Management of severe malaria

Plasmodium falciparum and other human malaria parasites can cause a variety of life-threatening syndromes. Diagnosis is difficult because none of these syndromes is unique to malaria, and parasitemia may be incidental rather than responsible for the illness. Malaria must be considered in the differential diagnosis of each of the severe syndromes it can cause – severe anemia, coma and convulsions, acidosis, hypoglycemia, shock, acute renal failure, intravascular hemolysis, acute respiratory distress syndrome and disseminated intravascular coagulation. The possibility of an alternative or additional infection must be considered and, in many circumstances, covered by initial emergency treatment. In the comatose patient the presence of a distinctive retinopathy is suggestive that malaria is the cause of the disease. Management must begin with emergency measures to ensure vital functions, followed by prompt provision of supportive measures (airway protection, glucose, fluids, oxygen, blood, antipyresis and anticonvulsants), and supervised referral to an appropriate available facility offering optimal clinical management. In a remote site, specific antimalarial therapy may be started with artesunate by suppository to cover the journey to hospital, where treatment can continue with intravenous or intramuscular quinine or with intravenous artesunate, followed by full artemisinin combination therapy as soon as oral treatment is possible. Identifying and managing severe disease events remains crucially important as malaria control measures successfully reduce the burden of the infection, with the possibility of waning of both immunity of hosts to the infection and familiarity of clinicians with the disease.

KEYWORDS: artemisinin drugs ■ artesunate suppositories ■ cerebral malaria ■ malarial complications ■ quinine ■ severe malaria ■ severe malarial anemia ■ supportive care ■ triage

Limangeni Mankhambo[1], Ajib Phiri[1], MacPherson Mallewa[1] & Malcolm Molyneux[1,2†]

[†]Author for correspondence
[1]Malawi–Liverpool–Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, Blantyre, Malawi
Tel.: +265 8888 36625
Fax: +265 1875 774
mmolyneux999@gmail.com
[2]School of Tropical Medicine, University of Liverpool, UK

Four species of *Plasmodium* have long been recognized to cause malaria in humans – *P. falciparum, P. vivax, P. malariae* and *P. ovale.* A fifth species has recently been added to this list, *P. knowlesi,* identified as an important cause of human disease in Malaysia [1]. Traditionally it has been taught that only *P. falciparum* causes severe and life-threatening disease, but recent evidence indicates that both *P. vivax* and *P. knowlesi* can also do so [2,3]. However, *P. falciparum* remains the principal cause of malaria complicated by severe syndromes, and this parasite is the major contributor to the worldwide malaria-attributable death toll, variously estimated at 0.75–3 million fatal cases per year [4]. The majority of deaths are in young children in Africa.

Even *P. falciparum* causes approximately 100-times as many mild illnesses as it does severe, and parasites are commonly tolerated without any symptoms among people living in areas of intense transmission. Severe disease may develop in individuals of any age who encounter *P. falciparum* for the first time and who do not obtain efficacious treatment promptly – hence those at greatest risk are young children in endemic areas, travelers to such areas and people of all ages living in areas with low levels or infrequent episodes of transmission.

Malaria is called severe when the characteristic febrile illness is complicated by any of a variety of systemic or organ dysfunctions, including severe anemia, acidosis, hypoglycemia, encephalopathy (altered consciousness, seizures), shock, disseminated intravascular coagulation (DIC), renal failure, intravascular hemolysis and acute respiratory distress syndrome (ARDS) [5]. The presence of any one or any combination of these syndromes in a patient with *P. falciparum* parasitemia constitutes a traditional diagnosis of severe malaria, provided that there is no other identifiable cause of the illness.

In areas with intense year-round transmission of *P. falciparum,* the most severe disease affects young children aged between 6 months and 3 years, severe anemia being the predominant complicating syndrome. In areas with less intense and seasonally varying transmission, slightly older children may be more commonly affected,

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with a relatively greater incidence of cerebral complications. Among children in Africa, acute renal failure, DIC and ARDS are rare, while these syndromes are common among nonimmune travelers and adults in low transmission areas who develop severe *P. falciparum* malaria.

The problem of diagnosis

None of the symptoms or complications that can result from *P. falciparum* infection is specific to malaria. All of the syndromes listed above can be caused by other conditions or infections. In a nonimmune traveler who develops malaria parasitemia, any associated syndrome is likely, although not certain, to be attributable to the infection. The principal diagnostic challenge in this situation is to consider the possibility of malaria and to examine blood films. In an endemic area the situation is very different: parasitemia is common in the asymptomatic population, and may merely be incidental to the presenting illness. In this situation, the diagnosis of malarial disease requires clinical judgment and the use of additional clues such as the density of parasitemia, the presence of thrombocytopenia and, in the comatose patient, the presence of the distinctive malarial retinopathy, and the absence of an alternative adequate diagnosis [6].

However, an illness may have dual or multiple contributing causes. In a parasitemic patient with an associated syndrome, it is not always possible to distinguish between complicated malaria, an alternative unrelated diagnosis (e.g., *Herpes simplex* encephalitis) and an additional or associated diagnosis (e.g., nontyphoidal *Salmonella* bacteremia), and each possibility has to be considered and either excluded or treated. A recent review of children admitted to a district hospital in Kenya concludes that *P. falciparum* parasitemia was, at least sometimes, biologically rather than merely coincidentally linked with each of three independent comorbidities studied: HIV infection, malnutrition and invasive bacterial infection [7].

The diagnostic principles listed in Box 1 are essential to the adequate management of severe malaria.

Treatment: general considerations

Diagnosis – of malaria infection, of each complication, and of possible additional or alternative diagnoses – is crucial to good management, which must consist of supportive care, treatment of specific complications and specific antiparasitic therapy. After the start of treatment, existing complications may become worse, and new complications may develop, despite optimal therapy; intensive monitoring is therefore essential to good management. The majority of episodes of severe malaria occur in communities located far from major hospital facilities; the patient's life may then depend upon optimal attention being paid at the simplest local dispensary or health post, followed by prompt referral to a hospital offering in-patient care, and admission to an intensive care unit in the unusual circumstance that such a unit is available. The care that can be offered at these three levels differs according to the level of sophistication of a country's health services; a fairly typical example is given in Table 1.

The principles of management of severe disease are the same whether the causal agent is *P. falciparum, P. vivax* or *P. knowlesi.* There are similar requirements for management of the life-threatened patient whether a child, a pregnant woman or a nonpregnant adult. Special considerations in pregnancy include the need to avoid fetotoxic drugs, the extra danger to the woman of any peripartum hemorrhage if already anemic from malaria, and the extra intravascular fluid load incurred after the second stage of labor, requiring careful management if she has renal impairment, pulmonary edema or ARDS.

Syndromes

Severe anemia

Severe anemia (all causes) is a major contributor to morbidity and mortality among children in the developing world [8], where 47% of children under the age of 5 years have anemia of some degree [9]. In children admitted to hospitals in Africa, 12–29% have severe anemia (hemoglobin concentration [Hb] ≤5g/dl), and among these the in-hospital case-fatality rate is 4–10% [10,11]. Malaria is an important contributor to severe anemia, but seldom the only one; other important etiologies include deficiencies of micronutrients (iron, vitamin A, folate and so on), other infectious diseases (HIV, intestinal helminths) and hemoglobinopathies [12]. Multiple etiologies are commonly present in the same individual with anemia. Many descriptive studies have shown a strong association between parasitemia and anemia, but the best evidence for a causal role of malaria in anemia comes from malaria-specific interventions: large trials of insecticide-treated nets [13] and of malaria-specific prophylaxis [14] in children in Africa have shown efficacy not only against malarial infections, but also against anemia and severe anemia. As with all malaria syndromes, the causal role of the parasite in the syndrome can rarely be proven in the individual

patient, although rapid improvement in the [Hb] after specific antimalarial therapy can provide convincing retrospective evidence.

In countries where *P. falciparum* transmission is intense, severe anemia is the leading presentation of severe malaria in children [8]. In these areas 1.4–5.7 million cases of severe malarial anemia (SMA) occur annually, and result in up to a million deaths [15]. The case-fatality rate of SMA is higher than that of severe anemia of other causes in children, and the risk of death in children with SMA increases with the presence of respiratory distress, impaired consciousness or bacteremia [16]. The peak age of presentation of SMA is 1–2 years, in contrast to that of cerebral malaria (CM; 2–5 years). Cross-sectional and other epidemiological data suggest that while malaria may be associated with a chronic,

Box 1. Diagnostic principles in severe malaria.

- Think of the possibility of malaria in a patient with any syndrome that malaria can cause.
- Obtain blood films and their results promptly, including speciation and quantification of any parasites.
- Repeat blood films if initially negative, even if provisional antimalarial therapy has been started.
- Monitor progress: other complications may develop.
- Manage in a facility capable of identifying and treating any complications that exist or may develop.
- Seek both additional and alternative diagnoses.

Table 1. Care of a severely ill patient with possible severe malaria, according to facility.

Activity	At health post	At district hospital	Additional in ICU
Emergency triage			
Secure airway	Position	Position, suction, O_2	Ventilation*
Deep breathing	Fluids – oral/ng	Bolus of iv. fluid	–
Coma/convulsion	Give glucose Oral/buccal/ng	Glucose, anticonvulsant/s iv. (or intra-osseous‡)	Paralysis and ventilation‡
Dehydration	Fluids – oral/ng	iv. line, fluid balance	Infusion pump
Hyperpyrexia (>39°C)	Rectal paracetamol*	Rectal paracetamol or other antipyretic	–
Diagnosis & differntial diagnosis			
	RDT‡ (dipstick for malaria diagnosis) Glucose stix*	Blood films, thick and thin for identification and quantitation of parasites	–
		[Hb], FBC, lactate	–
		Blood cultures	–
		Urea, creatinine, electrolytes, glucose	–
		Ophthalmoscopy	–
		Lumbar puncture pulse oximetry	CT scan*‡, EEG*‡
		Identify renal failure	–
		Chest x-ray‡	–
Supportive care			
	See triage above	Fluids: iv. line	Central line
		Fluid balance	–
		Identify renal failure	Dialysis‡
		Glucose – intravenous	Vasopressors
		Antipyretic/s	Inotropes
		Pulse oximetry → oxygen	Assist ventilation‡
		Anticonvulsant/s	–
		Blood transfusion‡	–
Specific therapy			
	Artesunate suppositories	iv. or im. quinine or iv. artesunate	Infusion pump
		Parenteral antibiotic/s	–

Health post is a peripheral unit without facilities for injections/infusions/admissions. District hospital is an average hospital with inpatient facilities, without formal ICU. ICU is a facility allowing artificial ventilation, intubation, cardiopulmonary monitoring and so on.
**If necessary.*
‡If available.
EEG: Electroencephalogram; FBC: Full blood count; ICU: Intensive care unit; im.: Intramuscular; iv.: Intravenous; RDT: Rapid diagnostic test.

gradual development of severe anemia [17], in many cases [Hb] falls rapidly, resulting in an acute, less well tolerated anemia.

Malaria causes anemia through disruption of parasitized red blood cells when schizonts are released, by the phagocytosis of parasitized erythrocytes in the spleen [18], by the additional hemolysis of unparasitized erythrocytes [19] and by impairment of erythropoiesis in bone marrow [20]. The importance of the latter mechanism is demonstrated both by histological appearances of the bone marrow and by the characteristic absence of circulating reticulocytes in an acute episode of symptomatic malaria. Within a few days of effective antimalarial treatment, there is a brisk reticulocytosis.

Treatment begins with assessment of vital functions. Distressed breathing in severe malarial anemia is more likely to be due to acidosis than to impaired myocardial function [21]. Deep breathing with clear lung fields on auscultation suggests acidosis, and a high blood lactate concentration may support this. General signs of dehydration or impaired peripheral perfusion should be sought, in addition to signs of cardiac failure.

Clinical assessment of fluid needs, the level of [Hb] and the availability of safe blood for transfusion help to determine whether and in what form blood transfusion should be given. WHO guidelines recommend that in malarious areas children with a [Hb] of 4 g/dl or less (hematocrit ≤ 12%) should be treated by blood transfusion, irrespective of other clinical features [22]. If there is distressed breathing, altered consciousness or a high-density parasitemia, transfusion should be given at [Hb] levels at or below 5 g/dl. In areas with low-intensity or sporadic malaria transmission, a higher cut-off (7 g/dl) may be used. A study in a well-equipped and well-staffed district hospital in Kenya demonstrated that adherence to the WHO guidelines for transfusion resulted in satisfactory outcomes in both the acute illness and subsequent recovery of [Hb] [23].

If the aim of blood transfusion is to correct both volume depletion and anemia, whole blood should be given (20 ml/kg) at a rate suiting the patient's needs. If correction of anemia is the only objective, packed or settled red cells may be given and should be administered slowly (10 ml/kg over 3–4 h).

Blood cultures of children with severe malaria have detected bacteremia in 7–14% [24,25], nontyphoidal *Salmonella* species being the most common isolates [26,27]. In a study of severe malaria in Malawian children, co-infection with nontyphoidal *Salmonella* was significantly more common among children with severe malarial anemia than among children with other forms of severe malaria [28], and in a large study of children presenting with severe anemia in the same population, nontyphoidal *Salmonella* bacteremia was associated with *P. falciparum* parasitemia [10].

The role of hematinics in the immediate follow-up of children treated for severe malarial anemia has been controversial. A large randomized controlled trial evaluating the effect of iron and folate supplements in a malaria-intense area of Zanzibar (Tanzania) was terminated prematurely because of a higher proportion of adverse events or death in the intervention groups [29]. In children with acute malaria, bone marrow iron stores are adequate [30]. Iron supplementation in the context of hemolysis in malarial anemia could theoretically result in an increase in the availability of free iron, a potent stimulator of bacterial growth and an important element in the metabolic pathway of nontyphi *Salmonellae* [31]. However, a recent Cochrane review of oral iron supplementation for preventing or treating anemia among children in malaria-endemic areas did not find an increased risk of malaria, other infectious outcomes or all-cause mortality associated with iron supplementation [32].

Encephalopathy

Cerebral malaria is characterized by altered consciousness, commonly accompanied by seizures. This complication may ensue when a symptomatic *P. falciparum* infection has persisted for several days, or it may, especially in a child, develop rapidly during the first few hours of a febrile illness. In young children, malaria is a common cause of febrile convulsions, in which consciousness is restored after the event, usually within minutes. For research purposes, a strict diagnosis of CM requires parasitemia, with the presence of unrousable coma persisting for more than 6 h after a recognized seizure, usually indicated by the patient's failure to localize a painful stimulus and corresponding to a Glasgow coma score of less than or equal to 11 out of 15 or, in children aged over 8 months, a Blantyre coma score of 2 out of 5 or less [33]. The definition also requires that there should be no identifiable alternative explanation for the encephalopathy, and no reversible metabolic derangement, such as hypoglycemia, if the correction of this restores consciousness.

The differential diagnosis includes all causes of global encephalopathy. As with all malaria-associated syndromes, there are no external diagnostic clinical features by which CM may be distinguished from other causes of encephalopathy.

However, a recently described group of retinal changes, visible on direct or indirect ophthalmoscopy at the bedside, are associated with CM and improve the specificity of clinical diagnosis [34]. Although more fully studied in children, these changes are also found in adults [35]. Malarial retinopathy was found to be closely associated with a post-mortem diagnosis of pediatric CM in a study in Malawi [36]. The retinopathy consists (see FIGURE 1) of any or all of four components: patchy whitening of the retina, especially in the perifoveal part of the macula, orange or white coloration of retinal vessels, white-centred hemorrhages and, sometimes, papilloedema. Only the first two of these changes are specific to severe malaria, and their presence in a comatose patient provides additional evidence for the diagnosis.

A patient with *P. falciparum* parasitemia and coma should always be treated for severe malaria, but absence of retinopathy increases the importance of considering additional or alternative diagnoses. The main value of retinopathy as a diagnostic indicator is in increasing the specificity of the diagnosis of severe ('cerebral') malaria when this is an enrolment criterion for a pathophysiological study or a clinical trial, and when it is an end point in a prophylactic or interventional study. Retinopathy may also provide a visible correlate of intracerebral events in studies of the pathogenesis and pathophysiology of malarial encephalopathy.

In exploring alternative diagnoses, lumbar puncture must be considered, and its benefits weighed against possible risks. Intracranial pressure is commonly raised in CM in children [37], but opening pressure at lumbar puncture is not a predictor of a fatal outcome [38]. CT scanning is suggestive of brain swelling in some adults, and in children MRI scans, brain morphology at autopsy and brain weights in fatal cases suggest the frequent presence of cerebral edema [36,39]. Brain histological studies using immunofluorescent techniques demonstrate that in fatal malaria in both adults and children, intracerebral endothelial cell junctions are damaged, suggesting impairment of the blood–brain barrier [40,41]; similar changes are found in the retina at autopsy [MANKHAMBO L, PHIRI A, MALLEWA M, MOLYNEUX M. UNPUBLISHED OBSERV.]. Despite these indicators of brain swelling, frank cerebral herniation is rarely found at autopsy, even in patients who had undergone lumbar puncture [36]. Small trials of therapies directed against cerebral edema have failed to demonstrate benefit [42,43].

An advantage of obtaining cerebrospinal fluid (CSF) is that clues to diagnoses other than malaria may be obtained. In a study of children presenting to hospital with encephalopathy in Malawi, 11% of children who died with an initial clinical diagnosis of CM actually died of rabies [44]. A variety of other viral infections were identified by examination of CSF for viruses in the same study [MANKHAMBO L, PHIRI A, MALLEWA M, MOLYNEUX M. UNPUBLISHED DATA]. In Kenya, herpes simplex virus was found in the CSF in four (9%) of 47 children admitted with a clinical diagnosis of CM [45]. In most endemic areas it is not

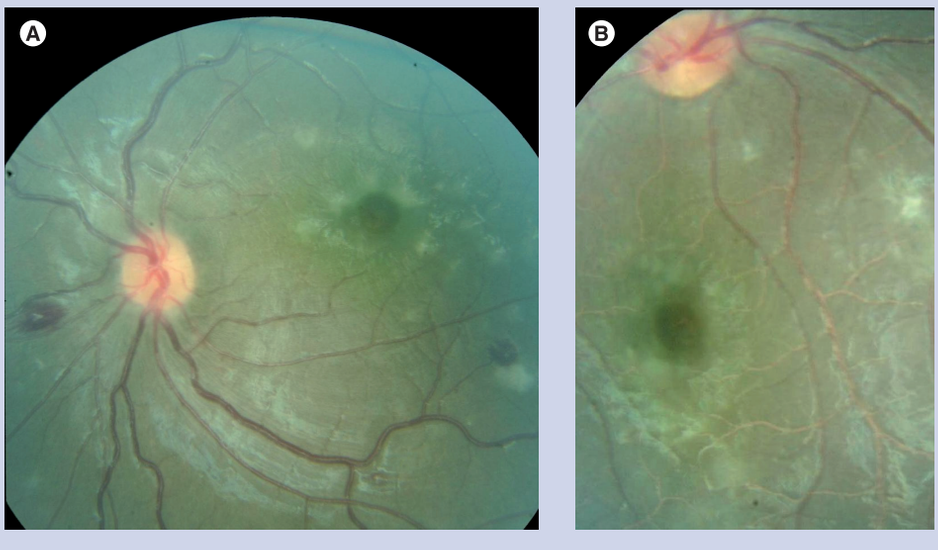

Figure 1. Malarial retinopathy in two children with cerebral malaria. (A) With patchy peri-foveal retinal whitening; note also three white-centred hemorrhages (photograph by S Glover). **(B)** With vessel whitening (lower half of picture) (photograph by S Glover).

possible to prove the presence of herpes simplex virus, and a combination of lymphocytosis in the CSF and focal neurological signs, in the absence of malarial retinopathy, are enough to warrant presumptive therapy with acyclovir.

Seizures are a common component of CM. Seizures may be simple or complex, brief or prolonged, and focal or generalized. They may be readily evident on clinical observation, or may be subtle, with only minor movements of fingers, lips or eyelids providing a clinical clue to their presence. Seizures may be detectable by electroencephalography in some patients who exhibit no detectable convulsive movements [46,47]. A clue to the occurrence of seizure in such circumstances may be a sudden deterioration in coma score, with or without an additional explanation such as hyopoglycemia or hyperpyrexia.

The management of CM requires identification and supportive treatment of systemic and metabolic abnormalities (hypoglycemia, hypovolemia, acidosis, hyperpyrexia, severe anemia), management of seizures and management of any organ failure. All of these must be combined with simultaneous specific antimalarial therapy (discussed later).

Diazepam administered intravenously or rectally is the recommended first-line treatment for seizures in malaria [22]. This may successfully terminate seizures, but they may persist or recur, probably owing to the short half-life of the drug in circulation. Further doses of diazepam may be given, but with increasing risk of causing respiratory depression, especially if accompanied by phenobarbitone. An alternative to diazepam is midazolam, which, being water-soluble, can be given by the buccal or intranasal route and has been shown to be at least as effective and as safe as diazepam [48]. Lorazepam, a longer acting benzodiazepine causing less respiratory depression than diazepam, has been shown to be better than the commonly used intramuscular paraldehyde in controlling seizures in Malawian children [49].

The management of CM has important potential implications for the subsequent well-being of the patient. Children with CM are more likely to develop epilepsy in subsequent months than those followed after noncerebral malaria. Among Malian children aged between 6 months and 14 years who were admitted to hospital with malaria, the incidence of epilepsy in the subsequent 3–4 years was nearly four-times higher in those whose presenting illness was CM than in those with noncerebral malaria [50]. Current studies are aiming to distinguish pre-existing epilepsy that may be triggered by malaria into an illness resembling CM, from epilepsy that develops only after, and probably as a consequence of, an episode of CM.

Acidosis & acidemia

The identification and importance of acidosis in the context of severe malarial anemia is discussed above. Acidosis is most commonly a result of tissue hypoxia, exacerbated by anemia, hypovolemia and hypotension, but it may be augmented by liver dysfunction, impaired renal function and production of lactate by the parasite [51,52]. Acidemia (low blood pH) indicates failure of hyperventilation to compensate adequately for metabolic acidosis [53]. Studies in children using stable isotope techniques confirm that increased lactate production by the host (resulting from anaerobic glycolysis) rather than reduced clearance is the main cause of the accumulation of lactic acid [54]. There is a strong association of altered acid–base status with disease severity and mortality, independent of other predictors of illness and death in malaria [53]. Inadequacy of the circulating intravascular volume, common in severe malaria and contributing to acidosis, may result from preceding vomiting, failure to drink, pyrexia, sweating and hyperventilation, commonly aggravated by peripheral vasodilatation. Appropriate volume expansion is therefore a central component of therapy [55]. The choice of rehydration fluid remains a subject of intense study. In the presence of severe anemia, volume depletion is best corrected by transfusion of whole blood. In the absence of severe anemia, the outcome is better with albumin than with saline infusions [56]. The possibility that crystalloid infusions in CM may exacerbate cerebral edema, and that volume depletion in this situation would be better corrected by a colloidal fluid, is currently under investigation in clinical trials.

Simultaneous correction of hypoglycemia and severe anemia, combined with specific antimalarial therapy, usually lead to correction of acidemia. Concurrent bacteremia must be looked for, and there is considerable justification for the administration of a broad-spectrum antibiotic in addition to antimalarial therapy in patients with malaria and acidosis. The control of acidemia becomes considerably more difficult in the presence of acute renal failure, when hemodialysis or hemofiltration may be required before acidosis can be corrected. There is no convincing role either for sodium bicarbonate or for the dehydrogenase activator dichloroacetate, which inhibits lactate release, in the treatment of acidosis.

Acute renal failure

While minor degrees of impairment of renal function are common in children with severe *P. falciparum* malaria, established acute renal failure is rare. By contrast, acute renal failure is an important complication in nonimmune adults, when it may be an isolated complication or may, more commonly, be one of several system disorders [57]. It has been reported in *P. vivax* infections in adults, including those in whom an associated low-grade *P. falciparum* could not be identified by PCR [58]. The clinical pattern in renal failure complicating *P. falciparum* malaria suggests acute tubular necrosis, a conclusion corroborated by postmortem studies in Vietnamese adults [57], in which moderate sequestration of both parasitized erythrocytes and host monocytes were also demonstrated in renal microvessels. The mechanisms leading to acute tubular necrosis have not been established, but presumably hypovolemia, hypotension, parasite sequestration and vasoconstriction may all contribute to the pathogenesis. Hemoglobinuria has classically been associated with acute renal failure [59], but the mechanism may be indirect through associated hemodynamic dysfunction, as free hemoglobin itself is not nephrotoxic, and hemoglobinuria is common in children who do not suffer renal impairment. Acute tubular acidosis may develop in severe malaria and contribute to systemic acidemia.

The management of renal failure in malaria requires the same intensive attention as acute renal failure of any cause, including dialysis when necessary. Peritoneal dialysis may be lifesaving when facilities for hemodialysis are not available [60].

Hypoglycemia

Hypoglycemia should be suspected in a patient whose level of consciousness suddenly deteriorates. Failure of hepatic gluconeogenesis appears to be the principal mechanism in malaria-associated hypoglycemia [61], exacerbated by glucose consumption by parasites in a patient with increased metabolic demands and increased anaerobic glycolysis. Plasma insulin concentrations are appropriately low, in contrast to the high levels found in the quinine-induced hypoglycemia to which pregnant women are particularly prone [62]. Hypoglycemia should be corrected urgently, but not excessively since glucose itself is a powerful stimulant of insulin secretion. Frequent monitoring is essential to achieve and maintain normoglycemia, since hypoglycemia may recur.

Pulmonary edema & acute respiratory distress syndrome

Severe breathlessness and hypoxemia may develop in a severe *P. falciparum* infection, accompanied by radiological changes suggesting either pulmonary edema or ARDS. These two complications are best distinguished by pulmonary artery pressure measurement, a high level suggesting fluid overload and requiring fluid restriction, diuretics and attention to renal function, while a normal or low level suggests ARDS, which may respond only to positive pressure ventilation. Both conditions must be distinguished from aspiration pneumonia complicating coma or a seizure, and from acidosis in which radiological changes are absent.

Specific antiparasitic therapy

Together with supportive measures for severe malaria, efficacious antiparasitic therapy must be started promptly.

In a remote or rural site, where many sufferers first encounter a health professional and where injections are not possible, artesunate administered by suppository can save lives if the referral journey to a larger center or hospital is likely to take more than 6 h [63].

In a randomized study of severe malaria treatments in hospital in 1259 adults and 202 children (89 aged <6 years) in Southeast Asia [64], the case fatality was significantly lower in those treated with intravenous artesunate (15%) than in those receiving intravenous quinine (22%), a reduction of 37%. Intravenous artesunate is now the recommended first-line therapy for adults with severe malaria in low-transmission areas [65]. It is likely that this recommendation will become standard for travelers from non-malarious areas once the drug is licensed [66]. In Britain and in the USA, the fact that the drug must be procured on a named-patient basis may cause an undesirable delay in starting antiparasitic treatment [67,68]. A large multicountry trial is in progress to compare intravenous artesunate with quinine in African children. A similar superiority of artesunate over quinine cannot be assumed, as there may be less quinine resistance in Africa than in Southeast Asia, and because of the considerable differences in the patterns and outcomes of severe malaria between African children and Asian adults. Meanwhile, parenteral quinine remains the usual antimalarial drug used for severe malaria in Africa (20 mg/kg of quinine dihydrochloride salt twice daily, either by slow infusion over 3 h per dose or by intramuscular injection [64]). Whether artesunate or

quinine is used for initial treatment, standard oral therapy should replace it as soon as the patient can take drugs by mouth.

Since there is no rapid and reliable bedside test for the sensitivity of a patient's parasites to the antimalarial drug being given, national policies rely on local drug-sensitivity patterns to determine recommended drug schedules.

Adjunctive therapies

Many of the life-threatening components of severe malaria may be in part the result of impaired, enhanced or indirect host responses to the invading parasite. This recognition has led to the investigation of numerous adjunctive therapies that could potentially correct some of these disturbances. Many such measures when added to the treatment of severe malaria have shown effects against metabolic, cellular or even clinical end points. However, demonstrating benefit against outcomes of importance to public health – reduced mortality or reduced long-term sequelae – requires randomized trials of a size that can rarely be achieved. Promising possibilities that have not yet been found to benefit important outcomes when added to the treatment of severe malaria include:

- Dexamethasone [42] or mannitol [43], aimed at reducing cerebral edema;
- Dichloroacetate, intended to reduce lactate production [69];
- *N*-acetylcysteine, antagonizing the known oxidant stress in severe malaria [70];
- Rosiglitazone, with the capacity to modulate exaggerated host innate responses [71];
- Pentoxyfylline to reduce the release of TNF-α [72];
- Monoclonal anti-TNF antibody to oppose effects of excessive TNF [73];
- Immunoglobulin from pooled sera of semi-immune adults [74];
- L-arginine to provide additional substrate for endothelial nitric oxide (NO) production, NO being diminished in proportion to the severity of malaria [75];
- Direct administration of NO to correct the same deficiency has been suggested but not trialed;
- Exchange blood transfusion, targeted at removing excessive circulating parasites, products or mediators [76].

Other potential adjunctive therapies, some specific to malaria, remain as promising possibilities: soluble receptors to prevent or reverse ligand specific binding of parasitized erythrocytes to endothelium or to other erythrocytes; molecules to scavenge free hemoglobin since this exacerbates local vascular nitric oxide deficiency; products to limit endothelial extrusion of von Willebrand factor strands that may promote microthrombus formation; and many others based on our increasing knowledge of pathogenetic mechanisms. It remains possible that some of these or new adjunctive therapies may yet prove beneficial in malaria treatment, but demonstrating benefit in the context of falling incidences of fatal disease presents a major challenge to trialists.

Addition of antibiotics in treatment of severe malaria

Bacterial infections may either mimic or complicate severe malaria syndromes, as discussed above under both severe anemia and CM. Clinicians must often admit uncertainty as to the agent/s causing their patient's disease, and administer both antimalarial and antibacterial drugs. There is an urgent need to develop new techniques that can increase diagnostic accuracy.

Future perspective

The past decade has seen a huge increase in the energy and funding applied to malaria control. Transmission is being reduced in many parts of the globe, elimination is being achieved in some areas, and the possibility of reinstating the goal of eradication is being debated. The consequence of this increased attention to malaria is likely to be a reduction in severe disease events, already observed in some parts of the world. In others this will take many years, and there is a real possibility that changes in transmission intensity, resulting from control programs, will alter levels of immunity and increase the susceptibilities of some age groups or populations to severe malaria.

Overall, the falling incidence makes clinical trials of new therapies more difficult. Accuracy in identification of severe malaria (important for monitoring progress) and competence in its management (important for public support) remain crucially necessary for the success of large-scale antimalaria campaigns, whether aimed at control or elimination of malaria.

The largest current gap in the provision of services for those with severe malaria is in communities most at risk. We urgently need rapid

diagnostic tests that can not only detect parasites, but can indicate whether a plasmodium is the cause of the patient's disease and can detect the significant presence of additional or alternative infections. Health services in endemic areas need enhanced networks of health providers at the village level, equipped with these simple diagnostics and with drugs that can be rapidly administered without sophisticated equipment both for malaria and for other life-threatening infections. In addition, we will need improved transport networks allowing prompt and safe referral to hospital facilities.

Current vaccines undergoing trials hold promise for partial prevention of infection and are likely to potentiate other control measures. New vaccines specifically aimed at ameliorating clinical complications – 'antidisease vaccines' – are a promising possibility that we can hope for in the coming decades. A vaccine against pregnancy malaria appears achievable quite soon.

The threat of parasite resistance to antimalarial drugs will continue. The widespread use of combinations of drugs with differing kinetics for uncomplicated malaria will result in millions of people having low-level companion drugs in circulation, a recipe for resistance-selection in high-transmission areas. Once the companion drug in an artemisinin combination therapy is ineffectual, the 3 days of artemisinin in standard treatments will fail. We urgently need new antimalarial drugs to provide alternatives, both to prevent and to cope with drug resistance.

Patients will be in need of competent diagnosis and management of severe malaria for many years to come.

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Executive summary

Context

- *Plasmodium falciparum* causes most of the severe disease and death due to malaria worldwide, but both *P. vivax* and *P. knowlesi* can also cause severe syndromes.
- In endemic areas there are many more mild than severe disease events caused by *P. falciparum*.
- The greater the intensity of transmission, the younger the people most affected.
- Children in high-transmission areas rarely suffer from acute renal failure, acute respiratory distress syndrome and disseminated intravascular coagulation, which are common in nonimmune adults.

Diagnosis

- None of the syndromes that may complicate malaria are unique to it, making specific diagnosis difficult.
- The presence of parasitemia does not prove that a patient is suffering from malaria, since many people in the community are parasitemic without their parasites causing illness.
- Alternative or additional infections may be present in a patient with apparent severe malaria.

Treatment: general considerations

- Treatment requires emergency care for vital functions, supportive measures for metabolic and systemic disorders, and specific antimalarial drugs.
- At each level of the health service at least some of these can be provided. Artesunate by suppositories improves the outlook for patients whose referral journey to hospital will take many hours.

Identifying & managing syndromes

- Severe anemia commonly goes unrecognized in the community. Malaria is an important but not unique contributor to severe anemia, maximally so in infants and toddlers in very intense-transmission areas.
- There is a significant association between malarial anemia and invasive non-typhi *Salmonellae* infection.
- The presence of a unique retinopathy can strengthen confidence in a diagnosis of malaria as the cause of coma.
- Bacterial and viral infections may either mimic or co-exist with severe malaria, and must sometimes be covered presumptively with appropriate treatment.
- Intravenous artesunate is the treatment of choice in areas of low-transmission intensity, while quinine by either the intramuscular or intravenous route continues to be used in areas of intense transmission.

Prospects

- Successful malaria control programs will reduce the incidence of severe disease, but this will take time.
- Clinical trials against severe disease will become more difficult as disease incidence falls.
- Control of transmission may paradoxically increase severe disease as immunity wanes.
- Parasite and vector resistance to drugs and insecticides, respectively, threaten control programs, and vigilance will remain crucially important for many years to come.

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