In Africa, malaria continues to be one of the most important causes of childhood morbidity and mortality. Most deaths, in children admitted to hospital with severe malaria, occur within the first 24 h (Newton and Krishna, 1998). In other words the majority of children die of the complications of severe malaria before they can benefit from the full effect of quinine. Therefore, improvements in outcome will require the implementation of supportive therapies directed at treating complications and correcting disordered physiology. A wide variety of adjunctive therapies have been evaluated but have not resulted in improved outcome (White, 1998). The introduction of other novel therapies needs to be based on a better understanding of the pathophysiological processes involved.

Over the last decade there have been considerable advances in the understanding of the clinical pathophysiology of malaria, principally as a result of detailed clinical and laboratory studies. Severe malaria in children was previously considered to comprise two major clinical syndromes (World Health Organization, 1990; Bruce-Chwatt, 1952; Carme et al., 1992; Colbourne and Edington, 1954; Greenwood et al., 1987; Molyneux et al., 1988; Musoke, 1966; Snow et al., 1994; Snow et al., 1997): cerebral malaria (secondary to intracerebral sequestration of parasites) (Beeson and Brown, 2002; Marsh, 1992) and severe malaria anaemia (Abdalla et al., 1980; Newton et al., 1997b; Phillips and Pasvol, 1992).
However, it has now been recognised that this model is too simplistic and in recent years severe malaria has been regarded as a complex syndrome affecting many organs. It also becomes apparent that metabolic acidosis, often manifesting as respiratory distress, is an important component of the severe malaria syndrome (Fig. 1) (Allen et al., 1996; Krishna et al., 1994; Marshall et al., 1996; Waller et al., 1995). This has led to a change in the understanding of the processes underlying severe malaria and an appreciation that severe malaria comprises systemic functional derangements resulting from the host–parasite interaction (Marsh, 1999).

**1. Cytokine activation and microcirculatory changes**

In both severe malaria (Day et al., 1999; Grau et al., 1989; Kern et al., 1989; Kwiatkowski et al., 1990) and sepsis (Bone, 1996; Hack et al., 1997; Hotchkiss and Karl, 2003; Santos and Wilmore, 1996) the release of a variety of toxins triggers the activation of host immune factors that include cytokines, such as tumour necrosis factor (TNF) and pro-inflammatory interleukins, oxygen free radicals and nitric oxide, which result in damage to host endothelium and tissues. The prevailing theory that the sepsis syndrome represents an over-stimulated immune response (Hotchkiss and Karl, 2003) has some parallels in severe malaria. Studies in African children have shown that raised levels of the inflammatory cytokines tumour necrosis factor-α, interleukin (IL)-1β, and IL-6 are associated with cerebral malaria (Grau et al., 1989; Kern et al., 1989; Kwiatkowski et al., 1990) and relatively...
low levels of the anti-inflammatory cytokine IL-10 are associated with severe malarial anaemia (SMA) (Kurtzhals et al., 1998). In Vietnamese adults with severe malaria, elevated plasma cytokines are associated with systemic pathologic abnormalities but not with cerebral involvement (Day et al., 1999). In children, the role of pro- and anti-inflammatory cytokines in other manifestations of severe falciparum malaria (particularly acidaosis) is not well defined (Torre et al., 2002). Since the manifestations of the host response in malaria are similar to the systemic inflammatory response syndrome (SIRS) or sepsis syndrome (Kumar et al., 2001; Levy et al., 2003; Saez-Llorens et al., 1995) it is logical to draw some parallels between what is known about septic shock and severe malaria. Potential endotoxin-mediated manifestations include endothelial damage which can lead to increased vascular permeability, leakage of colloid from the intravascular space, pathological vasodilatation and myocardial depression; ultimately resulting in hypovolaemia and impaired organ perfusion (Kumar et al., 2001) (Levin, 1987). In severe malaria, such haemodynamic changes could augment other pathophysiological processes specific to P. falciparum, such as microvascular obstruction secondary to cytoadhesion of PRBC to vascular endothelium (Kyes et al., 2001), rosetting (Chen et al., 2000) and reduced RBC deformability (Dondorp et al., 2002) all of which may result in impaired tissue perfusion.

2. Clinical manifestations of severe malaria in children

In order to illustrate current approaches to the management of severe malaria in childhood we will discuss the major clinical presentations rationalised into one of the five clinical scenarios. Although these scenarios are not mutually exclusive, they are presented as a means for discussing our current understanding of the disordered physiology seen in severe malaria, therapeutic challenges and areas requiring further research (Table 1).

When approaching any sick child with the clinical features of severe malaria the importance of a rapid, structured approach to cardiopulmonary and neurological assessment in deciding management priorities, should be stressed (Advanced paediatric life support: the practical approach, 1993; American Heart Association, 1997). This includes the initiation of generic supportive therapies, which are fundamental to the management of any critically ill child, irrespective

Table 1
Clinical spectrum of severe malaria in childhood

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical presentation</th>
<th>Mortality</th>
<th>Pathophysiology</th>
<th>Specific supportive treatments</th>
<th>Key areas for research</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coma; 'cerebral malaria'</td>
<td>&lt;5% (if post-ictal); &gt;5–10% (if coma prolonged)</td>
<td>Parasite sequestration; 'brain' swelling; impaired blood-brain barrier</td>
<td>Treat convulsions, (mannitol unproven)</td>
<td>Neuroprotective therapies</td>
</tr>
<tr>
<td>2</td>
<td>Respiratory distress ± prostration or lethargy ± hypoglycaemia</td>
<td>1–2%</td>
<td>Destruction of parasitised and non-parasitised red blood cells; impaired reticuloendothelial system</td>
<td>Volume replacement</td>
<td>Volume required; define most appropriate colloid or crystalloid</td>
</tr>
<tr>
<td>3</td>
<td>Severe anaemia, no respiratory distress or impaired consciousness; 'severe malaria anaemia'</td>
<td>10–15%; [&gt;35%]</td>
<td>Lactic acidosis; reduced red cell deformability; impaired perfusion and possible end-organ failure in children with coma and hypoglycaemia</td>
<td>Blood</td>
<td>Optimised timing and speed of transfusion; management to correct volume deficit; red cell substitutes</td>
</tr>
<tr>
<td>4</td>
<td>Severe anaemia + respiratory distress; [+ coma] ± hypoglycaemia</td>
<td>1–2%</td>
<td>Destoriation of parasitised and non-parasitised red blood cells; impaired reticuloendothelial system</td>
<td>Transfusion or haematinics</td>
<td>Rigorous testing of WHO guidelines on transfusion; reduce blood transfusion; role of blood substitutes</td>
</tr>
<tr>
<td>5</td>
<td>Deep coma + respiratory distress ± hypoglycaemia</td>
<td>&gt;20%</td>
<td>Multi organ involvement; neuro-metabolic disorder or role of hypoglycaemia</td>
<td>Supportive fluids</td>
<td>Safety of volume therapy? Improved understanding of metabolic derangement</td>
</tr>
</tbody>
</table>
of aetiology. For example, for a child with status epilepticus, clearing the airway by suction, provision of oxygen and correct positioning are as important and life saving as appropriate anti-convulsant therapy. Furthermore, optimal basic life support can be implemented with few resources and by non-specialist medical personnel. Current supportive therapies include the provision of intravenous fluids, the treatment of hypoglycaemia, hyperpyrexia and convulsions and the prevention of aspiration by nasogastric tube insertion and aspiration (World Health Organization, 2000).

3. Common clinical scenarios in severe malaria

The scenarios are considered in three groups: coma, acidosis and anaemia. Coma (so-called ‘pure’ cerebral malaria) and uncomplicated severe anaemia (haemoglobin < 5 g/dl) (scenarios 1 and 3) characterise the traditional model of severe malaria in children. In both cases prompt treatment with effective anti-malarials and appropriate supportive therapies will result in case fatalities around 5% in children with coma and 1% in children with severe anaemia (Marsh et al., 1995). It is children with respiratory distress, a clinical manifestation of metabolic acidosis, presenting with either impaired consciousness or anaemia who represent the greatest and most urgent therapeutic challenge and it is in this group that most deaths occur.

4. Scenario 1: coma

In falciparum malaria impairment of consciousness is not always synonymous with ‘cerebral malaria’. Decreased conscious level may result from a variety of metabolic and haemodynamic complications and this term should be restricted to children with sustained impairment of conscious level (inability to localise pain) after correction of hypoglycaemia and hypovolaemia. Characteristically, cerebral malaria presents with a 1–4-day history of fever and convulsions. Coma is frequently precipitated by a prolonged seizure. Within the group of children presenting primarily in coma (without other complications) there is considerable heterogeneity. In the majority of cases the provision of supportive therapies and the administration of quinine is accompanied by a successful resolution of coma over the subsequent 4–12 h. Neurological sequelae in this sub-group are generally infrequent. However, there are a number of children who, at presentation, are indistinguishable from children of good prognosis but then develop persistent deep coma, status epilepticus, posturing and brain stem features suggestive of raised intracranial pressure (ICP). Such children pose a significant therapeutic challenge since they often require multiple anti-convulsant medications, with the attendant risk of depression of respiratory drive which, in turn, will worsen brain-swelling. The most common seizures in severe malaria are focal motor or generalised tonic–clonic convulsions (Bondi, 1992; Crawley et al., 1996). However, around 25% of seizures are subtle or sub-clinical (detected with EEG) frequently manifesting as eye deviation, an irregular respiratory pattern or drooling (Crawley et al., 1998) (see picture 1). Intracranial pressure monitoring and post-mortem studies in this group of patients with a prolonged and complicated course have demonstrated brain-swelling is a major feature in fatal cases (Newton et al., 2000; Newton et al., 1994), particularly in the agonal stages (shown in picture 2). Fig. 3 shows the CSF pressures of children with severe malaria in fatal cases and survivors. The only sign that was associated with the greatest and most urgent therapeutic challenge and it is in this group that most deaths occur.

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5. Scenario 2: acidosis

In this group the chief clinical presentations are either lethargy or prostration in association with respiratory distress characterised by deep (Kassmaul) breathing (English et al., 1996a). Convulsions and hypoglycaemia are also frequent complications. Although respiratory distress can occur for several reasons, including lower respiratory tract infection, studies from Kilifi have shown that the vast majority of cases of malaria with respiratory distress are accompanied by metabolic acidosis (English et al., 1995; English et al., 1996a). The aetiology of the acidosis and its optimal management are still unresolved; although increased production and impaired metabolism of organic acids have been suggested as causes. Several factors which increase lactate production, are present in malaria including fever, severe anaemia, hypovolaemia, altered rheological properties of non-parasitized red blood cells (NPRBC), recent seizure activity, the products of parasite metabolism and decreased elimination through impaired hepatic blood flow and function (Agbenyega et al., 2003; Newton and Krishna, 1998). However, hyperlactataemia is not the only cause of acidosis in malaria. Ketoacidosis is a common finding in children with severe malaria in Kenya (English et al., 1997b; Maitland et al., 2003b) and Papua New Guinea (Allen et al., 1996). In Vietnam 63% of adults with severe malaria were acidic (serum base deficit > 3.3) but only 35% had lactataemia (lactate > 4 mmol/l). Serum base deficit (SBD) was the best correlate with a fatal outcome, while serum creatinine and lactate accounted for most of the variation in SBD. Impaired renal and hepatic function were important co-factors in the acidosis of severe malaria (Day et al., 2000).

Few studies have been conducted which assess the specific treatment of acidosis in children with malaria. In the past, sodium bicarbonate has been used to correct the acidosis; however, it has fallen out of favour since it fails to address the underlying processes and has not been shown to improve outcome (World Health Organization, 2000; White, 1998). Many caution against the use of 8.4% sodium bicarbonate as it results in hypernatraemia and hyperosmolality (Adrogue and Madias, 1998). Other concerns relate to experimental work demonstrating increased carbon dioxide production and worsening acidemia; paradoxical acidification of the cerebrospinal fluid; decreased myocardial contractility; increasing lactic acid production or decreasing metabolism of organic acids (Graf and Arieff, 1986; Narins, 1987). In chronic acidosis the administration of sodium bicarbonate has lead to a decrease in the delivery of oxygen to tissues by causing a left shift in the oxygen dissociation curve (Graf and Arieff, 1986; Narins, 1987). Sodium bicarbonate is not recommended in the WHO guidelines for the treatment of malaria complicated by acidosis nor is it recommended in general as first line treatment for the management of metabolic acidosis in conditions such as systemic sepsis or

Other experimental agents for the management of acidosis in children with severe malaria include sodium dichloroacetate (an inducer of pyruvate dehydrogenase) (Krishna et al., 1995) and N-acetylcysteine, an inhibitor of tumour necrosis factor that also impedes cytoadherence. A more rapid resolution in lactic acidosis than placebo was observed in both these studies but neither compound showed any effect on mortality.

The commonest cause of acidosis in a critically ill child is hypovolaemia. Most guidelines suggest that the initial management of uncompensated metabolic acidosis should focus primarily on improving tissue oxygenation, which includes volume expansion of the extracellular fluid compartment to correct hypovolaemia (Advanced paediatric life support: the practical approach, 1993; American Heart Association, 1997). Depending on the cause of the critical illness hypovolaemia may be secondary to factors such as leakage of fluid from the intravascular space, pathological vasodilatation, increased fluid losses and inadequate volume replacement (Levin, 1987). There has been an increasing appreciation that in children, unlike adults, hypotension is not a prerequisite for the diagnosis of hypovolaemia in sepsis (Saez-Llorens et al., 1995). On the contrary, hypotension is a late feature. Current guidelines for the emergency management of a critically-ill child, irrespective of aetiology, include rapid volume expansion with isotonic crystalloid fluid (Carcillo et al., 1991) and electrolyte correction (Khilnani, 1992) to optimise circulating blood volume and myocardial function. Retrospective (Maitland et al., 2003a), observational (English et al., 1996b) and interventional studies (Maitland et al., 2003b) all provide strong supportive evidence for a role for hypovolaemia in the acidosis of severe malaria in children. To date, the application of aggressive volume replacement in severe malaria has been relatively limited, due to concerns about potential complications such as increased intracranial pressure or pulmonary oedema. Phase I studies of volume replacement have recently reported the presence of hypovolaemia in children with acidosis, and the safe correction of both hypovolaemia and acidosis with either 0.9% saline or 4.5% albumin (Maitland et al., 2003b). However, randomised controlled trials are necessary to establish optimum fluid management.

6. Scenario 3: anaemia

The typical case of severe malarial anaemia is an infant presenting with a 3-4 day history of a fever, signs of pallor, lethargy and a haemoglobin concentration between 4 and 6 g/dl but with no evidence of respiratory distress or cardiovascular compromise. Should these children receive a blood transfusion as part of the routine management? In sub-Saharan Africa children are one of the chief recipients of transfused blood (Fleming, 1997). In many malaria endemic areas between 19 and 50% of children admitted to hospital receive a blood transfusion, principally for severe malaria anaemia (SMA) (Lackritz et al., 1992; Obonyo et al., 1998). Although transfusion may be lifesaving, the risk of transmission of HIV or other infections and of adverse reactions are significant. Furthermore, in many hospitals blood is in desperately short supply. In the absence of respiratory distress or coma in-patient mortality is relatively low (<1%) in children with SMA (Marsh et al., 1995). Current WHO recommendations for SMA suggest that only children with profound anaemia (Hb < 4 g/dl) should be transfused routinely in the absence of other complications (World Health Organization, 2000). Currently there are insufficient data to be sure whether routinely giving blood to clinically stable children with profound anaemia in endemic malarious areas reduces long-term morbidity and mortality.

7. Scenario 4: severe anaemia and respiratory distress

Unlike those with clinically stable anaemia, children with SMA (Hb < 5 g/dl) and respiratory distress have a considerable mortality (16%) (Marsh et al., 1995). The conscious level is often impaired ranging from lethargy to prostration and ultimately coma. Traditionally, these children were regarded as having biventricular heart failure (Hall, 1976) and have been treated with loop diuretics, digoxin, and gradual correction of anaemia by slow blood transfusion (reviewed in (English, 2000)). Recent clinical studies have cast doubt on the idea that respiratory distress is primarily due to congestive cardiac failure in the majority of children with SMA. Almost all of these children have an underlying acidosis, gen-
erally a severe lactic acidosis (English et al., 1997b; Maitland et al., 2003b). Key issues are impaired oxygen delivery due to a critical reduction in haemoglobin (English et al., 1997a) and impaired perfusion secondary to poorly deformable NPRBC (Dondorp et al., 2002). Observational studies have not convincingly demonstrated features of heart failure. On the contrary, central venous pressure measurements in a group of children with severe anaemia and respiratory distress were more indicative of hypovolaemia (English et al., 1996b; Maitland et al., 2003b). In these children urgent blood transfusion usually results in rapid clinical recovery, resolution of acidosis (English et al., 1996b; Maitland et al., 2003b) and improved in-vitro measures of red cell deformability (Dondorp et al., 2002). The children with the highest mortality (>30%) are those who present with SMA, respiratory distress and coma (Marsh et al., 1995). Death quickly ensues if blood is not rapidly available. Over 60% of the deaths from SMA occur in children who die before receiving a blood transfusion (Bojang et al., 1997; English et al., 2002). The routine supply of blood for transfusion requires dedicated personnel and resources, and the availability of volunteer donors, which in most hospitals is unsustainable. In children with SMA complicated by respiratory distress the speed of response is critical to survival. Thus, the application of simple clinical and laboratory guidelines identifying children likely to benefit most from treatment and reduce unnecessary blood transfusion may be important to securing the supply of safe blood products (English et al., 2002). Other potential alternatives include the use of blood substitutes such as bovine haemoglobin or haemoglobin substitutes; however, even if expense did not preclude their use, significant safety issues of artificial haemoglobins need to be addressed before these products could be considered for clinical trials (reviewed in Chang, 2000).

8. Scenario 5: coma and acidosis

One of the most challenging therapeutic scenarios facing the clinician is a child presenting in deep coma complicated by severe acidosis or cardiovascular evidence of impaired perfusion. Does our current understanding of the aetiology of coma or acidosis in severe malaria allow us to speculate on the optimum treatment? The aetiology of cerebral malaria is thought to be due, in part, to mechanical obstruction of the cerebral microvasculature mediated by a number of factors including the cytoadherence of parasitised red blood cells to the vascular endothelium (Kyes et al., 2001), rosetting (Chen et al., 2000), and decreased deformability of NPRBC leading to abnormal blood flow (Dondorp et al., 2000). Taken together these processes may result in reduced microvascular perfusion in which volume replacement aimed at improving circulation could potentially be beneficial. Fig. 4 shows the relationship between cerebral perfusion pressure and outcome, which lends support for a role for volume expansion (Newton et al., 1996). The counter to this argument is evidence of blood-brain barrier disruption (Adams et al., 2002; Brown et al., 2001; Brown et al., 2000), raised intracranial pressure (Newton et al., 1991), significant brain-swelling at post-mortem (Walker et al., 1992; White et al., 2001) and the presence of significantly more retinal haemorrhages in fatal cases (White et al., 2001) suggesting a significant cerebral insult accompanied by cerebral oedema (Sanni, 2001) in the presence of which volume replacement may be detrimental. Furthermore, children dying with cerebral malaria often have clinical signs (Newton et al., 1997a) and post-mortem features (Walker et al., 1992; White et al., 2001) compatible with transtentorial herniation and sonographic features of progressive intracranial hypertension during the agonal phases (Newton et al., 1996). The most likely cause of raised ICP in cerebral malaria is
an increase in cerebral blood volume (Newton et al., 2000). This dilemma is reminiscent of the similar predicament in the treatment of meningitis, in which it was customary in the past to volume restrict. Recent studies in meningitis have shown that when compared to volume expansion modest fluid restriction is detrimental to outcome (Herson and Todd, 1977; Powell et al., 1990). In severe malaria this issue can only be resolved through rigorously conducted clinical trials of volume replacement or volume restriction.

In conclusion, the last 10 years have seen a change in the understanding of the pathophysiological processes underlying severe malaria in children from a simplistic two-syndrome picture to one where severe malaria is seen as a complex syndrome affecting many organs. In particular, metabolic acidosis has been recognised as the single most important prognostic feature and the area where significant advances in treatment should be focused.

References


