

## Original Article

# Management of malaria with acute renal failure

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## Introduction

In parts of the world, such as Africa, where *Plasmodium falciparum* is endemic and its transmission is stable, severe malaria affects mainly children. Cerebral malaria and severe anaemia are common but multi-organ failure involving the kidneys or liver is very rare. Surviving children develop immunity and thus as adults rarely develop severe disease [1]. In contrast, in other tropical countries where transmission of *P. falciparum* is unstable and the risk of infection low, severe malaria can occur at any age. Severe malaria is defined as parasitaemia greater than 5% or vital organ dysfunction. Acute renal failure (ARF) is a common complication of severe falciparum malaria in non-immune individuals. At the Bangkok Hospital for Tropical Disease, 5,210 patients with falciparum malaria were admitted during the period 1991-1997 of whom 112 patients (2.12%) had ARF. In a recent study of 560 cases of severe adult malaria in Vietnam, 28% of patients had renal failure on admission and 41% at some stage, with 14% overall requiring dialysis [2]. Overall, however, ARF is not a common complication of malaria. During the Vietnam war, the reported incidence was 19 cases in 3,300 malarial admissions in 1965/6 and 8 of 2003 admissions in 1966/7 [3,4].

## Acute renal failure

### Immediate management

ARF is managed simultaneously with the treatment of malaria and the treatment of other complications (see table 1). Several important decisions must be taken when the patient is admitted:

- Is the malaria complicated or not?
- What is the best treatment for malaria?
- What is the immune status of the patient?
- General standard management.
- Identification and management of complications.

### Clinical features

**Diagnosis:** ARF is defined as either [5]:

- Plasma creatinine greater than 270  $\mu$  mol/l (> 3 mg/dl) even after fluid repletion.
- Oliguria (<400 ml per day).

**Presentation:** With severe malaria, 50% of patients will have a raised urea and creatinine at the time of admission. This reflects the dehydration and hypovolaemia that occurs with sweating, vomiting and diarrhoea. With fluid replacement the plasma concentrations of urea and creatinine usually return to the normal range. Patients are extremely catabolic (*hypercatabolic*) which will cause a disproportionate rise in the blood urea to creatinine ratio. This will be further exaggerated if the patient is dehydrated and has pre-renal failure with low urine volumes.

ARF usually develops simultaneously with other complications (see table 1), but can develop later

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when patients are already oedematous and sick with other complications.

Table 1. Complication of malaria

Manifestation	Definition
Cerebral	
• Impaired consciousness	Coma for > 30 minutes following convulsion and if no other explanation.
• Repeated convulsions	> 2 per 24 hours in the absence of hyperpyrexia.
Anaemia	Haematocrit < 15%, haemoglobin < 5 g/dl.
Acute renal failure	< 400 ml/day adult or < 12 ml/kg/day child, Creatinine > 270 µmol/l (> 3 mg/dl).
Pulmonary oedema	Low central venous pressure and pulmonary oedema in the absence of fluid overload.
Hypoglycaemia	Glucose < 2.2 mmol/l (< 40 mg/dl).
Shock	Systolic BP < 50 mmHg children (1-5 yrs) or < 70 mmHg in adult, or core-skin difference > 10°C.
Spontaneous bleeding	or disseminated intravascular coagulation (DIC).
Acidaemia	Arterial pH < 7.25, venous bicarbonate < 15 mmol/l.
Macroscopic haemoglobinuria	Haemoglobinuria, without G6PD-deficiency.
Severe weakness/prostration	
Hyperparasitaemia	>100 000/ul parasites/µL, or > 5% , >500 000/ul - high mortality.
Jaundice	Hyperbilirubinaemia > 50 µmol/l (> 3 mg/dl).
Hyperpyrexia	Rectal temperature > 40°C.

*Clinical course:* Oliguria usually occurs towards the end of the first week and lasts for one week. It is prolonged in elderly patients with underlying renovascular disease. Acute renal failure is commonly complicated by a septic shock syndrome and sometimes by septicaemia. When ARF develops after the acute phase it is more likely to be non-oliguric and dialysis not required [1].

There are many WHO criteria for severe complications of acute malaria [5] and there are differences between the features of severe malaria in adults and in children (table 2). The prognostic factors listed in table 3 reflect vital organ dysfunction and magnitude of the parasite burden. They are not absolute, and in fatal cases several factors usually coexist.

Table 2. Relative incidence of severe falciparum malaria complications

	Non-pregnant adults	Pregnant women	Children
Anemia	+	++	+++
Convulsions	+	+	+++
Hypoglycemia	+	+++	+++
Jaundice	+++	+++	+
Renal failure	+++	+++	-
Pulmonary edema	++	+++	+

From White NJ. Malaria. In: Cook CG (ed). Manson's Tropical Diseases. 12 edn. WB Saunders, London, 1996, pp 1144.

Table 3. Features indicating a poor prognosis in severe malaria

Clinical indicators:	Laboratory indicators:
Age under 3 years	Hyperparasitemia (>100,000/ul or >5%)
Deep coma	Peripheral shizontemia
Witnessed or reported convulsions	Peripheral leukocytosis (>12,000/ul)
Absent corneal reflexes	Packed cell volume less than 20%
Decerebrate rigidity	Hemoglobin <7.0 g/dl
Clinical signs of organ dysfunction (eg. renal failure, pulmonary edema)	Blood glucose less than 2.2 mmol/l (<40 mg/dl)
Retinal hemorrhages	Low CSF glucose
Shock	Blood urea > 21 mmol/l (>60 mg/dl)
	Creatinine more than 270 µmol/l (>3.0 mg/dl)
	High CSF lactic acid (>6 mmol/l)
	Raised venous lactic acid (>6 mmol/l)
	More than 3-fold elevation of serum liver enzymes (amino-transferases)

Derived from White NJ. Malaria in: Cook CG (ed). Manson's Tropical Diseases. 12 edn. WB Saunders, London, 1996, pp 1117 (ref 20)

*Treatment:* Patients should be evaluated carefully for hydration status. If patients have a reduced urine output, they may be either dehydrated and

hypovolaemic (pre-renal cause) or have established acute renal failure with acute tubular necrosis (ATN). In hypovolaemic patients, rehydration

should be attempted orally, or intravenously when necessary (see figure 1). Intravenous fluids must be given cautiously in case pulmonary oedema develops. Central venous pressure should be monitored and kept below 5 cm H<sub>2</sub>O.

We recommend that gastric acidity is reduced by proton pump inhibitors or histamine (H<sub>2</sub>) receptor antagonists. Early enteric feeding should be encouraged.

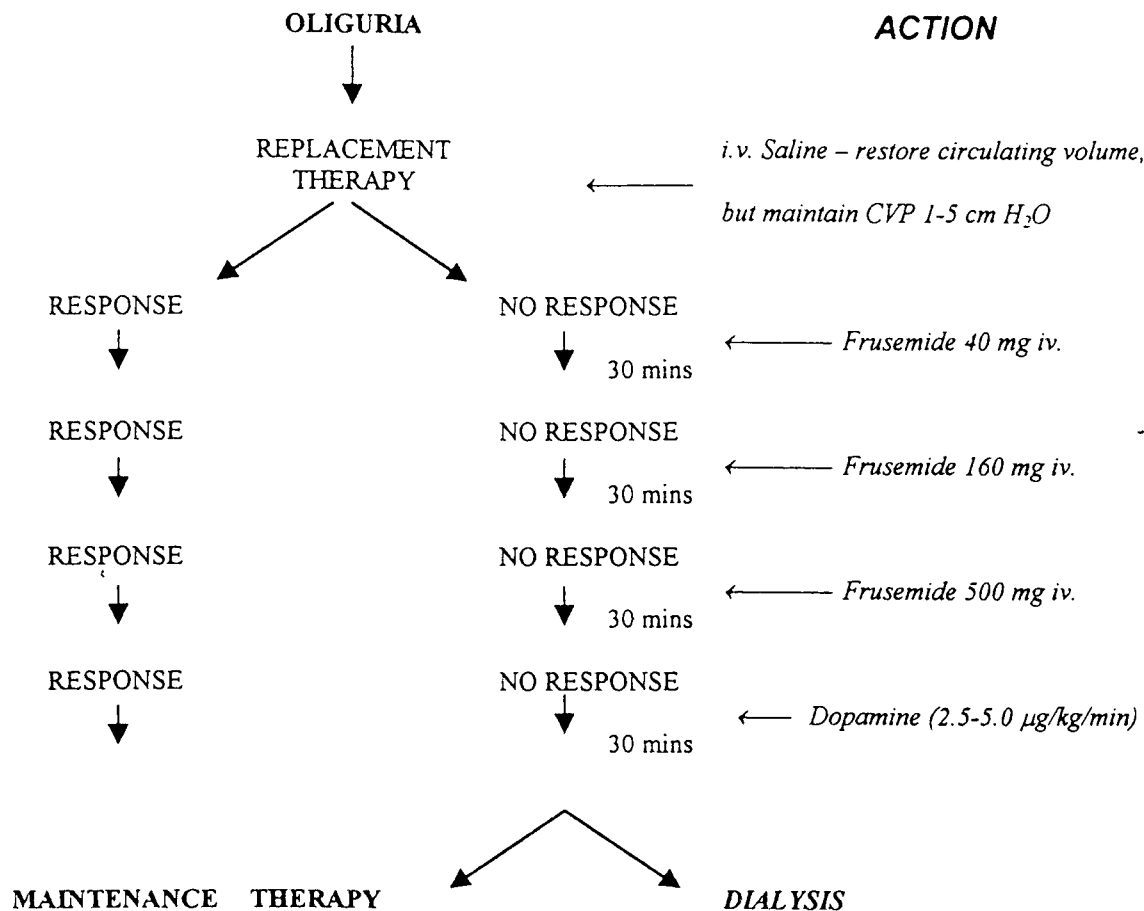


Fig. 1. Guidelines to fluid management

**Antimalarial therapy:** Parenteral antimalarial drugs should be given in severe malaria and quinine remains the drug of first choice in most parts of the world. It must be diluted and given slowly. 20 mg/kg of the dihydrochloride salt should be given over 4 hours as a loading dose, followed by 10 mg/kg infused over 2-8 hours every 8 hours for 7 days or until alternative drugs can be taken orally [6]. After 3 days the dose of quinine should be reduced by 30-50 % in patients with reduced renal clearance. Quinine can cause hyper-insulinaemia and hypoglycaemia.

Artemisinin derivatives are potent antimalarial drugs and are increasingly used in areas of chloroquine resistance, such as SE Asia [27]. They are not licensed for use yet in the UK.

**Complications and their management (see table 1)**

*Respiratory*

Pulmonary oedema can be due to iatrogenic intravenous fluid overload or to ARDS (adult respiratory distress syndrome) caused by low pressure pulmonary oedema [7]. It is a grave complication of severe malaria with high mortality (over 50%) and can even appear several days after therapy has started, at a time when the patient's general condition is improving and the peripheral parasitemia is diminishing. It is more common in association with renal failure, hyperparasitemia, hypoglycaemia and metabolic acidosis. Malaria in pregnancy usually has a high risk of pulmonary oedema, particularly after delivery.

Changes in respiration can be a warning sign of hypoglycaemia, metabolic acidosis, pneumonia, pulmonary oedema, or as a result of high fever alone.

#### *Cerebral malaria*

Cerebral malaria is defined as unrousable coma in a patient with asexual forms of *P. falciparum* in the peripheral blood and no other identifiable cause of unconsciousness [8].

In the tropics the list of differential diagnoses is large, but in practice obtaining an accurate history, completing a detailed clinical examination and performing a lumbar puncture excludes most of the alternative diagnoses (with the possible exception of viral encephalitis which may have to wait demonstration of virus or viral specific IgM in the CSF). It should also be noted that bacterial meningitis or other severe bacterial infections can co-exist with cerebral malaria.

#### *Hypoglycaemia*

Frequent monitoring of blood glucose is essential. Hypoglycaemia should be suspected in any patient whose consciousness is deteriorating, who develops convulsions or who has changed respiratory patterns. Hypoglycaemia should be reversed by slow intravenous injection of 0.5-1 ml/kg of 50% dextrose water, and prevented by administering a 10% dextrose infusion at 1-2 mg/kg per hour. The plasma glucose should be maintained between 4-8 mmol/l (80-120 mg/dl) and checked frequently.

#### *Haematological*

**Bleeding diathesis:** Thrombocytopenia is common, but platelet transfusion is indicated only if the patient has systemic bleeding. Thrombocytopenia *per se* is not an indication for platelet transfusion. Coagulation abnormality leading to systemic bleeding is uncommon. With sensitive measures, activation of the coagulation cascade can be detected in all patients with acute symptomatic malaria [9] but significant disseminated intravascular coagulation occurs in less than 5% of patients with severe disease [5]. Hepatic failure and prolonged prothrombin time is rare. Transfusion of coagulation factors is only indicated in patients with coagulation abnormality and systemic bleeding.

**Severe anaemia:** Anaemia develops very rapidly and blood transfusion is often required [10,11]. Anaemia results from a combination of bone marrow suppression and accelerated red cell destruction [12-14] of both parasitized and unparasitized red cells. Blood transfusion is indicated in patients with severe anaemia. Blood should be cross-matched on admission and transfused to maintain the haematocrit

over 21%. Transfusion rates should be slow to avoid volume overload, and it may be necessary to give a potent diuretic such as frusemide intravenously at the same time.

**Blackwater fever:** Massive intravascular haemolysis and haemoglobinuria can sometimes cause ARF. It is usually seen in patients with glucose-6-phosphate dehydrogenase deficiency [15].

#### *Metabolic acidosis*

This condition is serious and rapidly fatal. Lactic acidosis and renal impairment both contribute to hydrogen ion retention. Lactic acidosis results from the parasite, increased anaerobic glycolysis and a failure of hepatic gluconeogenesis [16]. Sodium bicarbonate (8.4%) may be given if arterial pH falls below 7.1. The pyruvate dehydrogenase activator dichloroacetate has proved promising in pilot clinical trials and experimental studies [17-19].

#### *Bacterial infections*

Gram-negative septicaemia [20], aspiration pneumonia and urinary tract infections may all occur and should be treated with appropriate antibiotics. Any patient who develops shock at any stage should be investigated as in one report 40% of patients had positive blood cultures. In our own experience (unpublished) almost all shock patients had negative blood culture and the causes of shock were considered to be due to multiple organ failure, severe metabolic acidosis, ARDS.

Endotoxemia originates from the gut, either by entry of gram-negative bacteria or endotoxin from the gut lumen [21,22], together with failure of normal hepatic clearance mechanisms [23].

#### *Hepatic dysfunction*

A cholestatic jaundice is common in severe malaria, although hepatic failure is very rare. Haemolysis also contributes to the hyperbilirubinaemia.

Hepatosplenomegaly is common and in Thailand half of the adults and children over six years of age with cerebral malaria have palpable liver or spleen. Massive splenomegaly is most unusual in severe malaria.

#### **Pathogenesis**

Numerous reports of examination of renal tissue by light microscopy describe the non-specific features of acute tubular necrosis, but there has been no systematic investigation of the renal ultrastructural changes seen by electron microscopy. Thus our concept of pathological changes in the glomerular and tubular microcirculation are derived from those seen in the cerebral circulation.

**Histology:** In the brain, extensive plugging of cerebral capillaries has been recognised for years. This is due to margination (adhesion to endothelium) and sludging (stasis and aggregation) of parasitised red cells. Fibrin formation leading to thrombosis is not a feature. In an electron microscopy study [24], occasional neutrophils were seen, but other leucocytes were not observed in significant numbers either inside or outside of vessels. There was a total absence of platelets. The endothelium frequently showed degenerative changes on the surface, disorganisation of cytoplasm, with pseudopodia sticking out from the endothelial surface.

In the kidney, by light microscopy, dilated peritubular capillaries and interlobular veins are congested with pigment-macrophages, parasitised red cells, young lymphocytes and plasma cells. Occasional platelet-fibrin thrombi are seen [25,26]. Tubular necrosis is seen in most cases involving distal and collecting tubules and rarely proximal convoluted tubules. Necrotic tubules, both in the cortex and medulla, contain granular haemoglobin casts [27]. The great majority of parasitised red blood cells in the kidney are in glomeruli and some are adherent to the endothelium. Very few are seen elsewhere [24].

## Outcome

Acute renal failure (ARF) is one of the three most common causes of death in severe malaria [28]. The outcome depends on the time between onset of symptoms and arrival to a health facility and on the available facility resources and health worker capacity to manage the complications. Most severely ill patients live in rural areas endemic for malaria where the facilities are limited.

Before 1980, the mortality rate of patients with severe complicated malaria was 29 - 50% [29,30]. Moreover, in cases with lung complications, the mortality rate rose to 60 - 75% [29,31]. During the Vietnam war the mortality from ARF fell from 50% to 15-20% once dialysis facilities became available [30]. Since 1980, with early dialysis for renal failure and full respiratory support, the mortality rate of complicated malaria has declined to 10 - 20%. In Vietnam the mortality of ARF with malaria has fallen from 75% to 26% with the introduction of peritoneal dialysis [32].

In our own study of 122 patients with malarial acute renal failure admitted to the Bangkok Hospital for Tropical Disease, during the period 1991-1997, 101 (90.2%) patients received hemodialysis [33]. Ninety-three patients were oliguric and the remainder were non-oliguric. The overall mortality was 11%. Of the 12 patients who died, 11 were jaundiced and eight had cerebral malaria.

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