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How Do We Treat Children with Severe Malaria?

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1. Introduction

Malaria imposes a profound burden on global public health; over one third of the world's population (~2 billion people) live in malaria-endemic areas, with ~1 billion people estimated to carry parasites at any one time (Guerin et al., 2002). The greatest burden of malaria falls on sub-Saharan Africa (SSA), where it causes between 200–450 million disease episodes each year and over 1 million deaths. Most of these deaths are in children <5 years. Throughout the world the burden of malaria is increasing, especially in sub-Saharan Africa, mainly attributed to drug and insecticide resistance and social and environmental changes. Couple this to the worldwide increase in international travel, increases in the numbers of legal and illegal economic migrants, as well as in refugees seeking asylum from wars or political unrest, it is not surprising that there is a parallel rise in imported malaria. Nevertheless, in the UK and other European countries malaria is still a rare cause of hospital admission, few paediatricians have ever seen a case of severe malaria. Management of severe malaria should not only focus upon the choice of antimalarial agents, but should include comprehensive management of the child (Maitland et al., 2005a).

2. Epidemiological Considerations

The resurgence of malaria in most tropical countries equates with an increased risk to travellers. Throughout the world, many countries are reporting an increasing number of cases of imported malaria. There are four species of malaria parasite known to naturally infect man. In the UK, other European countries and America there has been a steady rise in the number and proportion of the potentially lethal falciparum malaria. In the UK over two thousand cases of malaria are imported

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every year, however over two decades the predominant type has changed from vivax to falciparum malaria. Half of all cases occur in people visiting friends or relatives overseas, and increased migration from Africa (rather than from India) means that more of these visits are now to areas where falciparum malaria is common. Two thirds of UK falciparum cases occur in London, the vast majority in the African population. A large proportion of total imported cases are in those who have taken no prophylaxis in highly malarious areas. Approximately 13% of these cases were children <15 years (Travel, 2003).

3. Pre-hospital Management

Once infected by *P. falciparum*, without prompt diagnosis and appropriate treatment, progression to severe malaria is likely in a non-immune child. This should always be assumed even for children raised in malaria-endemic areas but now residing in non-malarious areas. Immunity requires years of repeated infection and rapidly wanes when the person is no longer exposed to infective mosquito bites. When a child presents with a possible travel-associated or tropical illness it is important to take a detailed travel and exposure history. Important points to focus upon include a full vaccination history; whether malaria chemoprophylaxis was taken correctly, if indicated; whether specific measures were employed to prevent insect bites. Nevertheless, as malaria prophylaxis and preventative measure are never 100% effective malaria should be considered in any patient presenting with a fever who has travelled to or come from an endemic area (for details visit: http://www.cdc.gov/travel/diseases.htm#malaria or http://www.who.int/topics/malaria/en/). The usual presentation is with fever within two weeks of exposure but in children the presentation can sometimes be with non-specific symptoms including cough, headache, malaise, vomiting and diarrhoea. Common supportive findings in malaria include splenomegaly, mild thrombocytopaenia, anaemia and mild jaundice. Although most patients present within a few weeks or months of their return, presentation may be delayed particularly in the semi-immune, those who have taken prophylaxis and in *P. vivax*, *P. ovale* and *P. malariae* infections. The assessment of the child should include a full clinical examination to exclude any of the severity features (see Box 2.1). Although most cases of *P. falciparum* malaria presenting to health services in the UK are uncomplicated, up to 10% become severe and life-threatening, principally due to delays in diagnosis and inadequate treatment (Bradley, 2003; Ladhani et al., 2003). In uncomplicated disease the clinical features of malaria are similar in both children and adults, however in severe disease the clinical spectrum, complications and management differ. While the clinical symptoms and signs do not help distinguish the infecting Plasmodium species, the travel history is extremely helpful (especially if travelled to Africa where *P. falciparum* is the most common species) in imported malaria cases and in guiding drug selection. Non-infectious diseases specialists are more likely to make errors in therapy than are infectious diseases specialists so prompt referral or consultation is recommended. Specialist advice is recommended for children infected with *P. falciparum* returning from South East Asia, where multi-drug resistant malaria is endemic.

Box 2.1. Clinical features and priorities for management

Recognition of Severe Malaria
High priority: emergency management

- Depressed conscious state (any degree)
- Intercurrent seizures
- Hypoglycaemia <3 mmols
- Evidence of shock
- Hypoxia (oxygen saturations <95%)
- Metabolic acidosis (base deficit >8)
- Severe hyperkalaemia (potassium >5.5 mmols/L)

Intermediate risk: need for high dependency care
Haemoglobin <10 g/dl
History of convulsions during this illness
Hyperparasitaemia >5%
Visible jaundice
P. falciparum in a child with sickle cell disease

- **Low risk: need admission for parenteral medication**

Vomiting Unable to take or comply with oral medication

- **Low Risk: need for observation**

None of the above
Admit and observe on oral treatment

Adapted from BMJ paper

4. Parasitological Diagnosis

In general any fever starting within 8 days of entry into a malaria endemic area is probably not malaria. However, the presumptive diagnosis of malaria should prompt urgent referral for *immediate* diagnosis and management. Failure to expedite appropriate referral may lead to the development of life-threatening disease. Thick and thin blood films, processed from an EDTA sample by the local haematology laboratory are the mainstay of diagnosis. Three thick films taken 12 hours apart excludes most malaria infections in any patient exposed to malaria. If clinical suspicion is high, further films are warranted. Thick films are necessary to diagnose malaria and thin film is required to define species and stages. Failure to prepare and rigorously examine a *thick film* may lead to a falsely negative malaria film especially in non-immune patients who often present with scant parasitaemia. Despite this, some scanty infections may escape detection. There are a number of other tests that are used to detect parasitaemia. The tests detect parasite derived histidine-rich protein 2 (HRP-2) e.g. *Para*Sight F®, ICT malaria P.f.®; parasite lactate dehydrogenase (OptiMal®) or parasite nuclear material (quantitative buffy coat (QBC)). In general, these are quick and simple to use, distinguish between the major forms of

human malaria, and may have some advantages over microscopy, particularly in children with low-density parasitaemia, a characteristic that often applies to those who have been on prophylaxis (Moody and Chiodini, 2002; Palmer et al., 2003).

5. Assessment and Triage of Children with Severe Malaria

As for any other sick child presenting to hospital the initial management of a child with suspected malaria should be guided by a rapid, structured, triage assessment, aimed at identifying emergency and priority signs (1997; Group, 2001) (Box 2.1). The sequence of clinical assessment should remain (1) the early recognition of impending respiratory failure (2) the detection of shock and (3) a neurological assessment. This approach, will guide early management towards the complications that are the most commonly life-threatening. Emergency management should not be delayed while the diagnosis of malaria is confirmed. Unless there is likely to be an undue delay, the administration of specific antimalarial drugs can usually be deferred until resuscitation treatments have been given and the diagnosis confirmed. Nevertheless, if the clinical suspicion of malaria is high, an intravenous infusion of quinine should be started empirically following initial resuscitation, even if the results are delayed. Experimental treatments, such as exchange transfusion, have no role to play in the initial management of children with suspected malaria, and may distract attention from providing urgent and simple life-saving interventions.

It is now clear that severe malaria encompasses a complex syndrome affecting many organs resulting in biochemical and haematological derangements which have many features in common with the pathophysiological derangement seen in children with the sepsis syndrome (Maitland and Newton, 2005). Among these, metabolic acidosis (manifesting as respiratory distress) has emerged as a central feature of severe malaria, and is widely recognized as the best independent predictor of a fatal outcome in both adults (Day et al., 2000) and children (Allen et al., 1996; Newton et al., 1998; Taylor et al., 1993; Waller et al., 1995), mortality being greatest in children in whom acidosis and impaired consciousness co-exist. In malaria-endemic areas, most deaths occur within hours of admission, principally from the failure of the clinician to recognize impending circulatory collapse or respiratory compromise. The latter is particularly true in children with prolonged seizures. Raised intracranial pressure (ICP) may complicate cases presenting in coma (Newton et al., 1998), prompting a cautious approach to volume resuscitation in such children.

5.1. Generic Approached to Management

The airway must be secured, oxygenation optimised, vascular access established, hypoglycaemia, if present should be corrected (5 ml/kg of 10% dextrose). Seizures are common however, in African children with severe malaria around 25% of seizures are subtle or sub-clinical (demonstrated by EEG) (Crawley et al., 1996) The presence of respiratory depression, irregular breathing, drooling, eye deviation or occasionally bizarre posturing should alert the clinician to either the presence of

complex seizures. After ensuring adequate airway and respiratory support specific management should follow the evidence-based consensus guideline advocated by the Advance Paediatric Life support Group (Group, 2001). Seizure prophylaxis is not recommended (Crawley et al., 2000).

5.2. Identification and Management of Shock

Severe falciparum malaria is frequently complicated by features of shock. In a retrospective review of cases presenting to Kilifi District hospital factors associated with a fatal outcome included deep breathing or acidosis (base deficit below −8), hypotension (systolic blood pressure <80 mmHg), raised plasma creatinine (>80 μmols/l), low oxygen saturation (<90%), dehydration and hypoglycaemia (<2.5 mmols/L). Shock was present in 212/372 (57%) children, of whom 37 (17.5%) died, and was absent in 160, of who only 7 (4.4%) died ($\chi^2 = 14.9$; P = 0.001 (Table 2.1) (Maitland et al., 2003a). Delayed capillary refill time (≥2 s) is a reasonable prognostic indicator, especially in children with a decreased conscious level (Pamba and Maitland, 2004). These data suggest that impaired tissue perfusion may play a role in the mortality of severe malaria. Moreover, these results suggest that volume resuscitation, an important life saving intervention in children with hypovolaemia, should be considered in severe malaria with evidence of impaired tissue perfusion.

Table 2.1. Triage parameters and electrolyte derangement suggesting urgent need for intervention in the critically ill child

Parameter	n (%)	Case Fatality (%)
Airway and respiration:		
Hypoxia (O_2 sats <90%)[a]	86/501 (17.1)	30
Respiratory rate >60 br.pm	83/501 (16.6)	20
Deep "acidotic" breathing	104/515 (20.2)	31
Cardiovascular and hydration:		
Severe tachycardia (>160 bpm)	81/503 (16.1)	17
Hypotension (<80 mmHg)	66/507 (13)	26
Capillary refill time >2 secs	165/496 (33.3)	15
Neurological:		
Seizures	303/515 (58.8)	8.3
Prostration[b]	353/514 (68.7)	13
Blantyre Coma Score ≤2	266/509 (52.3)	16
Laboratory:		
Severe acidosis (pH < 7.2)	96/436 (22)	36
Raised creatinine (>80 μmols/L)	96/469 (20.4)	26
Hypoglycaemia (<2.5 mmols/L)	58/478 (12.1)	28
Hyperkalaemia (>5.5 mmols/L)	61/493 (12.3)	28
Hyponatraemia (<125 mmols/L)	21/493 (4.3)	14
Hypokalaemia (<3 mmols/L)	16/493 (3.2)	6

[a]Measured by pulse oximeter;
[b]inability to sit unsupported or breast feed.

We have demonstrated that volume depletion (measured by central venous pressure) was present on admission in the majority of children with severe malaria complicated by acidosis. We also demonstrated that volume expansion safely corrects the hemodynamic abnormalities and is associated with improved organ function and reduction in acidosis (Maitland et al., 2003b).

5.2.1. Volume Resuscitation

Several resuscitation fluids are available for the treatment of severe dehydration or shock in children. Simple electrolyte solutions are of proven benefit in most situations where excess water and electrolyte depletion has resulted from severe diarrhoea or vomiting. In conditions such as septic shock or severe malaria there is still debate over the optimum solution and, in the latter condition, over the safety of volume resuscitation. As in sepsis, some advocate the use of colloidal solutions, which will restore both water and electrolytes and plasma oncotic pressure, thus reducing the risk of potentiating, raised intracranial pressure. There is undoubtedly some risk that aggressive volume expansion would accentuate ICP. Non-colloidal containing solutions such as isotonic saline will move rapidly from the intravascular compartment into the tissues with the potential risk of accentuating raised ICP and pulmonary oedema. This situation is reminiscent of the similar dilemma in the treatment of meningitis, in which it was customary in the past to volume restrict (Herson and Todd, 1977; Powell et al., 1990). Recent studies in meningitis have shown that when compared to volume expansion modest fluid restriction is detrimental to outcome. We have shown in a Phase II randomised controlled trial (RCT), that volume resuscitation with between 20 and 40 mls/kg of either 0.9% saline or 4.5% human albumin solution (HAS), safely corrects the haemodynamic features of shock and improves renal function in Kenyan children with severe malaria (Maitland et al., 2005b; Maitland et al., 2005c). Pulmonary oedema was a rare complication of volume expansion (<0.5%) (Maitland et al., 2005c).

We advise the cautious use of fluid resuscitation when treating children presenting in coma. In the same trial children presenting in coma with the features of shock 11 out of 24 (46%) receiving saline died compared to only 1 out of 21 (5%) receiving HAS (relative risk 9.6; 95% CI 1.4 to 68; P = 0.002) (Maitland et al., 2005c). Until further data become available from larger trials we recommend that HAS should be considered the resuscitation fluid of choice in the subgroup of children who present with coma and features of shock. Volume resuscitation should proceed cautiously and be terminated once there is a satisfactory cardiovascular response to the volume challenge. A urine output of <1 ml/kg/hr, in the absence of urinary retention, indicates impaired renal perfusion secondary to hypovolaemia, and is a good non-invasive guide to fluid management. If the patient is still shocked, or if the shocked state returns, then treatment of shock should take priority, since cerebral perfusion depends on an adequate blood pressure.

Re-evaluation of the respiratory and circulatory status after each intervention is important. For any child with persisting features of shock after having received 40 mls/kg of fluid, we recommend elective tracheal intubation, mechanical ventila-

tion and placement of a central venous catheter to guide further fluid management (Group, 2001). Patients with severe acidosis may self ventilate pCO2 to very low levels as compensation for the metabolic acidosis. Great care should be taken when initiating ventilation to avoid a sudden rise of pCO2, even to normal levels, before acidosis has been partially corrected.

5.3. The Child with Impaired Consciousness (GCS ≤ 8)

Rapid assessment of neurological function should include an assessment of the conscious level (AVPU or Children's GCS scale are adequate), pupillary size and reaction to light, in addition to observation of the child's posture and convulsive movements, if present. Other CNS infections or intracranial haemorrhage should be considered as an alternative diagnosis in a child with neck stiffness or a full fontanelle. The presentation of an acute neurological syndrome characterised by impaired consciousness, convulsions, abnormal neurological signs, and opisthotonic posturing are cardinal features of cerebral malaria (2000). However, these features may also suggest raised ICP in a small proportion of children (Newton et al., 1991a; Walker et al., 1992; Waller et al., 1991b). Initial management should include maintenance of the airway, support of breathing and immediate correction of hypoglycaemia and volume deficits. These interventions will correct hypoxia, hypoglycaemia or shock, which maybe potential contributors to the depressed conscious level. Children who remain unconscious (GCS ≤ 8) or have features suggestive of raised ICP warrant elective intubation and ventilation. For those with seizures, the decision to ventilate may be delayed if they are in a post-ictal state, as long as the airway is patent. Repeated seizures and motor posturing movements are commonly seen in severe malaria. In sub-Saharan Africa abnormal motor posturing (AMP) manifesting as decorticate, decerebrate or opisthotonus is often observed since few hospitals have facilities for paralysis and ventilation. However, the pathogenesis of these signs and prognosis of each type of posturing is unclear (Idro et al., 2004; Molyneux et al., 1989; Newton et al., 1997; Newton and Krishna, 1998; Schmutzhard and Gerstenbrand, 1984). Raised ICP, cerebral ischaemia, hypoxia, hypoglycaemia, and hyponatraemia are suggested as causes of AMP. The relationship AMP and raised ICP has yet to be established, nevertheless, owing to the potential risk of raised ICP ventilation should aim to optimise the pCO2 in the normal range, as there is no evidence that hyperventilation is beneficial in raised ICP. To date, the only clinical sign that was associated with the development of intermediate or severe intracranial hypertension, was a sluggish or absent pupillary response (Newton et al., 1997). Other signs (such as absent or extensor motor response, pupillary dilatation, decerebrate posturing, or absent oculocephalic reflexes) were not (Newton et al., 1997). Recent studies in children in Malawi have demonstrated a retinopathy that is peculiar to severe malaria, consisting of patchy whitening of the retina both in the macular and extra-macular areas, pale opacification of retinal vessels, and white-centred haemorrhages (Lewallen et al., 1999) (Figure 3). In children who died histopathological examinations of retina, parietal and cerebellar sections of the brains showed a correlation between the density of

haemorrhages in the retina with their density in the brain (Lewallen et al., 2000; Lewallen, 2000; White et al., 2001). The presence of the retinopathy may help guide management (Taylor et al., 2004).

6. Monitoring

6.1. Blood Tests

Once the diagnosis is made, repeat blood films for parasite counts may be useful in following the progress of the disease. However, the paediatrician should be aware that, as quinine acts upon the later stages (schizonts), which are the generally sequestered in the microcirculation and thus not generally visible to the microscopist examining the blood film (that generally examines the circulating younger ring stages), peripheral parasitemia might continue to increase over the first 24 hours. In cases presenting from Africa (where quinine resistance is rarely encountered), this rarely indicates quinine resistance, and should not cause undue alarm. The addition or development of features indicating clinical severity should be used to guide initial and subsequent management rather than the parasitaemia alone.

6.2. Other Laboratory Investigations

To determine the range of biochemical and haematological derangements the following basic blood tests should be performed: full blood count, electrolytes (including potassium magnesium, phosphate and calcium) (Maitland et al., 2005d), urea (BUN) or creatinine, blood glucose, lactate and a blood gas. These should be measured serially, at least 12 hourly, if the child remains critically ill. Additional blood should be obtained for blood cultures and for blood grouping, in case a transfusion is required subsequently.

7. General Management

7.1. Antimalarial Medication

Parenteral quinine remains the first line anti-malarial drug for patients with severe falciparum malaria. Parenteral quinine, prescribed as quinine dihydrochloride (122 mg salt contains 100 mg quinine base) remains the first line treatment of severe falciparum malaria given as an initial loading dose of 20 mg salt/kg IV over 4 hours then 10 mg/kg IV tds. Intravenous quinine should be prescribed for any child with *P. falciparum* malaria who is unable to take oral medication or is vomiting. Mefloquine is a synthetic analogue of quinine and the *quinine loading dose should be omitted if the patient has taken mefloquine prophylaxis* in the previous 24 hours or received a treatment dose within the previous 3 days. Quinine should be prescribed for 7 days however once the child can take oral medication. Further treatment with another antimalarial is recommended (since its bitter taste precludes

Table 2.2. Antimalarial treatments

Drug	Uncomplicated Malaria (oral medication)	Complicated Malaria (parenteral medication)
Proguanil with Atovaquone (Malarone®)	Daily dose for 3 days: **Paediatric tablets** 5–8 kg: 2 paediatric 25 mg tablets, 9–10 kg: 3 paediatric 25 mg tablets given once daily **Adult tablets** 21–30 kg: 2 adult 100 mg tabs, 31–40 kg: 3 adult (100 mg) tabs, >40 kg: 4 adult (100 mg) tabs given once daily	**Quinine hydrochloride:** Loading dose 20 mg salt/kg IV (over 4 hours) then 10 mg/kg IV (over 4 hours) 8 hourly for 7 days. Or if oral medications tolerated before 7 days then switch to *complete course* of oral medication (Malarone®, mefloquine or artemether with lumefantrine) as for uncomplicated malaria[1]
Mefloquine (Lariam®)	15 mg base/kg followed by a second dose of 10 mg/kg 8–24 hours later[2] Given at 0, 8, 24, 36, 48 and 60 hours 5–<15 kg: 1 tab; 15–<25 kg 2 tabs; 25–<35 kg 3 tabs; ≥35 kg: 4 tabs (adult dose) Give with milk or similar as bioavailability significantly enhanced with fat.	
Artemether with lumefantrin (Riamet® or Coartem®)		

[1]Avoid prescribing oral quinine in children as the bitter taste may affect compliance.
[2]Repeat dose if vomited within 30 minutes.

its oral prescription to children). Mefloquine (Lariam®), Atovaquone-proguanil (Malarone®) or Lumefantrine-artemether (Coartem®, Novartis, Basel, Switzerland is currently the only fixed ratio artemether combination therapy that has been developed up to international standards) are potential follow on therapies. See Table 2.2 for doses. For those returning from Southeast Asia, where quinine resistance is problematic, advice regarding the use of intravenous artesunate should be sought from one of the regional centres. Other anticipated complications and management are covered in Box 2.2.

7.2. Role of Exchange Transfusion

Exchange transfusion has been advocated for hyper-parasitaemia (>10%) in adult ICU settings, despite no evidence to suggest that it confers a better outcome (Riddle et al., 2002). Even when parasitaemia exceeds 25%, the vast majority of children respond rapidly to the treatments outlined above. In those with persistent acidosis, and multi-organ impairment not responsive to the resuscitation treatments outlined above, exchange transfusion may be considered as a means of rapidly reducing the level of abnormal red cells, or parasite toxins. This treatment however remains experimental.

Box 2.2. Anticipated complications

Very common

- **Hypoglycaemia (blood glucose <3 mmols):** correlates with disease severity.
- **Hyperpyrexia:** increases the risk of convulsions in children and should be treated with antipyretics/tepid sponging. Ibuprofen superior to paracetamol fever reduction, dose should be reduced in cases complicated by impaired renal function.
- **Seizures and Posturing** – see under emergency management

Common

- **Electrolytes derangement:**
  - hyperkalaemia complicates cases with severe metabolic acidosis at admission.
  - hypokalaemia, hypophosphataemia and hypomagnesaemia only apparent postadmission. Serial monitoring of plasma electrolytes is suggested.

  Treatment should follow standard APLS guidelines
- **Metabolic Acidosis:**
  - Resolves with the correction of hypovolaemia and treatment of anaemia by blood transfusion
  - No evidence to support the use of sodium bicarbonate.
- **Severe malaria anaemia:**
  - Most cases will experience some reduction of haemoglobin, and do not require transfusion. Decision to transfuse influenced by the parasitaemia level and clinical condition of the child.
  - Transfuse if the Hb falls below an absolute value of 10 g/dl.

Uncommon

- **Secondary bacterial infection** may occur and empiric broad-spectrum antibiotics are warranted
- **Coagulation activation:** Bleeding is rare despite the customary thrombocytopenia of severe malaria (platelet counts often $<50 \times 10^9$/L)

8. Outcome

Once recognised and adequately treated the outcome from severe malaria is generally favourable. Experience from the non-immune or semi-immune adults with severe malaria suggest that the complication of jaundice, renal failure, pulmonary oedema and adult respiratory distress syndrome are more frequent. Whilst transient renal impairment, secondary to hypovolaemic shock, is common in children with severe malaria from hyperendemic areas. Renal function generally corrects with the provision of volume expansion. There have been case reports from India demonstrating that children of an older age are more likely to have the adult phenotype of

severe malaria including renal failure and ARDS suggesting that more data are needed to determine whether the management prescribed above is appropriate for children with severe malaria who are not ordinarily resident in malaria endemic areas.

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