Published in final edited form as:
Expert Rev Anti Infect Ther. 2010 September ; 8(9): 997–1008. doi:10.1586/eri.10.90.

Adjunctive therapy for cerebral malaria and other severe forms of *Plasmodium falciparum* malaria

Chandy C John[1,†], **Elizabeth Kutamba**[2], **Keith Mugarura**[2], and **Robert O Opoka**[2]

[1] Center for Global Pediatrics, 717 Delaware Street SE, Room 363, Minneapolis, MN 55455, USA
[2] Department of Paediatrics and Child Health, Mulago Hospital and Makerere University, Kampala, Uganda

Abstract

Severe malaria due to *Plasmodium falciparum* causes more than 800,000 deaths every year. Primary therapy with quinine or artesunate is generally effective in controlling *P. falciparum* parasitemia, but mortality from cerebral malaria and other forms of severe malaria remains unacceptably high. Long-term cognitive impairment is also common in children with cerebral malaria. Of the numerous adjunctive therapies for cerebral malaria and severe malaria studied over the past five decades, only one (albumin) was associated with a reduction in mortality. In this article, we review past and ongoing studies of adjunctive therapy, and examine the evidence of efficacy for newer therapies, including inhibitors of cytoadherence (e.g., levamisole), immune modulators (e.g., rosiglitazone), agents that increase nitric oxide levels (e.g., arginine) and neuroprotective agents (e.g., erythropoietin).

Keywords

adjunctive; cerebral; human; malaria; *Plasmodium falciparum*; severe; treatment

Malaria remains a major cause of morbidity and mortality throughout the world. In 2008, there were an estimated 243 million cases of malaria and 863,000 deaths from malaria worldwide. The vast majority of cases (85%) were in Africa, with the remainder occurring in Southeast Asia (10%), South America and the Eastern Mediterranean regions [1]. In Africa, children and pregnant women are the most affected. An African child has between 1.6 and 5.4 episodes of malaria fever each year, and one in every five (20%) childhood deaths is due to the effects of the disease [1].

Severe malaria and malaria-related mortality are most often due to *Plasmodium falciparum*, particularly in Africa. The manifestation of severe malaria varies according to age group and transmission intensity [2–4], but severe malarial anemia is the most common form of severe malaria, and cerebral malaria (CM) among the deadliest. Severe malarial anemia accounts for up to 64% of all severe malaria in children under 5 years of age [5–8]. CM usually accounts for less than 10% of hospital admissions for malaria, but has a very high mortality rate (13–

[†]Author for correspondence: Tel.: +1 612 625 8383 Fax: +1 612 625 2920 ccj@umn.edu.

Financial & competing interests disclosure
This work was supported in part by a grant from the National Institute of Neurologic Disorders and Stroke (grant 5R01-NS055349) to Chandy C John. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

21%) [5–7,9,10]. Importantly, African children who survive the acute episode of CM often have long-term cognitive (~25%) [11,12] and neurologic (1.1–4.4%) [11,13] deficits. There is some evidence of neuropsychiatric problems after CM in adults in Asia [14], but neither neuropsychiatric or cognitive problems have been studied systematically in these populations.

Pathogenesis of CM & other forms of severe malaria

The classic pathologic feature of human CM is sequestration of infected and noninfected red cells in the venules and capillaries of the brain [15]. On the blood side of the blood–brain barrier (BBB), parasitized red blood cells (pRBCs) activate endothelial cells, and monocytes and platelets are attracted to the sites of sequestered, adherent pRBCs, impeding vessel flow, leading to local tissue hypoxia and ischemia. Endothelial activation is also associated with release of proinflammatory cytokines, notably TNF-α [16]. TNF-α upregulates cellular adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which may lead to further cytoadherence of erythrocytes and sequestration [17]. In addition, it has been proposed that excessive TNF-α may lead to exaggerated sickness behavior, and a local 'shutdown' of activity in affected areas of the brain [18]. Other cytokines are also associated with CM pathogenesis and mortality, including low serum levels of RANTES [19], elevated serum levels of IFN-γ, macrophage inflammatory protein (MIP)-1β, IL-6, IL-10 [19], IL-1 receptor antagonist (IL-1ra), monocyte chemoattractant protein (MCP), granulocyte colony-stimulating factor (G-CSF) [20] and interferon inducible protein-10 (IP-10) [21]. A few factors have been associated with decreased mortality in CM, notably VEGF [21]. Low levels of nitric oxide (NO) are present in uncomplicated and severe malaria, and individuals with the lowest levels of NO have increased mortality [22]. On the brain parenchyma side of the BBB, astrocytes, microglia and perivascular macrophages may be activated by NO, cytokines or *P. falciparum* exoantigens crossing the BBB, and produce cytokines and chemokines intrathecally, leading to local neuronal damage [23,24]. Although sequestration is the pathologic hallmark of CM, sequestration alone seems unlikely to lead to the coma that is an essential element in the pathogenesis of CM. The clinical picture of CM is likely to be due to some combination of the effects of sequestration, metabolic changes such as hypoglycemia and metabolic acidosis, and the effects of systemic and CNS proinflammatory cytokine production.

Very few studies have assessed the pathogenesis of neurologic and cognitive deficits in CM. One study demonstrated that elevated levels of erythropoietin (EPO) are associated with decreased acute neurologic deficits [25], but did not assess long-term neurologic deficits. Another study showed that elevated cerebrospinal fluid but not serum levels of TNF were associated with persistent neurologic and cognitive deficits, while elevated cerebrospinal fluid levels of G-CSF and IL-8 were associated with protection from persistent neurologic deficits [26]. The lack of data on factors associated with long-term cognitive impairment is a major barrier to considerations of adjunctive therapy to prevent this serious complication.

Primary therapy for severe malaria, including cerebral malaria

Primary treatment for severe malaria is parenteral quinine or arte-misinin derivatives. Artemisinin derivatives have many advantages over quinine, most notably a far better safety profile, with fewer serious side effects. A large multicenter, multi-country, open-label randomized clinical trial on the treatment of malaria in Southeast Asia definitively showed decreased mortality with artesunate (15%) as compared with quinine (22%) treatment [27]. The study included both children and adults, but the vast majority of patients treated were adults. As a result of this study, artesunate or artemisinin derivates are now the treatment of choice for severe malaria in Southeast Asia. In children, particularly children in Africa, the evidence for the superiority of artemisinin derivates is less clear. A recent systematic review

of artemisinin derivatives versus quinine for the treatment of severe malaria in children found no evidence that parental artesunate was superior to quinine, but most studies had fairly small enrollment [28]. A large, multicenter randomized clinical trial is currently underway in Africa comparing artesuate with quinine for the treatment of malaria, and this trial should more authoritatively answer the question of whether artesunate is superior treatment to quinine for African children.

Adjunctive therapy for CM & severe malaria

Even under optimal conditions, the case–fatality rate in severe malaria treated with either artemisinin derivatives or quinine remains unacceptably high. In an effort to reduce malaria-related mortality, numerous adjunctive therapies that may alter malaria-induced abnormalities in physiology have been tested. Adjunctive therapy is defined as any additional therapy that modifies physiologic processes caused by malaria. These therapies may act directly on specific biologic pathways altered by malaria or more generally on end-stage factors produced in malaria by a number of different specific processes. Thus, this article includes agents that target factors believed to be key in the pathophysiological processes of severe malaria (e.g., elevated levels of TNF-α or low levels of NO) or agents that control end-stage factors associated with poor clinical outcomes (e.g., hypovolemia or metabolic acidosis). In a number of instances, these interventions were successful in reducing mortality in murine models of severe malaria [29], but results in human studies have been disappointing. Of all the interventions to date, only albumin infusion has led to a significant decrease in mortality, and this finding was from a single small study [30]. A few interventions have shown promise in reducing morbidity.

Adjunctive therapies assessed in randomized clinical trials

Therapies that have been assessed in randomized clinical trials or (in the case of exchange blood transfusion [EBT]) in numerous clinical studies are summarized in Table 1. Adjunctive therapies that have been tested in patients with CM or severe malaria include treatments that:

- Modulate the immune response to *P. falciparum* (dexametha-sone, intravenous immunoglobulin, monoclonal antibodies to TNF-α, pentoxifylline and curdlan sulfate)
- Reduce iron burden (iron chelation with desferrioxamine or deferipone)
- Reduce oxidative stress (*N*-acetylcysteine [NAC])
- Counteract the prothrombotic state (heparin and aspirin)
- Reduce parasitemia (EBT)
- Expand volume and potentially decrease acidosis (albumin)
- Decrease intracranial pressure and cerebral edema (mannitol and dexamethasone)
- Prevent seizure activity (prophylactic phenobarbital)

Modulation of the immune response

Since the immune response to *P. falciparum* appears to play an important role in the development of CM, many adjunctive therapies tested have attempted to alter specific presumably deleterious immune responses. Therapies assessed include medications that reduce systemic inflammation (dexamethasone and intravenous immunoglobulin), modify the immune response to *P. falciparum* (curdlan sulfate) or lower TNF-α levels (anti-TNF-α antibodies and pentoxifylline).

Dexamethasone was assessed at different doses in two independent clinical trials of severe malaria in Thailand [31] and Indonesia [32]. In both trials, dexamethasone treatment did not decrease mortality, and in the trial in Thailand, individuals receiving dexamethasone had a higher risk of complications (pneumonia and gastrointestinal bleeding) than those receiving placebo. Similarly, treatment with intravenous immunoglobulin resulted in a trend toward increased mortality and neurologic sequelae in children receiving the immunoglobulin [33]. The lack of efficacy may reflect that the injury from the inflammatory response has already occurred and cannot be modified. Curdlan sulfate, a sulfated 1–3, β-D-glucan, inhibits *P. falciparum* growth *in vitro* and downregulates the immune response to *P. falciparum*. Two small randomized controlled trials showed relative safety and faster fever clearance in the group that received curdlan sulfate [34], but no additional studies on efficacy have been completed.

Therapies to counteract the effects of TNF-α include monoclonal antibodies to TNF-α and inhibitors of TNF-α synthesis. A large trial of monoclonal antibodies to TNF-α in children with CM showed no difference in mortality, but an increase in neurologic sequelae with this therapy [35]. Pentoxifylline, a phosphodiesterase inhibitor, inhibits TNF-α synthesis and increases intracellular cyclic AMP. It reduced circulating TNF-α and IL-6 and produced clinical improvement in severe falciparum malaria, including CM, in some studies [36,37] but not others [38,39].

Reduction of iron burden

An iron chelator like deferoxamine could have antimalarial activity through its action of withholding iron from the parasite, an element crucial for its metabolic pathways. In addition, it inhibits iron-induced peroxidant damage to cells and subcellular structures, which can be another beneficial effect for patients with severe falciparum malaria [40]. Studies of deferoxamine and the oral iron chelator deferipone showed no differences in mortality in children with CM (deferoxamine) [41] or adults with severe malaria (deferipone) [42], but in both studies parasite clearance times were shorter in the iron chelator treatment group. However, the largest study to date of deferoxamine, a multicenter study in Zambia, showed a trend toward increased mortality with deferoxamine in one of the study sites [43]. At present, there is insufficient evidence to indicate the usefulness of iron chelators in the management of severe malaria.

Reduction of oxidative stress

Markers of oxidative stress are increased in severe malaria and are thought to contribute to malaria morbidity [44]. NAC is a widely used, safe and well-tolerated antioxidant. It is the main treatment for acute paracetamol poisoning, acting through direct scavenging of free radicals and replenishment of glutathione and cysteine. It has been suggested that NAC may be beneficial in the treatment of severe malaria, through similar mechanisms, but studies of NAC in severe malaria have so far yielded disappointing results. A pilot study in Western Thailand showed that intravenous NAC was associated with faster normalization of lactate levels [45], but a subsequent, larger study showed no difference in lactate clearance, coma recovery or mortality between groups, and parasite clearance times were slightly prolonged in those who received NAC [46].

Anticoagulation

Severe malaria is associated with prothrombotic factors, including elevated levels of endothelial microparticles [47] and other factors that can lead to local formation of microthrombi. Apart from its anticoagulation properties, heparin also prevents the formation of rosettes of infected red blood cells (RBCs), a phenomenon seen in severe malaria and thought to relate to pathogenesis [48]. An earlier study in which heparin or aspirin or neither drug was

given to travelers who presented with severe malaria in Germany showed no difference in mortality or any other outcome with either treatment [49].

Reduction of parasitemia through EBT

Exchange blood transfusion is used in conjunction with anti-malarial chemotherapy to rapidly reduce high malaria parasitemia, which has been associated with increased morbidity and mortality. EBT exchanges blood densely populated with infected RBCs for blood that is free of infected RBCs. EBT is thought to reduce antigenic stimulus and the proinflammatory responses to these antigens, and also to reduce RBC clearance and hemolysis, since transfused cells are not infected and have normal deformability. No randomized clinical trial has ever been conducted on EBT, and it is unlikely that such trials will ever be conducted, since EBT, despite a lack of definitive evidence for efficacy, is considered standard of care for patients with high-level parasitemia. A meta-analysis of studies in which individuals received EBT concluded that there was no difference in mortality or other outcomes for those who received EBT versus those who did not, but individuals who received EBT had higher baseline parasitemia and disease severity [50]. Experts recommend that for very sick patients in the presence of adequate facilities, a parasitemia of above 15% is an indication for EBT [51]. The procedure requires expertise and intense monitoring, which limits its suitability in resource-limited settings in developing countries. Blood substitutes may be considered in the future, but there are no current trials investigating blood substitutes as an alternative to EBT.

Volume expansion or correction of acidosis

Use of plasma expanders such as albumin can improve micro-circulation, correct hypoglycemia and reduce lactic acidosis. A study of Kenyan children with severe malaria documented significantly lower mortality among patients who received albumin (3.6%) compared with those who received saline (18%), although resolution of acidosis did not differ between the groups [52]. A trial comparing albumin and the synthetic colloid gelofusine similarly suggested a comparative advantage for albumin [53]. The studies did not compare albumin with standard maintenance fluid therapy without volume expansion, and have been criticized because of the lack of evidence that volume expansion is required in patients with severe malaria [54]. To address this issue, a large multicenter trial is currently being conducted in multiple hospital sites in Africa comparing volume expansion with albumin or saline to standard maintenance fluids in children with severe febrile illness and evidence of impaired perfusion.

Dichloroacetate (DCA), an activator of pyruvate dehydrogenase, reduces hyperlactatemia and acidosis complicating severe malaria. A study from Thailand demonstrated a drop in lactate levels in adults with severe malaria who received DCA as compared with saline [55], but no further trials on DCA efficacy in severe malaria have been reported.

Reduction of intracranial pressure

Mannitol is an osmotic diuretic that lowers intracranial pressure (ICP) by creating an osmotic gradient that draws water from brain parenchyma into the brain capillaries. It also slows production of cerebrospinal fluid, which further reduces intracranial pressure. In a Kenyan study of ICP in patients with CM, mannitol was able to reduce moderate elevations in ICP, but was ineffective in severely elevated ICP. Significantly, mannitol did not reduce mortality [56]. A subsequent clinical trial of mannitol versus placebo in Ugandan children with CM found no difference between mannitol and placebo-treated children in mortality, coma duration or any other clinical outcome [57].

Prevention of seizure activity

Seizures are a prominent feature in CM and repeated seizures have been associated with poor outcome [58]. Control of seizures has therefore been proposed as one of the ways of improving survival in CM. However, phenobarbital, the primary medication generally available for seizure prophylaxis, has not been shown to reduce mortality in individuals with CM. An early study of older children in Thailand showed a reduction of seizures but no difference in mortality with a low dose (3.5 mg/kg) given intramuscularly [59]. However, a study in Kenyan children using a larger intramuscular dose of phenobarbital (20 mg/kg) showed increased mortality in the children who received phenobarbital [60], although their seizures were reduced in number. The increased mortality was particularly high in children who received more than three doses of diazepam, and was associated with respiratory arrest, probably from the combined respiratory depression caused by phenobarbital and diazepam. Currently, seizure prophylaxis is not recommended in children with CM, as there are no data on whether an alternate dosage of phenobarbital or use of a different antiseizure medication might lead to a reduction in mortality.

Potential future adjunctive therapy for severe malaria & CM

In addition to the agents already tested, improved understanding of severe malaria and CM pathogenesis has led to further potential adjunctive therapies that might decrease the morbidity and mortality seen with these diseases. An area of particular interest is neurologic and cognitive impairment following CM. Studies have shown that CM is associated with short-term neurologic deficits [11,61] and that approximately one in every four children with CM will demonstrate long-term cognitive impairment [9,11], making this a major public health problem in sub-Saharan Africa. Adjunctive therapies that not only reduce mortality but also decrease the risk of long-term cognitive morbidity in children with severe malaria are urgently needed.

Among the areas in which adjunctive therapy for severe malaria and CM may be developed are:

- Agents that inhibit cytoadherance (*P. falciparum* erythrocyte membrane protein-1 [PfEMP1] inhibitors, levamisole and glycosaminoglycans)
- Immune modulators (rosiglitazone and pantethine)
- Agents that increase NO levels (arginine and inhaled NO)
- Neuroprotective agents (EPO)

Inhibition of cytoadherance

Inhibition of PfEMP1 binding to endothelial cells

The *var* gene-encoded PfEMP1 plays a major role in sequestration. PfEMP1 enables the parasite to adhere to the endothelial linings of blood vessels (cytoadherence) and aids in attraction of noninfected erythrocytes to the infected RBCs (rosetting) [62]. Agents that block PfEMP1 binding and hence interrupt cyto-adherence and sequestration are therefore potential adjunct therapies for severe malaria. Different ligands (aptamers) have been tried. In one study, high-affinity ligands (aptamers) were able at high concentrations to completely disrupt rosette formation *in vitro*, suggesting that this may be an avenue for therapeutic intervention [63]. Further studies on aptamer safety and *in vivo* efficacy are required to determine if these agents will move on to clinical trials.

Levamisole

CD36 is one of the major vascular receptors that mediates the binding of infected RBCs to the vascular endothelium, a process that leads to sequestration. Levamisole inhibits the binding of infected RBCs, resulting in decreased cytoadhesion. In a randomized clinical trial of individuals with uncomplicated malaria, the use of levamisole together with quinine resulted in almost compete prevention of early trophozoite sequestration and greater than 65% prevention of midtrophozoite sequestration [64]. A trial of levamisole in severe malaria is currently underway.

Glycosaminoglycans

Sulfated glyconconjugates, such as heparin, disrupt rosette formation [48], but have also been shown to enhance the adhesion of infected RBCs to dermal microvascular endothelial cells [65]. A new form of heparin, depolymerized by periodate treatment to generate novel glycans (d-glycosaminoglycans [d-GAGs]) that lack anticoagulant activity, has been produced [66]. *In vitro* studies demonstrated that d-GAGs disrupted rosettes, and inhibited merozoite invasion of erythrocytes and endothelial binding of *P. falciparum*-infected erythrocytes, and *in vivo* studies of *P. falciparum* in nonhuman primates showed that sequestered parasites were released following d-GAG injection [67]. If d-GAGs prove to be safe in humans, they may provide effective adjunctive therapy that prevents sequestration, and by this action decreases the risk of severe malaria.

Immune modulation

In murine studies, the peroxisome proliferator-activated receptor-γ agonist rosiglitazone modulated the innate host immune response to malaria by enhancing phagocytosis of infected RBCs and decreasing inflammatory responses to infection by inhibition of specific signaling pathways [68]. Phase I and II trials show that rosiglitazone was well tolerated compared with standard therapy for uncomplicated *P. falciparum* malaria and resulted in increased parasite clearance and decreased inflammatory biomarkers associated with adverse malaria outcomes [69]. Rosiglitazone may be a promising adjunct therapy for malaria, but it also makes fat cells more responsive to insulin, and this could be a problem for children in Africa with severe malaria, where hypoglycemia is a common complication of severe malaria and is associated with an increased risk of death [70].

Other immune modulators, such as low-molecular-weight thiol pantethine, have been proposed. Pantethine modulates one of the early steps of the inflammation–coagulation cascade, the transbilayer translocation of phosphatidylserine at the cell surface, and in this way lowers platelet response to activation by thrombin and collagen and decreases circulating endothelial microparticles and preserves BBB integrity [71]. Pantethine has been used in trials for other diseases in humans, and is well tolerated [72]; therefore, it could be considered for clinical trials in severe malaria.

Increasing NO levels

Nitric oxide is believed to play a significant role in the pathogenesis of severe malaria [73]. Low serum NO levels are seen in individuals with malaria, and the lowest levels are seen in children who die of CM [22]. L-arginine is the substrate for NO synthase and by improving NO bioavailability, endothelial function may be improved. Phase I trials have shown that arginine is safe and well tolerated in adults with moderate-to-severe malaria, and that arginine infusion is associated with recovery of endothelial function [74]. A Phase II trial is now ongoing in Indonesia among adult patients. An alternative method to improve NO bioavailability would be to use inhaled NO, which has proven to be safe and effective in a number of other disease

states in adults and children, and has shown evidence of a neuroprotective effect in neonates [75]. A clinical trial of inhaled NO in severe malaria is currently planned in Uganda.

Neuroprotection

Due to its anti-inflammatory, antioxidant and anti-apoptotic effects, EPO has been proposed as a possible adjuvant therapy for CM. African children with high levels of EPO during a malaria episode were found to have a better clinical outcome than their counterparts with lower levels, suggesting that EPO provided some form of neuroprotection [25]. Murine studies are encouraging and suggest that recombinant EPO may lead to earlier clinical recovery, increased survival and a degree of neuroprotection [76]. However, recombinant human EPO therapy in cancer and chronic kidney disease has resulted in increased thrombo-embolic complications and/or death in several studies [77,78], and a recent large clinical trial in stroke victims also demonstrated an increased death rate in those who received EPO [79]. CM is an acute event and does not have the chronic procoagulatory state seen in cancer and renal failure, but the elevated levels of endothelial microparticles seen in CM [47] could increase the risk of microthrombus formation, and this could be exacerbated by EPO therapy. A small safety trial in Mali showed no evidence of increased mortality from EPO therapy in children with severe malaria when compared with historical mortality rates [80], but the ability of this study to detect some of the potential adverse effects of EPO (e.g., increased thrombus formation) was limited. A trial of EPO therapy in severe malaria is currently ongoing in Mali [81].

Conclusion

The numerous trials of adjunctive therapy for severe malaria and CM have had generally disappointing results, with no single therapy showing unequivocal benefit in multiple studies, and many therapies yielding conflicting results in different studies. A significant increase in the understanding of malaria pathogenesis has led to several potential new therapies that have shown initial promise, and clinical trials of several of these therapies are currently ongoing. The next decade should provide us with answers as to whether these new therapies herald a breakthrough for treatment of severe malaria or add to the past track record of a lack of success in adjunctive therapy.

Expert commentary

Adjunctive therapy for severe malaria must be assessed in light of the larger field of interventions to combat malaria at every level. The introduction of insectide-treated bednets, artemisinin combination therapy and indoor residual spraying have led to dramatic declines in malaria incidence in several areas of Africa [82–84]. These large-scale interventions to prevent malaria are the ultimate solution to reduction of severe malaria and its complications. Nonetheless, in many areas malaria remains a leading cause of death in children under 5 years of age. Furthermore, drug and insectide resistance have the potential to rapidly undo the progress seen in the reduction of malaria incidence in the past decade. For this reason, it is imperative that work on adjunctive therapy continues, to reduce the burden of morbidity and mortality from severe malaria.

In this article, we have highlighted both the past failures in adjunctive therapy and the areas of promise for future work. It is perhaps instructive that even in industrialized nations, the most effective ‘adjunctive’ therapy for severe infectious illness such as sepsis is improved supportive care in an intensive care unit, including optimal monitoring, fluid management, ventilation and pressure support. These options are not available in most areas of the developing countries where malaria is endemic. Malaria pathogenesis is complex, and a single adjunctive intervention targeting one pathway may not dramatically reduce mortality and morbidity in

severe malaria, but multiple moderately successful interventions may lead to a larger reduction in combination than any single intervention.

A major question remains in the area of primary therapy: is artesunate more effective than quinine in the treatment of African children with severe malaria, as it is in Asian children and adults with severe malaria [27]? This question should be answered by the African Quinine vs Artesunate in Severe Malaria Trial (AQUAMAT), which is currently scheduled to end in December 2010. The effects of adjunctive therapies may differ if administered with artesunate as opposed to quinine, since artesunate has other properties including prevention of sequestration by the killing of ring-form parasites [85], so this additional factor may also need to be taken into account in future trials of adjunctive therapy.

Five-year view

Despite more than four decades of clinical trials of adjunctive therapy for severe malaria, not a single intervention to date has reached the point of such clearly proven efficacy that it is routinely used in severe malaria. Numerous therapies that appeared effective in murine models of severe malaria did not prove effective in human trials. Many of the clinical trials lacked the power to detect all but a very large difference. Finally, a number of therapies, such as high-dose steroids and prophylactic phenobarbital, actually proved to be harmful. In light of these bleak data, it is reasonable to question whether any progress on adjunctive therapy for severe malaria is likely in the next 5 years.

There are reasons for optimism despite the lack of past success. Albumin, one of the few therapies that showed modest success in a small clinical trial, is now undergoing a large multicenter trial of efficacy. Better understanding of the parasite and of disease pathogenesis has led to assessment of newer therapies such as L-arginine and levamisole, which have shown promise in early trials, albeit for clinical end points other than severe morbidity or mortality. New studies of CM pathogenesis, involving novel testing such as CNS imaging by MRI and assessment of endothelial cell biology, could lead to further assessment of new adjunctive interventions for CM and severe malaria.

Even if the trials outlined above are successful in identifying successful new adjunctive therapies for severe malaria, the lack of healthcare resources in most developing countries remains a major stumbling block to implementation of these therapies. Albumin, for example, is expensive and must be kept refrigerated and, like most of the therapies proposed, must be given intravenously. Provision of such therapy will almost certainly require external funding. Given the importance of the therapy, one hopes that successful interventions will be subsidized. Prevention of uncomplicated malaria remains the best way to reduce severe malaria and its associated mortality and morbidity, but until malaria is eliminated, therapies to improve outcomes in severe malaria will remain important. In the next 5 years, one or more successful therapies for severe malaria may be discovered, but widespread implementation of such therapy is probably beyond the 5-year horizon.

Key issues

- Malaria remains a major cause of morbidity and mortality, particularly among children in sub-Saharan Africa. More than 200 million cases of malaria occur every year, leading to more than 800,000 deaths.
- Despite primary therapy that is effective against the parasite (quinine and artesunate), mortality and morbidity from severe malaria remain high.

- Cerebral malaria is among the deadliest forms of severe malaria, with mortality ranging from 13 to 21%. Long-term cognitive impairment occurs in approximately 25% of children with cerebral malaria.
- Trials of adjunctive therapy for severe malaria to date have been disappointing. Several therapies were harmful (dexamethasone, intravenous immunoglobulin and prophylactic phenobarbital), and others were either not effective or had mixed results. A number of therapies that were successful in mouse malaria models were not effective in humans.
- Albumin is the only adjunctive therapy to date associated with reduced mortality in children with severe malaria, and this finding was from a single, small study in which both treatment groups received volume expansion. A multicenter randomized clinical trial comparing volume expansion with albumin or saline to treatment with maintenance fluids in febrile children with impaired perfusion is currently being conducted.
- A better understanding of severe malaria pathogenesis must be the foundation of effective adjunctive therapy. Several recent studies have provided new insights into severe malaria and cerebral malaria pathogenesis, including the mechanisms underlying endothelial cell response to *Plasmodium falciparum* infection, the role of nitric oxide in endothelial dysfunction, and the relationship of CNS proinflammatory responses to *P. falciparum* infection and cognitive sequelae in cerebral malaria.
- New therapies being considered as adjunctive therapy in severe malaria include inhibitors of cytoadherence (levamisole and glycosaminoglycans), immune modulators (rosiglitazone and pantethine), agents that increase nitric oxide levels (L-arginine and inhaled nitric oxide) and neuroprotective agents (erythropoietin). Among these agents, levamisole and arginine may be the most promising, based on preliminary studies, but no large trials in severe malaria have yet been completed with either of these therapies.
- Implementation of effective adjunctive therapy, if such a therapy is found, will probably require subsidization in developing countries, and could be difficult to implement even with subsidization, given the infrastructure required for administration of some of these therapies.
- Ultimately, prevention of malaria is the most effective method of reducing severe malaria. However, until malaria is eradicated, development of effective adjunctive therapy for severe malaria remains important if childhood mortality in developing countries is to decrease.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. WHO. World malaria report 2008. WHO; Geneva, Switzerland: 2008.
2. Snow RW, Marsh K. The consequences of reducing transmission of *Plasmodium falciparum* in Africa. Adv Parasitol 2002;52:235–264. [PubMed: 12521262]

3. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature 2005;434(7030):214–217. [PubMed: 15759000]

4. Idro R, Aloyo J, Mayende L, Bitarakwate E, John CC, Kivumbi GW. Severe malaria in children in areas with low, moderate and high transmission intensity in Uganda. Trop Med Int Health 2006;11(1): 115–124. [PubMed: 16398762]

5. Murphy SC, Breman JG. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. Am J Trop Med Hyg 2001;64(1–2 Suppl):57–67. [PubMed: 11425178]

6. Reyburn H, Mbatia R, Drakeley C, et al. Association of transmission intensity and age with clinical manifestations and case fatality of severe *Plasmodium falciparum* malaria. JAMA 2005;293(12): 1461–1470. [PubMed: 15784869]

7. Oduro AR, Koram KA, Rogers W, et al. Severe falciparum malaria in young children of the Kassena-Nankana district of northern Ghana. Malar J 2007;6:96. [PubMed: 17662142]

8. Kahigwa E, Schellenberg D, Sanz S, et al. Risk factors for presentation to hospital with severe anaemia in Tanzanian children: a case–control study. Trop Med Int Health 2002;7(10):823–830. [PubMed: 12358616]

9•. John CC, Bangirana P, Byarugaba J, et al. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics 2008;122(1):e92–e99. First study to prospectively document long-term cognitive impairment in children with cerebral malaria. [PubMed: 18541616]

10. Imbert P, Sartelet I, Rogier C, Ka S, Baujat G, Candito D. Severe malaria among children in a low seasonal transmission area, Dakar, Senegal: influence of age on clinical presentation. Trans R Soc Trop Med Hyg 1997;91(1):22–24. [PubMed: 9093619]

11. Boivin MJ, Bangirana P, Byarugaba J, et al. Cognitive impairment after cerebral malaria in children: a prospective study. Pediatrics 2007;119(2):e360–e366. [PubMed: 17224457]

12. Boivin MJ. Effects of early cerebral malaria on cognitive ability in Senegalese children. J Dev Behav Pediatr 2002;23(5):353–364. [PubMed: 12394524]

13. van Hensbroek MB, Palmer A, Jaffar S, Schneider G, Kwiatkowski D. Residual neurologic sequelae after childhood cerebral malaria. J Pediatr 1997;131(1 Pt 1):125–129. [PubMed: 9255203]

14. Roze E, Thiebaut MM, Mazevet D, et al. Neurologic sequelae after severe falciparum malaria in adult travelers. Eur Neurol 2001;46(4):192–197. [PubMed: 11721125]

15••. Taylor TE, Fu WJ, Carr RA, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. Nat Med 2004;10(2):143–145. Highlights the importance of sequestration as a hallmark of brain pathology in autopsies of children with true cerebral malaria. [PubMed: 14745442]

16••. Grau GE, Taylor TE, Molyneux ME, et al. Tumor necrosis factor and disease severity in children with falciparum malaria. N Engl J Med 1989;320(24):1586–1591. Early study documenting increasing levels of TNF-α with increasing disease severity in malaria. [PubMed: 2657427]

17•. Clark IA, Alleva LM. Is human malarial coma caused, or merely deepened, by sequestration? Trends Parasitol 2009;25(7):314–318. Debates whether sequestration is a cause or a secondary phenomenon in cerebral malaria. [PubMed: 19541540]

18. Clark IA, Budd AC, Alleva LM. Sickness behaviour pushed too far – the basis of the syndrome seen in severe protozoal, bacterial and viral diseases and post-trauma. Malar J 2008;7:208. [PubMed: 18854046]

19. John CC, Opika-Opoka R, Byarugaba J, Idro R, Boivin MJ. Low levels of RANTES are associated with mortality in children with cerebral malaria. J Infect Dis 2006;194(6):837–845. [PubMed: 16941352]

20. John CC, Park GS, Sam-Agudu N, Opoka RO, Boivin MJ. Elevated serum levels of IL-1ra in children with *Plasmodium falciparum* malaria are associated with increased severity of disease. Cytokine 2008;41(3):204–208. [PubMed: 18282763]

21. Jain V, Armah HB, Tongren JE, et al. Plasma IP-10, apoptotic and angiogenic factors associated with fatal cerebral malaria in India. Malar J 2008;7:83. [PubMed: 18489763]

22•. Anstey NM, Weinberg JB, Hassanali MY, et al. Nitric oxide in Tanzanian children with malaria: inverse relationship between malaria severity and nitric oxide production/nitric oxide synthase type

2 expression. J Exp Med 1996;184(2):557–567. Showed that nitric oxide levels are reduced, not elevated, in children with severe malaria. [PubMed: 8760809]

23. Medana IM, Hunt NH, Chan-Ling T. Early activation of microglia in the pathogenesis of fatal murine cerebral malaria. Glia 1997;19(2):91–103. [PubMed: 9034826]
24. Jennings VM, Lal AA, Hunter RL. Evidence for multiple pathologic and protective mechanisms of murine cerebral malaria. Infect Immun 1998;66(12):5972–5979. [PubMed: 9826380]
25•. Casals-Pascual C, Idro R, Gicheru N, et al. High levels of erythropoietin are associated with protection against neurological sequelae in African children with cerebral malaria. Proc Natl Acad Sci USA 2008;105(7):2634–2639. Describes elevated levels of erythropoietin in children with cerebral malaria who did not develop neurologic deficits, suggesting erythropoietin could be neuroprotective in these children. [PubMed: 18263734]
26••. John CC, Panoskaltsis-Mortari A, Opoka RO, et al. Cerebrospinal fluid cytokine levels and cognitive impairment in cerebral malaria. Am J Trop Med Hyg 2008;78(2):198–205. Provides evidence of production of proinflammatory cytokines by brain parenchymal cells in children with cerebral malaria. [PubMed: 18256412]
27••. Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–725. Established artesunate as the treatment of choice for severe malaria in adults in Southeast Asia, as it was associated with reduced mortality when compared with quinine. [PubMed: 16125588]
28. Praygod G, de Frey A, Eisenhut M. Artemisinin derivatives versus quinine in treating severe malaria in children: a systematic review. Malar J 2008;7:210. [PubMed: 18928535]
29. White NJ, Turner GD, Medana IM, Dondorp AM, Day NP. The murine cerebral malaria phenomenon. Trends Parasitol 2010;26(1):11–15. [PubMed: 19932638]
30••. Maitland K, Pamba A, English M, et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis 2005;40(4):538–545. Only clinical trial to date to provide evidence of decreased mortality with an adjunctive therapy in severe malaria. [PubMed: 15712076]
31••. Warrell DA, Looareesuwan S, Warrell MJ, et al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. N Engl J Med 1982;306(6):313–319. Established that steroids were harmful, not helpful, in cerebral malaria. [PubMed: 7033788]
32. Hoffman SL, Rustama D, Punjabi NH, et al. High-dose dexamethasone in quinine-treated patients with cerebral malaria: a double-blind, placebo-controlled trial. J Infect Dis 1988;158(2):325–331. [PubMed: 3042874]
33. Taylor TE, Molyneux ME, Wirima JJ, Borgstein A, Goldring JD, Hommel M. Intravenous immunoglobulin in the treatment of paediatric cerebral malaria. Clin Exp Immunol 1992;90(3):357–362. [PubMed: 1458672]
34. Havlik I, Looareesuwan S, Vannaphan S, et al. Curdlan sulphate in human severe/cerebral *Plasmodium falciparum* malaria. Trans R Soc Trop Med Hyg 2005;99(5):333–340. [PubMed: 15780339]
35. van Hensbroek MB, Palmer A, Onyiorah E, et al. The effect of a monoclonal antibody to tumor necrosis factor on survival from childhood cerebral malaria. J Infect Dis 1996;174(5):1091–1097. [PubMed: 8896514]
36. Das BK, Mishra S, Padhi PK, et al. Pentoxifylline adjunct improves prognosis of human cerebral malaria in adults. Trop Med Int Health 2003;8(8):680–684. [PubMed: 12869088]
37. Di Perri G, Di Perri IG, Monteiro GB, et al. Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. J Infect Dis 1995;171(5):1317–1322. [PubMed: 7751709]
38. Hemmer CJ, Hort G, Chiwakata CB, et al. Supportive pentoxifylline in falciparum malaria: no effect on tumor necrosis factor α levels or clinical outcome: a prospective, randomized, placebo-controlled study. Am J Trop Med Hyg 1997;56(4):397–403. [PubMed: 9158047]
39. Looareesuwan S, Wilairatana P, Vannaphan S, et al. Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand. Am J Trop Med Hyg 1998;58(3):348–353. [PubMed: 9546417]
40. Gordeuk VR, Loyevsky M. Antimalarial effect of iron chelators. Adv Exp Med Biol 2002;509:251–272. [PubMed: 12572998]

41. Gordeuk V, Thuma P, Brittenham G, et al. Effect of iron chelation therapy on recovery from deep coma in children with cerebral malaria. N Engl J Med 1992;327(21):1473–1477. [PubMed: 1406879]
42. Mohanty D, Ghosh K, Pathare AV, Karnad D. Deferiprone (L1) as an adjuvant therapy for *Plasmodium falciparum* malaria. Indian J Med Res 2002;115:17–21. [PubMed: 12424933]
43. Thuma PE, Mabeza GF, Biemba G, et al. Effect of iron chelation therapy on mortality in Zambian children with cerebral malaria. Trans R Soc Trop Med Hyg 1998;92(2):214–218. [PubMed: 9764337]
44. Griffiths MJ, Ndungu F, Baird KL, Muller DP, Marsh K, Newton CR. Oxidative stress and erythrocyte damage in Kenyan children with severe *Plasmodium falciparum* malaria. Br J Haematol 2001;113 (2):486–491. [PubMed: 11380421]
45. Watt G, Jongsakul K, Ruangvirayuth R. A pilot study of *N*-acetylcysteine as adjunctive therapy for severe malaria. Q JM 2002;95(5):285–290.
46. Charunwatthana P, Abul Faiz M, Ruangveerayut R, et al. *N*-acetylcysteine as adjunctive treatment in severe malaria: a randomized, double-blinded placebo-controlled clinical trial. Crit Care Med 2009;37(2):516–522. [PubMed: 19114891]
47. Combes V, Taylor TE, Juhan-Vague I, et al. Circulating endothelial microparticles in malawian children with severe falciparum malaria complicated with coma. JAMA 2004;291(21):2542–2544. [PubMed: 15173142]
48. Rogerson SJ, Reeder JC, al-Yaman F, Brown GV. Sulfated glycoconjugates as disrupters of *Plasmodium falciparum* erythrocyte rosettes. Am J Trop Med Hyg 1994;51(2):198–203. [PubMed: 7521140]
49. Hemmer CJ, Kern P, Holst FG, Nawroth PP, Dietrich M. Neither heparin nor acetylsalicylic acid influence the clinical course in human *Plasmodium falciparum* malaria: a prospective randomized study. Am J Trop Med Hyg 1991;45(5):608–612. [PubMed: 1951871]
50. Riddle MS, Jackson JL, Sanders JW, Blazes DL. Exchange transfusion as an adjunct therapy in severe *Plasmodium falciparum* malaria: a meta-analysis. Clin Infect Dis 2002;34(9):1192–1198. [PubMed: 11941545]
51. White NJ. The treatment of malaria. N Engl J Med 1996;335:800–806. [PubMed: 8703186]
52. Maitland K, Nadel S, Pollard AJ, Williams TN, Newton CR, Levin M. Management of severe malaria in children: proposed guidelines for the United Kingdom. Br Med J 2005;331(7512):337–343. [PubMed: 16081449]
53. Akech S, Gwer S, Idro R, et al. Volume expansion with albumin compared to gelofusine in children with severe malaria: results of a controlled trial. PLoS Clin Trials 2006;1(5):e21. [PubMed: 16998584]
54. Woodrow CJ, Planche T. Phase III trial of albumin in malaria still lacks scientific justification. PLoS Clin Trials 2007;2(2):e1. [PubMed: 17369877]
55. Krishna S, Supanaranond W, Pukrittayakamee S, Kuile FT, Ruprah M, White NJ. The disposition and effects of two doses of dichloroacetate in adults with severe falciparum malaria. Br J Clin Pharmacol 1996;41(1):29–34. [PubMed: 8824690]
56. Newton CR, Crawley J, Sowumni A, et al. Intracranial hypertension in Africans with cerebral malaria. Arch Dis Child 1997;76(3):219–226. [PubMed: 9135262]
57. Namutangula B, Ndeezi G, Byarugaba JS, Tumwine JK. Mannitol as adjunct therapy for childhood cerebral malaria in Uganda: a randomized clinical trial. Malar J 2007;6:138. [PubMed: 17958887]
58. Crawley J, Smith S, Kirkham F, Muthinji P, Waruiru C, Marsh K. Seizures and status epilepticus in childhood cerebral malaria. Q JM 1996;89(8):591–597.
59. White NJ, Looareesuwan S, Phillips RE, Chanthavanich P, Warrell DA. Single dose phenobarbitone prevents convulsions in cerebral malaria. Lancet 1988;2(8602):64–66. [PubMed: 2898696]
60•. Crawley J, Waruiru C, Mithwani S, et al. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. Lancet 2000;355(9205): 701–706. Documented increased mortality with prophylactic phenobarbital in African children with cerebral malaria. [PubMed: 10703801]
61. Idro R, Carter JA, Fegan G, Neville BG, Newton CR. Risk factors for persisting neurological and cognitive impairments following cerebral malaria. Arch Dis Child 2006;91(2):142–148. [PubMed: 16326798]

62. Chen Q, Pettersson F, Vogt AM, et al. Immunization with PfEMP1-DBL1α generates antibodies that disrupt rosettes and protect against the sequestration of *Plasmodium falciparum*-infected erythrocytes. Vaccine 2004;22(21–22):2701–2712. [PubMed: 15246600]
63. Barfod A, Persson T, Lindh J. *In vitro* selection of RNA aptamers against a conserved region of the *Plasmodium falciparum* erythrocyte membrane protein 1. Parasitol Res 2009;105(6):1557–1566. [PubMed: 19693540]
64. Dondorp AM, Silamut K, Charunwatthana P, et al. Levamisole inhibits sequestration of infected red blood cells in patients with falciparum malaria. J Infect Dis 2007;196(3):460–466. [PubMed: 17597461]
65. McCormick CJ, Newbold CI, Berendt AR. Sulfated glycoconjugates enhance CD36-dependent adhesion of *Plasmodium falciparum*-infected erythrocytes to human microvascular endothelial cells. Blood 2000;96(1):327–333. [PubMed: 10891469]
66. Vogt AM, Barragan A, Chen Q, Kironde F, Spillmann D, Wahlgren M. Heparan sulfate on endothelial cells mediates the binding of *Plasmodium falciparum*-infected erythrocytes via the DBL1α domain of PfEMP1. Blood 2003;101(6):2405–2411. [PubMed: 12433689]
67. Vogt AM, Pettersson F, Moll K, et al. Release of sequestered malaria parasites upon injection of a glycosaminoglycan. PLoS Pathog 2006;2(9):e100. [PubMed: 17009869]
68. Serghides L, Patel SN, Ayi K, et al. Rosiglitazone modulates the innate immune response to *Plasmodium falciparum* infection and improves outcome in experimental cerebral malaria. J Infect Dis 2009;199(10):1536–1545. [PubMed: 19392627]
69. Boggild AK, Krudsood S, Patel SN, et al. Use of peroxisome proliferator-activated receptor γ agonists as adjunctive treatment for *Plasmodium falciparum* malaria: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2009;49(6):841–849. [PubMed: 19673614]
70. Marsh K, English M, Crawley J, Peshu N. The pathogenesis of severe malaria in African children. Ann Trop Med Parasitol 1996;90(4):395–402. [PubMed: 8944083]
71. Penet MF, Abou-Hamdan M, Coltel N, et al. Protection against cerebral malaria by the low-molecular-weight thiol pantethine. Proc Natl Acad Sci USA 2008;105(4):1321–1326. [PubMed: 18195363]
72. Vecsei L, Widerlov E. Preclinical and clinical studies with cysteamine and pantethine related to the central nervous system. Prog Neuropsychopharmacol Biol Psychiatry 1990;14(6):835–862. [PubMed: 2277850]
73. Weinberg JB, Lopansri BK, Mwaikambo E, Granger DL. Arginine, nitric oxide, carbon monoxide, and endothelial function in severe malaria. Curr Opin Infect Dis 2008;21(5):468–475. [PubMed: 18725795]
74. Yeo TW, Lampah DA, Gitawati R, et al. Recovery of endothelial function in severe falciparum malaria: relationship with improvement in plasma L-arginine and blood lactate concentrations. J Infect Dis 2008;198(4):602–608. [PubMed: 18605903]
75. Marks JD, Schreiber MD. Inhaled nitric oxide and neuroprotection in preterm infants. Clin Perinatol 2008;35(4):793–807. viii. [PubMed: 19026341]
76. Wiese L, Hempel C, Penkowa M, Kirkby N, Kurtzhals JAL. Recombinant human erythropoietin increases survival and reduces neuronal apoptosis in a murine model of cerebral malaria. Malar J 2008;7:3. [PubMed: 18179698]
77. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299(8):914–924. [PubMed: 18314434]
78. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355(20):2085–2098. [PubMed: 17108343]
79. Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke 2009;40(12):e647–e656. [PubMed: 19834012]
80. Picot S, Bienvenu AL, Konate S, et al. Safety of epoietin β-quinine drug combination in children with cerebral malaria in Mali. Malar J 2009;8:169. [PubMed: 19630971]
81. Casals-Pascual C, Idro R, Picot S, Roberts DJ, Newton CR. Can erythropoietin be used to prevent brain damage in cerebral malaria? Trends Parasitol 2009;25(1):30–36. [PubMed: 19008152]
82. Okiro EA, Alegana VA, Noor AM, Mutheu JJ, Juma E, Snow RW. Malaria paediatric hospitalization between 1999 and 2008 across Kenya. BMC Med 2009;7:75. [PubMed: 20003178]

83. O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet 2008;372(9649):1555–1562. [PubMed: 18984188]

84. Ceesay SJ, Casals-Pascual C, Erskine J, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet 2008;372(9649):1545–1554. [PubMed: 18984187]

85. Dondorp AM. Clinical significance of sequestration in adults with severe malaria. Transfus Clin Biol 2008;15(1–2):56–57. [PubMed: 18501654]

Expert Rev Anti Infect Ther. Author manuscript; available in PMC 2011 July 1.

Table 1

Randomized clinical trials of adjunctive therapy in severe malaria.

Author, year, country	Therapy	Dosage and route	Study design	Type of severe malaria	Age	Sample size (n)	Outcome	Ref.
Immunomodulation								
Warrell *et al.*, 1982, Thailand	Dexamethasone	2 mg/kg iv. over 48 h	RCT, DB, PC	Cerebral malaria	6–70 years	100	No difference in mortality; increased coma duration and complications (pneumonia, gastrointestinal bleeding) in patients receiving dexamethasone	[31]
Hoffman *et al.*, 1988, Indonesia	Dexamethasone	11.4 mg/kg iv. over 48 h	RCT, DB, PC	Stuporous or comatose patients	18 months to 42 years	38	No difference in mortality, duration of coma or parasite clearance time	[32]
Taylor *et al.*, 1992, Malawi	IVIG	400 mg/kg iv. over 3 h	RCT, DB, PC	Cerebral malaria	1–12 years	31	Trends toward increased mortality and neurologic sequelae with IVIG treatment	[33]
Havlik *et al.*, 2005, Thailand	Curdlan sulfate	Varying dose iv.	Two RCTs, PC	Severe malaria	>12 years	62	Faster fever clearance, no difference in parasite clearance times with curdlan sulfate	[34]
van Hensbroek *et al.*, 1996, The Gambia	Anti-TNF monoclonal antibody	5 mg/kg iv. × one dose	RCT, DB, PC	Cerebral malaria	1–9 years	610	No difference in mortality; increased neurologic sequelae in children who received antibody	[35]
Das *et al.*, 2003, India	POF	10 mg/kg/day iv. × 3 days	RCT	Cerebral malaria	>18 years	52	Trend toward lower mortality, and faster resolution time and lower TNF levels on day 3 in POF group	[36]
DiPerri *et al.*, 1995, Burundi	POF	10 mg/kg/day iv. × 3 days	RCT	Cerebral malaria	<14 years	56	Shorter coma and trend toward lower mortality in children receiving POF	[37]
Hemmer *et al.*, 1997, Germany	POF	20 mg/kg/day iv. × 5 days	RCT, PC	Severe and uncomplicated malaria	22–69 years	51	More side effects (nausea and abdominal discomfort) in POF than placebo; no	[38]

Author, year, country	Therapy	Dosage and route	Study design	Type of severe malaria	Age	Sample size (n)	Outcome	Ref.
							difference in TNF levels or clinical outcomes	
Looareesuwan *et al.*, 1998, Thailand	POF	0.83 mg/kg/h or 1.66 mg/kg/h iv. × 72 h	RCT, PC	Severe malaria	16–60 years	45	No difference in any clinical outcome or parasite clearance time	[39]
Iron chelation								
Gordeuk *et al.*, 1992, Zambia	Deferoxamine	100 mg/kg/day iv. × 2 days	RCT, DB, PC	Cerebral malaria	<6 years	83	No difference in mortality or coma duration; decreased parasite clearance time with deferoxamine	[41]
Thuma *et al.*, 1998, Zambia	Deferoxamine	100 mg/kg/day iv. × 3 days	RCT, PC	Cerebral malaria	<6 years	352	Trend toward increased mortality in one center with deferoxamine, trend toward shorter coma time with deferoxamine	[43]
Mohanty *et al.*, 1998, India	Deferipone	75 mg/kg/day p.o./ NG × 10 days	RCT, DB, PC	Severe malaria	>18 years	45	No difference in mortality, faster resolution of coma and fever, decreased parasite clearance time	[42]
Antioxidant								
Watt *et al.*, 2002, Thailand	*N*-acetylcysteine	300 mg/kg iv. over 20 h	RCT, DB, PC	Severe malaria	>18 years (only males)	30	Faster normalization of lactate levels, trend toward earlier switch to oral medications	[45]
Charunwatthana *et al.*, 2009, Thailand and Bangladesh	*N*-acetylcysteine	300 mg/kg iv. over 20 h	RCT, DB, PC	Severe malaria	>16 years	108	No difference in mortality, lactate clearance or coma recovery times between groups. Slightly longer parasite clearance time with *N*-acetylcysteine	[46]
Anticoagulant								
Hemmer *et al.*, 1991, Germany	Heparin or aspirin	Heparin 70 U/kg/day sc. × 5 days; ASA 500 mg iv. days 0, 2	RCT	Severe malaria	>14 years	97	No difference in fever or parasite clearance, or time to discharge between groups	[49]

Author, year, country	Therapy	Dosage and route	Study design	Type of severe malaria	Age	Sample size (n)	Outcome	Ref.
		and 4; control group received neither drug						
Exchange transfusion								
Riddle *et al.*, 2002, multiple	EBT		Meta-analysis of eight studies; no RCT to date	Severe malaria			No difference between those who received EBT and those who did not, but baseline parasitemia and malaria severity were higher in those who received EBT	[50]
Volume expansion/correction of acidosis								
Maitland *et al.*, 2005, Kenya	Albumin	4.5% iv., 20 ml/kg × one dose	RCT, albumin vs saline vs control	Severe malaria with acidosis	Children (ages not given)	150	Lower mortality with albumin than saline	[52]
Akech *et al.*, 2006, Kenya	Albumin	4.5% iv., 20 ml/kg × one dose	RCT, albumin vs gelofusine	Severe malaria, acidosis and clinical features of shock	Children >3 months of age	88	Trend toward lower mortality with albumin than with gelofusine	[53]
Krishna *et al.*, 1996, Thailand	Dichloroacetate	46 mg/kg iv., two doses 12 h apart	RCT, dichloroacetate vs saline	Severe malaria	>18 years	20	Greater decrease in lactate concentration in those who received dichloroacetate	[55]
Reduction of cerebral edema								
Namutangula *et al.*, 2007, Uganda	Mannitol Dexamethasone	1 g/kg iv. × one dose See studies [31] and [32] at start of table	RCT, DB, PC	Cerebral malaria	6–60 months	156	No difference in mortality or duration of coma	[57]
Seizure prophylaxis								
White *et al.*, 1988, Thailand	Phenobarbital	3.5 mg/kg im. × one dose	RCT, DB, PC	Cerebral malaria	>6 years	46	Decreased seizures	[59]
Crawley *et al.*, 2000, Kenya	Phenobarbital	20 mg/kg im. × one dose	RCT, PC	Cerebral malaria	9 months– 13 years	340	Increased mortality, decreased seizures	[60]

ASA: Acetylsalicylic acid; DB: Double blind; EBT: Exchange blood transfusion; im.: Intramuscular; iv.: Intravenous; IVIG: Intravenous immunoglobulin; NG: Nasogastric tube; PC: Placebo controlled; p.o.: Per oral; POF: Pentoxifylline; RCT: Randomized controlled trial; sc.: Subcutaneous.