The Management of Patients with Severe Malaria

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Abstract. Severe malaria is a global problem, claiming at least 1 million lives annually. Few adequately powered clinical studies have been directed at improving the management of severe malaria over the years, but this situation is slowly changing. The antimalarial treatment of severe disease is being transformed by the development and deployment of the water-soluble artemisinin derivative artesunate. Parenteral artesunate is now the treatment of choice in low-transmission areas and in the 2nd and 3rd trimesters of pregnancy, and research is underway into whether it should replace quinine as the treatment of choice in African children. Development of good manufacturing practice (GMP) formulations should make parenteral artesunate more widely available in the near future. The development of artesunate suppositories offers another exciting prospect, the ability to treat patients with severe disease in remote rural settings, delaying the evolution of disease and buying them time to reach a health care facility. No adjunctive therapy has been shown to improve the outcome of severe malaria, but most studies have been underpowered. Future trials of interventions shown to be promising in pilot studies should be large and adequately powered. This will require multicenter designs and necessitate close collaboration between groups, as well as agreement on the research agenda. We suggest a list of candidate interventions for debate.

INTRODUCTION

Falciparum malaria remains a major cause of morbidity and mortality throughout the tropical world, with as many as 500 million cases annually causing 1–3 million deaths. Most cases of malaria are uncomplicated and can be treated successfully with appropriate oral antimalarial drugs. However, in a proportion of patients, particularly in nonimmune individuals and/or where treatment has been delayed or ineffective drugs (chloroquine in most areas of the world) or substandard counterfeit drugs given, life-threatening severe disease can evolve requiring hospitalization, parenteral antimalarial therapy, and the treatment of complications. Severe malaria is often a multisystem disorder, presenting with multiple complications, each requiring specific management. In most of the malaria-endemic world, sophisticated intensive care facilities are not available and treatment is necessarily resource-limited. The mortality associated with severe malaria remains high, ranging from 10% to 50% depending on the setting. In this context, the main objective of the management of severe malaria is to prevent the patient from dying. Prevention of long-term sequelae and recrudescence (the usual primary endpoint of antimalarial trials in uncomplicated malaria) are secondary objectives.

The World Health Organization coordinated the production of guidelines for the management of severe and complicated malaria in 1990 and again in 2000, which also contain strict definitions of severe malaria, useful for standardizing clinical research. More recently, in 2006, WHO published evidence-based guidelines for the treatment of malaria, which include extensive advice on the management of severe malaria as well as a clinically useful distillation of the WHO severe malaria definitions (Table 1).

Unfortunately, the clinical evidence base on which to base guidelines is small, as most of the clinical trials on severe malaria management have been either negative, underpowered, or both. Until the SEQUAMAT trial in 2005, no proposed intervention in severe malaria had ever been shown to reduce mortality. This review will briefly recapitulate the evidence for current “best practice” but will also concentrate on the many gaps in our knowledge and how they might be addressed.

INITIAL ASSESSMENT AND MANAGEMENT

Severe malaria is a medical emergency. Initial management is based on that of any acutely and severely ill patient. The initial rapid clinical assessment should focus on the airway and circulation and include assessments of conscious level, respiratory status, and state of hydration. Hypoglycemia should be ruled out or, if the patient is comatose, treated empirically. Convulsions, which can present with subtle symptoms, especially in children, should be treated promptly. Intravenous rehydration should be commenced if indicated, oxygen given if there is clinical or blood gas evidence of respiratory distress or hypoxia, and an appropriate antimalarial drug administered. If the presence of severe malaria is suspected (Table 1), the patient should be transferred to the highest level of care available (preferably an intensive care unit).

In areas of high transmission, peripheral parasitemia is common and relatively uninformative unless very high, and other common infections may produce clinical pictures similar to the spectrum of syndromes produced by severe malaria. In cases with impaired consciousness, a lumbar puncture should be performed to exclude meningitis and the possibility of bacterial sepsis considered in all seriously ill individuals. Blood cultures are rarely available in endemic areas, but where they have been done systematically, bacteremias were found in a significant proportion of clinically severe patients with parasitemia. Clearly if there are focal signs suggesting a bacterial infection (such as pneumonia), broad-spectrum antibiotic cover should be given. However, at present there is no robust method of excluding bacterial sepsis in patients with parasitemia and “severe malaria” in high-transmission areas. In the absence of such a test, a strong case can be made...
Parenteral quinine remains at present the drug of choice for severe malaria. Treatment involves the use of 10–20 mg/kg/day given intramuscularly over 4 hours. Where intravenous infusion is not practicable, quinine can be given by deep intramuscular injection, although this can cause sterile abscesses, which in turn have been associated with a lethal form of tetanus. Although so far no clinical trials have addressed this issue, intramuscular artemether has since been shown to be a valid treatment for severe malaria. Artemisinin derivatives are the most rapidly acting of all antimalarial drugs. However, the advantage of using artemisinin derivatives in African childhood severe malaria is due to this or to the absence of a true treatment effect; in the Asian patients (mainly adults), artemether was associated with a modest, but significantly lower mortality than quinine [OR (99% CI) 0.8 (0.62 to 1.02), P = 0.08], but this effect was not seen in African patients (mainly children). Intramuscular artemether has since been shown to be erratically absorbed (unlike intramuscular artesunate, which was rapidly absorbed and quickly hydrolyzed to DHA); it is unclear whether artemether’s lack of effect on mortality in African children is due to this or to the absence of a true difference in efficacy between quinine and the artemisinin derivatives in African childhood severe malaria. Hence, the need for evidence from randomized clinical trials comparing quinine and artemesunate in African children. AQUAMAT (African Quinine versus Artesunate in Severe Malaria Trial), a multicenter study based on the SEAQUAMAT design, is currently underway. This trial plans to recruit 5,306 patients (including 202 children) in 4 south and southeast Asian countries. 1261 patients (including 202 children) in 4 south and southeast Asian countries were recruited into SEAQUAMAT (South and Southeast Asian Quinine versus Artesunate in Severe Malaria Trial), the largest ever clinical drug trial in severe malaria. Mortality in those randomized to artesunate was 15% (107 of 730) compared with 22% (164 of 731) in quinine recipients; a relative reduction of 34.7% (95% CI 18.5–47.6%; P = 0.0002). The NNT (Number Needed to Treat to save one life) was 11.1 (95% CI 5.8–121) in Bangladesh, 12.6 (7.3 to 45) in Burma, 16.6 in Indonesia, and 21.2 in India. The mortality difference was particularly marked in those patients with large numbers of circulating young parasites, consistent with the hypothesis that artesunate’s advantage lies in its ability to kill young parasites before they sequester (unpublished observations). As a result of the SEAQUAMAT study, parenteral artemesunate is now recommended by WHO as the drug of choice for the treatment of severe malaria in low-transmission areas and in the second and third trimesters of pregnancy (Table 2).

The current recommendation for treating severe malaria patients in high-transmission areas is either quinine or an artemisinin derivative. This patient group consists mainly of African children, who bear the largest part of the global malaria disease burden and for whom the potential advantage for parenteral artesunate is not as clear-cut as in southeast Asian adults. Severe malaria in children progresses more rapidly than in adults, leaving a smaller time window for the killing of young parasites by artemesunate to deliver a clinical advantage. In the 1980s and 1990s under WHO oversight, a number of studies were carried out in both Africa and Asia comparing quinine with artemether, a lipid-soluble artemisinin derivative administered intramuscularly (it can also be given rectally, but not intravenously). An individual patient data meta-analysis showed that, whereas overall there was no significant difference in mortality between the two drugs [14% vs. 17%, odds ratio (95% confidence interval) 0.8 (0.62 to 1.02), P = 0.08], there was substantial heterogeneity in the treatment effect; in the Asian patients (mainly adults), artemether was associated with a modest, but significantly lower mortality than quinine [OR (99% CI) 0.59 (0.35 to 1.01), P = 0.012], but this effect was not seen in African patients (mainly children). Intramuscular artemether has since been shown to be erratically absorbed (unlike intramuscular artesunate, which was rapidly absorbed and quickly hydrolyzed to DHA); it is unclear whether artemether’s lack of effect on mortality in African children is due to this or to the absence of a true difference in efficacy between quinine and the artemisinin derivatives in African childhood severe malaria; hence the need for evidence from randomized clinical trials comparing quinine and artemesunate in African children. AQUAMAT (African Quinine versus Artesunate in Severe Malaria Trial), a multicenter study based on the SEAQUAMAT design, is currently underway. This trial plans to recruit 5,306 patients by 2010, and is powered to detect a 25% reduction in mortality from 8% to 6%.

The only widely available parenteral artemesunate formulation is made by Guilin Pharmaceutical factory in China.
Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is first available. Artesunate 2.4 mg/kg body weight (bw) i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended choice in low-transmission areas or outside malaria-endemic areas.

For children in high-transmission areas, the following antimalarial medicines are recommended as there is insufficient evidence to recommend any of these antimalarial medicines over another for severe malaria:

- Artesunate 2.4 mg/kg bw i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day;
- Artemether 3.2 mg/kg bw i.m. given on admission then 1.6 mg/kg bw per day;
- Quinine 20 mg salt/kg bw on admission (i.v. infusion or divided i.m. injection), then 10 mg/kg bw every 8 h; infusion rate should not exceed 5 mg sali/kg bw per hour.

Animal toxicity studies have raised concerns about possible neurotoxicity with high doses of the artemisinin derivative drugs, but so far, despite widespread use, neurotoxicity has not been reported in humans. The animal neurotoxicity appears particularly related to high sustained levels produced by administration of lipophilic artemisinin derivatives such as artemether, which suggests that if a problem with neurotoxicity did exist (and there is no evidence of this to date), then water-soluble derivatives such as artesunate would be much safer.

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Artesunate suppositories. Most patients with malaria in the rural tropics live far from the nearest health clinic or hospital, and many develop severe disease and die before reaching a health facility where parenteral treatment can be given. Deployment of artesunate suppositories in rural areas offers the prospect of effective early treatment of malaria, preventing clinical deterioration and buying time to reach a hospital. The use of suppositories containing artemisinin or one of its derivatives for the treatment of severe malaria in both adults and children was pioneered in Viet Nam in the early 1990s. Subsequently, the WHO sponsored the development of GMP-manufactured rectal artesunate capsules, which appear to be reasonably well absorbed and are effective for the treatment of moderately severe malaria. A large phase III study of early deployment has been completed and will report soon, and it appears likely that rectal artesunate will obtain U.S. FDA registration in the near future. Home- or village-based deployment of rectal artesunate in rural areas of the tropics may play an important role in reducing malaria-associated morbidity and mortality. Further research needs to be conducted on how best to achieve this, in particular, at what level to deploy the suppositories (family, village health worker, etc.), whether they will be socially and culturally acceptable, and assessment of practical problems concerning their administration (early passing of suppository, multiple dosing, potential paradoxical delays in referral, etc.). As a high proportion of sick individuals will have severe bacterial sepsis rather than severe malaria, the question of antibiotic cover arises. A suppository containing both artesunate and an antibiotic (preferably one with some antimalarial activity) may be the next logical step and is currently the subject of preliminary research into its feasibility.

**Supportive Care and Management of Complications**

Good nursing care is essential in the management of severe malaria, with particular attention to fluid balance, manage-

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<thead>
<tr>
<th>Table 2</th>
<th>Extracts from current WHO guidelines for the treatment of severe malaria® (reproduced with permission)</th>
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<tbody>
<tr>
<td><strong>Summary of recommendations on the treatment of severe malaria</strong></td>
<td>Level of evidence</td>
</tr>
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<td><strong>Summary of recommendations on pre-referral treatment for severe falciparum malaria</strong></td>
<td>T, E</td>
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<td><strong>Recommendation for treatment for severe falciparum malaria in pregnant women</strong></td>
<td>T, O, E</td>
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<tr>
<td>Use the parenteral antimalarial treatment locally available for severe malaria in full doses. Where available, AS is the first and artemether the second option in the second and third trimesters. In the first trimester, until more evidence becomes available, both artesunate and quinine may be considered as options.</td>
<td>O, E</td>
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® Levels of evidence: S, formal systematic reviews, such as a Cochrane Review, including more than one randomized controlled trial. T, comparative trials without formal systematic review; O, observational studies (e.g., surveillance or pharmacological data); E, expert opinion/consensus.

1 On June 21, 2007, the U.S. FDA approved an Investigational New Drug protocol that will allow the Centers for Disease Control and Prevention to make intravenous artesunate available to clinicians who request it for patients who have severe malaria.
ment of the unconscious patient, and detection of potentially lethal complications such as hypoglycemia.

**Coma.** In Western ICUs, mechanical ventilation is often used in the unconscious cerebral malaria patient to protect the airway, although its efficacy in terms of prevention of mortality and sequelae has not been proven. In a small study of Kenyan children with cerebral malaria and raised intracranial pressures, mannitol, an anti-osmotic agent, was successful in reducing intracranial pressure for short periods, but no convincing clinical evidence exists to support its routine use.

**Convulsions.** Seizures in cerebral malaria should be treated with rectal diazepam, intravenous lorazepam, paraldehyde, or other standard anticonvulsants, after high-flow oxygen and appropriate airway management have been initiated. Prophylactic phenobarbitone was shown to reduce seizure incidence in adult cerebral malaria, but a study in children using a single intramuscular dose of 20 mg/kg reduced seizures but increased mortality, possibly through respiratory depression caused by an interaction with diazepam. Prophylactic anticonvulsive therapy is therefore currently not recommended.

**Acute renal failure.** Whereas in African children malaria-associated acute renal failure is extremely rare, it is a relatively common complication of severe malaria in nonimmune adults and children. It has an untreated mortality of > 70% and should be treated with adequate renal replacement therapy—preferably by hemofiltration when available, as this has been shown to be superior to peritoneal dialysis in terms of mortality and cost-effectiveness. The role of hemodialysis has not been assessed in a randomized trial, but it is likely to be superior to peritoneal dialysis in the hemodynamically stable patient.

**Hemodynamic shock.** Shock in severe malaria (“algid malaria”) carries a high mortality in both adults and children. It should be treated initially with oxygen and fluids (with monitoring of central venous pressure if available), though, as in children, it is unclear how aggressive the volume expansion should be in terms of safety and effectiveness. Massive hemorrhage, from the gastrointestinal tract or rarely a ruptured spleen, should be excluded. A septic screen including blood cultures should be performed and appropriate broad-spectrum antibiotics administered to cover the possibility of bacterial sepsis. If inotropes are necessary, dopamine has been used safely in malaria, and dobutamine and norepinephrine may also be used though there is little experience with them in severe malaria. Epinephrine should be avoided as it induces serious lactic acidosis.

**Fluid resuscitation.** The role of aggressive fluid resuscitation in the management of severe malaria, particularly in children, is unclear and currently controversial. The debate centers around whether hypovolemia plays an important role in the pathophysiology of severe malaria, causing poor tissue perfusion, leading to anaerobic glycolysis and consequent acidosis. Advocates of aggressive fluid repletion suggest that the standards of care applied in resource-rich settings for severely ill children with bacterial sepsis should be extrapolated to severe malaria, while those against argue that there is no evidence that severe dehydration occurs in severe malaria and are concerned that overzealous rehydration may lead to pulmonary and cerebral edema. There is at present insufficient evidence either way, as all clinical studies conducted so far have been small and unsatisfactory. A large multicenter clinical trial is planned that will hopefully provide some answers, but in the meantime, intravenous fluid regimens should be guided by clinical judgment and, if available, by central venous pressure monitoring.

**Acidosis.** Metabolic acidosis, a common complication of severe malaria, is strongly associated with fatal outcome in both adults and children. Lactic acid is an important contributor, but impaired renal bicarbonate handling and the presence of other as yet unidentified acids also play major roles.

Dichloroacetate (which stimulates pyruvate dehydrogenase) has been shown to reduce plasma lactate in severe malaria, but to have no effect on pHi, possibly because of the multifactorial etiology of the acidosis. Hemofiltration has been shown to rapidly eliminate acidosis in malaria patients with renal failure, even in the presence of lactic acidosis. Early hemofiltration may be a useful strategy in patients with acidosis and renal impairment who have not yet developed established renal failure, but this has not yet been evaluated in a clinical trial.

**Anemia.** This is present in almost all patients with severe malaria but occurs most prominently in young children. Benefits of blood transfusion should outweigh the risks (especially of HIV and other pathogens). There is no clear evidence supporting specific hemoglobin cut-off levels, and a number of figures are quoted in reviews and guidelines. In adults, the threshold for blood transfusion is commonly set at a hematocrit < 20%. Clinical evidence from Kenya has led to proposed threshold hemoglobin levels for African children of 5 g/dL if there is co-existing respiratory distress, impaired consciousness, or hyperparasitemia or at an absolute cut-off of 4 g/dL.

**ARDS.** This feared complication has a high mortality rate and can develop several days after admission and onset of treatment. Clinical research is needed into both the pathophysiology and treatment of this condition. The etiology is poorly understood, and treatment in malaria is currently based on expert opinion and extrapolation from studies on ARDS associated with other conditions.

**OTHER ADJUNCTIVE THERAPIES**

The malaria literature contains many small trials of potential adjunctive therapies for severe malaria. Most of these studies to date have been underpowered, and in a recent review many were found to have “inadequate methodological quality.” In many cases, meta-analyses have been conducted with multiple small trials in attempts to make sense of the data, but still the power was usually insufficient to draw conclusions. An exception is the placebo-controlled trial of anti-TNF trial in the Gambia reported in 1996, which recruited 610 patients, 124 of whom died. There was no mortality difference and a suggestion of an increased incidence of sequelae in the treatment group. The classic 1982 dexamethasone study from Thailand on the other hand, although well-conducted and the largest study ever in severe malaria at the time (N = 100), is underpowered by today’s standards and may conceal a type II error. A meta-analysis combining it with the second malaria steroid trial from Indonesia concluded that there was insufficient power to exclude a mortality effect either way. A meta-analysis of trials on the use of iron chelators also concluded that, although no clear benefit was demon-
strated, there is not enough data to draw a definitive conclusion.\textsuperscript{54}

Exchange blood transfusion is a popular adjunctive therapy, particularly in well-resourced settings. There are a number of rationales for its use in severe malaria, including removal of parasitized erythrocytes, removal of cytokines and other soluble toxins and mediators, and improving the rheology of the blood unparasitized erythrocytes by replacing unparasitized erythrocytes with reduced deformability.\textsuperscript{55} However, no adequately powered randomized controlled clinical trial has been performed, and a meta-analysis of small studies and case series showed no clear benefit (although the transfused patient group was significantly sicker than the control group).\textsuperscript{56}

Two adjuvant candidates aimed at the disease process in general are the antioxidant N-acetylcysteine (NAC) and the antihelmintic drug levamisole. NAC has been the subject of several small studies, in one of which it was shown to increase lactate clearance.\textsuperscript{57} Levamisole, which inhibits binding of parasitized erythrocytes to CD36 in vitro and in uncomplicated malaria\textsuperscript{58} has not yet been trialed in severe malaria.\textsuperscript{59}

**FUTURE DIRECTIONS**

The evidence base for the treatment of severe malaria is lamentably small given the global importance of the disease and the number of deaths it causes. Fewer than 10,000 patients have ever been randomized into treatment trials of severe malaria, an astonishingly small figure given the \( \approx 10 \) million cases of severe malaria annually and our inadequate knowledge of how it should best be managed. Clearly, underfunding has played a major role in the past, but in recent years this problem has begun to be addressed as the global community has started making major investments in tackling the main infectious-disease killers. There has been an associated slow but steady development of clinical research capacity in the malaria-endemic world, and although there is a long way to go, it is for the first time becoming practical to conduct large, adequately powered clinical trials of candidate treatments for severe malaria. Major funding and logistical challenges are still associated with such projects, and research capacity building has to be an integral part of the planning. The considerable problem of agreeing on the research agenda must also be kept in mind, as only a limited number of such multicenter trials can be conducted at any one time. Only by forming multinational collaborations can we hope to address important clinical research questions with sufficient statistical power.

Which new treatments or clinical management strategies warrant assessment in these multi-center studies? In Table 3 we list a number of candidates along with a subjective assessment of the evidence supporting their inclusion and the level of controversy such a trial is likely to generate. Several have been mentioned already in this review, whereas others are more speculative and may require study in smaller trials with surrogate marker endpoints before a larger study can be justified. This is necessarily a personal list, and we are sure to have omitted a number of worthy contenders. The main objective is to stimulate debate and, ultimately, some degree of agreement. This is a prerequisite for the development of collaborations and networks to carry out the studies.

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