

## Management of severe falciparum malaria

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Received : 16-09-03  
Review completed : 05-11-03  
Accepted : 29-11-03  
PubMed ID : 15047999  
J Postgrad Med 2004;50:45-50

### ABSTRACT

*Plasmodium falciparum* is the most common cause of severe and life-threatening malaria. Falciparum malaria causes over one million deaths every year. In Africa, a vast majority of these deaths occur in children under five years of age. The presentation of severe malaria varies with age and geographical distribution. The mortality rate is higher in adults than in children but African children develop neuro-cognitive sequelae following severe malaria more frequently. The management of severe malaria includes prompt administration of appropriate parenteral anti-malarial agents and early recognition and treatment of the complications. In children, the complications include metabolic acidosis (often caused by hypovolaemia), hypoglycaemia, hyperlactacidaemia, severe anaemia, seizures and raised intracranial pressure. In adults, renal failure and pulmonary oedema are more common causes of death. In contrast, concomitant bacterial infections occur more frequently in children and are associated with mortality in children. Admission to critical or intensive care units may help reduce the mortality, and the frequency and severity of sequelae related to severe malaria.

**KEY WORDS:** Severe malaria, *Plasmodium falciparum*, critical care, intensive care

*Plasmodium falciparum* is the most common cause of severe (life-threatening) malaria. It affects all age groups, although the reported mortality varies considerably depending upon the age, immunity, clinical complications and access to appropriate treatment.<sup>1</sup> The mortality is higher in adults with severe falciparum malaria than in children with similar disease,<sup>2</sup> as evidenced by the fact that mortality amongst South East Asian adults with renal failure due to severe malaria is 45% while the mortality amongst Kenyan children with severe anaemia is only 1%.<sup>4</sup> Intensive care with facilities for ventilation and haemodialysis appears to reduce the mortality.<sup>5,6</sup> This review sets out the criteria of severe falciparum malaria and discusses the management of life-threatening complications in resource-poor countries.

The presentation of severe falciparum malaria differs between children in endemic areas and non-immune adults. In areas of

high malaria transmission, severe malaria mainly affects children under five years of age.<sup>1</sup> In other areas, all age groups are at risk of developing severe malaria. In addition, the diagnosis of severe malaria must always be considered in travellers and migrant workers who have entered malaria endemic regions.<sup>1</sup> Besides mosquito bites, malaria can also be transmitted via blood transfusions or contaminated needles. Severe malaria is life-threatening and results from organ dysfunction or following the use of ineffective or inappropriate anti-malarial treatment. The World Health Organisation (WHO) has suggested criteria for the definition of severe malaria in both adults and children (Table 1)<sup>1</sup> and produced a handbook outlining the management.<sup>7</sup>

### Differences in the Clinical Presentation of Severe Malaria in Adults and Children

In children living in endemic areas, the commonest present-

**Table 1: Life-threatening complications of severe malaria**

System involved	Manifestations of systemic dysfunction
Neurological	Prostration / inability to sit unsupported Impaired consciousness or coma Generalised convulsions
Respiratory	Respiratory distress [acidotic/ Kussmaul breathing] Pulmonary oedema and adult respiratory distress syndrome
Cardiovascular	Circulatory collapse [algid malaria]
Renal	Acute renal failure
Haematological	Severe normocytic anaemia (Haemoglobin < 5 g/dl) Jaundice* Abnormal bleeding Haemoglobinuria
Metabolic	Hypoglycaemia (Whole blood glucose < 2.2 mmol/l) Metabolic acidosis with respiratory distress
Other	High fever Hyperparasitaemia

\* Jaundice has a poor prognosis only in the presence of other features of severe disease.



ing syndromes associated with severe malaria include central nervous system involvement which may present with impaired consciousness ranging from prostration to cerebral malaria (CM) or recurrent convulsions, respiratory distress (acidosis) or symptomatic anaemia.<sup>2,4</sup> The WHO defines CM as unarousable coma (unable to localise a painful stimulus) in the presence of asexual parasitaemia with the exclusion of other encephalopathies. However, any patient with an impaired level of consciousness should be treated as severe malaria. Metabolic complications include hypoglycaemia, metabolic acidosis, lactic acidemia and electrolyte imbalance. Children presenting with impaired consciousness or respiratory distress are at highest risk of death from severe malaria.<sup>4</sup> Even these manifestations show a predilection for certain ages. Younger children are more likely to present with severe anaemia than with CM. However, respiratory distress could be present in younger children or could even accompany CM.<sup>8</sup> Respiratory distress is a manifestation of metabolic acidosis. Adults also develop acidosis and CM, but pulmonary oedema and renal failure occur more frequently (Table 2) and are associated with an increased mortality.<sup>1,2</sup>

The diagnosis of malaria is based upon detecting the asexual forms of the parasites, in the blood smear stained with Giemsa or Field's stain. In cases where the laboratory diagnosis is unavailable or unreliable, a history of exposure within the last year, particularly within the preceding 10 weeks and the suggestive clinical picture should prompt the physician to start anti-malarial treatment.<sup>1</sup> The need to recognise severe malaria in both adults and children is important as this allows the immediate institution of optimal treatment in the hospital – either with increased nursing care in a general ward or preferably by admission to an intensive care unit (ICU) or high dependency unit (HDU), where requisite monitoring, nursing and therapeutic facilities are available. Table 3 provides a list of criteria that should prompt the clinician to admit the patient to an ICU or HDU.

The differential diagnosis of severe malaria is wide but the conditions that should be actively considered and excluded are: septicaemia, typhoid fever, pyelonephritis, lobar pneumonia, viral hepatitis, meningitis, encephalitis, Reyes syndrome, drug effects and poisoning.<sup>1,7</sup>

## **Management of Severe Malaria**

The treatment for malaria involves initial stabilisation of the patient, detection of complications and the start of parenteral anti-malarials.

### ***Immediate management***

The initial stabilisation of the patient involves the use of advanced life support techniques that are applicable to both adults and children. The key steps are:

1. Assess the Airway, Breathing and Circulation and intervene where necessary.
2. Fix a wide bore cannula and draw blood for emergency investigations that would help establish diagnosis, detect complications, predict prognosis and pre-empt emergencies. These include slide for the detection of malarial parasites, estimation of haemoglobin (Hb) concentration or haematocrit, blood glucose level and determination of blood group for cross match. Other relevant investigations that need to be carried out are outlined in Table 4.
3. Treat hypoglycaemia.
4. Assess the level of consciousness using a coma scale appropriate for the age – the Glasgow coma score (GCS) in adults and the Blantyre coma score (BCS) in children. A nasogastric tube should be inserted in all unconscious patients and the stomach contents should be emptied to prevent aspiration.
5. Record the following vital signs: temperature, pulse, blood pressure (BP), respiratory rate and capillary refill time (CRT).
6. Weigh the patient, calculate the dose of anti-malarial drugs and start treatment.
7. Assess state of hydration; consider catheterisation of the urinary bladder (to measure urine output and specific gravity) and insertion of a line to measure central venous pressure (CVP).
8. Plan first 8 hours of intravenous fluids.
9. Unconscious patients should have a lumbar puncture (LP) so that CNS infections, especially acute bacterial meningitis could be excluded with certainty. The LP may have to be delayed if there are signs of raised intracranial pressure (ICP). However, the patient should be put on anti-microbial and anti-viral (if available) therapy, until the LP can be carried out and results of CSF examination are

**Table 2: Differences in the clinical features of severe malaria in adults and children**

Clinical features	Children	Adults	Prognosis
Prostration	Common	Common	Reasonable
Coma	Infrequent	Infrequent	Poor
Kussmaul (deep) breathing (acidosis)	Common	Rare	Poor
Multiple convulsions	Common	Rare	Reasonable
Severe anaemia	Common	Rare	Reasonable
Renal failure	Rare	Uncommon	Very poor
Pulmonary oedema	Rare	Uncommon	Very poor
Bacteraemia	Common	Common	Poor
Jaundice	Rare	Common	Poor
Circulatory collapse	Rare	Rare	Very poor
Abnormal bleeding	Rare	Rare	Very poor
Haemoglobinuria	Rare	Rare	Reasonable



**Table 3: Criteria for admission of patients with severe malaria to ICU**

Acidosis	: Base excess < -8
Parasitaemia	: Endemic areas: More than 20% Non-endemic areas: More than 10%
Coma	: Summated Glasgow Coma Score <sup>1</sup> less than or equal to 8 or Blantyre Coma Score <sup>1</sup> less than or equal to 2
Hypoglycaemia	: Blood glucose level less than 2.2mmol/l
Renal dysfunction	: Urine output less than 0.5ml/kg/hr
Pulmonary oedema	

**Table 4: Investigations to detect complications of severe malaria**

<i>Blood for</i>	
Parasite count	
Blood glucose level	
Complete Haemogram (Haemoglobin estimation, White Cell Count and platelet count)	
Blood Group determination and cross match	
Blood gas analysis	
Serum Electrolytes estimation	
Blood Urea or creatinine level	
Blood culture	
Coagulation indices	
Estimation of serum/ plasma levels of liver enzymes	
<i>CSF for</i>	
Microscopic examination including cell count	
Estimation of CSF levels of glucose and protein (to exclude other CNS infections)	
<i>Urine for</i>	
Determination of specific gravity	
Microscopic examination inclusive of cell count	
<i>Chest X-ray for</i>	
Detection of pulmonary oedema or infection	

available.

10. Detect and treat the complications of severe malaria. These have been outlined in Table 1.

### **Anti-malarial Therapy**

Treatment with effective anti-malarial agents is the only therapeutic intervention that has been shown to reduce mortality in severe malaria. Anti-malarial agents should be administered parenterally to patients with severe malaria, since

gastrointestinal absorption may be erratic. In a life-threatening situation such as severe malaria, all efforts should be directed to ensure that effective levels of these drugs are attained in patients. The cinchona alkaloids (e.g. quinine) or artemisinin derivatives are the usual drugs of choice in such a situation.

#### **Quinine**

Quinine can be administered intravenously, intramuscularly or orally, but only the parenteral routes are recommended in the presence of severe malaria. Quinine dihydrochloride salts are used parentally as the first line of treatment in most parts of the world. It acts on the mature trophozoite stages only. Quinine has 85% bioavailability when given intramuscularly, even in young children.<sup>9</sup> A loading dose of quinine allows for parasiticidal concentrations to be achieved quickly.<sup>10</sup> A meta-analysis showed that a loading dose of quinine reduced fever clearance time and parasite clearance time but the data was not sufficient to detect an effect on the risk of death or convulsions.<sup>11</sup> Higher loading doses and shorter intervals between doses are used in adults in Asia where the parasites are less sensitive to quinine as compared to children in Africa (Table 5).<sup>9,12</sup>

Since oral quinine is bitter and is associated with unpleasant side-effects in conscious patients, other anti-malarial drugs are often used to shorten the course of quinine. In Asia, a seven-day course of tetracycline or doxycycline is administered to adults, and clindamycin to children or pregnant women. In Africa, a single dose of sulphadoxine- pyrimethamine (SP) is often used, but its' efficacy is decreasing. However, it is prudent to administer at least 5-7 days of quinine. In SE Asia, a longer course of quinine is sometimes used.

Quinine has a strong stimulant effect on pancreatic insulin secretion and leads to iatrogenic hypoglycaemia,<sup>9</sup> especially in pregnant women. In the doses used for the treatment of malaria it does not appear to cause significant cardiotoxicity, but it is advisable to monitor the electrocardiogram while the loading dose is administered. Cinchonism (tinnitus, high-tone hearing impairment, nausea, dysphoria and vomiting) often leads to poor compliance with the seven-day regime. Although quinine may cause contractions of the pregnant uterus and has been associated with effects on the foetus, it remains the most widely used drug for the treatment of severe malaria during pregnancy.

**Table 5: Parenteral anti-malarial therapy for severe falciparum malaria**

Anti-malarial	Loading dose	Maintenance dose
<b>Cinchona alkaloids</b>		
Quinine dihydrochloride	20 mg salt /kg over 4 hours in adults <sup>9*</sup>	10 mg salt /kg over 4 hours repeated every 8 hours
Intravenous (IV) route	15 mg salt /kg over 2 hours in African children <sup>12 *</sup>	10 mg salt /kg over 4 hours repeated every 12 hours
Quinine dihydrochloride	20 mg salt/kg (dilute IV formulation to 60 mg/ml	10 mg salt/kg repeated every 8–12 hours
Intramuscular (IM) route	given by deep IM injection divided between both anterior thighs)*	
Quinidine gluconate <sup>†</sup> IV route	20mg salt/kg infused over 4 hours	10mg salt/kg infused over 4 hours every 8–12 hours
<b>Artemisinin derivatives</b>		
Artesunate IV route	2.4 mg/kg	1.2 mg/kg repeated at 12 and 24 hours, then 1.2 mg/kg daily
Artemether IM route	3.2 mg/kg	1.6 mg/kg repeated 12–24 hourly

\*The loading dose is to be avoided in a patient who has received quinine, mefloquine or quinidine within the last 24 hours. †Monitor the QRS and QTc during treatment



### **Quinidine**

Quinidine, a d-isomer of quinine is more effective as an anti-malarial but is also more cardiotoxic. Systemic hypotension and significant QTc prolongation are more commonly seen with quinidine.<sup>13</sup> It is used mainly in the USA. It is rarely used in other parts of the world and except when quinine and artemisinin derivatives are not available.

### **Artemisinin derivatives**

Artemether and artesunate are increasingly being used in the treatment of severe malaria. Treatment is initiated with a loading dose that is followed by a once-daily dose regimen. Such a schedule is more convenient than that used for the administration of cinchona alkaloids. Artemisinin derivatives have the advantage of clearing the parasitaemia at a faster rate than that seen with quinine. This is due to the fact that artemisinin and its derivatives are fatal for all stages of the parasite. However, it should be clarified that the trials that compared the efficacy and safety of quinine and artemether, failed to demonstrate any difference in the mortality or frequency or severity of residual neurological sequelae.<sup>14</sup> It is worth mentioning that a recent study suggests that artesunate may be more effective.<sup>15</sup>

The artemisinin derivatives have relatively few side-effects, although severe allergic reactions have been reported. The reticulocyte count may drop transiently in the first week of treatment, although, this does not appear to aggravate the anaemia associated with malaria. Artemisinin-induced neurotoxicity was detected in animal models, although there have been no reports of neurotoxicity in human subjects on necropsy.<sup>16</sup> These compounds should be used in combination with other anti-malarials to prevent the development of resistance.<sup>17</sup>

### **Other anti-malarials**

Other anti-malarial drugs such as halofantrine, mefloquine, atavaquone, SP, doxycycline, and tetracycline are not recommended in severe and complicated malaria as primary treatment. Parasite resistance has developed to these drugs, when they are used alone. Mefloquine administered by the nasogastric route in patients with CM showed rapid but incomplete absorption<sup>18</sup> suggesting that this route is unreliable in patients with severe malaria. These anti-malarials may be used in the latter stages of the management of severe malaria to reduce the period of parenteral treatment, improve compliance and cure, and prevent the development of resistance to the parenteral anti-malarials.

## **Supportive Therapies**

Adjunct therapy may reduce mortality since over a third of the patients die within 12 hours of admission, before the anti-malarials have had time to work.<sup>8</sup> Supportive therapy is aimed at reversal or termination of patho-physiological mechanisms that lead to potentially fatal complications.

### **Antibiotics**

Blood cultures have detected bacteraemia in 7-14% of patients admitted with severe malaria.<sup>19</sup> Non-typhoid *Salmonella* sep-

ticaemia is the most common co-infection in children with severe malaria. In patients with a reduced level of consciousness, the differential diagnosis of meningitis must be entertained and broad-spectrum anti-microbial agents should be administered until the diagnosis can be excluded.<sup>6,20</sup>

### **Anticonvulsants**

Seizures are common in children with severe *falciparum* malaria, but occur less frequently in adults. The pathogenesis of seizures in severe malaria is not clear, but they may be caused by the sequestration of parasites in the brain, hypoglycaemia, hyperpyrexia in children prone to febrile seizures and sepsis or meningitis.<sup>8</sup> Seizures may not be detected clinically, particularly in CM.<sup>21</sup> Although prophylactic phenobarbitone may prevent seizures in adults with CM,<sup>22</sup> it is associated with an increased risk of mortality in children.<sup>23</sup> The management of seizures should include correction of the underlying cause, such as hypoglycaemia. Anticonvulsants should be administered for seizures lasting more than five minutes. Benzodiazepines are the most widely used and available anticonvulsants, but may cause respiratory depression.<sup>21</sup> Other anticonvulsants e.g. paraldehyde have less deleterious effects on respiration. With repeated or prolonged seizures, phenytoin, phenobarbitone, fosphenytoin,<sup>24</sup> chlormethiazole and thiopentone have been used.<sup>21</sup> These longer acting anticonvulsants require continued monitoring of vital signs for at least 4 hours after administration.

### **Blood transfusion and exchange transfusion**

Blood transfusion is life-saving in severe malarial anaemia. The indication for blood transfusion depends on the availability of pathogen-free compatible fresh blood, haemoglobin level, and fluid balance status.<sup>25</sup> In malaria endemic areas, children with haemoglobin concentration less than 4 g/dl or presence of respiratory distress or parasitaemia greater than 10%, with haemoglobin concentration between 4 and 5 g/dl should receive blood transfusion. The role of loop diuretics in children during transfusion is not established. In a well-hydrated adult, a haematocrit value below 20% should be an indication for undertaking blood transfusion. The clinical condition of these individuals should be closely monitored to detect the development of fluid overload. Small doses of loop diuretics may avoid circulatory overload in adults during blood transfusion.

### **Exchange transfusion**

Exchange transfusion has been thought to benefit patients with high parasite counts. The rationale is to remove infected red cells and thereby reduce the parasite burden, to reduce antigen load, to remove parasite-derived toxins and metabolites, and to correct anaemia.<sup>26</sup> In non-immune patients with severe falciparum malaria, indications for undertaking exchange transfusions include parasitaemia exceeding 30%, irrespective of clinical features, response to therapy or absence of poor prognostic features. It is recommended that the procedure should be undertaken even if parasitaemia is above 10%, if the patient has features suggestive of severe disease or if the individual has demonstrated failure to respond to treatment after 12-24 hours or if poor prognostic factors such as advanced age, or presence of late-stage parasites (schizonts) in the periph-



eral blood are present.<sup>1</sup> Patients with anaemia with circulatory overload may benefit from an exchange transfusion. This procedure should be attempted only in units that can supply pathogen-free compatible fresh blood and when facilities for haemodynamic monitoring during and after the procedure are available. It should be noted that a meta-analysis studying the efficacy of exchange transfusion in patients with severe malaria failed to show any benefit,<sup>27</sup> and randomised control trials have not been conducted.

### *Dialysis*

The indications for dialysis in acute renal failure due to severe falciparum malaria are similar to other causes of renal failure. The mortality in acute renal failure without dialysis is 50-75%.<sup>28</sup> Early diagnosis of established renal failure and institution of dialysis are important in preventing mortality. A rapidly rising creatinine level is the most sensitive indicator of the need for dialysis. Peritoneal dialysis reduces mortality,<sup>28</sup> but haemofiltration is even more effective<sup>3</sup> and is associated with an improved outcome.<sup>3,6</sup>

### *Fluids*

The role of fluids in severe falciparum malaria is controversial and appears to be different in children as compared to adults. The fluid requirements must be assessed in each patient. Evidence shows that African children with severe malaria may be hypovolaemic due to reduced intake or increased losses and they develop respiratory distress because they are acidotic.<sup>29</sup> They rarely develop pulmonary oedema. Hypovolaemia is corrected by boluses of fluids that improve circulation. In adults, fluids must be used cautiously as they are at a greater risk of developing pulmonary oedema and circulatory overload. Fluid administration should be stopped and diuretics given if pulmonary oedema is suspected. The jugular venous pressure (JVP) may help in assessing the fluid status in older children and adults, but monitoring the CVP is very helpful during the administration of fluids. There is no evidence to show that fluid restriction improves the outcome in CM.

Electrolyte derangements, particularly hyponatraemia are an important consideration in the choice of fluids to be administered. Isotonic (0.9%) saline is used to correct hypovolaemia. Maintenance fluids must contain sufficient glucose to prevent hypoglycaemia. When anaemia is present, blood transfusion should be considered as a therapeutic intervention. Fresh blood improves acidosis and red cell deformability found in falciparum malaria.

### *Inotropic support*

Although shock (algid malaria) is rare, it is associated with death. Inotropic support may be required after correction of hypovolaemia.<sup>1</sup> Dopamine appears to provide better inotropic support than adrenaline in adults with severe malaria.<sup>30</sup>

### *Hypoglycaemia*

Hypoglycaemia is a common complication, particularly in children and pregnant women. Often, it cannot be detected clinically; hence frequent checking of blood glucose levels is mandatory, particularly in patients with impaired consciousness.

Correction with 50% dextrose appears to be safe in adults,<sup>31</sup> but this has not been established in children.

### *Raised intracranial pressure*

Raised intracranial pressure (ICP) is frequently detected in African children with CM.<sup>32</sup> It is less frequently seen in other populations, as only 20% of Thai adults with CM demonstrated raised ICP.<sup>33</sup> Recent studies from India suggest that brain swelling is common in adults.<sup>34</sup> The treatment of raised ICP in malaria remains controversial. Mannitol reduces the ICP<sup>35</sup> but no randomised controlled trials have been conducted to show that it reduces sequelae or mortality.

### *Ventilation*

Prompt endo-tracheal intubation by experienced personnel and mechanical ventilation may be a life-saving procedure. The indications for mechanical ventilation depend upon the resources, particularly the medical and nursing staff. Acute respiratory distress syndrome, poor respiratory effort, aspiration pneumonia, acute pulmonary oedema and deep coma may benefit from ventilatory support. Care must be taken to ensure frequent suction and adequate humidification during ventilation while maintaining a PaCO<sub>2</sub> below 4.0 (KPa) since a rise in the PaCO<sub>2</sub> may increase ICP and precipitate death.<sup>36</sup>

### *Therapies not recommended in the treatment of malaria*

There are many therapies that have been tried in severe malaria, but there is insufficient evidence to recommend their use. The role of antipyretics remains controversial, since studies have been conducted in patients with non-severe malaria only.<sup>37</sup> Paracetamol prolonged parasite clearance in two studies of uncomplicated malaria, but has not been studied in severe disease. Ibuprofen appears to be more effective than paracetamol in uncomplicated malaria<sup>38</sup> but should be avoided in patients with abnormal bleeding. Corticosteroids have not shown any benefit when used in CM, and their use was associated with significant side-effects.<sup>39</sup> Likewise, there is little evidence to recommend the use of low molecular weight dextran, adrenaline, cyclosporin A, and hyper immune serum in patients with CM.<sup>1</sup> Use of Dichloroacetate and anti-TNF antibodies has not shown any beneficial effects on survival in malaria.

### *Pregnancy*

In pregnancy, both symptomatic and asymptomatic malaria can cause morbidity and mortality to both mother and the unborn foetus. Primigravida women in endemic areas and non-immune pregnant women (particularly during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester) are at greatest risk. Pregnant women with malaria are particularly prone to hypoglycaemia, pulmonary oedema and anaemia.

## **Conclusion**

Severe falciparum malaria remains among the leading causes of morbidity and mortality in the world. The mortality can be reduced by early recognition of the features of severe malaria, prompt administration of appropriate anti-malarials and treatment of complications, preferably in an ICU setting. Clinicians must have a high index of suspicion, especially with trav-





ellers to areas where malaria remains endemic. A high standard of nursing care and continued observation in the acute stage of the disease are important for reducing mortality.

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