be a major research priority, given the limited evidence presented to support an association between electrolyte deficiencies and adverse outcome.

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