

7. SEVERE MALARIA ^{13,23}

Unless *P. falciparum* malaria is promptly diagnosed and treated, the clinical picture may deteriorate rapidly. There is significant morbidity and mortality associated with the occurrence of severe malaria.

Young children, pregnant women, immunosuppressed patients and any non-immune persons are at risk for the development of complications. One can assume that all South Africans living in the malaria areas in this country and all South African travellers are non-immune.

7.1 FEATURES INDICATING SEVERE MALARIA

Clinical Features

- Impaired consciousness, convulsions
- Respiratory distress: acidosis, ARDS, pulmonary oedema
- Jaundice
- Bleeding
- Shock

Biochemical Features

- Renal impairment – serum creatinine >265 µmol/liter or rapidly rising creatinine or urine output <400 ml/day (adult)
- Acidosis (plasma bicarbonate <15 mmol/liter) (serum lactate > 5 mmol/liter)
- Hepatic impairment (transaminases > 3 times normal)
- Hypoglycaemia (blood glucose < 2.2 mmol/liter)
- Hypoxia (pO₂ - < 8 Kpa in room air)

Haematological Features

- Parasitaemia ≥ 5%, or ≥ 3+
- Haemoglobin < 6 g/l or haematocrit <20%
- ≥ 5% neutrophils contain malaria pigment
- Presence of schizonts of *P. falciparum* in peripheral blood smear
- Evidence of DIC

7.2 TREATMENT

The patient should be treated in the highest level of care available. Treatment must include specific anti-malarial chemotherapy and management of complications.

7.3 CHEMOTHERAPY

Quinine is the drug of choice for the treatment of severe malaria in South Africa. Intravenous quinine is the preferred route of administration, especially where the patient is comatose, vomiting or severely ill. Quinine administration is always by **slow**, rate controlled intravenous administration, **never by bolus injection**. Where intravenous quinine administration is not feasible, not available or considered unsafe, the intramuscular route may be used initially.

7.4 LOADING DOSES ^{23,28,29}

In severe malaria an **initial loading dose must be given, by slow intravenous infusion over 4 hours**. The rationale for the loading dose is to rapidly reach a therapeutic level.

The loading dose of quinine is quinine dihydrochloride salt, **20 mg/kg** body weight diluted in 5 - 10 ml/kg body weight of dextrose water over 4 hours. **The loading dose is given strictly according to body weight.** The disposition of quinine in very obese patients is not known. It has been suggested that there is a ceiling dose above which quinine should not be given, but there is no evidence to support this.

The loading dose should be omitted if the patient has received quinine, quinidine or halofantrine, in the preceding 24 hours, or mefloquine in the preceding 7 days. In these cases, ECG monitoring is advisable.

7.5 MAINTENANCE DOSES ^{23,28}

Six to eight hours after starting the loading dose, a maintenance dose of quinine dihydrochloride salt, 10 mg/kg diluted in 5 - 10 ml/kg body weight of a dextrose containing solution should be commenced and infused over 4 - 6 hours. Intravenous quinine should be administered every 8 hours until the patient can take oral medication (usually by 48 hours). For obese patients, the maintenance dose should be calculated according to ideal body weight, ideal body weight can be calculated for adults by a formula as follows:

Males: IBW (Kg) = 0.9 x height in cms-88 Females: IBW (Dg) = 0.9 x height in cms-92
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The total duration of therapy is 7 - 10 days.

The use of additional drugs, tetracycline or clindamycin, do not add initial therapeutic benefit for the severe malaria and may contribute to drug side effects. They should be added once the patient is improving.

Once the patient is improving oral treatment should be continued as per the recommendations for uncomplicated malaria. The dose of quinine should be reduced in renal failure. (See 7.8.4)

Quinine has a narrow therapeutic window, although serious side effects (cardiovascular or nervous system) during antimalarial treatment are unusual. The most frequent side effect during intravenous therapy is hypoglycaemia, especially in pregnant women and children. Hypotension, heart block, ventricular arrhythmias, and neurological problems, including convulsions and visual disturbances, occur rarely.

7.6 OTHER CHEMOTHERAPEUTIC OPTIONS ^{17,30}

In cases of suspected quinine resistance, where there has been a poor parasitological response to quinine, an artemisinin derivative may be considered when available. The only parenteral artemisinin currently available in South Africa is arteether. Slow absorption from the intramuscular depot site in severe malaria may compromise efficacy (See 6.1.3.2).

7.7 GENERAL MANAGEMENT OF SEVERE MALARIA

The following measures should be applied in the management of all patients with clinically diagnosed or suspected severe malaria:

- Patients should be admitted to the highest level of care available, ideally an intensive care unit. Good nursing care is vital.
- Appropriate antimalarial chemotherapy must be commenced urgently. Ideally the drug should be given intravenously initially.
- If parasitological confirmation of malaria is not readily available, a blood film should be made and treatment started on the basis of the clinical presentation, in very ill patients with febrile disease with no other obvious cause.

- Doses must be calculated on a mg/kg of body weight basis. A loading dose of drug should be administered initially. It is therefore important, whenever possible, to weigh the patient. This is particularly important for children. Do not confuse the doses of salt and base. Quinine doses are usually prescribed as salt (10 mg of salt = 8.3 mg of base).
- Other treatable causes of coma (e.g. meningitis, hypoglycaemia and severe anaemia) should be excluded.
- A rapid initial check of the blood glucose level and frequent monitoring for hypoglycaemia are important. Where this is not possible, glucose should be given.
- Regular monitoring of the core temperature, respiratory rate, blood pressure, level of consciousness and other vital signs is mandatory.
- Laboratory measurements should include: regular checks of haemoglobin, glucose, urea and creatinine, electrolytes and liver functions and acid-base status where possible and parasite density.
- Monitor fluid balance carefully. Avoid over- and under-hydration. Fluid overload is extremely dangerous as it may precipitate potentially fatal respiratory failure. Hypovolaemia however, may potentiate renal failure, metabolic acidosis and circulatory collapse. Accurate recording of fluid input and output is essential. Frequent central venous pressure (CVP) monitoring is recommended; maintain the CVP between >0-5cms of water.
- Monitor urine output constantly and carefully observe for the appearance of haemoglobinuria.
- Reduce high body temperatures (>39°C) by vigorous tepid sponging and fanning. Antipyretics may also be given. Avoid aspirin-containing compounds and non steroidal anti-inflammatory drugs.
- Look for and manage any complicating or associated infections. A broad-spectrum antibiotic is recommended.

7.8 COMPLICATIONS^{11,13,23}

7.8.1 Anaemia

Definition

A haemoglobin level ≤ 6 gms/dl or a haematocrit $\leq 20\%$.

Anaemia is a common complication of malaria, especially in young children and pregnant women. It occurs as a result of haemolysis and/or bone marrow dysfunction. Severe anaemia may manifest as cardiac failure, shock, hypoxia or confusion.

Management

Blood transfusion (packed cells) should be considered in patients in whom the Hb is 6 gm/dl or less, or the haematocrit is less than 20%, especially those with cardiovascular decompensation and shock. Caution should be exercised and fluid overload should be avoided.

7.8.2 Hypoglycaemia

Definition

A blood glucose level < 2.2 mmol/l.

Hypoglycaemia is common in severe malaria, particularly in pregnancy, in children, and in patients on intravenous quinine. Blood glucose should be monitored 4 - 6 hourly. Hypoglycaemia may not always present with classical symptoms of sweating, anxiety,

dilatation of pupils or tachycardia. It must always be excluded in patients with malaria who present with depressed levels of consciousness, including coma and convulsions.

Management

Adults: 50ml of 50% dextrose water given intravenously as a bolus.

Children: 1 ml of 50% dextrose water/kg body weight, intravenously

This should be followed by continuous intravenous infusion of 5 or 10% dextrose solution. Avoid fluid overload.

7.8.3 Cerebral malaria

Definition

Any patient with a depressed level of consciousness, ranging from agitation or confusion, to coma.

Cerebral malaria can resemble bacterial or viral infections of the central nervous system, or any cause of raised intracranial pressure. The clinical features are not specific; the patient may be flaccid, spastic, exhibit meningism, photophobia or symmetrical upper motor neurone signs. Papilloedema or cerebral oedema are not usually found. It is very important to exclude hypoglycaemia. If meningitis is suspected, a lumbar puncture should be performed. Cerebral malaria may occur as an isolated complication, or as part of multi-organ failure.

Convulsions may occur as a result of cerebral malaria, accompanying fever or in association with hypoglycaemia.

Management

Prophylactic anti-convulsants are currently not recommended. Treatment of convulsions is with standard anti-convulsant treatment.

Supportive treatment should include: treatment of convulsions, monitoring of level of consciousness and protection of the airway. Dexamethasone and mannitol are not recommended.

7.8.4 Renal failure

Definition

A serum creatinine greater than 265 $\mu\text{mol/l}$, or a rapidly rising creatinine, and/or a urine output of less than 0.5 ml/kg/hr or less than 400 ml/day in an adult should be regarded as renal failure. Rarely the patients may present in a polyuric phase. Renal failure is generally a (early) complication of malaria in adults, and occurs rarely in children. Hypovolaemia, sequestration of parasitised red cells in the renal vasculature, intravascular haemolysis and haemoglobinuria are incriminated in the development of renal dysfunction in malaria. This may lead to acute tubular necrosis and renal failure. Acute renal failure is usually reversible with appropriate management.

Management

Dehydration, if present, must be corrected carefully. Excessive administration of fluids should be avoided to minimise the risk of pulmonary oedema. A central venous catheter should be inserted where possible and the CVP maintained between 0-5 cms of water. Meticulous attention to fluid intake and output is essential.

Early dialysis is recommended, where available, as renal failure in malaria occurs against a background of a hypercatabolic state. Veno-venous hemofiltration is the most effective mode of dialysis in malaria.

Patients with impaired renal function require a reduction in maintenance quinine dihydrochloride salt to 5 - 7 mg/kg every 8 hours, after 48 hours of treatment with the full dose. Quinine is not removed by dialysis.

7.8.5 Circulatory collapse

Definition

Systolic blood pressure less than 80 mmHg in adults or less than 50 mmHg in children, and the patient's limbs are cold and clammy.

Circulatory collapse may be seen in patients with metabolic acidosis, severe anaemia, dehydration, ARDS, a ruptured spleen or septicaemia.

Management

Ideally, a central venous catheter should be inserted and hypovolaemia corrected with an appropriate volume expander (blood or plasma) or isotonic saline. Start inotropes if the CVP is between 0-5 cms and the patient is still shocked, and start broad spectrum antibiotics.

7.8.6 Metabolic acidosis

Measurement of acid-base status is a very useful tool in assessing a patient with malaria. Metabolic acidosis, especially lactic acidosis, is an important indicator of severe malaria, even if no other complications are present and is a poor prognostic sign. Metabolic acidosis may present as shock and/or respiratory distress; in children severe anaemia may present with metabolic acidosis.

Management

Correct any reversible cause of acidosis, in particular dehydration and severe anaemia. Take care not to give excessive fluid. The routine use of bicarbonate is not recommended.

7.8.7 Respiratory complications

Acute respiratory distress syndrome (ARDS) is an uncommon, but often fatal complication of severe malaria, and is a particularly severe problem in pregnant woman. ARDS may appear several days after chemotherapy has been started, and the general condition of the patient appears to have improved. Iatrogenic overadministration of fluids may contribute to the development of ARDS.

An increase in the respiratory rate, bilateral crepitations, clinical and laboratory evidence of cyanosis, confusion, agitation, or a saturation less than 90%, should alert the clinician to the possibility of ARDS. Pulmonary oedema as a result of iatrogenic fluid overload, or pneumonia should also be considered.

Management

Treatment depends on the severity of the respiratory complications. Fluids must be restricted. Diuretics should be given where indicated. Oxygen should be administered, and in some patients ventilatory support may be required.

7.8.8 Hepatic dysfunction

Although a raised indirect bilirubin due to haemolysis is a frequent finding in malaria, the clinical presence of jaundice or the finding of raised hepatic transaminases (greater or equal to 3x normal) should alert the clinician to the probability of severe malaria. The presence of jaundice combined with renal failure and acidosis is cause for great concern.

7.8.9 Disseminated Intravascular Coagulation (DIC)

DIC is rare in patients with severe malaria. Moderate degrees of thrombocytopenia are noted in the majority of cases of uncomplicated malaria, but bleeding is not common. However severe degrees of thrombocytopenia may be an indication of severe malaria and may be associated with bleeding. With effective malaria treatment, platelet counts return to normal within a few days. DIC is mostly associated with multi-organ failure, or hyperparasitaemia, and may in some cases be due to secondary bacterial infection or septicaemia.

Management

Fresh whole blood if indicated, and available; and platelet transfusions if the platelet count is very low or there is evidence of bleeding.

7.8.10 Secondary infections

Secondary bacterial infections may complicate malaria: aspiration pneumonia, urinary tract infections in catheterised patients, and nosocomial infections in hospitalised patients. In a significant number of patients with severe malaria, especially in children, bacteraemia and septicaemia have been noted, and Gram-negative and Gram-positive bacteria have been cultured. This syndrome is associated with high mortality, and is a particular problem in children.

Management

Antibiotics should be given to all children with severe malaria, and to any patient in whom septicaemia is suspected. Although this is a bigger problem in children, most guidelines recommend antibiotics for adults too as the features of bacterial and malarial sepsis overlap. A broad-spectrum antibiotic should be administered to cover both Gram-positive and Gram-negative bacteria.

7.8.11 Hyperparasitaemia

In general, peripheral parasite counts above 5% should be regarded as severe malaria as this is associated with increased morbidity. Low parasite counts do not exclude severe malaria or complications, and a parasite count must always be interpreted together with the clinical picture and other laboratory findings. Parasite counts are not always accurate, and counts can vary cyclically, depending on when the smear is taken.

The peripheral parasite count does not accurately reflect the parasite load. In highly endemic malarious areas, semi-immune persons may tolerate high parasite densities, without clinical symptoms and complications. The presence of schizonts of *P. falciparum* in a peripheral blood smear is an important indicator of severe malaria.

Management

The patient should be managed with a rapidly acting effective antimalarial drug; either quinine or an artemisinin-containing compound and intravenous therapy should be considered. The patient should be especially monitored for complications, even if these are not present initially.

Exchange transfusion possibly has a role to play in patients with hyperparasitaemia whose parasite counts increase or fail to decrease significantly on appropriate chemotherapy.

7.8.12 Malarial haemoglobinuria

The pathogenesis is unknown. The condition is seen in patients with G-6-PD deficiency, who are treated with antimalarial drugs, notably oxidant drugs like primaquine. Rarely, the condition is seen in patients with severe malaria and in those with malaria treated with quinine. Intravascular haemolysis leads to anaemia, passage of haemoglobin in the urine, and varying degrees of renal failure.

Management

Continue appropriate malaria chemotherapy: quinine may be continued (primaquine must be avoided). Supportive therapy should include blood transfusions for severe anaemia, adequate fluids and renal dialysis where indicated.

7.8.13 Exchange transfusion³¹

The role of exchange transfusion in severe malaria is controversial and there are no controlled studies to support its use.

Exchange transfusion may be considered for use in selected patients e.g. patients with hyperparasitaemia in whom the parasite count increases despite appropriate chemotherapy, and patients who develop multi-organ dysfunction despite appropriate chemotherapy.

The requirements for exchange transfusion include a safe blood supply, a skilled operator and a haemodynamically stable patient. The exchange volume should be 4 - 10 litres of blood for an adult.

7.8.14 Splenic rupture

Splenic rupture is a rare complication of malaria, and is more common in *P. vivax* infections