MANIFESTATION AND OUTCOME OF SEVERE MALARIA IN CHILDREN IN NORTHERN GHANA

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Abstract. The symptoms of severe malaria and their contribution to mortality were assessed in 290 children in northern Ghana. Common symptoms were severe anemia (55%), prostration (33%), respiratory distress (23%), convulsions (20%), and impaired consciousness (19%). Age influenced this pattern. The fatality rate was 11.2%. In multivariate analysis, circulatory collapse, impaired consciousness, hypoglycemia, and malnutrition independently predicted death. Children with severe malaria by the current World Health Organization (WHO) classification, but not by the previous one (1990), showed relatively mild clinical manifestations and a low case fatality rate (3.2%). In hospitalized children with severe malaria in northern Ghana, severe anemia is the leading manifestation, but itself does not contribute to mortality. In this region, malnutrition and circulatory collapse were important predictors of fatal malaria. The current WHO criteria serve well in identifying life-threatening disease, but also include rather mild cases that may complicate the allocation of immediate care in settings with limited resources.

INTRODUCTION

Severe *Plasmodium falciparum* malaria annually causes at least one million deaths, most of which occur in African children less than five years of age.[1] Drug resistance and demographic development will contribute to a further increase in malaria morbidity and mortality.[2,3]

Severe anemia, cerebral malaria, and metabolic acidosis are considered the major clinical manifestations in severe childhood malaria. However, there is a remarkable shortage of clinical description of severe malaria in different endemic regions. The disease pattern and the relative contribution of individual symptoms to mortality differ with endemicity, geographic location, access to health services, and age, among other factors.[1,4–12] Revised standard criteria of severe malaria have been proposed by the World Health Organization (WHO) (2000) to identify children at high risk.[1] Although no classification will meet all requirements, its main aim is to guide treatment and predict disease outcome. In Senegal, the revised definition proved to be less specific than the previous WHO version (1990), but equally sensitive in identifying life-threatening disease.[10,13]

We report the results of a study on children with severe malaria in the remote northern region of Ghana. This study had three major aims: 1) to describe the clinical spectrum of severe malaria, 2) to assess predictors of fatal outcome, and 3) to evaluate the revised WHO classification of severe malaria with respect to clinical relevance and applicability in this setting.

PATIENTS AND METHODS

The study was conducted at the Teaching Hospital in Tamale, the capital of the northern Region of Ghana. Despite a population of approximately 300,000, the city has a rural character with hamlets and thatched, mud-wall huts scattered over a vast area. Malaria transmission in northern Ghana is perennial but highly seasonal.[14] Climate and vegetation are savanna-type with rains from May to October, and a dry season from November to April. In the near-by district of Kassena-Nankana, an average of 300 infective anopheline bites per person per year has been estimated.[15] Entomologic data for the study area are not available. In a survey in the northern region in the rainy season 2002, almost two-thirds of 2,100 children had microscopically detectable parasitemia indicating a hyperendemic malaria situation (Mockenhaupt FP and others, unpublished data). Chloroquine treatment constitutes the predominant means of malaria control. Clinical treatment failure of chloroquine in uncomplicated malaria was observed in 29% in a recent trial and resistant *P. falciparum* genotypes were detected in 84%.[16,17] The pediatric ward at Tamale Teaching Hospital comprises 55 beds; facilities for intensive care do not exist.

Between August and November 2002, children six months to nine years of age with signs of severe malaria were examined by a pediatrician (SG). Rectal temperature, heart rate, respiratory rate, and blood pressure were documented. Malnutrition was defined as a weight-for-age (WAZ) score < -2 based on National Center for Health Statistics (Hyattsville, MD) reference data. Malaria parasites were counted on Giemsa-stained thick blood films per 200 white blood cells. Hyperparasitemia was defined as a parasite density $> 250,000$ asexual parasites/μL of blood. Hemoglobin (Hb), blood glucose, and lactate were measured (vario photometer; Diaglobal, Berlin, Germany). Severe anemia, hypoglycemia, and hyperlactatemia were defined as Hb <5 g/dL, glucose <40 mg/dL [<2.2 mmol/L], and lactate ≥ 5 mmol/L,[18] respectively. Severe malaria was defined by an asexual *P. falciparum* parasitemia, at least one of the following WHO (2000) criteria,[1] and by the absence of detectable, non-malarious causes for these symptoms: 1) severe anemia; 2) prostration, defined as the inability to sit or eat although otherwise able to do so; 3) respiratory distress, defined as sustained nasal flaring, subcostal recessions, or Kussmaul breathing; 4) multiple convulsions, defined as a respective history within the preceding 24 hours plus one directly observed convulsion; 5) impaired consciousness, defined as a Blantyre score ≤ 4;[19] 6) clinical jaundice; 7) hemoglobinuria, verified by dipstick (Combur; Roche

Diagnostics, Basel, Switzerland); 8) circulatory collapse, defined as a systolic blood pressure <60 and <80 mm of Hg in children ≤5 and >5 years of age, respectively, plus cool limbs or weak or absent peripheral pulses; 9) abnormal bleeding; and 10) pulmonary edema. Assessment of prostration and consciousness was postponed for at least one hour if a post-ictal state or previous anticonvulsive treatment was present or suspected. The term cerebral malaria was reserved for a Blantyre score ≤2. Two hundred ninety children fulfilled one or more of these criteria. Informed written consent was obtained from the parents of the patients. The study protocol was reviewed and approved by the Ethics Committee of the University for Development Studies in Tamale.

Patients were treated with artesunate (Plasmotrim; Mepha Pharma, Aesch, Switzerland) for five days at a dose of 5 mg/kg of body weight (double dose on first day) applied orally, as suppositories, or via nasogastral tube as judged appropriate and adjusted to the nearest manageable fraction. Additional treatment included intravenous or oral glucose substitution, intravenous rehydration, paracetamol, diazepam, and phenobarbital as appropriate. All patients with severe anemia received blood transfusions.

Parasite densities were normalized by log_{10} transformation and geometric mean parasite densities (GMPDs) and 95% confidence intervals (CIs) were calculated. Continuous variables were compared by Student's t-tests, Mann-Whitney U tests, or Kruskal-Wallis-tests. Proportions were compared by chi-square tests or Fisher's exact test. Logistic regression models including sex and age and with stepwise backward removal of factors not associated in multivariate analysis ($P > 0.05$) were used to assess associations between symptoms, and to estimate predictors of mortality and sequelae.

RESULTS

The median age of the 290 children (155 girls and 135 boys) was 24 months (range = 6–102). The mean ± SD temperature, GMPD (95% CI), and median Hb (range) were 38.6 ± 1.1°C, 29,512 (21,904–39,763)/μL, and 4.9 (1.5–13.4) g/dL, respectively. Malnutrition was seen in 42% (123 of 290) of the children, and the mean WAZ score was –1.6.

Manifestations of severe malaria. Severe anemia defined severe malaria in more than half of the patients followed by prostration and respiratory distress (Table 1). Multiple convulsions and impaired consciousness each occurred in approximately 20% of the children. Anemia decreased in frequency with age. Opposite trends were seen for prostration, jaundice, hemoglobinuria, hyperparasitemia, and hypoglycemia. In addition, convulsions and impaired consciousness tended to become more frequent in older children (Table 1). The median age (range) of children with severe anemia, but without cerebral involvement (prostration, convulsions, or impaired consciousness, n = 88), was 21.5 months (6–97) as compared with 27.5 (6–102) in patients with cerebral involvement (n = 186; $P < 0.0001$).

The mean number of symptoms defining severe malaria was 1.7. One, two, three, and four defining criteria were present in 48%, 39%, 10%, and 3% of the children, respectively. In 24% of the children (n = 69), severe anemia was the only manifestation. Hemoglobinuria and circulatory collapse always occurred in combination with at least one of the other criteria.

Associations between symptoms and baseline characteristics of the children were analyzed (Table 2). Anemia was associated with hyperlactatemia, malnutrition, and absence of hyperparasitemia. Hemoglobin and log_{10} parasite density correlated positively ($R = 0.36$, $P < 0.0001$). In respiratory distress and impaired consciousness, both hypoglycemia and hyperlactatemia were increased in frequency. Impaired consciousness occurred more frequently in girls (23.9%, 37 of 155) than in boys (14.1%, 19 of 135; $P = 0.04$), as did hypoglycemia (21.3%, 33 of 155 versus 11.9%, 16 of 135; $P = 0.03$) and hyperlactatemia (46.5%, 72 of 155 versus 31.1%, 42 of 135; $P = 0.007$). In multivariate analysis, the increased risk of impaired consciousness in girls lost statistical significance (odds ratio [OR] = 1.6, 95% CI = 0.8–3.1,

TABLE 1
Proportions of children with symptoms and conditions of severe malaria according to age groups

	All	Age groups		
		<2 years	≥2 <4 years	≥4 years
No.	290	99	129	62
Proportion with criterion (%, no.)				
Severe anemia	55.2 (160)	77.8 (77)	47.3 (61)*	35.8 (22)*†
Prostration	33.4 (97)	26.3 (26)	34.9 (45)	41.9 (26)*†
Respiratory distress	22.8 (66)	30.3 (30)	17.8 (23)*	21.0 (13)
Multiple convulsions	20.3 (59)	17.2 (17)	20.9 (27)	24.2 (15)
Impaired consciousness	19.3 (56)	14.1 (14)	20.9 (27)	24.2 (15)
Jaundice	11.7 (34)	2.0 (2)	12.4 (16)*	25.8 (16)*†
Circulatory collapse	3.4 (10)	4.0 (4)	2.3 (3)	4.8 (3)
Hemoglobinuria	2.8 (8)	0 (0)	3.1 (4)	6.5 (4)*†
Pulmonary edema	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal bleeding	0 (0)	0 (0)	0 (0)	0 (0)
Proportion with other conditions				
Cerebral malaria	16.9 (49)	11.1 (11)	19.4 (25)	21.0 (13)
Hyperparasitemia	22.1 (64)	15.2 (15)	22.5 (29)	32.3 (20)*†
Hypoglycemia	16.9 (49)	10.1 (10)	19.4 (25)	22.6 (14)*†
Hyperlactatemia	39.3 (114)	42.4 (42)	32.6 (42)	48.4 (30)
Hyperpyrexia (> 40°C)‡	8.1 (23)	8.2 (8)	9.6 (12)	4.9 (3)

* Significant difference to age group <2 years old ($P < 0.05$).
† Significant trend with age groups ($P < 0.05$, by chi-square test for trend).
‡ n = 283.

TABLE 2
Univariate and multivariate analysis of factors associated with symptoms defining severe malaria*

Symptom	Factor	Univariate analysis		Multivariate analysis	
		Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Anemia	Hyperparasitemia	0.2 (0.1–0.4)	< 0.0001	0.2 (0.1–0.4)	< 0.0001
	Malnutrition	1.8 (1.1–3.0)	0.02	1.7 (1.0–2.9)	0.05
	Hyperpyrexia†	0.4 (0.2–1.0)	0.04	–	
	Hyperlactatemia	1.5 (0.9–2.5)	0.09	2.2 (1.2–3.9)	0.007
Respiratory distress	Hypoglycemia	2.6 (1.3–5.3)	0.003	2.1 (1.0–4.2)	0.05
	Hyperlactatemia	2.6 (1.5–4.8)	0.0005	2.2 (1.2–4.1)	0.009
Multiple convulsions	Hyperpyrexia†	2.7 (1.0–7.3)	0.03	2.7 (1.1–6.7)	0.03
Impaired consciousness	Hyperparasitemia	2.4 (1.2–4.8)	0.006	–	
	Hypoglycemia	8.0 (3.8–16.6)	< 0.0001	7.4 (3.7–14.7)	< 0.0001
	Hyperlactatemia	2.7 (1.4–5.1)	0.0008	–	
Jaundice	Hyperparasitemia	2.1 (0.9–4.9)	0.05	–	
Circulatory collapse	Hyperparasitemia	5.7 (1.3–28.4)	0.009	4.0 (1.0–15.5)	0.05
	Hypoglycemia	13.2 (2.8–81.2)	0.0002	10.5 (2.6–43.6)	0.001
	Hyperlactatemia	6.6 (1.3–64.2)	0.02	–	

* Analysis included hyperparasitemia, hypoglycemia, hyperlactatemia, malnutrition, and hyperpyrexia (>40°C) as independent variables. Logistic regression models include sex and age (months); factors were stepwise removed if their association with the outcome variable was not significant (P > 0.05). CI = confidence interval.
† n = 283.

P = 0.16). In patients with multiple convulsions compared with those without multiple convulsions, parasite density was higher (GMPD = 64,863/μL, 95% CI = 39,620–106,191 versus 24,099/μL, 95% CI = 17,011–34,140, P = 0.009) and hyperpyrexia was more frequent. The mean ± SD body temperature was also increased in prostration (38.8 ± 1.0°C versus 38.5 ± 1.1°C; P = 0.04).

Outcome. Of the 290 children, five dropped out of the study, and 32 died (case fatality rate [CFR] = 11.2%). Twenty, seven, and five children died within 24 hours, 24–48 hours, and 48–72 hours after hospitalization, respectively. Neither age nor parasite density influenced outcome. In the age groups <2, 2 to <4, and ≥4 years old, CFRs were 9.3% (9 of 97), 11.8% (15 of 127), and 13.1% (8 of 61), respectively. The GMPD was 29,648/μL in children who survived and 29,242/μL in patients who died (P = 0.98). The CFRs increased with the number of symptoms defining severe ma-laria (1, 2.9%; 2, 14.5%; 3, 31%; and 4, 30%; χ^2_{trend} = 24.2, P < 0.0001). In univariate analysis, factors associated with mortality were circulatory collapse, impaired consciousness, respiratory distress, hypoglycemia, hyperlactatemia, hyperparasitemia, and malnutrition (Table 3). Risk of death due to prostration increased when analysis was restricted to conscious patients (n = 231, OR = 2.9, 95% CI = 0.8–13.6, P = 0.08). Multivariate analysis revealed four independent predictors of fatal outcome: circulatory collapse, impaired consciousness, hypoglycemia, and malnutrition (Table 3). In this model, prostration increased the risk of death with borderline statistical significance (OR = 3.5, 95% CI = 0.8–15.1, P = 0.09). All patients who died had one or more of four symptoms, namely impaired consciousness, circulatory collapse, convulsions, and prostration. 96% (47 of 49), 82% (93 of 114), and 84% (54 of 64) of patients with hypoglycemia, hyperlactatemia, and hyperparasitemia, respectively, fell into

TABLE 3
Symptoms and case fatality rates among 285 children with severe malaria*

Condition	Case fatality rate (%)	Univariate analysis		Multivariate analysis	
		Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Defining criterion					
Circulatory collapse	77.8	35.1 (6.1–354)	< 0.0001	31.4 (4.7–207)	0.0003
Impaired consciousness	37.0	10.7 (4.5–25.9)	< 0.0001	8.1 (3.1–21.1)	< 0.0001
Respiratory distress	20.0	2.6 (1.2–6.1)	0.01	–	
Hemoglobinuria	12.5	1.1 (0.0–9.3)	1.0	–	
Multiple convulsions	12.1	1.1 (0.4–2.9)	0.82	–	
Severe anemia	10.1	0.8 (0.4–1.7)	0.51	–	
Jaundice	8.8	0.7 (0.1–2.6)	0.78	–	
Prostration	8.2	0.6 (0.2–1.5)	0.25	–	
Other conditions					
Cerebral malaria	36.2	8.4 (3.6–20.1)	< 0.0001	–†	
Hypoglycemia	35.4	8.1 (3.4–19.3)	< 0.0001	2.9 (1.1–7.7)	0.03
Hyperlactatemia	19.5	3.9 (1.7–9.3)	0.0003	–	
Hyperparasitemia	18.8	2.3 (1.0–5.4)	0.03	–	
Malnutrition	16.0	2.2 (1.0–5.1)	0.03	2.8 (1.1–7.0)	0.03
Hyperpyrexia (>40°C)‡	4.3	0.4 (0.0–2.5)	0.48	–	

* Factors were stepwise removed from the logistic regression models if they were not associated (P > 0.05). Multivariate odds ratios are adjusted for age (months) and sex. CI = confidence interval.
† In the logistic regression model replacing impaired consciousness, adjusted odd ratio = 5.4 (95% CI = 2.1–14.3); P = 0.0006.
‡ n = 283.

this group. The CFRs among children with overlaps of these four conditions are shown in Figure 1.

None of the children with exclusive anemia (0 of 67), respiratory distress (0 of 5), or jaundice (0 of 9) died. In the largest subgroup of children with severe anemia (n = 158), mortality was associated with female sex (OR = 4.9, 95% CI = 1.3–27.4, P = 0.01), impaired consciousness (OR = 8.5, 95% CI = 2.3–29.7, P = 0.0004), hypoglycemia (OR = 7.9, 95% CI = 2.2–27.4, P = 0.0005), and hyperlactatemia (OR = 6.5, 95% CI = 1.7–36.5, P = 0.002) in univariate analysis, and with impaired consciousness (OR = 39.4, 95% CI =4.5–346, P = 0.0009) and prostration (OR = 17.3, 95% CI = 2.0–148, P = 0.009) in multivariate analysis.

Neurologic sequelae at discharge were observed in six (2.4%) of 253 survivors (spasticity and deafness, n = 2; paralysis of right arm, n = 1; prostration, n = 2; non-defined defect, n = 1). Multivariate analysis identified hypoglycemia (OR = 20.1, 95% CI = 2.6–155, P = 0.004), multiple convulsions (OR = 8.7, 95% CI = 1.2–60.5, P = 0.03), and increasing age (months, OR = 1.05, 955 CI = 1.01–1.1, P = 0.02) as independent predictors of neurologic defects.

Comparison of previous and current classifications of severe malaria. Of the 290 children, 194 (66.9%) had severe malaria as defined by a modification of the previous WHO (1990) definition (Table 4). Among the remaining 96 patients, the leading symptoms were prostration (n = 44, 46%) and severe anemia (n = 43, 45%). Other conditions were respiratory distress (n = 19, 20%), jaundice (n = 17, 18%), and impaired consciousness (n = 1, 1%). Children who were not identified as severe malaria cases by the 1990 WHO criteria tended to be of higher age, had lower parasite densities and less hyperlactatemia, and exhibited an approximately five-fold lower CFR.

DISCUSSION

In northern Ghana, severe anemia is the predominant manifestation of severe childhood malaria and affects mainly young children. Cerebral involvement is comparatively rare and seems to occur more frequently in older patients. This pattern resembles the situation in highly endemic regions and confirms previously reported age-related differences in disease manifestation.[1,4,7,8,20]

Our hospital-based data need to be interpreted with caution because they may represent only part of the picture of severe malaria in northern Ghana. One reason for this is that community access to treatment and health-seeking behavior can influence disease manifestation and its assessment.[21] In Senegal and in The Gambia, both with relatively lower malaria transmission, children with severe malaria were generally older than those in Tamale and cerebral malaria was more prevalent than severe anemia.[10,12] The same was found in Ouagadougou, Burkina Faso, located only 200 miles to the north of Tamale.[20] These differences may partially be due to the more intense malaria transmission in northern Ghana,[15] but may involve other factors as well. In contrast to previous studies,[5,6,13] severe malarial anemia in our patients was not defined by a certain threshold of parasite density that may have contributed to its comparatively high proportion. A further limitation applies to the number of statistical tests performed in this study. As a matter of course, the possibility of type 1 errors cannot completely be excluded and results should be interpreted with adequate caution.

The pathogenesis of severe malaria is complex and may vary geographically. In northern Ghana, severe anemia was associated with young age, malnutrition, and hyperlactatemia, but not with hyperparasitemia. In Tanzanian children, *P. falciparum* parasitemia outweighed malnutrition as a cause of severe anemia whereas in Burkina Faso, malnutrition was considered more important.[21,22] Surprisingly in the present study, anemia occurred more frequently at low parasite densities. However, this is consistent with findings from southern Ghana where more than 80% of severely anemic children exhibited no parasitemia but presented with detectable plasma levels of soluble malaria antigens.[23] This finding may reflect chronic and/or repeated infections during the preceding rainy season that eventually lead to a gradual decrease in Hb concentrations. This view is supported by Koram and others, who reported a decrease in Hb levels in children from northern Ghana at the end of the high transmission season.[24] Moreover, the low prevalence of hyperpyrexia in our patients with severe anemia provides evidence for a chronic course of
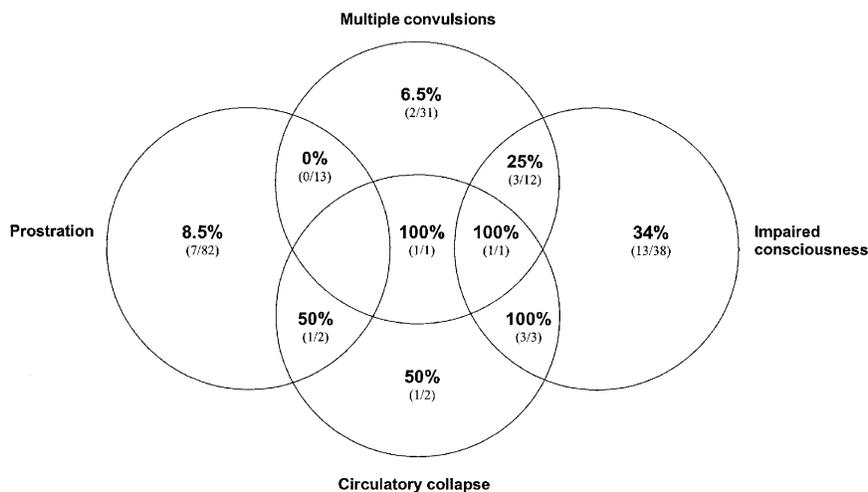

FIGURE 1. Case fatality rates in children with overlapping symptoms of severe malaria in northern Ghana.

TABLE 4
Comparison of children diagnosed as severe malaria cases by modified World Health Organization (WHO) (1990) criteria and those in addition by WHO (2000) criteria*

Parameter	WHO (1990) criteria† fulfilled	Additional WHO (2000) criteria fulfilled	P
No.	194	96	
Sex (female:male)	106:88	49:47	0.56
Age, months; median (range)	24 (6–102)	24 (8–97)	0.08
GMPD (/μL, 95% CI)	47,973 (35,308–65,181)	11,041 (5,994–20,336)	< 0.0001
Hb (g/dL) median (range)	4.8 (2.1–12.0)	5.3 (1.5–13.4)	0.47
Anemia at parasite density			
<10.000/μL, % (no.)	0 (0)	44.8 (43)	0.01
Hypoglycemia, % (no.)	25.3 (49)	0 (0)	< 0.0001
Hyperlactatemia, % (no.)	47.4 (92)	22.9 (22)	< 0.0001
Hyperparasitemia, % (no.)	22.7 (44)	20.8 (20)	0.72
Hyperpyrexia, % (no.)‡	9.5 (18)	5.3 (5)	0.22
Malnutrition, % (no.)	41.8 (81)	43.8 (42)	0.75
Case fatality rate, % (no.)	15.3 (29/190)	3.2 (3/95)	0.002
Deaths predicted, % (no.)	90.6 (30/32)	9.4% (3/32)	0.002

* GMPD = geometric mean parasite density; CI = confidence interval; Hb = hemoglobin.
† Modified from the original WHO (1990) criteria,[13] severe malaria was defined as *Plasmodium falciparum* parasitemia plus at least one of the following: Blantyre coma score ≤3, severe anemia (Hb <5 g/dL plus ≥10.000 parasites/μL), renal failure (clinical criterion), or (see Patients and Methods section): hypoglycemia, circulatory collapse, spontaneous bleeding, multiple convulsions, pulmonary edema, or hemoglobinuria.
‡ n = 283.

the disease. This corresponds to findings in a study of Tanzanian children with severe anemia who were frequently asymptomatic or showed nonspecific symptoms.[25] Among the other symptoms of severe malaria, respiratory distress was associated with hypoglycemia and hyperlactatemia. In accordance with previous observations from Kenya,[5] this suggests that metabolic acidosis rather than anemia and cardiac failure is the underlying cause in respiratory distress. Impaired consciousness, hyperlactatemia, and hypoglycemia were more common in girls than in boys. This may be caused by sex-related differences in health-seeking behavior and/or genetic factors. Jaundice increased in frequency with age, but viral hepatitis cannot be ruled out as a possible cause. The association between hyperparasitemia and jaundice supports the role of hemolysis in the latter. Hemolysis due to sickle-cell disease or glucose-6-phosphate dehydrogenase has yet to be excluded.

The fatality rate associated with severe malaria depends on, among other things, the predominant symptoms that, in turn, have implications for treatment. In the present study, 11% of the children died of severe malaria. The CFR was within the lower range reported in recent studies from Africa.[1,5,10,12,20] Similar to other hospital settings,[1,5,12] the majority of children, especially those with circulatory collapse, died within 24 hours after admission, emphasizing the need for triage and early treatment. As in previous studies,[1,5,9–12,20] hypoglycemia leading to acidosis and impaired consciousness indicated a poor prognosis. This condition can easily be treated by glucose infusion. A bolus infusion of normal saline may also reduce overall mortality, although this contrasts with common practice in many African hospitals because of concerns of volume overload.[11,26] Malnutrition predicted death in children with severe malaria. Some dehydrated children may have been categorized as malnourished and thus biased this association. Nevertheless, the few data available suggest that malnutrition in fact increases the risk of dying from severe malaria.[6,9,27] Severe anemia *per se* was not a cause of fatal outcome. This agrees with previous findings from The Gambia.[12] Severe anemia without respiratory distress or impaired consciousness resulted in a low CRF in Kenya.[5]

In the present study area, children with circulatory collapse, impaired consciousness, malnutrition, hypoglycemia, and to a lesser degree, prostration have to be classified as high-risk patients. In these children, artemisinine-based suppositories may be an option for immediate treatment prior to transfer because such a regimen is fast-acting, highly effective, and can be administered easily.[28]

For medical facilities with limited resources, criteria for diagnosis of life-threatening malaria must be simple and robust, rapidly assessable, and independent of laboratory protocols if possible. According to the 2000 WHO criteria, three patients were identified with subsequent fatal outcome who would have been excluded by the 1990 WHO definition. The higher sensitivity, together with fewer laboratory parameters required, argue strongly in favor of the revised classification. Conversely, the broader definition may also lead to an increase in hospitalization or referral to intensive care. In Dakar, Senegal, children considered as severe cases by the 2000 WHO criteria, but not by the former, required a reduced number of therapeutic interventions; none of the patients died.[10] In the present study, children with severe malaria identified exclusively by the 2000 WHO criteria fell into two major overlapping groups, i.e., prostration and severe anemia at low parasite density. These patients exhibited a relatively low fatality rate. However, without a transfusion, a substantial number of these children would have died.[29] In Tamale, the 2000 WHO definition of severe malaria proved to be clinically feasible and sensitive. Thus, in areas of similar disease patterns and limited resources, the revised WHO criteria may serve well in identifying high-risk children. In comparison with the previous classification, the revised definition provides a simplified tool for rapid and sensitive diagnosis of severe malaria, taking into account a slight loss in specificity. If higher specificity is of importance, as in studies on pathophysiology or on genetic influences on disease progression, the stricter 1990 definition may retain its usefulness.

In conclusion, severe malaria in northern Ghana is characterized by a high proportion of severe anemia and a high fatality rate connected with circulatory collapse and impaired consciousness. Intermittent preventive treatment has been

shown to reduce malaria-associated anemia at the community level.[30] This as well as early diagnosis and prompt treatment of high-risk patients could substantially lower childhood mortality in this region.

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