A CASE REPORT ON BLACK WATER FEVER AND LITERATURE REVIEW

Ghafoor S, Ali N, Mehmood A & Noor M.

INTRODUCTION

Malaria is endemic throughout most of the tropics. Of the approximately 3.2 billion people living in endemic areas, there are 350 to 500 million symptomatic cases of malaria annually with an estimated 1 million deaths each year[1]. Nearly all serious illnesses and deaths due to malaria are caused by Plasmodium falciparum.

Severe malaria is acute malaria with major signs of organ dysfunction and/or high level of parasitemia. In endemic areas, young children and pregnant women are at high risk for severe malaria. Older children and adults develop partial immunity after repeated infections; these groups are thus at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria parasites and so are at high risk for severe disease.

CASE REPORT

A 35 years farmer farming in Bannu his home town woke up with high grade fever with rigors and chills went to local doctor received antimalarial artemether. Next day fever dropped but he developed deep jaundice, nausea, dark color urine 'like coffee'.

On admission we found severe anemia, thrombocytopenia and renal failure and remarkable jaundice. There was no spleenomegaly hepatomegaly. Blood smear was positive for P. falciparum and P. vivax. G6PD enzyme levels were normal. Heamodialysis was performed immediately started on quinine injectable with iv fluids. Four pints of packed cells were transfused. After five sessions of dialysis he became polyuric. Was discharged home and at follow up after 2 weeks had normal renal function.

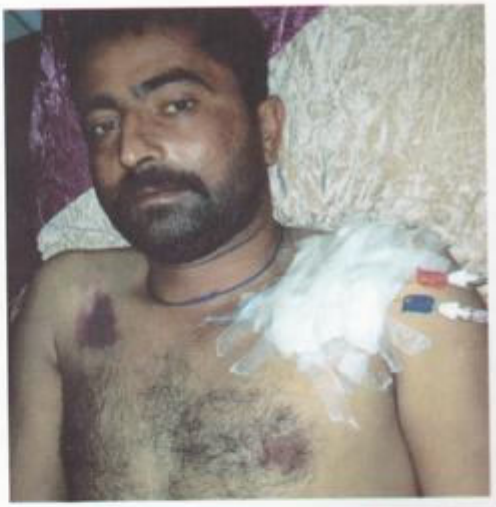
DEFINITION

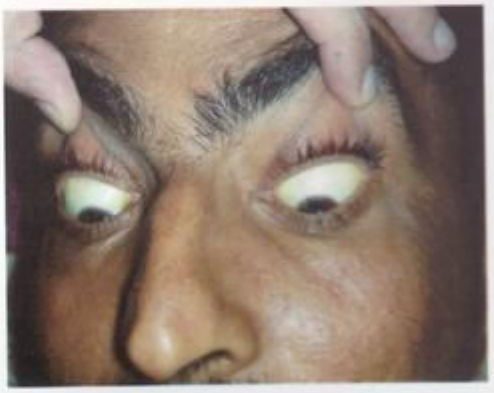
Severe malaria is generally defined as acute malaria with high levels of parasitemia (> 5 percent) and/or major signs of organ dysfunction.

- Altered consciousness with or without convulsions
- Respiratory distress or acute respiratory distress syndrome (ARDS)
- Circulatory collapse
- Renal failure, hemoglobinuria ("blackwater fever")

Lab results

Hb	4.5 g/dl
Platelet count	50,000
LDH	890
P.falciparum gametocytes	+++
Bilirubin	15 mg/dl
Dir.bil	9 mg/dl
AST	50U/L
ALT	40U/L
URINE heamoglobin	++
Urea	345
Creatinine	7 mg/dl





- Hepatic failure
- Disseminated intravascular coagulation
- Severe anemia
- Hypoglycemia

The clinical manifestations of severe malaria vary with age and geography. In areas where malaria is endemic, young children (ages 2 to 5 years) are at high risk for severe malaria, as are pregnant women. Older children and adults develop partial immunity after repeated infection, and thus are at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria parasites and so are at high risk for progression to severe disease if infected with P. falciparum[3,4]. For this reason, it is important to consider malaria in the differential diagnosis of all febrile patients with a history of travel to areas where the disease is endemic. Seizures, hypoglycemia, and severe anemia are relatively more common in children, whereas acute renal failure, jaundice, and pulmonary edema are more common in adults. Cerebral malaria (with coma), shock, acidosis and respiratory arrest may occur at any age.

DIAGNOSIS

The diagnosis of malaria and degree of parasitemia is established by blood smear. In general, the heavier the parasitemia, the sicker the patient, but there are many asymptomatic patients with high parasitemia, and patients with severe malaria can present with low density infection.

CLINICAL MANAGEMENT

General principles

Death due to severe malaria can occur within hours of presentation, so prompt assessment and initiation of antimalarial therapy is essential. Patients should be evaluated with attention to findings consistent with malaria as well as additional and/or alternative causes of presenting symptoms. A full neurologic assessment should be performed; including assessment of the Glasgow coma scale is suitable for adults. Temperature, heart rate and rhythm, respiratory rate and rhythm, blood pressure oxygen saturation, and weight should be noted, as should capillary refill and degree of pallor.

Of primary importance in the treatment of malaria is the provision of prompt, effective therapy and concurrent supportive care to manage life-threatening complications of the disease. Supportive measures (e.g., oxygen, ventilatory support, cardiac monitoring, and pulse oximetry) should be instituted as needed. During this time, intravenous catheters should be placed and finger prick blood samples should be obtained for laboratory tests needed immediately. Point-of-care testing machines can be used for rapid determination of hematocrit, packed cell volume (PCV) or hemoglobin, glucose, and lactate. Parasitemia can also be determined quickly but requires a microscope. Additional tests can be done if/when indicated: electrolytes, full blood count, type and cross, blood culture, and clotting studies. Unconscious patients should have a lumbar puncture to rule out concomitant bacterial meningitis in the absence of contraindications (e.g., papilledema). These tasks should overlap with institution of antimalarial treatment as well as other ancillary therapies as needed (including anticonvulsants, intravenous glucose and fluids, antipyretics, antibiotics, and blood transfusion).

Repeat clinical assessments should be performed every two to four hours for prompt detection and management of complications (in an intensive care setting, if possible). If the coma score decreases after initiation of treatment, investigations should focus on the possibility of seizures, hypoglycemia, or worsening anemia. Repeat laboratory assessments of parasitemia, hemoglobin/hematocrit, glucose, and lactate should be performed in six hour intervals used to guide management decisions[5].

Antimalarial therapy

There are two major classes of drugs available for parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Quinine has been mainstay of antimalarial therapy for centuries and remains the preferred treatment in many

reas. However, data comparing quinine and temisinins suggest that intravenous artesunate is referable for treatment of adults with severe falciparum alaria (in areas where intravenous artesunate of reliple quality is readily available)[2]. In other areas, intrenous quinine (or quinidine in the United States) reains the drug of choice.

Quinine/quinidine — Intravenous quinine remains the treatment of choice for children in Africa and for areas where intravenous artesunate of reliable quality is not readily available. As noted above, the mortality benefit of artesunate over quinine has been observed among adults surviving >24 hours after starting treatment[6]. Since half of pediatric deaths occur within the first 24 hours after starting treatment, the mortality benefit in this group is not certain. A multi-center study comparing artesunate and quinine among African children with severe malaria is underway, and the preferred approach to therapy may be modified on the basis of subsequent findings.

Intravenous quinine dihydrochloride 20 mg salt/kg (in 5 percent dextrose) loading dose over 4 hours, followed by 20 to 30 mg salt/kg divided into two to three equal administrations of 10 mg salt/kg (over 2 hours) at 8 or 12 hour intervals (maximum 1800 mg salt/day). Solutions diluted to 60 mg/mL quinine dihydrochloride are less painful than more concentrated preparations[7].

If intravenous infusions cannot be given, uinine can be administered via intramuscular injecon. Two injections of 10 mg/kg quinine (diluted to 60 100 mg/mL) should be administered 4 hours apart. he anterior thigh is preferred over the gluteal region minimize the risk of sciatic nerve damage.

rereferral treatment

The risk of death due to severe malaria is greatst in the first 24 hours of illness. In rural endemic aras where patients with severe malaria cannot begin travenous therapy immediately, patients should be eated with a prereferral dose of intramuscular or trarectal therapy and triaged to an acute care facily. Options include intramuscular administration of uinine or an artemisinin, or rectal administration of rtesunate.

ompleting therapy

In general, the total duration of therapy with quiine/quinidine for severe malaria is 7 days. The total uration of therapy with artemisinin based therapy is 3 ays.

Patients completing oral quinine treatment hould also receive a second agent. Options for co dministration with quinine include 7 days of doxycycline or tetracycline (or clindamycin for children or regnant women). Options for oral artemisinin combiation therapy are outlined in detail separately.

Respiratory status

Hypoxemia is not common in the setting of severe malaria; oxygen saturation <90 percent should raise suspicion for a concomitant lower respiratory tract infection. Pulmonary edema may develop, particularly in the settings of renal impairment or severe malarial anemia. Acute respiratory distress syndrome (ARDS) can also complicate severe malaria. The approach to ventilatory management ranges from supplemental oxygen to mechanical ventilation with positive end expiratory pressure (PEEP).

Neurologic status

The standard clinical case definition of cerebral malaria includes the following criteria[2]:

- Blantyre coma score d"2
- P. falciparum parasitemia (any density)
- No other identifiable cause of coma (eg, hypoglycemia, meningitis, or a post-ictal state)[2].
- **Lumbar puncture** — Patients with altered sensorium should undergo lumbar puncture (in the absence of contraindications) to exclude concomitant bacterial meningitis. If clinical instability or papilledema on ocular fundus examination preclude lumbar puncture, presumptive antibiotic therapy for bacterial meningitis should be initiated.

Seizure management — Seizures occur in up to 70 percent of children with severe malaria; subclinical seizures occur in 15 to 20 percent of cases[8]. Seizures may be generalized or focal, and the clinical signs may be subtle (nystagmus, irregular respirations, hypoventilation, or a drop in the Blantyre coma score). It is also important to evaluate for causes of seizure besides cerebral malaria (eg hypoglycemia, fever) and to treat accordingly as outlined in the following sections.

Benzodiazepines are useful first line agents for seizure treatment. Diazepam (0.4 mg/kg) can be administered intravenously or per rectum; lorazepam (0.1 mg/kg) can be administered intravenously or interosseously. These doses can be repeated once if seizures do not cease within 5 minutes of the initial dose. Benzodiazepines should not be combined due to risk of respiratory depression. If seizures are not controllable with benzodiazepines, other options include phenobarbitone (phenobarbital 15 to 20 mg/kg, slow IV push) or phenytoin (18 mg/kg diluted in 100 mL normal saline, infused over 20 minutes).

If seizures recur, repeat single doses of benzodiazepine may be administered. Alternatively, maintenance doses of phenobarbital (5 to 15 mg/kg/day, administered orally, via NG tube, or via slow IV push in divided doses every 12 hours) or phenytoin (5 mg/kg/day IV) may be initiated.

Patients with severe malaria should not receive routine seizure prophylaxis in the absence of clinical seizure activity. In a study of 340 children with cerebral malaria randomized to receive phenobarbital (20 mg/kg) or placebo upon admission to hospital, the mortality in the phenobarbital group was significantly higher than the placebo group (18 versus 8 percent)[9].

Anemia and coagulopathy — Removal of infected and uninfected erythrocytes from the circulation is associated with rapid development of anemia. Patients with severe anemia may present with or without altered consciousness. Course of repeated malaria infections, so patients can be fully alert with hemoglobin concentrations of 2 to 3 g/dL (hematocrit <10 percent). Evaluation for pallor of the conjunctivae, nailbeds, and palms can provide a rough estimate of the degree of anemia, since blood vessels in these areas are close to the surface. The degree of anemia and the level of parasitemia may be useful parameters for predicting the need for a blood transfusion and for determining the volume of blood to transfuse, but there have been no conclusive studies in this area. In general, 10 mL/kg of packed red blood cells or 20 mL/kg of whole blood transfused over 2 to 4 hours is appropriate. Blood should be typed and cross-matched prior to infusion.

Coagulopathy — clinically evident disseminated intravascular coagulation in the setting of severe malaria is rare (<5 percent), but profound thrombocytopenia is common, and the microcirculation in many organs is occluded by fibrin thrombi[10]. The approach to this complication is discussed in detail separately.

Hypoglycemia — Hypoglycemia (blood glucose <40 mg/dL or <2.2 mmol/L) is a common complication of malaria and a marker of severe disease[11,12]. It should be suspected in any patient who is comatose or who deteriorates suddenly.

Clinical manifestations of hypoglycemia include seizure and altered consciousness, although these are not reliable clinical indicators and blood glucose concentration should be assessed as part of routine evaluation.

Hypoglycemic patients should have intravenous access established promptly, followed by administration of initial bolus of dextrose (0.25 g/kg of body weight). This is usually achieved with 2.5 mL/kg of 10 percent dextrose solution, since extravasation of higher concentrations of glucose can cause severe tissue damage. Blood glucose measurement after 15 minutes should be repeated, with administration of repeat boluses until the patient is normoglycemic. If glucose measurement is not possible, comatose patients with parasitemia at the time of initial assessment should receive a bolus of 2.5 mL/kg of 10 percent dextrose solution.

Maintenance intravenous fluids should contain at least 5 percent dextrose; patients with recurrent hypoglycemia should receive 10 percent dextrose (10 percent dextrose can be prepared quickly by withdrawing 100 mL from a one liter bag of a 5 percent dextrose solution and replacing it with 100 mL of a 50 percent dextrose solution.

Patients presenting with normoglycemia can develop hypoglycemia during the course of treatment. In addition, those managed promptly for hypoglycemia at presentation can have subsequent recurrent hypoglycemia. Therefore, blood glucose should be monitored closely during the course of illness with prompt management as outlined above.

Volume management — The intravascular volume status in the setting of severe malaria is uncertain; there are data to both support and refute the presence of hypovolemia in the setting of severe malaria infection[13,14]. Adults with malaria appear to be more vulnerable to fluid overload than children; there is a thin line between underhydration (and thus worsening renal impairment) and overhydration (and risking pulmonary and cerebral edema). Therefore, fluid requirements should be assessed on an individual basis. Reliable markers of intravascular volume depletion in patients with severe malaria include cool peripheries, delayed capillary refill, low venous pressure and low urine output. Deep breathing (reflecting lactic acidosis) may also be a reasonable indicator of hypovolemia. In the setting of acute renal failure, institution of renal replacement therapy is appropriate if feasible. Hemofiltration is associated with lower mortality than peritoneal dialysis.

Nutrition — Nutritional supplementation should be provided by nasogastric tube (NG) for patients with prolonged coma who are unable to eat and drink within 24 to 48 hours.

Fever — High fevers (>38.5°C) are common in the setting of malaria infection and may reflect the host response to endogenous pyrogens released at the time of schizont rupture[15]. The optimal approach to treatment of fever is uncertain, although use of antipyretics in patients with high fever is appropriate given the association between high fever and convulsions[2].

Paracetamol (acetaminophen; 15 mg/kg every 6 hours; maximum dose 1000 mg), is a reasonable antipyretic agent; oral therapy can be used for patients able to swallow. Otherwise, suppository formulations are acceptable[2]. If fever persists, ibuprofen (10 mg/kg every 6 hours; maximum dose 1200 mg per day) can be administered (orally or via nasogastric tube) alone or on an alternating schedule with paracetamol every 3 hours.

Bacterial Infection — Bacteremia is an important contributor to morbidity and mortality in the setting of severe malaria, and severe anemia has been implicated as a primary risk factor for nontyphoidal Salmonella septicemia[16,17].

PREGNANCY

Pregnant women are more likely to develop severe P. falciparum malaria than other adults, particularly in the second and third trimesters. Complications such as hypoglycemia and pulmonary edema are more common than in non pregnant individuals. Maternal mortality can approach 50 percent, and fetal death and premature labor are common.

Prompt antimalarial therapy and supportive care should be administered as outlined in the preceding sections. If there is a choice of therapy, artesunate or artemether are preferred over quinine in the second and third trimesters since quinine is associated with recurrent hypoglycemia.

SUMMARY AND RECOMMENDATIONS

- Severe malaria is acute malaria with major signs of organ dysfunction and/or high level of parasitemia in endemic areas, young children and pregnant women are at high risk for severe malaria. Older children and adults develop partial immunity after repeated infections and therefore are at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria parasites and so are at high risk for severe disease.
- The diagnosis of malaria and degree of parasitemia is established by blood smear. In general, the heavier the parasitemia, the sicker the patient, but there are many asymptomatic patients with high parasitemia, and patients with severe malaria can present with low density infection.
- For treatment of non pregnant adults with severe falciparum malaria we suggest intravenous artesunate (in areas where intravenous artesunate of reliable quality is readily available). Treatment of children with severe falciparum malaria we suggest treatment with intravenous quinine.
- For treatment of pregnant women with severe falciparum malaria in the second and third trimesters we suggest intravenous artesunate (in areas where intravenous artesunate of reliable quality is readily available of pregnant women with severe falciparum malaria in the first trimester we suggest intravenous quinine.
- The total duration of therapy with quinine/quinidine for severe malaria is 7 days. The total duration of therapy with artemisinin based therapy is 3 days. After the acute stage of illness has been treated with parenteral therapy and the patient can swallow, a complete course of oral therapy (selected on the basis of known parasite drug susceptibility or national treatment guidelines) should be administered.
- We recommend administration of pre-referral treatment to patients in rural endemic areas with suspected severe malaria who cannot begin intravenous therapy immediately.
- Death due to severe malaria can occur within hours of presentation, so prompt assessment and initiation of antimalarial therapy are essential, and followed by concurrent supportive care to manage life-threatening complications of the disease:

— Pulmonary complications of severe malaria include pulmonary edema, acute respiratory distress syndrome, and lower respiratory tract infection. Management requirements may range from supplementary oxygen to mechanical ventilation.

— Neurologic complications include altered sensorium, seizure and coma. Seizures should be managed as outlined above.

— Hematologic complications include severe anemia and coagulopathy. Decisions regarding transfusion should be tailored to individual patient circumstances.

— Hypoglycemia (blood glucose <40 mg/dL or <2.2 mmol/L) is a common complication of malaria and a marker of severe disease; it should be suspected in any patient who deteriorates suddenly. Hypoglycemic patients should have intravenous access established promptly followed by administration of 50 percent dextrose (1 mL/kg) with repeat blood glucose measurement after 15 minutes.

— Hypovolemia should be assessed on an individual basis. Adults with malaria appear to be more vulnerable to fluid overload than children; there is a thin dividing line between underhydration (and thus worsening renal impairment) and overhydration (and risk of pulmonary edema.

REFERENCES

1. World Malaria Report 2005, Geneva, World Health Organization, 2005.
2. WHO guidelines for the treatment of malaria. Geneva, World Health Organization, 2006. Available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (Accessed Oct 22, 2008).