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## 1.-BACKGROUND

Alterations of blood glucose homeostasis are a common problem in paediatric emergency departments in Africa and are associated with a wide variety of disorders and diseases[1]. Hyperglycaemia in severely ill non-diabetic and diabetic patients is a well-known factor for increased morbidity and mortality[2,3]. The prevalence of hyperglycaemic 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]. Hyperglycaemia is a risk factor for death in malaria and non-malaria endemic areas [4,5]. Regarding to its aetiology, 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 hypoglycaemia upon admission is estimated between 6.4 and 7.3% among all paediatric hospitalizations in different African countries [5,8,9]. Hypoglycaemia in children is associated with malaria, diarrhoea and other life-threatening diseases, including meningitis and sepsis as a factor negatively contributing to their outcome. Clinical hypoglycaemia 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 hypoglycaemia episode is a challenging task for clinicians, including endocrinologists. The "critical sample" is the blood sample obtained during the hypoglycaemia 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 hyperglycaemia and hypoglycaemia 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].

Hypoglycaemia 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]. Hypoglycaemia 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 focussed on malarial-associated hypoglycaemia, aiming to describe its incidence, burden, pathophysiology and consequences for children living in malaria-endemic areas.

## **2.- 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: “hypoglycaemia”, “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 hypoglycaemia. Our outcomes of interest were related to the pathophysiology and prognosis of hypoglycaemia in the context of malaria. A total of 86 papers were included in this review.

### 3.- THE BURDEN OF HYPOGLYCAEMIA

Hypoglycemia is a condition characterized by an abnormally low level of blood sugar. There is a considerable variability in the thresholds used to define hypoglycaemia 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 hypoglycaemia has been established, irrespectively of the underlying disease, by the World Health Organization (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 hypoglycaemia due to high prevalence of malaria, diarrhea, malnutrition, and other life-threatening diseases often complicated by hypoglycemia[21].

In the neonatal period, hypoglycaemia 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 hypoglycaemia among newborns from developing settings remains a mystery as regular control of glycaemia is seldom performed.

Severely malnourished children are another population particularly vulnerable to hypoglycaemia. It has been estimated that malnutrition contributes to at least one third of deaths in children <5 years and the presence of hypoglycaemia 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 hypoglycaemia[26].

#### **4.-CLINICAL FEATURES OF HYPOGLYCAEMIA**

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, 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 system and of the adrenal medullae, the two components of the sympathoadrenal system, to the neurogenic symptoms, as well as to the increments in circulating norepinephrine and to 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, 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, i.e., loss of the alarm symptoms of hypoglycemia. Thus, patients with hypoglycemia often tolerate abnormally low plasma glucose concentrations without clinical symptomatology (subclinical hypoglycaemia). Hypoglycaemia is, therefore, frequently undetected. None of these symptoms is specific to hypoglycemia and clinical signs may mimic other diseases[20,28].

## 5.- ALTERATIONS OF BLOOD GLUCOSE RELATED TO MALARIA

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 *Plasmodium 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 anaemia, dark urine, hypoglycaemia, jaundice, respiratory distress, shock, and/or renal failure[33].

### Malaria-related hypoglycaemia

Hypoglycaemia, as a defining feature of severe malaria[20], is considered when glycaemia is  $<2.2$  mmol/l or 40mg/dl[33], and indicates a poor prognosis, predominantly when accompanied by acidaemia ( $\text{pH}<7.3$ ) or hyperlactataemia (lactate  $>5$ mmol/l)[34]. It is also a treatable cause of coma and convulsions[20].

The prevalence of malaria-associated hypoglycaemia 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 hypoglycaemia with an associated mortality of 18.8% (OR 1.8 versus non-hypoglycaemic patients)[35]. Data from children younger than 15 years admitted with malaria in a rural hospital from Mozambique showed a prevalence of 1.0% of hypoglycaemia (rising up to 3.7% if only considering severe malaria patients) on admission, associated to a high CFR

(16.2%)[14]. Admission hypoglycaemia was also reported in 8.4% of 1420 children with malaria in a rural hospital from Kenya[5].

### **Malaria-related hyperglycaemia**

Hyperglycaemia is a frequent finding in acute infections as response to stress. In acute *P. falciparum* malaria, however, specific hypoglycaemic mechanisms usually overcome the hyperglycaemic response. Malaria is a peculiar infectious disease with respect to glucose metabolism as hypoglycaemia instead of hyperglycaemia is a common complication, especially in children and pregnant women[14,15,36-40]. Hyperglycaemia 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].

### **Dysglycaemia and other *Plasmodium* species**

*Plasmodium vivax* is increasingly recognized as a cause of severe disease[41,42]. Hypoglycaemia prevalence described in Asiatic children infected with *Plasmodium vivax* was as high as 3%, albeit with no apparent serious consequences (CFR 0%)[42]. In African adults with *Plasmodium* infection, hypoglycaemia was detected in 7.7%, lower than in patients with *Plasmodium falciparum* malaria (11.5%). CFR were also lower among *Plasmodium 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 *Plasmodium vivax* malaria than *Plasmodium falciparum* malaria[44]. Most of the American and Asiatic studies in children with malaria comparing *Plasmodium vivax* and *Plasmodium falciparum* or mixed infections describe low prevalence of hypoglycaemia on admission (0,8-3%),

even for *Plasmodium falciparum* mono-infections[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 hypoglycaemia in such settings when compared to Sub-Saharan Africa may be related to a protective genetic factor associated with ethnic group.

*Plasmodium 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 *Plasmodium knowlesi* in macaques seems to be glycolysis[48,49] but, this species, to our knowledge, has not been associated with hypoglycaemia in humans[47]. *Plasmodium ovale* and *Plasmodium malariae*, both traditionally considered benign malaria species, have only extraordinarily been associated with severe disease[50,51], but not as a cause of hypoglycaemia.

## **6.- THE PATHOPHYSIOLOGY OF MALARIA-RELATED HYPOGLYCAEMIA**

### **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 hypoglycaemia. 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 glycaemic instability witnessed in critical illness and potentially impairs normal mechanisms for defending against hypoglycaemia.

Decreased levels of glycaemia 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 and 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, hypoglycaemia is associated with increased glucose turnover and quinine-induced hyperinsulinaemia, which causes increased peripheral uptake of glucose[54,56,57] and may cause low glycaemia during quinine treatment, especially in pregnant women[15,58]. Indeed, pregnant women are a particularly high-risk group for severe malaria. Hypoglycaemia is a recognized complication of malaria in pregnancy, but its pathophysiology is not well understood. Glucose production in pregnant women with non-severe *Plasmodium falciparum* infection is higher compared to healthy pregnant patients, delaying the normal occurrence of hypoglycaemia secondary to fasting [59]. These data indicate that stimulation of glucose production by malaria protects pregnant women from hypoglycaemia and that pathophysiology of malaria-related hypoglycaemia in pregnancy probably is more related to prolonged fasting or treatment (quinine) induced[15,59]. Although fasting is also a recognized risk factor causing hypoglycaemia 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 hypoglycaemia, is that pre-treatment hypoglycaemia is more common in children [36] whereas data in African children indicate that hypoglycaemia 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 and suggested causes of malaria-related hypoglycaemia**

The mechanism underlying hypoglycaemia in malaria is not fully explained by pathophysiological data. Causes suggested in identified studies can be divided into two groups: (1) related to quinine therapy and (2) not related to quinine therapy. The second group can be divided into two types of etiological causes (i) related to increased glucose utilization and (ii) related to alterations in glucose production.

### **1.- Hyperinsulinaemia secondary to quinine therapy**

Quinine-associated hyperinsulinaemia 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 hyperinsulinaemia seems to be well balanced, making hypoglycaemia less frequent in quinine-treated children than it would be expected[62]. However, data in children show that hyperinsulinaemia rarely accompanies hypoglycaemia either on admission or during quinine treatment[53,61,62]. Ogetti et al found no evidence of a dose-response relationship between quinine and any degree of hypoglycaemia 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 hypoglycaemia.

### **2.- Hypoglycaemia 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 only about 20% in uncomplicated *Plasmodium falciparum* malaria [37,39]. Plasmodium-infected erythrocytes can consume glucose up to 30-100 times the rate of uninfected erythrocytes[33,63] If the infection progresses, the risk of hypoglycaemia increases as host glucose production becomes insufficient for host and parasite 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 hypoglycaemia 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 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 hypoglycaemia in children with *Plasmodium falciparum* malaria, but data on glucose production in these children are scarce. In contrast, in adults with severe *Plasmodium 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 hypoglycaemia in malaria[33,59,65]. Previous studies in Kenyan children with uncomplicated *Plasmodium 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 hypoglycaemic paediatric 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 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 *Plasmodium 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 hypoglycaemia 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 glycogen stores are usually low. Thus, they are only able to maintain a normal plasma glucose level for a maximum fasting period of 12-24 hours[72]. However, some studies have described that regulation of glycogenolysis during fasting seems to be driven by the necessity to guarantee glucose output and maintain euglycemia[70]. That could suggest that glycogen depletion might not be important in causing hypoglycaemia in malaria after an overnight fast.

### ***Fasting and hypoglycaemia***

Severe illness 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 hours of fasting[71]. In the fasting state, plasma glucose levels are maintained within narrow limits by a delicate balance between endogenous glucose production that derives from both glycogenolysis, 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[72]. . Studies performed in children with malaria described that this age group can maintain a normal plasma glucose concentration for at least 26 hours of fasting[73] unlike healthy adults which seem capable of maintaining normal plasma glucose levels for up to 86 hours of fasting[74] and have demonstrated a relationship between fasting, hypoglycaemia, severity of disease and mortality[5,52]. 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].

## 7.- PROGNOSIS AND CONSEQUENCES OF MALARIA-RELATED HYPOGLYCAEMIA

### Morbidity and mortality related to hypoglycaemia

As we have previously described, hypoglycaemia 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 hypoglycaemic patients[14,16].

A systematic review and meta-analysis of descriptive and interventional studies of severe childhood *Plasmodium falciparum* malaria compared clinical features and outcomes in different regions. Asian children presented less frequently hypoglycaemia than African children (1% [0–3%], versus 10% [CI95 7–13%]  $p < 0.05$ ) and hypoglycaemia-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 hypoglycaemia on admission of 3.1% associated to a very high CFR (61.5%)[16]. Table 2 summarizes hypoglycaemia associated case fatality rates from different studies.

Data from randomized controlled trials evaluating whether outcomes improve following treatment of hypoglycaemia 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 sugar administration are more effective to correct hypoglycaemia but no data related to morbidity or mortality were provided[76].

## **Is there a threshold for hypoglycaemia?**

There is no universally applicable definition of hypoglycaemia, 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 hypoglycaemia 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 to intermediate levels of low glycaemia[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 hypoglycaemia whenever glycaemia 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 hypoglycaemia should be reviewed in order to improve the hospital management of children with malaria and hypoglycaemia and their prognosis.

## **8.- MANAGEMENT OF MALARIA-RELATED**

### **HYPOGLYCAEMIA**

According to WHO algorithms[20], hypoglycaemia in children with severe malaria should be corrected if glucose is  $<3.0$  mmol/l. The evolution of blood glucose is dynamic and hypoglycaemia 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 glycaemia falls at around 3 mmol/L, the patient may present alarm signs of clinical hypoglycaemia 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 intravenous solution containing dextrose, or milk or sugary solutions via nasogastric tube[20].

In relation to the route utilized to correct hypoglycaemia, the WHO guidelines recommend oral correction if the child is able to feed or intravenous (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 hypoglycaemic 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 to the use of alternative treatments (oral sugar group; sublingual sugar group; 8ml of dextrose 30% IV group, and water group) in children with moderate hypoglycaemia. The authors concluded that sublingual administration was effective in moderately hypoglycaemic children[76]. A second study assessed the efficacy of IV 10% glucose and sublingual sugar in the treatment of hypoglycaemia 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 hypoglycaemia in the sublingual sugar group occurred faster than with intravenous 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 36m/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 hypoglycaemia[76].

Current WHO recommendations related to solution administration to correct hypoglycaemia in children with impaired consciousness propose the administration of 5ml/kg of 10% glucose or IV dextrose solution rapidly. A second assessment of the blood glucose after 30 minutes should be conducted followed by a repeated dose of the IV dextrose (5ml/kg) if glycaemia is low (<3mmol/l). In order to prevent further hypoglycaemia 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 to give 2ml/kg of 10% dextrose water or 0.5ml/kg of 50% dextrose water in 1:1 dilution with similar outcomes[8].

Regarding the requirements for specific antimalarial treatment, Ogetti et al assessed the association between antimalarial treatment and incidence of hypoglycaemia, and the quinine dose-response relationship in Kenyan children with severe malaria (15mg/kg versus 20mg/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 hypoglycaemia (8% versus 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 to reduce substantially mortality in African children with severe malaria. Additionally, the incidence of post-treatment hypoglycaemia was less frequent in patients assigned to the artesunate group than in those assigned to the quinine group[56,79].

## **9.- PREVENTION AND EARLY DETECTION OF HYPOGLYCAEMIA**

Given the abundant evidence suggesting that hypoglycaemia causes an increased mortality and morbidity[14,16,78]., and given the strength of the association of malaria-

related hypoglycaemia and mortality, and the low associated risk of the intervention, it would appear reasonable to establish all possible measures to prevent hypoglycaemia. Ensuring a prompt and adequate prophylactic supply of glucose through nasogastric tube or glucose drip would appear as a necessary measure to avoid hypoglycaemia in very ill children who are unable to feed[80]. Hypoglycaemia 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 hypoglycaemia episode has been corrected, a new hypoglycaemia episode may occur if the situation leading to the first hypoglycaemia 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 hospital of developed countries, has resulted in increased use of point-of-care glucose (POCG) devices in such settings. However, multiple factors affect the accuracy of POCG. 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 POCG devices failed the International Organization for Standardization testing criteria in 4.9% to 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 hypoglycaemia, this necessarily implies increasing the nursing workload and the associated costs, which unfortunately limits its implementation in resource-limited countries. At this stage, prevention of hypoglycaemia in critically children with malaria is probably best accomplished by the combination of accurate measuring techniques, frequent blood glucose monitoring and early recognition of hypoglycaemia symptoms.

## 10.- FIVE-YEAR VIEW: *The way forward*

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

Continuous glucose monitors (CGM) can potentially obviate these limitations. A CGM is a device that measures glucose levels continuously, taking readings every 5 minutes (288 per day), 24 hours 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 and colleagues noted CGM had good correlation with results obtained using laboratory measurements ( $r = 0.48$ ). [82], they still require a daily comparison with blood glycaemia, 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 hypoglycaemia episodes, and a comprehensive description of the dynamics and evolution of blood glucose. This would help establishing some preliminary risk factors for hypoglycaemia during the first days of illness, and help 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 paediatric intensive care units of developed countries[82,83], may help improve our understanding of the real burden and associated pathophysiology of childhood hypoglycaemia. As malaria seldom occurs in developed countries, we need to bring this technology to endemic areas.

Their major inconvenience at the moment is related to their high cost, 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 glycaemia 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 hypoglycaemia.

In addition to improving our capacity to detect and routinely monitor continuously blood glucose levels, better and faster ways of managing hypoglycaemia should be developed. In this respect, sublingual mucosa has shown to be an excellent alternative route for the administration of glucose among moderately hypoglycaemic children. A preliminary study suggests that sublingual sugar or pre-prepared dextrose gel are both promising treatments for the prevention and correction of hypoglycaemia in children with hypoglycaemia, 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 hypoglycaemia in children with malaria and its potential impact on decreasing CFR should be conducted.

## 11.- EXPERT COMMENTARY

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

A standardized definition of hypoglycaemia and the thresholds associated to mortality should be a priority. A high CRF has been demonstrated among moderately hypoglycaemic children with malaria[16]. The threshold for intervention should also be reviewed in order to improve the hospital management of children with malaria and hypoglycaemia 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 hypoglycaemia. 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 hypoglycaemia[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 glycaemia at the bedside, measures to correct a likely hypoglycaemia (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 hypoglycaemia and the low risk of adverse events associated with treatment.

Correction of hypoglycaemia 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 hypoglycaemia in children unable to feed. The sublingual or oral routes for sugar administration seem both 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.

## 12.- KEY ISSUES

- Hypoglycaemia is a common problem among paediatric emergency admissions in Africa, and is associated with a wide variety of disorders and diseases
- Hypoglycaemia 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 glycaemia 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

- Hypoglycaemia 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 in our understanding of the true incidence of hypoglycaemia 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 glycaemia correction on decreasing associated CFR.

## 13. FIGURES AND TABLES

### Figure legends:

Figure 1: Flow chart diagram for Article selection

### Tables:

Table 1. Different thresholds found in the literature for defining hypoglycaemia

Threshold (mg/dl)	Threshold (mmol/l)	Context	Reference
40	2.2	Newborns	Hospital care for children WHO 2013[20][24]
40	2.2	Severe malaria	Tropical Medicine and International Health[33]
45	2.5	Severe malaria	Hospital care for children WHO 2013[20]
45	2.5	Well-nourished children Severe infection	, Hospital care for children WHO 2013[20]
54	3.0	Severe malnutrition	Hospital care for children WHO 2013[20]
54	3.0	Severe malaria	Ogetti et al[78] 2010, Zijlmans et al[73] 2008
60	3.3	Severe malaria	Graz et al 2008[77]

Table 2. Associated case fatality rates (CFR) found in the literature for different hypoglycaemia thresholds

<b>Threshold (mmol/l)</b>	<b>CFR (%)</b>	<b>Author</b>
2.2	61.5	Willcox et al [16]
	35.4	Mockenhaupt et al[85]
	30	Lon et al [86]
	21.7	Marsh et al [17]
	18.8	Jallow et al[35]
	16.2	Bassat et al [14]
	3.3	Kendjo [19]
2.2 - 4.3	46.2	Willcox et al [16]
3.0	11	Ogetti et al [78]
4.4 – 8.2	13.4	Willcox et al [16]

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### **Reference annotations**

\*\*Willcox ML, Forster M, Dicko MI, Graz B, Mayon-White R, Barennes H. Blood glucose and prognosis in children with presumed severe malaria: is there a threshold for 'hypoglycaemia'? *Trop Med Int Health*. 15(2),232-40 (2010).

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

\*Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, et al. Indicators of life-threatening malaria in African children. *N Engl J Med*. 332(21),1399-404(1995).

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

\*Manning L, Laman M, Davis WA, Davis TM. Clinical Features and Outcome in Children with Severe Plasmodium falciparum Malaria: A Meta-Analysis. *PLoS One*.9(2),e86737 (2014).

*Of interest because it is a meta-analysis of prospective studies of severe malaria whose data highlight that recent estimates of declining global malaria mortality are not replicated by improved outcomes for children hospitalized with that diagnoses.*

\*\*Barennes H, Valea I, Nagot N, Van de Perre P, Pussard E. Sublingual sugar administration as an alternative to intravenous dextrose administration to correct hypoglycemia among children in the tropics. *Pediatrics*. 116(5),e648-53 (2005).

*Of considerable interest because it is a preliminary study that suggests that sublingual sugar is a promising treatment for the prevention and correction of moderate hypoglycaemia in children with malaria.*

\*\*Graz B, Dicko M, Willcox ML, Lambert B, Falquet J, Forster M, et al. Sublingual sugar for hypoglycaemia in children with severe malaria: a pilot clinical study. *Malar J*. 7,242 (2008).

*Of considerable interest because it is a preliminary study that suggests that sublingual sugar is a promising treatment for the prevention and correction of hypoglycaemia in children with severe malaria.*

\*\*Bridges BC, Preissig CM, Maher KO, Rigby MR. Continuous glucose monitors prove highly accurate in critically ill children. *Crit Care*.14(5),R176 (2010).

*Of considerable interest because it is one of the largest studies to date, CGM values have a clinically acceptable correlation with the blood glucose values.*

## **15.- FINANCIAL DISCLOSURE**

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