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Role of Nutritional Interventions in the Management of Pediatric Malaria

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Abstract
This study aimed at investigating the role of nutritional interventions in the management of pediatric malaria, as Malaria is a leading cause of morbidity and mortality for many of these people, and imposes a substantial economic and social burden on these societies. Though precise data are lacking, most estimates agree that malaria causes 800,000 to 1,000,000 deaths per year. The proportion of childhood deaths caused by malaria appears to have been rising during the last three decades. Approximately 81% of malaria cases and 91% of malaria deaths occur in the African Region, where it remains one of the commonest causes of death and serious morbidity, especially for children and pregnant women; approximately 86% of malaria deaths globally are of children under 5 years of age.

1.1 Introduction

Nearly two billion people, roughly a third of the world's population, live in malaria-endemic areas (Tusting, Willey, Lucas, Thompson, Kafy, Smith & Lindsay, 2013).

Malaria is a leading cause of morbidity and mortality for many of these people, and imposes a substantial economic and social burden on these societies. Of the four species of Plasmodia that cause human disease, Plasmodium falciparum causes the greatest burden of disease and death worldwide (Osei & Hamer, 2008).

Though precise data are lacking, most estimates agree that malaria causes 800,000 to 1,000,000 deaths per year. The proportion of childhood deaths caused by malaria appears to have been rising during the last three decades (Snow, Trape & Marsh, 2001).

The epidemiology of malaria in children is difficult to assess as most of clinical symptoms are non-specific and most of the cases occur in settings where no routine testing is available.

Malaria remains a leading cause of ill health. More than 40% of the world's population (approximately 3 billion people) are exposed to malaria in 108 endemic countries. It caused between 655 000 and 1.240.000[1] deaths in 2010. Approximately 81% of malaria cases and 91% of malaria deaths occur in the African Region, where it remains one of the commonest causes of death and serious morbidity, especially for children and pregnant women; approximately 86% of malaria deaths globally are of children under 5 years of age. In fact children are at highest risk for severe disease and death between six months and five years of age: during this period children are most vulnerable as they have lost maternal immunity and they haven't yet developed specific immunity to infection. However this does not mean that younger infants are exempt from the death toll, the contrary is true given the fact that in addition to the well-known inoculum through the blood meal of an infected female anopheles and through infusion of infected blood products, neonates and young infants might also be vertically infected by plasmodia crossing the placenta (Schumacher & Spinelli, 2012).

The epidemiology of falciparum malaria has been changing over the past 10 years, with declining numbers of clinical cases reported in different parts of the world. In Africa, malaria deaths have been cut by one third within the last decade; outside of Africa, 35 out of the 53 countries affected by malaria, have reduced cases by 50% in the same time period. In countries where access to malaria control interventions has improved most significantly, overall child mortality rates have fallen by approximately 20%, a percentage more than twice that of all childhood death attributable to malaria. Part of this reduction may be due to the fact now recognized that malaria is also an important risk factor for other severe infections, namely bacteremia in African children (Obaro & Greenwood, 2011).

1.2 Clinical features

The clinical manifestations of malaria, the severity and course of a clinical attack depends on the species and strain of the infecting plasmodium parasite, as well as the age, genetic constitution (ethnicity), immune status, malaria specific immunity, and nutritional status of the child, the mode of transmission of infection, whether the individual was on prophylaxis or had previous exposure to antimalarial drugs, as the latter may present with only minimal symptoms or signs (Bostrom, Giusti, Arama, Persson, Dara, Traore, Dolo, Doumbo & Troye-Blomberg, 2012).

The malaria paroxysm results from the lysis of parasitized red blood cells and release of merozoites into the circulation at the completion of asexual reproduction. The paroxysm is characterized by fever and chills accompanied by constitutional symptoms, alternating with periods of fatigue but otherwise relative wellness. Although periodicity of the paroxysm in primary attacks is thought to be pathognomonic for malaria species, this periodicity may take several days to become established, may not occur at all in asynchronous infections, or may

be modified by previous immunity or treatment. In patients with previous malaria who are partially immune, merozoite release by erithrocytic schizonts and the accompanying febrile paroxysms are synchronous: approximately every 48 hours for *P.vivax* and *P.ovale* and every 72 hours for *P.malariae*. *P.falciparum* infections are usually asynchronous, resulting in no periodic febrile episodes, at least during the first days of illness (Agrawal & Teach, 2006).

Since severe malaria is a multisystem, multi-organ disease, children frequently present with a combination of the classical clinical phenotypes: cerebral malaria (CM), severe malarial anemia (SMA), respiratory distress, and hypoglycaemia.

The former two, CM and SMA, are the most common complications of malaria in children. Cerebral malaria is defined by WHO as unarousable coma in a patient with *P.falciparum* parasitaemia in who other causes of encephalopathy have been excluded. Children with CM may develop focal neurological signs, decerebrated or decorticated posturing due to raised intracranial pressure, decreased level of consciousness or coma, behavioral changes, hallucinations, and seizures. Seizures can be protracted or multiple and may be followed by a long postictal state or they may be difficult to recognize if they present only by conjugate eye deviation, nystagmus, oral automatisms, salivation, and hypoventilation. Although most children with CM regain consciousness within 48 h and seem to make a full neurological recovery, approximately 20% die and up to 10% have persistent neurological sequelae. These are particularly associated with protracted or multiple seizures which may cause cognitive deficiency and/or epilepsy (Crowley, Chu, Love & Nosten, 2010).

1.3 Complications

Many studies have attempted to decipher which aspects lead malaria infection to severe disease in some, yet remain asymptomatic in others. The likelihood of death is increased in children with pre-existing health problems such as anemia, malnutrition and immunocompromised states. A splenic patients develop rapidly progressive malaria.

Malaria complications result from hemolytic anemia and microvascular obstruction with subsequent tissue ischemia. Features of severe or complicated malaria include respiratory distress, acidosis (pH <7.3), hypoglycaemia (<2.2 mmol/l), elevated aminotransferases, severe anemia (Hb <5 g/dl), and high parasitaemia (defined as >5%–10% infected erythrocytes or more than 500 000 infected erythrocytes per microliter).

It is important to remember that there are no clinical features that are pathognomonic for severe malaria. The well-known clinical (fever, impaired consciousness, seizures, vomiting, respiratory distress) and laboratory (severe anemia, thrombocytopenia, hypoglycaemia, metabolic acidosis, and hyperlactatemia) features of severe falciparum malaria in children, are equally typical for severe sepsis. Leukocytosis does not allow for discrimination either, as it has been described in up to 20% of young children with severe malaria (Ladhani, Lowe, Cole, Kowuondo & Newton, 2002).

This can be (partially) explained by the activation of the same cytokine pathways in both conditions: Releasing debris from both, parasites and erythrocytes, including the so called malaria toxin glycosylphosphatidylinositol as well as malarial pigment (haemozoin) leads to the activation of peripheral blood mononuclear cells and consequently kicks off the cascade of pro-inflammatory cytokines which probably determines disease severity. Last but not least bacteremia may complicate malaria in up to 8% of severe cases, especially in younger patients, increasing the risk for fatal outcome (Berkley, Mwarumba, Bramhan, Lowe & Marsh, 1999).

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Malarial retinopathy (retinal abnormalities consisting of two unique features - patchy retinal whitening and focal changes of vessel color) is highly specific, (Beare, Lewallen, Taylor & Molyneux, 2011) so not necessary (Postels & Birbeck, 2011) for malarial encephalopathy not only in children.

Increasing evidence shows involvement of the angiopoietin-Tie-2 with retinopathy and mortality in paediatric cerebral malaria (Conroy, Glover, Hawkes, Erdman, Seydel, Taylor, Molyneux & Kain, 2012).

Severe malarial anemia (defined as hemoglobin concentration < 5 g/dl in the presence of *P.falciparum* parasitaemia) is more common in children than in adults. While mortality of SMA is low in asymptomatic children (approx. 1%), the presence of respiratory distress and metabolic acidosis is often (up to 30%) associated with a fatal outcome. According to the world malaria report 2011, the fatality rate for high risk populations approaches 40%.

The role of iron supplementation in the prevention and treatment of anemia in malaria-endemic regions has been much debated. Iron deficiency has an adverse effect on child health, cognitive development and overall survival, and WHO guidelines thus recommend routine iron supplementation for children aged 6 months to 24 months living in areas where anemia prevalence is 40% or more. Alterations of iron metabolism in the human host are, however, thought to increase resistance to infection by restricting the availability of iron to microorganisms. With effective malaria control, iron supplementation should not be withheld from children with anemia in endemic areas.

Not only does the severity of malaria infection change with age, but the clinical manifestation of disease does as well: CM occurs more often in children aged 3 to 6 years; SMA is most likely to develop in children younger than 2 years. CM is more often associated with dehydration, hypoglycaemia, acidosis and respiratory distress; SMA is more often associated with spleen and liver enlargement.

Respiratory distress (deep breathing, Kussmaul's respiration) is a clinical sign of metabolic acidosis, and has emerged as a powerful independent predictor of fatal outcome in falciparum malaria. It can be misinterpreted as cardiac failure and circulatory overload, especially if associated with severe tachycardia.

1.4 Congenital Malaria

Pregnant women are more likely than others to be inoculated with and infected by malaria parasites and are more prone to severe forms, making adverse outcomes particularly common in prim gravida women and their offspring.

Besides the mother, Malaria can infect also the placenta and the fetus, leading to low birth weight through intrauterine growth retardation and/or prematurity. Estimates for malaria induced low birth weight range from 7.8–45.3 of every 1000 live births and the associated mortality risks during the first month of life is about 40 times that of babies with normal birth weight (Murphy & Breman, 2001).

The parasite concentration dependent correlation between maternal peripheral blood parasitaemia, placental, and umbilical cord-blood (fetal) parasitaemia has long been known (Redd, Wirima, Steketee, Breman & Heymann, 1996).

All four types of human malaria can be transmitted congenitally, but the disease most often is associated with *P.vivax*. That congenital malaria is not seen more frequently is due in part to the effective barrier function of the placenta. Although congenital malaria develops in 0.1% of immune and 10% of no immune mothers in endemic areas, placental infection occurs in as many as one third of pregnant women. In endemic areas, distinguishing malaria acquired congenitally from that acquired by post-natal transmission from mosquitoes is difficult.

The onset of symptoms is insidious and usually occurs at 2 to 8 weeks of age. The typical malaria paroxysm is usually absent, with the infant presenting instead more sepsis like symptoms: irritability, poor feeding, vomiting and diarrhoea. Fever and hepatosplenomegaly may be found on physical examination. The most common laboratory finding is anemia, but thrombocytopenia and (unspecific) hyerbilirubinaemia are also common. Therapy for the infected species of malaria is curative, but in contrast to the mother, the infant does not need treatment of the exoerythrocytic stages of the parasite.

Interestingly, new evidence suggests that a subset of those vertically affected infants is also at higher risk of malaria infections later in life.

Imported Malaria occurs in children in many non-endemic countries. Over 1000 imported cases in children are diagnosed in Europe each year. Returning to country of origin to visit friends and relatives is the main risk factor. Over three quarters of these individuals did not take the recommended malarial chemoprophylaxis for the region to which they were travelling. The diagnosis often is delayed because of lack of consideration of malaria as a cause of illness and unfamiliarity with the disease. In children with acquired immunity, the signs and symptoms of disease may be subtle and nonspecific, but fever is universal. The diagnosis of malaria should be considered in every child with fever or a history of recent fever who has visited a malaria-endemic area, irrespective of antimalarial prophylactic. The differential diagnosis of fever in a patient with recent international travel history is broad. Common causes of fever by symptom complex are indicated in table 1.

Table 1: Differential diagnosis of malaria

Intermittent fevers: borreliosis, brucellosis, trypanosomiasis, kala azar (visceral leishmanasis), babesiosis, sequential common infections, mononucleosis, rat-bite fever, idiopathic periodic fever, familial Mediterranean fever, lymphoma, juvenile reumathoid arthritis
Fever and headache: meningitis, encephalitis, sinusitis, influenza, typhus, enteroviral infection, tuberculosis, pneumonia, occult bacteraemia, common viral infections
Fever, abdominal pain, vomiting, diarrhoea, and malaise: enteric (typhoid) fever, viral or bacterial gastroenteritis, hepatitis, pyelonephritis, schistosomiasis (Katayama fever), amebias
Fever and jaundice with recent tropical travel: dengue fever, viral hemorrhagic fever, leptospirosis, yellow fever, plague, hepatitis, enteric (typhoid) fever, typhus, haemolytic- uremic syndrome (Shigella, E.coli)

1.5 Diagnosis

WHO guidelines recommend prompt and accurate parasitological confirmation of malaria diagnosis by optic microscopy or rapid diagnostic tests based on lateral flow immunochromatography as part of an effective disease management, as delays in diagnosis are associated with an increased risk of severe malaria, requirement for intensive care and death.

As in adults, the gold-standard diagnosis of malaria rests on demonstration of the parasite in peripheral blood smears of a febrile child. Both thick and thin blood smears should be examined: the thick smear has the advantage of concentrating the parasites and thus increasing diagnostic sensitivity. The thin smear allows for positive identification of the malaria species.

In malaria endemic regions, there is a tendency to treat all fevers as malaria, particularly in high risk groups such as young children. As a result it is not uncommon for malaria to be clinically diagnosed and treated without microscopic confirmation or despite a negative blood smear.

The results of a retrospective study conducted in Uganda among children up to 15 years of age, with a diagnosis of malaria, provide evidence that children who did not have microscopy performed or had a negative blood smear had a higher risk of death than those with a positive blood smear. The higher mortality in children diagnosed and treated for malaria without microscopic confirmation is likely due at least in part to misdiagnosis and a lack of treatment for conditions other than malaria. These results argue for microscopy or rapid diagnostic testing of all children admitted with a presumptive diagnosis of malaria and evaluation of other causes of disease in children with negative results.

In addition, in falciparum malaria, the percentage of parasitized red blood cells, the presence of *P.falciparum* schizonts and pigment deposits in peripheral polymorph nuclear leukocytes may indicate severe malaria.[11]

Serological tests provide confirmation of past malaria infection, but they don't help in the diagnosis of acute infections for treatment purposes. Furthermore, due to persisting maternal antibodies, their use in infants and young children is even more limited.

Additional diagnostic tests for malaria include but are not limited to rapid dipstick tests and polymerase chain reaction. There are now commercially available whole-blood rapid dipstick tests for falciparum malaria that are based on the qualitative detection of the histidine-rich protein 2 antigen of *P.falciparum*; however, their sensitivity and specificity depend on the pre-test probability making it difficult to express clear recommendations. In a recent study from Burkina Faso, designed to evaluate the accuracy of a rapid diagnostic test on the diagnosis of malaria infection and of malaria-attributable fever during low and high transmission season, the overall performance of the sensitivity of the test was below the WHO-recommended threshold of 95%. During the rainy season, almost 90% of febrile children below 1 year, and almost 85% of those between 1 and 4 years, had a positive rapid test, but a positive malaria test result had a Positive Predictive Value of only 82% and 69%, respectively.

1.6 Management and treatment

1.6.1 Uncomplicated Malaria

Treatment of malaria depends on the (presumptive) identification of the species of Plasmodium causing the infection, knowledge of the presence of resistant organisms in the area in which the malaria was contracted, national guidelines, antimalarial availability, individual patient factors and whether the malarial illness is categorized as either uncomplicated or severe.

For falciparum malaria, the urgent initiation of appropriate therapy is especially critical, because

P.falciparum infections can cause rapidly progressive illness and death.

In endemic areas children with uncomplicated malaria, low parasitaemia, no vomiting and who maintain their nutrition and hydration orally may be treated with oral antimalarial, on an outpatient basis.[10]

Where possible and feasible, a thick and thin blood smear, FBCs, electrolytes, blood glucose, and renal and liver function tests should be performed on all patients hospitalized, as well as testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency, if *P.vivax* cannot be excluded.

Drug combinations, rather than monotherapy, are now seen to be the best solution for treating malaria, but the primary problem with using drug combinations in Africa is cost: in much of the continent people have malaria several times a year, and treatment cost – including procurement of drugs - could be prohibitive both for governments and households. This is one of the reasons why too many cases in Africa are still treated with monotherapy with a high risk of treatment failure.

Artemisinin and its derivatives are now a standard component, due to their high plasmodium killing rates and their capacity to target both, sexual and asexual stages they prevent both, clinical deterioration and transmission. Combination of an artemisinin derivative with a long-acting antimalarial drug reduces treatment duration to only 3 days. Artemisinin are generally safe and well tolerated, and are recommended by WHO as first-line treatment for *P. falciparum* and chloroquine-resistant *P.vivax* infection. The main artemisinin-based combination therapies (ACTs) are artesunate combined with either mefloquine or amodiaquine, artemether combined with lumefantrine, and dihydroartemisinin with piperaquine. The artemisinin derivatives are safe and well tolerated by young children, and so the choice of ACTs will be determined largely by the safety and tolerability of the partner drug.

Sulfadoxine-pyrimethamine should be avoided in the first weeks of life because it competitively displaces bilirubin with the potential to aggravate neonatal hyperbilibinaemia. Furthermore the correct dosing in young children still needs to be defined. Primaquine should also be avoided in the first month and in children known to have severe G6PD deficiency.

Alternatives such as clindamycin and doxycycline may also be given, but only in children >8 years because of risk of dental hypoplasia and permanent teeth discoloration. With these exceptions there is no evidence for specific serious toxicity for any of the other currently recommended antimalarial treatments in infancy.

Chloroquine remains recommended for the treatment of infections caused by *P.malariae, P.ovale* and *P.knowlesi*, also ACT seem to be equally effective.

In *P.vivax* and *P.ovale* infections, patients recovered from the first episode of illness may have additional attacks, or relapses, after months or even years without symptoms, because these Plasmodium species have dormant liver stage parasites (hypnozoites) that may reactivate. Treatment with primaquine phosphate for 14 days should be included in the treatment of the first attack to eradicate the hepatic hypnozoites.

Of course, HIV-infected children should receive prompt, effective antimalarial treatment according to the WHO guidelines. While there is evidence that Lopinavir/ritonavir based antiretroviral treatment can lower the risk for malaria in children other combinations may be associated with a higher incidence of neutropenia (artesunate and amodiaquine) or hepatotoxicity (artesunate and amodiaquine plus efavirenz).

1.6.2 Severe Malaria

As already said earlier, the risk of death from severe malaria is greatest in the first 24 hours.

Patients with severe malaria infections or those unable to take oral medications should thus be hospitalized and managed as any emergency: airway patency should be checked, and oxygen should be given. Intravenous access should be rapidly established to allow for lab work (including blood cultures when possible) and parenteral antimalarial therapy.

If referral to a treatment facility able to administer IV treatment cannot be accomplished within 6 h, pre-referral treatment with intramuscular artesunate, artemether, or quinine, or rectal artesunate (10 mg/kg BW single dose) is recommended. The patient should than be referred to a facility where complete parenteral treatment can be given. Only if referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication to be than continued with a full course of the recommended ACT for uncomplicated malaria.

Indications for hospitalization include cerebral malaria, severe anemia, haemoglobinuria, renal failure, pulmonary oedema, coagulopathy, severe thrombocytopenia, shock, high parasitaemia, metabolic acidosis, hypoglycaemia, intractable vomiting, dehydration, seizures, or altered level of consciousness. Among them, respiratory distress and impaired consciousness are indicators of a poor prognosis that should trigger immediate parenteral antimalarial treatment with any effective antimalarial first available. So eventually less efficacious as in non-malaria associated seizures, intravenous diazepam should be administered for any seizure lasting more than 5 minutes.

For parenteral treatment of severe malaria the cinchona alkaloids (quinine and – in the US quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil) can be used. However, recent evidence from the AQUAMAT trial, a multi-centre study conducted in African children hospitalized with severe malaria,

showed a significant mortality reduction by 22.5% in the artesunate group when compared to the quinine group. The superiority of parenteral artesunate over quinine for the treatment of severe malaria in both adults and children and in different regions of the world is reflected also in the latest Cochrane Review.

Artesunate seems to offer additional advantages, ranging from ease of administration (no cardiac monitoring) to the reduction in the incidence of convulsions, coma, and hypoglycaemia developing after discharge.

For children, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW im given on admission then 1.6 mg/kg BW per day; or quinine 20 mg salt/kg BW on admission (IV infusion or divided im injection), then 10 mg/kg BW every 8 h; infusion rate should not exceed 5 mg salt/ kg BW per hour.

Children with anemia associated with severe malaria may require blood transfusion. Platelet transfusions for thrombocytopenia are generally not recommended because thrombocytopenia is not associated with bleeding problems in children.

Blood glucose should be monitored every 4 h and haemoglobin and parasite count at least daily.

Empirical parenteral antibiotic treatment with a third-generation cephalosporin or even a quinolone should also be given as co-infection with malaria and (multidrug resistant) gram-negative bacteria, like non-typhoidal salmonellae, are more frequent than previously thought and may not always be identified by current WHO guidelines.

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