In the developing world, hypoglycemiam is a frequent complication among admitted children, particularly in malaria-endemic areas, and a defining feature of severe malaria and associated with high case fatality rates (CFR). This complication could be much more common than currently considered, particularly because it frequently occurs without a direct immediate clinical translation. Its etiology has not yet been fully understood and is likely to be multifactorial. Routine screening and treatment of hypoglycemia, as recommended by international guidelines, may be challenging to perform in developing countries on account of the limited resources available. In this review, we discuss the published literature in relation with the incidence, risk factors, and consequences of hypoglycemia among malaria patients, aiming to improve our current understanding of this common and life-threatening complication of malaria.

**KEYWORDS:** children • continuous glucose monitor • glucose consumption • glucose homeostasis • hyperinsulinemia • hypoglycemia • malaria • sublingual glucose

**Background**

Alterations of blood glucose homeostasis are a common problem in pediatric emergency departments in Africa and are associated with a wide variety of disorders and diseases [1]. Hyperglycemia in severely ill non-diabetic and diabetic patients is a well-known factor for increased morbidity and mortality [2,3]. The prevalence of hyperglycemia in children on admission in the tropics is estimated between 2.9 and 11% [4,5]. It has been associated with a greater need for intensive care and worse prognosis in critically ill children in the absence of insulin-dependent diabetes mellitus [4,6]. Hyperglycemia is a risk factor for death in malaria and non-malaria endemic areas [4,5]. Regarding its etiology, it has been described as part of the body’s stress response to hypovolemic or acute illness, such as sepsis and trauma [2,7].

In the other spectrum, the prevalence of hypoglycemia upon admission is estimated between 6.4 and 7.3% among all pediatric hospitalizations in different African countries [5,8,9]. Hypoglycemia in children is associated with malaria, diarrhea and other life-threatening diseases, including meningitis and sepsis as a factor negatively contributing to their outcome. Clinical hypoglycemia is a risk factor for mortality in critical illness, even if only detected as a single episode, increasing the associated mortality from 39.5 to 55.9% [10,11].

Determining the cause of a hypoglycemia episode is a challenging task for clinicians, including endocrinologists. The ‘critical sample’ is the blood sample obtained during the hypoglycemia episode, necessary to screen glucose metabolites and the hormonal pathways involved in glucose homeostasis. It is a challenging sample to obtain and thus seldom available [12,13]. In resource-poor countries, both hyperglycemia and hypoglycemia may be aggravated by the local idiosyncrasies, including an altered nutritional status, delay in arrival and admission to hospital, use of potentially toxic herbal preparations and lack of health facilities [4,5].

Hypoglycemia is a defining feature of severe malaria and the most frequent metabolic complication of severe *Plasmodium falciparum* malaria, particularly in children and pregnant women [14,15]. Hypoglycemia is an independent risk factor of mortality in children with malaria [14,16–19]. Its pathophysiology in patients with malaria is unclear and a clearer understanding of its underlying mechanisms would be essential to improve the management and the prognosis in these children.

In this review, we have focused on malaria-associated hypoglycemia, aiming to describe its
incidence, burden, pathophysiology and consequences for children living in malaria-endemic areas.

Search methodology
Articles were identified through electronic searches of Pubmed, Health InterNetwork Access to Research Initiative (HINARI) and The Cochrane Library without any language or date restrictions. Pubmed was searched through the use of a broad sensitive filter using the following combination of search terms: ‘hypoglycemia’, ‘malaria’ and ‘children’ yielding 183 results, while the same search found out 363 results when the term ‘children’ was dropped (Figure 1). Limits were applied to exclude studies on animals. The references of the retrieved papers were further hand searched for additional studies. Unpublished literature was not searched. The population of interest for this article was restricted to children with confirmed malaria complicated with hypoglycemia. Our outcomes of interest were related to the pathophysiology and prognosis of hypoglycemia in the context of malaria. A total of 86 papers were included in this review.

The burden of hypoglycemia
Hypoglycemia is a condition characterized by an abnormally low level of blood sugar. There is a considerable variability in the thresholds used to define hypoglycemia in the different age groups and diseases among the identified studies. These definitions are based mainly on expert opinion and are still not clear (Table 1). The defining current threshold for hypoglycemia has been established, irrespective of the underlying disease, by the WHO as <2.5 mmol/l in an adequately-nourished child, <3 mmol/l in a severely malnourished child and 2.2 in newborns [20].

Children from limited-resource frequently suffer hypoglycemia due to high prevalence of malaria, diarrhea, malnutrition and other life-threatening diseases often complicated by hypoglycemia [21].

In the neonatal period, hypoglycemia is a significant cause of morbidity and mortality, and lack of detection or improper management can lead to neurological sequelae or death [22,23]. Newborns rely on their mothers for feeding. Frequent health conditions such as prematurity, asphyxia, infections and difficult breathing impair proper nutrition. Moreover, homeostatic mechanisms are not as efficient as in older children. Newborns are thus highly vulnerable to the development of alterations in blood glucose, although the true burden of hypoglycemia among newborns from developing settings remains a mystery as regular control of glycemia is seldom performed.

Severely malnourished children are another population particularly vulnerable to hypoglycemia. It has been estimated that malnutrition contributes to at least one-third of deaths in children <5 years, and the presence of hypoglycemia is potentially a major factor contributing to such a poor prognosis [24]. In these patients, various factors such as lack of exogenous nutritional intake, decreased absorption of disaccharides because of intestinal villous atrophy, increased oxidative stress or glucose uptake by intestinal bacteria compromise glucose homeostasis [25]. The prognosis in severe malnutrition improves when rigorously applying the WHO management of malnutrition guidelines, which take into special consideration the prevention and early treatment of sepsis and hypoglycemia [26].

Clinical features of hypoglycemia
Symptoms of hypoglycemia are classified as neuroglycopenic and neurogenic. The counter-regulatory hormonal response starts at a plasma glucose concentration below 3.8 mmol/l, whereas symptoms of neuroglycopenia (neurological symptoms derived from insufficient glucose reaching the central nervous system cells) arise at a concentration below 2.9 mmol/l [27]. Neurogenic or autonomic symptoms (tremulousness, palpitations, anxiety, sweating, hunger and paresthesias) are the result of the perception of physiological changes caused by the central nervous system-mediated sympathoadrenal discharge triggered by hypoglycemia. The relative contributions of the sympathetic nervous

Figure 1. Flow chart diagram for article selection.
system and of the adrenal medullae, the two components of the sympatoadrenal system, to the neurogenic symptoms, as well as to the increments in circulating norepinephrine and the hemodynamic changes that occur during hypoglycemia, are largely unknown. Neuroglycopenic symptoms (confusion, drowsiness, odd behavior, speech difficulties, incoordination, sensation of warmth, weakness or fatigue, severe cognitive failure, seizure and coma) are the result of brain glucose deprivation. The glycemic threshold for symptoms of hypoglycemia decreases following recent episodes of hypoglycemia, leading to the syndrome of hypoglycemia unawareness, that is, loss of the alarm symptoms associated mortality of 18.8% (odds ratio 1.8 vs non-hypoglycemic patients) [35]. Data from children younger than 15 years admitted with malaria in a rural hospital from Mozambique showed a hypoglycemia prevalence of 1.0% (rising up to 3.7% if only considering severe malaria patients) on admission, associated to a high case fatality rates (CFR) (16.2%) [14]. Admission hypoglycemia was also reported in 8.4% of 1420 children with malaria in a rural hospital from Kenya [5].

**Malaria-related hyperglycemia**

Hyperglycemia is a frequent finding in acute infections as response to stress. In acute *P. falciparum* malaria, however, specific hypoglycemic mechanisms usually overcome the hyperglycemic response. Malaria is a peculiar infectious disease with respect to glucose metabolism as hypoglycemia instead of hyperglycemia is a common complication, especially in children and pregnant women [14,15,36–40]. Hyperglycemia was associated with more frequent seizures in children with severe malaria from Mali. However, in the same study, it was associated with fewer deaths and considered a potentially protective mechanism in children with severe malaria [16].

**Dysglycemia & other Plasmodium species**

*P. vivax* is increasingly recognized as a cause of severe disease [41,42]. Hypoglycemia prevalence described in Asiatic children infected with *P. vivax* was as high as 3%, albeit with no apparent serious consequences (CFR 0%) [42]. In African adults with *Plasmodium* infection, hypoglycemia was detected in 7.7%, lower than in patients with *P. falciparum* malaria (11.5%). CFR were also lower among *P. vivax*-infected individuals [43]. However, an Indian study showed that several complications, including acute kidney injury, jaundice, severe anemia, metabolic acidosis, shock, hyperpyrexia, hypoglycemia or generalized tonic–clonic seizures were more prevalent in patients with *P. vivax* malaria than *P. falciparum* malaria [44]. Most of the American and Asiatic studies in children with

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**Table 1. Different thresholds found in the literature for defining hypoglycemia.**

| Study (year) | Threshold (mg/dl) | Threshold (mmol/l) | Context | Ref. |
|-------------|-------------------|-------------------|---------|------|
| Hospital care for children WHO (2013) | 40 | 2.2 | Newborns | [20,24] |
| Transactions of the royal society of tropical medicine and hygiene | 40 | 2.2 | Severe malaria | [33] |
| Hospital care for children WHO (2013) | 45 | 2.5 | Severe malaria | [20] |
| Hospital care for children WHO (2013) | 45 | 2.5 | Well-nourished children | [20] |
| Hospital care for children WHO (2013) | 54 | 3.0 | Severe malnutrition | [20] |
| Zijlmans et al. (2008); Ogeti et al. (2010) | 54 | 3.0 | Severe malaria | [73,78] |
| Graz et al. (2008) | 60 | 3.3 | Severe malaria | [77] |

The prevalence of malaria-associated hypoglycemia seems to vary in different parts of the world and in different age groups. Jallow et al. reported data from 2042 hospitalized malaria patients, of whom 21.9% presented hypoglycemia with an associated mortality of 18.8% (odds ratio 1.8 vs non-hypoglycemic patients) [35]. Data from children younger than 15 years admitted with malaria in a rural hospital from Mozambique showed a hypoglycemia prevalence of 1.0% (rising up to 3.7% if only considering severe malaria patients) on admission, associated to a high case fatality rates (CFR) (16.2%) [14]. Admission hypoglycemia was also reported in 8.4% of 1420 children with malaria in a rural hospital from Kenya [5].

**Malaria-related hypoglycemia**

In 2012, there were an estimated 207 million cases of malaria (range 135–287 million, around 80% occurring in Africa), which caused approximately 627,000 malaria deaths (range 473,000–789,000). An estimated 3.4 billion people continue to be at risk of malaria, mostly in Africa and south-east Asia [29]. Although most of the *P. falciparum* malaria cases are uncomplicated [30], up to 1–2% can be severe or life threatening [31,32].

In children, severe malaria is defined as asexual forms of *Plasmodium spp.* detected in peripheral blood and at least one of the following: impaired consciousness or coma, prostration, multiple seizures, hyperlactatemia or metabolic acidosis, severe anemia, dark urine, hypoglycemia, jaundice, respiratory distress, shock and/or renal failure [33].

**Malaria-related hypoglycemia**

Hypoglycemia, as a defining feature of severe malaria [20], is considered when glycemia is <2.2 mmol/l or 40 mg/dl [33] and indicates a poor prognosis, predominantly when accompanied by acidemia (pH <7.3) or hyperlactatemia (lactate >5 mmol/l) [34]. It is also a treatable cause of coma and convulsions [20].
malaria comparing *P. vivax* and *P. falciparum* or mixed infections describe low prevalence of hypoglycemia on admission (0.8–3%), even for *P. falciparum* monoinfections [41,42,45]. This could suggest that the nutritional status of Asiatic or American children, including hepatic glycogen stock (which may reflect differences in duration and/or severity of illness), is better than that of African children. Alternatively, the lower incidence of hypoglycemia in such settings when compared to Sub-Saharan Africa may be related to a protective genetic factor associated with ethnic group.

*P. knowlesi* has been recently identified as the ‘fifth human malaria species’. This zoonotic malaria may frequently cause severe or even life-threatening disease [46,47]. The main source of metabolic energy for the erythrocytic stages of the parasite *P. knowlesi* in macaques seems to be glycolysis [48,49] but, this species, to our knowledge, has not been associated with hypoglycemia in humans [47]. *P. ovale* and *P. malariae*, both traditionally considered benign malaria species, have only extraordinarily been associated with severe disease [50,51], but not as a cause of hypoglycemia.

**The pathophysiology of malaria-related hypoglycemia**

**Many causes for a disease**

In contrast to managing and overcoming an acute environmental stressor, alterations in metabolic demand during critical illness are likely to further impact the normal response to hypoglycemia. This combined with therapies that affect glucose metabolism (such as, for instance, quinine) and the catabolic state of severe illness likely predisposes a patient to the glycemic instability witnessed in critical illness and potentially impairs normal mechanisms for defending against hypoglycemia.

Decreased levels of glycemia secondary to the consumption of glucose by the *Plasmodium* parasite, hyperinsulinism caused by quinine, impaired gluconeogenesis and lack of adequate supplementation/oral intake are possible explanations in cases of severe malaria or even uncomplicated malaria [38,52-54].

**Differences between children, adults & pregnant women**

Some studies have revealed that there are differences in the regulation of glucose metabolism between adults and children older than 2 years with *falciparum* malaria and various degrees of severity [39,55]. In adults, hypoglycemia is associated with increased glucose turnover and quinine-induced hyperinsulinemia, which causes increased peripheral uptake of glucose [54,56,57] and may cause low glycemia during quinine treatment, especially in pregnant women [15,58]. Indeed, pregnant women are a particularly high-risk group for severe malaria. Hypoglycemia is a recognized complication of malaria in pregnancy, but its pathophysiology is not well understood. Glucose production in pregnant women with non-severe *P. falciparum* infection is higher compared to healthy pregnant patients, delaying the normal occurrence of hypoglycemia secondary to fasting [59].

These data indicate that stimulation of glucose production by malaria protects pregnant women from hypoglycemia and that pathophysiology of malaria-related hypoglycemia in pregnancy probably is more related to prolonged fasting or treatment (quinine) induced [55,59]. Although fasting is also a recognized risk factor causing hypoglycemia in children, metabolic adaptation of glucose metabolism differs between this age group and adults [60]. Other differences among adults and children related to the incidence of hypoglycemia is that pretreatment hypoglycemia is more common in children [36], whereas data in African children indicate that hypoglycemia related to quinine treatment is rare [36-40,53,61].

All this suggests that glucose metabolism differs in children and adults with severe malaria.

**Risk factors & suggested causes of malaria-related hypoglycemia**

The mechanism underlying hypoglycemia in malaria is not fully explained by pathophysiological data. Causes suggested in identified studies can be divided into two groups: related to quinine therapy and not related to quinine therapy. The second group can be divided into two types of etiological causes: related to increased glucose utilization and related to alterations in glucose production.

Hyperinsulinemia secondary to quinine therapy

Quinine-associated hyperinsulinemia has been described in children, although infrequently [61]. However, basal plasma glucose is usually increased in uncomplicated malaria, suggesting reduced tissue sensitivity to insulin [37]. Such hyperinsulinemia seems to be well balanced, making hypoglycemia less frequent in quinine-treated children than would be expected [62]. However, data in children show that hyperinsulinemia rarely accompanies hypoglycemia either on admission or during quinine treatment [53,61,62]. Ogeti et al. found no evidence of a dose–response relationship between quinine and any degree of hypoglycemia in children with severe malaria after admission, describing instead other markers of disease severity and disruption in the maintenance of the glucose supply associated to hypoglycemia.

Hypoglycemia not related to quinine therapy

**Increased glucose utilization**

Isotope-turnover studies have shown that basal plasma glucose utilization is increased approximately by 50% in severe malaria [37].

**Increased glucose consumption by the *Plasmodium* parasite**

In patients with severe malaria, glucose demand increases approximately by 50%, while this increase is only about 20% in uncomplicated *P. falciparum* malaria [37,39]. *Plasmodium*-infected erythrocytes can consume glucose up to 30 to 100-times the rate of uninfected erythrocytes [53,63]. If the infection progresses, the risk of hypoglycemia increases as host glucose production becomes insufficient for both the host’s and the parasite’s needs. The high-power metabolism of *Plasmodium* leads to a significantly increased glucose consumption of infected erythrocytes [64], but is considered a ‘contributing factor’ rather than the ‘causative factor’ of hypoglycemia.
because of the big difference in glucose demand between the parasites and the severely ill patient [65].

Increased glucose utilization by the host
In the host, the high metabolic demands of a severe illness such as severe *P. falciparum* malaria will increase the glucose needs much more than what a non-severe malaria episode would do. Different studies have shown that the glucose clearance rate, which can be estimated at 20% in uncomplicated malaria, can increase up to 40–70% in severe malaria [37,57].

Alterations in glucose production
Plasma glucose is derived from exogenous supply (enteral or parenteral nutrition) or from endogenous production. Glucose is produced mainly (~90%) in the liver by gluconeogenesis and glycogenolysis, and to a smaller extent (~10%) in the kidney by gluconeogenesis only. Limited glucose production capacity could play a role in the pathophysiology of hypoglycemia in children with *P. falciparum* malaria, but data on glucose production in these children are scarce. In contrast, in adults with severe *P. falciparum* malaria, there is an inverse correlation between plasma glucose concentration and glucose production, suggesting that increased peripheral glucose uptake rather than decreased production was the most important determinant for glucose concentration [57].

Impaired hepatic gluconeogenesis
Failure of hepatic gluconeogenesis is considered to be an important causative factor of hypoglycemia in malaria [33,59,65]. Previous studies in Kenyan children with uncomplicated *P. falciparum* malaria showed that glucose production was an important determinant of the plasma glucose concentration [40], and glucose production seemed to be largely dependent on gluconeogenesis. It has been described that hypoglycemic pediatric patients with malaria have low rates of gluconeogenesis and low contribution of glycogen as a source of glucose production [38,40]. However, subsequent studies, using reliable methods [55,66] to measure glucose kinetics, have found an increase in gluconeogenesis in different populations of patients with *P. falciparum* malaria with varying degrees of severity. Gluconeogenesis contributed 56% to glucose production in children with uncomplicated malaria (no differences among very young and older children) in a study from Surinam [67]. Similarly, in another study, glucose production was also much higher in children with severe malaria than in uncomplicated infection [36,38]. Also, in adults with uncomplicated *falciparum* malaria, glucose production and gluconeogenesis were significantly higher in the malaria patients compared with a group of healthy controls (p = 0.003 and <0.0001, respectively) [68]. In the same order of magnitude, non-severe *P. falciparum* infection in pregnant women resulted in higher glucose production and higher glucose levels, compared to healthy pregnant patients [68]. Gluconeogenic precursors in plasma are increased in severe malaria patients [53,54] and may be explained by anaerobic glycolysis, impaired liver function or other hepatic alterations, but not by inhibition of gluconeogenesis [33,69]. Therefore, it would appear more likely that the hypoglycemia caused by a decreasing hepatic gluconeogenesis occurs mainly in case of liver failure, an uncommon complication among malaria patients [20,37].

Glycogen store depletion
Children have a limited tolerance for fasting because of usually low glycogen stores. Thus, they are only able to maintain a normal plasma glucose level for a maximum fasting period of 12–24 h [70]. However, some studies have described that regulation of glycoenolysis during fasting seems to be driven by the necessity to guarantee glucose output and maintain euglycemia [71]. That could suggest that glycogen depletion might not be important in causing hypoglycemia in malaria after an overnight fast.

Fasting & hypoglycemia
Severe illness, such as severe malaria, induces anorexia and even inability to feed, particularly among young children. Fasting is considered a major risk factor for hypoglycemia in children. Healthy children are able to maintain a normal plasma glucose concentration for up to 24 h of fasting [72]. In the fasting state, plasma glucose levels are maintained within narrow limits by a delicate balance between endogenous glucose production that derives from both glycoenolysis, the breakdown of glycogen, and gluconeogenesis, the production of glucose from lactate, glycerol or several amino acids and glucose utilization. More than 90% of the required energy is provided by glucose, making the brain highly vulnerable to alterations in the plasma glucose levels [70]. Studies performed in children with malaria described that this age group can maintain a normal plasma glucose concentration for at least 26 h of fasting [73] unlike healthy adults which seem capable of maintaining normal plasma glucose levels for up to 86 h of fasting [74] and have demonstrated a relationship between fasting, hypoglycemia, severity of disease and mortality [532]. These data suggest that the most important determinant for hypoglycemia in young children with severe and non-severe malaria seems to be the duration of fasting [73].

Prognosis & consequences of malaria-related hypoglycemia
Morbidity & mortality related to hypoglycemia
As we have previously described, hypoglycemia is a defining feature of severe malaria [20] and indicates a poor prognosis. Its impact can be easily understood when assessing the mortality risk in patients with malaria. Indeed, mortality in severe malaria may increase from 8–13.4% in patients with normal blood glucose levels to 24–61.5% in the hypoglycemic patients [14,16].

A systematic review and meta-analysis of descriptive and interventional studies of severe childhood *P. falciparum* malaria compared clinical features and outcomes in different regions. Asian children presented less frequently with hypoglycemia than African children (1% [0–3%], vs 10% [95% CI: 7–13%] p < 0.05) and hypoglycemia-associated CFR in Asian children...
with severe malaria seemed to be lower than in those from other regions [30]. A prospective study of children with severe malaria conducted in Mali showed a prevalence of hypoglycemia on admission of 3.1% associated with a very high CFR (61.5%) [16]. Table 2 summarizes hypoglycemia associated case fatality rates from different studies.

Data from randomized controlled trials evaluating whether outcomes improve following treatment of hypoglycemia are scarce [21]. A study published a decrease in death rates of cerebral malaria after systematic dextrose 10% infusion [75]. Similarly, another study performed in a tropical setting proved that sublingual and intravenous (iv.) sugar administration is more effective to correct hypoglycemia, but no data related to morbidity or mortality were provided [76].

### Table 2. Associated case fatality rates found in the literature for different hypoglycemia thresholds.

| Study (year)          | Threshold (mmol/l) | CFR (%) | Ref. |
|-----------------------|--------------------|---------|------|
| Willcox et al. (2010) | 2.2                | 61.5    | [16] |
| Mockenhaupt et al. (2004) | 35.4              |         | [85] |
| Lon et al. (2013)     | 30                 |         | [86] |
| Marsh et al. (1995)   | 21.7               |         | [17] |
| Jallow et al. (2012)  | 18.8               |         | [35] |
| Bassat et al. (2008)  | 16.2               |         | [14] |
| Kendjo (2013)         | 3.3                |         | [19] |
| Willcox et al. (2010) | 2.2–4.3            | 46.2    | [16] |
| Ogetii et al. (2010)  | 3.0                | 11      | [78] |
| Willcox et al. (2010) | 4.4–8.2            | 13.4    | [16] |

CFR: Case fatality rates.

### Is there a threshold for hypoglycemia?

There is no universally applicable definition of hypoglycemia, and several different thresholds have been proposed (Table 1). It has not yet been fully elucidated which is the exact threshold of blood glucose that defines a worse prognosis in children with severe malaria. Most studies of severe malaria have used the threshold of <2.2 mmol/l to define hypoglycemia in severe malaria [14,16,33] although the latest threshold proposed by WHO is 2.5 mmol/l [20]. However, an increased risk of death has been associated with intermediate levels of low glycemia [16], so establishing a higher threshold should be considered. Defining the thresholds of hypoglycemia with high risk or morbidity and mortality for improving the prognosis should be a priority. WHO guidelines consider severe hypoglycemia whenever glycemia is less than 2.5 mmol/l but recommend correction when blood glucose <3.0 mmol/l is detected [20]. The most adequate threshold for intervention is not clear, and different limits have been used [16,20,33,77]. It is uncertain whether the same cut-off is also the most optimal for predicting poor outcome [16,21]. Thus, the optimal threshold for malaria-related hypoglycemia should be reviewed in order to improve the hospital management of children with malaria and hypoglycemia and their prognosis.

### Management of malaria-related hypoglycemia

According to WHO algorithms [20], hypoglycemia in children with severe malaria should be corrected if glucose is <3.0 mmol/l. The evolution of blood glucose is dynamic and hypoglycemia may occur and go undetected in severe patients in the time lapse between two assessments, even when they presented blood glucose within normal limits on admission. If glycemia falls at around 3 mmol/l, the patient may present alarm signs of clinical hypoglycemia if not corrected by endogenous contra-regulation metabolic pathways or by exogenous intakes [20]. In non-severely ill children or when the child is capable of eating, feeding is recommended as part of standard management, using a nasogastric tube if necessary [20]. WHO guidelines state that after initial correction, the child must be fed as soon as possible or must receive iv. solution containing dextrose or milk or sugary solutions via nasogastric tube [20].

In relation to the route utilized to correct hypoglycemia, the WHO guidelines recommend oral correction if the child is able to feed or iv. access in children with impaired consciousness [20]. Intravenous infusions are rarely feasible in rural Africa because of the lack of simple equipment or trained staff and can be difficult to administer in young children. An alternative route is via the sublingual mucosa, and it is possible to give simple sugar rather than glucose as shown previously among African hypoglycemic children, regardless of the underlying hypoglycemia etiology [76,77]. There are studies comparing iv. and other routes of administering glucose. Barennes et al. compared outcomes associated with the use of alternative treatments (oral sugar group; sublingual sugar group; 8 ml of dextrose 30% iv. group and water group) in children with moderate hypoglycemia. The authors concluded that sublingual administration was effective in moderately hypoglycemic children [76]. A second study assessed the efficacy of iv. 10% glucose and sublingual sugar in the treatment of hypoglycemia in children with severe malaria. There were no significant differences between groups with regard to treatment response (71% in sublingual sugar group and 67% in iv. glucose group), p = 0.81), and interestingly, correction of hypoglycemia in the sublingual sugar group occurred faster than with iv. glucose because there were delays in setting up the infusion (difficulty to find a venous access due to small or very ill child) [77]. Sublingual absorption appears to be faster than the oral route with an overall mean gain of 36 mg/dl (95% CI: 17.6–54.5) [76]. So, sublingual sugar or ready-to-use oral dextrose gel could be good examples of rapid and highly effective point-of-care treatment of hypoglycemia [76].

Current WHO recommendations related to solution administration to correct hypoglycemia in children with impaired consciousness propose the administration of 5 ml/kg of 10% glucose or iv. dextrose solution rapidly. A second assessment of the blood glucose after 30 mins should be conducted followed
by a repeated dose of the iv. dextrose (5 ml/kg) if glycemia is low (<3 mmol/l). In order to prevent further hypoglycemia in an unconscious child, it is important to give 10% dextrose in normal saline or Ringer’s lactate for maintenance infusion [20]. Although the majority of Sub-Saharan African countries follow the WHO recommendations, other African national guidelines recommend giving 2 ml/kg of 10% dextrose water or 0.5 ml/kg of 50% dextrose water in 1:1 dilution with similar outcomes [8].

Regarding the requirements for specific antimalarial treatment, Ogeti et al. assessed the association between antimalarial treatment and incidence of hypoglycemia and the quinine dose–response relationship in Kenyan children with severe malaria (15 vs 20 mg/kg). They found no relationship between quinine dosage 20 mg/kg loading (plus 10 mg/kg 8-hourly) versus 15 mg/kg loading (plus 10 mg/kg 12-hourly) and the incidence or severity of hypoglycemia (8 vs 5%, p = 0.07) [78]. Different studies have analyzed the safety profile of artesunate in comparison to quinine for the treatment of severe malaria. Artesunate has clearly demonstrated the ability to reduce substantially mortality in African children with severe malaria. Additionally, the incidence of post-treatment hypoglycemia was less frequent in patients assigned to the artesunate group than in those assigned to the quinine group [56,79].

Prevention & early detection of hypoglycemia

Given the abundant evidence suggesting that hypoglycemia causes increased mortality and morbidity [14,16,78], and given the strength of the association of malaria-related hypoglycemia and mortality, and the low associated risk of the intervention, it would appear reasonable to establish all possible measures to prevent hypoglycemia.

Ensuring a prompt and adequate prophylactic supply of glucose through nasogastric tube or glucose drip would appear a necessary measure to avoid hypoglycemia in very ill children who are unable to feed [80]. Hypoglycemia is often asymptomatic and only detected in routine blood testing. The glycaemia assessment is done using classic devices that need a finger prick each time the glucose level must be assessed, or rely on obtaining venous blood from an existing catheter. However, this clinical surveillance requires the adequate presence of human personnel near the patient. After the hypoglycemia episode has been corrected, a new hypoglycemia episode may occur if the situation leading to the first hypoglycemia has not changed and a single correction may probably not be enough to correct it permanently.

Due to the ease of use and rapidity of results, the implementation of strict glucose control in most intensive care units from hospitals of developed countries has resulted in increased use of point-of-care glucose devices in such settings. However, multiple factors affect the accuracy of point-of-care glucose. Glucose meters, a type of POC device frequently used in health care facilities of resource poor countries, tend to overestimate blood glucose compared to laboratory measurements, which are currently considered the gold standard methodology. Paired samples from different point-of-care glucose devices failed the International Organization for Standardization testing criteria in 4.9–13.4% of cases [81]. Moreover, although the use of algorithms and protocols including tight glycemic control (through frequent pricking) could decrease the incidence of hypoglycemia, this necessarily implies increasing the nursing workload and the associated costs, which unfortunately limits its implementation in resource-limited countries. Prevention of hypoglycemia in critically ill children with malaria is probably best accomplished by the combination of accurate measuring techniques, frequent blood glucose monitoring and early recognition of hypoglycemia symptoms.

Five-year view: the way forward

Most studies describing the incidence of hypoglycemia and the adverse prognostic associated consequences are based on the determination of glycemia at a fixed point, usually admission. Few studies in developing countries have monitored glycemia beyond admission and throughout the whole duration of treatment. Understanding the real incidence of hypoglycemia, clinical or subclinical, in pediatric patients during their hospital stay is necessary to establish better ways of preventing its occurrence and recurrence.

Continuous glucose monitors (CGMs) can potentially obviate these limitations. A CGM is a device that measures glucose levels continuously, taking readings every 5 min (288 per day), 24 h a day through the use of a subcutaneous sensor that measures the interstitial glucose level, closely related to the blood glucose level. Contrary to the capillary glucose test, this device does not take any amount of sample (blood or others) with these readings. These devices, routinely used in developed countries in adults and children for the monitoring of diabetes mellitus Type I, are safe and reasonably accurate, can be inserted superficially in the skin and carried by the patient for a maximum of 7 days with no need for replacement. As Branco et al. noted that CGM had good correlation with results obtained using laboratory measurements (r = 0.48) [82], they still require a daily comparison with blood glycemia, in order to calibrate the CGM, and maximize the validity of the measurements.

During the first days of hospitalization, which are the most critical days in patients with risk conditions such as malaria, CGM could allow a better detection of hypoglycemia episodes, and a comprehensive description of the dynamics and evolution of blood glucose. This would help in establishing some preliminary risk factors for hypoglycemia during the first days of illness and help in detecting those patients who could most benefit from additional supplementation and a more thorough control to improve prognosis during hospitalization.

The utilization of CGM, currently being introduced slowly in pediatric intensive care units of developed countries [82,83], may help improve our understanding of the real burden and associated pathophysiology of childhood hypoglycemia. As malaria seldom occurs in developed countries, we need to bring this technology to endemic areas.

At the present, the major inconvenience is the high cost of CGM, which is the most limiting factor to propose their wider
use in resource-constrained settings. Moreover, we still have not established the effect of detecting and/or preventing low glycemia levels that are not associated with clinical symptomatology on patient prognosis. Larger studies in this direction should be undertaken to assess the real effectiveness of CGM use in detecting and treating subclinical episodes of hypoglycemia.

In addition to improving our capacity to detect and routinely and continuously monitor blood glucose levels, better and faster ways of managing hypoglycemia should be developed. In this respect, sublingual mucosa has been shown to be an excellent alternative route for the administration of glucose among moderately hypoglycemic children. A preliminary study suggests that sublingual sugar or pre-prepared dextrose gel are both promising treatments for the prevention and correction of hypoglycemia in children with hypoglycemia, including that secondary to severe malaria [77]. Further confirmatory studies should be done to understand the advantages of bypassing the need for parenteral routes. Although it has already been established that moderate and severe hypoglycemia in critically ill patients are associated with an increased risk of death [84], randomized clinical trials assessing the benefit of correcting hypoglycemia in children with malaria and its potential impact on decreasing CFR should be conducted.

**Expert commentary**

Our review highlights the importance of hypoglycemia as a contributing factor for the adverse prognosis of many infections in children, particularly malaria. As a consequence of this, the measurement on admission and throughout hospitalization of glycemia appears a necessary practice in order to prematurely detect low blood glucose levels and manage them adequately. As this review has consistently shown, hypoglycemia can lead to death if undetected, but can also be rapidly corrected if detected on time.

A standardized definition of hypoglycemia and the thresholds associated with mortality should be a priority. A high CFR has been demonstrated among moderately hypoglycemic children with malaria [16]. The threshold for intervention should also be reviewed in order to improve the hospital management of children with malaria and hypoglycemia and the prognosis. Future large pragmatic randomized trials would help define optimal treatment thresholds.

Most of the time, low blood glucose concentration is not associated with the development of the classic clinical manifestations of hypoglycemia. The absence of clinical symptoms does not indicate that glucose concentration is normal or has not fallen below optimal level for maintaining brain metabolism. The incidence of hypoglycemia during the first days of hospitalization has been seldom studied in the context of malaria. It is possible that the lower the blood glucose on admission, the greater the risk of subsequent development of severe hypoglycemia [16,61]. Assessing blood glucose on admission should be complemented by appropriate surveillance for potential new episodes during hospitalization. Symptoms, signs and conditions that are associated with an increased risk of hypoglycemia should be checked, and their presence used to promote the implementation of corrective measures that can save lives. Irrespective of the capacity of measuring glycemia at the bedside, measures to correct likely hypoglycemia (suspected clinically or as a preventive measure in children with high risk of developing it) should be quickly instituted, given the high mortality associated with hypoglycemia and the low risk of adverse events associated with treatment.

Correction of hypoglycemia is an important therapeutic measure, although it is not clear whether this is sufficient to improve the prognosis. In resource-constrained settings where dextrose infusion is not available or is operationally challenging, other alternatives to parenteral administration should be investigated and promoted in order to correct hypoglycemia in children unable to feed. Both the sublingual or oral routes for sugar administration seem to be promising alternatives. Clinical trials have been performed among moderately and severely hypoglycemic African children, comparing sublingual sugar administration with oral water, oral sugar and dextrose infusion administrations with encouraging results [76,77].

The scientific community should focus research into new diagnostic procedures and therapeutic alternatives accessible for developing countries with limited resources.

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Key issues

- Hypoglycemia is a common problem among pediatric emergency admissions in Africa and is associated with a wide variety of disorders and diseases.
- Hypoglycemia is the most important metabolic complication of severe Plasmodium falciparum malaria, particularly in children and pregnant women.
- This complication could be much more frequent than currently considered, mostly because often it may be under detected due to its subclinical incidence.
- Decreased levels of glycemia secondary to the consumption of glucose by the Plasmodium parasite, hyperinsulinism caused by quinine, impaired gluconeogenesis and lack of adequate supplementation/oral intake are possible underlying mechanisms, but several knowledge gaps persist in our understanding of its pathophysiology.
- Hypoglycemia is an independent risk factor for death in children with malaria and understanding its pathophysiology is essential for implementing the required prevention and management strategies, so as to improve the prognosis in these children.
- In malaria, defining the specific thresholds of hypoglycemia associated with a high risk of mortality should be a priority.
- Modern technologies that allow the minimally invasive continuous monitoring of blood glucose should be utilized to further advance our understanding of the true incidence of hypoglycemia throughout hospitalization and to readily detect those patients who could most benefit from additional glucose supplementation during hospitalization.
- In resource-constrained settings where dextrose infusion is not available or intravenous lines are operationally challenging, other more feasible alternatives for glucose administration should be investigated.
- Randomized clinical trials should be conducted to evaluate alternative routes of administration of glucose and to assess the impact of glycemia correction on decreasing associated CFR.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Zijlmans WC, van Kempen AA, Settie MJ, et al. Adaptation of glucose metabolism to fasting in young children with infectious diseases: a perspective. J Pediatr Endocrinol Metab 2013;27(1-2):5-13

2. Kraft R, Herndon DN, McIak RP, et al. Bacterial respiratory tract infections are promoted by systemic hyperglycemia after severe burn injury in pediatric patients. Burns 2014;40(3):428-35

3. Mekitarian Filho E, Carvalho WB, Troster EJ. [Hyperglycemia, morbidity and mortality in critically ill children: critical analysis based on a systematic review]. Rev Assoc Med Bras 2009;55(4):475-83

4. Sambany E, Pussard E, Rajaonarivo C, et al. Childhood dysglycemia: prevalence and outcome in a referral hospital. PLoS One 2013;8(5):e55193

5. Osier FH, Berkley JA, Ross A, et al. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: prevalence and outcome. Arch Dis Child 2003;88(7):621-5

6. Faustino EV, Apkon M. Persistent hyperglycemia in critically ill children. J Pediatr 2005;146(1):30-4

7. Hirata Y, Tomioka H, Sekiya R, et al. Association of hyperglycemia on admission and during hospitalization with mortality in diabetic patients admitted for pneumonia. Intern Med 2013;52(21):2431-8

8. Elusian JB, Adejuyigbe EA, Adeodu OO. Hypoglycaemia in a Nigerian paediatric emergency ward. J Trop Pediatr 2006;52(2):96-102

9. Solomon T, Felix JM, Samuel M, et al. Hypoglycaemia in paediatric admissions in Mozambique. Lancer 1994;343(8890):149-50

10. Krinsley JS. Glycemic control in the critically ill - 3 domains and diabetic status means one size does not fit all!. Crit Care 2013;17(2):131

11. Rattarasarn C. Hypoglycemia in sepsis: risk factors and clinical characteristics. J Med Assoc Thai 1997;80(12):760-6

12. Hoc FM. Hypoglycemia in infants and children. Adv Pediatr 2008;55:367-84

13. Lteif AN, Schwenk WF. Hypoglycemia in infants and children. Endocrinol Metab Clin North Am 1999;28(3):619-46; vii

14. Basat Q, Guinovart C, Sigauque B, et al. Malaria in rural Mozambique. Part II: children admitted to hospital. Malar J 2008;7:37

15. Loaereswuan S, Phillips RE, White NJ, et al. Quinine and severe falciparum malaria in late pregnancy. Lancet 1985;2(8445):4-8

16. Willcox ML, Forster M, Dicko MI, et al. Blood glucose and prognosis in children with presumed severe malaria: is there a threshold for 'hypoglycaemia'? Trop Med Int Health 2010;15(2):232-40

- Of considerable interest because it is one of the few studies that study and show data of high CFR in children with malaria and intermediate levels of low glycemia.

17. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. N Engl J Med 1995;332(21):1399-404

- Of interest because it is a prospective study of a large number of children admitted to a Kenyan hospital that identified indicators of life-threatening malaria in children.

18. Nadim B, Mtove G, Amos B, et al. Blood glucose as a predictor of mortality in children admitted to the hospital with febrile illness in Tanzania. Am J Trop Med Hyg 2013;89(2):232-7

19. Kendjo E, Agbenyega T, Bojang K, et al. Mortality patterns and site heterogeneity of severe malaria in African children. PLoS One 2013;8(3):e58686

20. World Health Organization. Pocket book for hospital care of children: guidelines for the management of common illness with limited resources. 2nd edition. WHO; Geneva: 2013
27. Service FJ. Hypoglycemic disorders. N Engl J Med 1995;332(17):1144-52
28. Cryer PE. Symptoms of hypoglycemia, thresholds for their occurrence, and hypoglycemia unawareness. Endocrinol Metab Clin North Am 1999;28(3):495-500; v-vi
29. World Health Organization. World malaria report 2013. World Health Organization; Geneva: 2013
30. Manning L, Laman M, Law I, et al. Features and prognosis of severe malaria caused by Plasmodium falciparum, Plasmodium vivax and mixed Plasmodium species in Papua New Guinean children. PLoS One 2011;6(12):e29203
31. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet 2008;371(9608):243-60
32. Collins S, Dent N, Binns P, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. J Pediatr 2012; 161(1):88-93
33. World Health Organization. Severe falciparum malaria. Trans R Soc Trop Med Hyg 2000(Suppl 1):1-90
34. Krishna S, Waller DW, ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. Trans R Soc Trop Med Hyg 1988(1):67-73
35. Jallow M, Casals-Pascual C, Ackerman H, et al. Clinical features of severe malaria associated with death: a 13-year observational study in the Gambia. PLoS One 2012;7(9):e45645
36. Agbenyega T, Angus BJ, Bedu-Addo G, et al. Glucose and lactate kinetics in children with severe malaria. J Clin Endocrinol Metab 2000;85(4):1569-76
37. Binh TQ, Davis TM, Johnston W, et al. Glucose metabolism in severe malaria: minimal model analysis of the intravenous glucose tolerance test incorporating a stable glucose label. Metabolism 1997;46(12):1435-40
38. Dekker E, Hellestein MK, Romijn JA, et al. Glucose homeostasis in children with falciparum malaria: precursor supply limits gluconeogenesis and glucose production. J Clin Endocrinol Metab 1997;82(8):2514-21
39. Dekker E, Romijn JA, Ekberg K, et al. Glucose production and gluconeogenesis in adults with uncomplicated falciparum malaria. Am J Physiol 1997;272(6 Pt 1): E1059-64
40. Dekker E, Romijn JA, Waruiru C, et al. The relationship between glucose production and plasma glucose concentration in children with falciparum malaria. Trans R Soc Trop Med Hyg 1996; 90(6):654-7
41. Goyal JP, Makwana AM. Comparison of Clinical Profile between P. vivax and P. falciparum Malaria in Children: a Tertiary Care Centre Perspective from India. Malar Res Treat 2014;2014:132672
42. Bhattacharjee P, Dubey S, Gupta VK, et al. The clinicopathologic manifestations of Plasmodium vivax malaria in children: a growing menace. J Clin Diagn Res 2013; 7(5):861-7
43. Abdallah TM, Abdeen MT, Ahmed IS, et al. Severe Plasmodium falciparum and Plasmodium vivax malaria among adults at Kassala Hospital, eastern Sudan. Malar J 2013;12:148
44. Nandwani S, Pande A, Saluja M. Clinical profile of severe malaria: study from a tertiary care center in north India. J Parasit Dis 2014;38(1):11-15
45. Manning L, Laman M, Law I, et al. Features and prognosis of severe malaria caused by Plasmodium falciparum, Plasmodium vivax and mixed Plasmodium species in Papua New Guinean children. PLoS One 2011;6(12):e29203
46. Barber BE, William T, Grigg MJ, et al. A prospective comparative study of knowlesi, falciparum, and vivax malaria in Sabah, Malaysia: high proportion with severe disease from Plasmodium knowlesi and Plasmodium vivax but no mortality with early referral and artesunate therapy. Clin Infect Dis 2013;56(3):383-97
47. Rajahram GS, Barber BE, William T, et al. Deaths due to Plasmodium knowlesi malaria in Sabah, Malaysia: association with reporting as Plasmodium malariae and delayed parenteral artesunate. Malar J 2012;11:284
48. Shakespeare PG, Trigg PL. Glucose catabolism by the simian malaria parasite Plasmodium knowlesi. Nature 1973; 241(5391):538-40
49. Devuakul K, Maegraith BG. Blood sugar and tissue glycogen in infections in Macaca mulatta with the Nuri strain of Plasmodium knowlesi. Ann Trop Med Parasitol 1958; 52(3):366-75
50. Descheemaker PN, Mira JP, Bruneel F, et al. Near-fatal multiple organ dysfunction syndrome induced by Plasmodium malariae. Emerg Infect Dis 2009;15(5):832-4
51. Strydom KA, Isaak F, Fren J. Plasmodium ovale: a case of not-so-benign tertian malaria. Malar J 2014;13:85
52. Kawo NG, Msengi AE, Swai AB, et al. Hypoglycaemia and cerebral malaria. Lancet 1990;336(8723):1128-9
53. White NJ, Miller KD, Marsh K, et al. Hypoglycaemia in African children with severe malaria. Lancet 1987;1(8535):708-11
54. White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycaemia and hyperinsulinemia in falciparum malaria. N Engl J Med 1983;309(2):61-6
55. Thien HV, Kager PA, Sauerwein HP. Hypoglycaemia in falciparum malaria: is fasting an unrecognized and insufficiently emphasized risk factor? Trends Parasitol 2006;22(9):410-15
56. Rolling T, Wichmann D, Schmiedel S, et al. Artesunate versus quinine in the treatment of severe imported malaria: comparative analysis of adverse events focussing on delayed haemolysis. Malar J 2013;12:241
57. Davis TM, Looareesuwan S, Puportayakamee S, et al. Glucose turnover
in severe falciparum malaria. Metabolism 1993;42(3):334-40
58. Davis TM, Suputtamongkol Y, Spencer JL, et al. Glucose turnover in pregnant women with acute malaria. Clin Sci (Lond) 1994; 86(1):83-90
59. van Thien H, Ackermans MT, Weverling GJ, et al. Influence of prolonged starvation on glucose kinetics in pregnant women infected with Plasmodium falciparum. Clin Nutr 2004;23(1):59-67
60. Haymond MW, Karl IE, Clarke WL, et al. Differences in circulating gluconeogenic substrates during short-term fasting in men, women, and children. Metabolism 1982; 31(1):33-42
61. Taylor TE, Molyneux ME, Wirima JJ, et al. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. N Engl J Med 1988;319(16): 1040-7
62. Davis TM, Pukrittayakamee S, Supanaranond W, et al. Glucose metabolism in quinine-treated patients with uncomplicated falciparum malaria. Clin Endocrinol (Oxf) 1990;33(6):739-49
63. Roth E Jr. Plasmodium falciparum carbohydrate metabolism: a connection between host cell and parasite. Blood Cells 1990;16(2-3):453-60; discussion 461-456
64. Urscher M, Alich R, Deponte M. The glyoxalase system of malaria parasites–implications for cell biology and general glyoxalase research. Semin Cell Dev Biol 2001;22(3):262-70
65. White NJ. Malaria. In: Cook GC, Zumla AI, editors. 21st edn. Manson’s tropical diseases. W.B. Saunders; London: 2003
66. Landau BR. Stable isotope techniques for the study of gluconeogenesis in man. Horm Metab Res 1997;29(7):334-6
67. Zijlmans WC, van Kempen AA, Ackermans MT, et al. Very young children with uncomplicated falciparum malaria have a higher risk of hypoglycaemia: a study from Suriname. Trop Med Int Health 2008; 13(5):626-34
68. van Thien H, Weverling GJ, Ackermans MT, et al. FFAs are not involved in regulation of gluconeogenesis and glycolysis in adults with uncomplicated P. falciparum malaria. Am J Physiol Endocrinol Metab 2004;287(4):E609-15
69. Pukrittayakamee S, Krishna S, Ter Kuile F, et al. Alanine metabolism in acute falciparum malaria. Trop Med Int Health 2002;7(11):911-18
70. Robinson PJ, Rapoport SI. Glucose transport and metabolism in the brain. Am J Physiol 1986;250(1 Pt 2):R127-36
71. Sprangers F, Thien HV, Ackermans MT, et al. Glycogenolysis during short-term fasting in malaria and healthy subjects—the potential regulatory role of glycogen content on glycogen breakdown: a hypothesis. Clin Nutr 2004;23(5):1051-9
72. Zijlmans WC, van Kempen AA, Serlie MJ, Sauerwein HP. Glucose metabolism in children: influence of age, fasting, and infectious diseases. Metabolism 2009;58(9):1356-65
73. Zijlmans W, van Kempen A, Ackermans M, et al. Glucose kinetics during fasting in young children with severe and non-severe malaria in Suriname. Am J Trop Med Hyg 2008;79(4):605-12
74. Corssmit EP, Romijn JA, Sauerwein HP. Glucose metabolism in uncomplicated P. falciparum malaria. Am J Physiol 2000;278(4):E763-73
75. Gbadoe AD, Amenyah KA, Sauerwein HP, et al. Alanine metabolism in acute falciparum malaria. Clin Nutr 2004;23(5):1051-9
76. Barennes H, Valea I, Nagot N, et al. Sublingual sugar for hypoglycaemia in children with severe malaria. Cochrane Database Syst Rev 2005;(3):CD004927
77. Graz B, Dicko M, Willcox ML, et al. Sublingual sugar is a promising treatment for the prevention and correction of hypoglycaemia in children with severe malaria. Malar J 2008;7:242
78. Ogetii GN, Akech S, Jemutai J, et al. Hypoglycaemia in severe malaria, clinical associations and relationship to quinine dosage. BMC Infect Dis 2010;10:334
79. Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet 2010;376(9753):1647-57
80. Hirshberg E, Lacroix J, Sward K, et al. Blood glucose control in critically ill adults and children: a survey on stated practice. Crit Care 2008;13(3):1328-35
81. Hoedemakers CW, Klein Gunnewick JM, Prinsen MA, et al. Accuracy of bedside glucose measurement from three glucometers in critically ill patients. Crit Care Med 2008;36(11):3062-6
82. Branco RG, Chavan A, Tasker RC. Pilot evaluation of continuous subcutaneous glucose monitoring in children with multiple organ dysfunction syndrome. Pediatr Crit Care Med 2009;10(3):415-19
83. Bridges BC, Preissig CM, Maher KO, Rigby MR. Continuous glucose monitors prove highly accurate in critically ill children. Crit Care 2010;14(5):R176
84. Finfer S, Liu B, Chittock DR, et al. Hypoglycaemia and risk of death in critically ill patients. N Engl J Med 2012;367(12): 1108-18
85. Mockenhaupt FP, Ehrhardt S, Burkhardt J, et al. Manifestation and outcome of severe malaria in children in northern Ghana. Am J Trop Med Hyg 2004;71(2):167-72
86. Lon C, Timmermans A, Buathong N, et al. Severe malaria in Battambang Referral Hospital, an area of multidrug resistance in Western-Cambodia: a retrospective analysis of cases from 2006-2009. Malar J 2013;12:217