

Management of severe/complicated falciparum malaria

Anand.M, Atul Saroch, Navneet Sharma

Malaria is one of the most dreaded diseases in humans in terms of mortality and morbidity as it cannot be diagnosed clinically with reasonable accuracy. All fever cases clinically suspected of malaria should be investigated for confirmation of malaria either by rapid diagnostic test (RDT) or by microscopy. Early diagnosis and complete treatment is one of the key strategies of National Malaria Control Program. Malaria should be suspected in patients residing in endemic areas that present with fever. It should also be suspected in those febrile patients who have recently visited an endemic area. Although malaria is known to mimic the signs and symptoms of many common infectious diseases, the other causes should also be suspected and investigated.

Clinically malaria is classified into uncomplicated and complicated or severe malaria. Uncomplicated malaria is defined as symptomatic malaria without signs of vital organ dysfunction. Fever is the cardinal symptom of malaria. It can be intermittent with or without periodicity or continuous. Many cases have chills and rigors. The fever is often accompanied by headache, myalgia, arthralgia, anorexia, nausea and vomiting. The symptoms of malaria can be non-specific and mimic other diseases like viral infections, enteric fever etc. Complicated falciparum malaria or severe malaria is characterized organ failure (Table 1) as evidenced by one or more of the following features:

- Impaired consciousness / coma
- Repeated generalized convulsions
- Renal failure (Serum Creatinine >3 mg/dl; urine output <400 ml/24hrs)
- Jaundice (Serum Bilirubin >3 mg/dl)
- Severe anaemia (Hb <5 g/dl)
- Pulmonary oedema – Cardiogenic and non-cardiogenic
- Hypoglycaemia (Plasma Glucose <40 mg/dl)
- Metabolic acidosis (arterial pH <7.25 or plasma bicarbonate level of <12 mmol/l)
- Circulatory collapse/shock (Systolic BP <80 mm Hg, MAP <65 mmHg, core skin temperature difference of $>10^{\circ}\text{C}$)
- Abnormal bleeding and Disseminated Intravascular Coagulation
- Haemoglobinuria
- Hyperthermia (Temperature $>104^{\circ}\text{F}$)
- Hyperparasitaemia ($>5\%$ parasitized RBCs in low endemic and $>10\%$ in hyperendemic areas)

Table 1: Clinical Features and Mechanisms of causation in Severe Complicate Malaria:

Syndrome	Clinical Features	Mechanism of Causation
Severe Anemia	Shock, impaired consciousness, respiratory distress, CHF	↓ RBC production (reduced erythropoietin levels, pro-inflammatory cytokines), hemophagocytosis, antibody and complement mediated RBC destruction
Cerebral Malaria	Impaired consciousness, seizures, decerebration or decortication, long term neurological deficits	Microvascular obstruction (parasites, rosettes of RBC's), parasite toxin (GPI)
Miscellaneous	Hypoglycemia, DIC	Proinflammatory cytokines, parasite products, cytoadherence of parasitized RBC's
Metabolic Acidosis	Tachypnea, respiratory distress, hypoxia, ↑ serum lactate, renal failure	↓ tissue perfusion, hypovolemia, ↓ Cardiac Output, pro-inflammatory cytokines & parasite products
Renal Failure	Impaired consciousness, ↓urine output, vomiting, asterixis, pericardial rub	Hypovolemia, cytoadherence, microvascular obstruction, acute tubular necrosis, hemoglobinuria (pigment nephropathy), microangiopathy, transient glomerulonephritis (post-infectious)

Abbreviations: RBC, red blood cells; GPI, glycosylphosphatidylinositol; DIC, disseminated intravascular coagulation; CHF, congestive heart failure

Diagnosis

Diagnosis of malaria involves identification of malaria parasite (blood smear & microscopy) or its antigens/products in the blood of the patients (Rapid diagnostic tests or RDT's). The interpretation of tests is subjected to many factors, like quality of the test kit, the methodology and the maintenance of cold chain. The most important factor is the nature of the test with antigen based RDTs being more reliable and informative than antibody based tests. Since these tests have a very high negative predictive value, a properly done negative test does rule out malaria. Repeated tests (RDT) may have to be done in doubtful cases or based upon a strong clinical suspicion. The national guidelines for treatment of malaria have incorporated RDTs as an important component of diagnosis and recommend it to be the preferred test as it is simple, reliable and can be performed with minimum training / expertise.

In patients where clinical suspicion of malaria is high, the gold standard still remains peripheral smear (thick and thin) examination, however the yield may be only 30-35%. Duration of the illness, level of parasitemia, expertise of the technician and the method of examination may all have a bearing on the result of the malarial tests.

Buffy coat examination and PCR can be done in selective cases but are recommended mostly in research settings.

Table 2: Poor prognostic indicators in Severe/Complicated Malaria:

Clinical	Laboratory
Marked agitation	Severe anemia (PCV <15%)
Hyperventilation	Leucocytosis (> 12,000/μl)
Hypothermia (<36.5° C)	Platelet count (<50,000/μl)
Bleeding	Hypoglycemia (<2.2mmol/l)
Deep coma	Hyperlactaemia (>5mmol/l)
Convulsion	Acidosis (pH <7.3)
Anuria	S.creatinine (>3 mg/dl)
Shock	S.bilirubin (>3 mg/dl)
	Elevated liver enzymes (AST/ALT 3 times upper limit of normal, 5-nucleotidase also elevated)
	Elevated urate (>600 μmol/l)
	Prothrombin time (prolonged > 3 s)
	Fibrinogen level (<200 mg/dl)
	Parasitology- Hyperparasitemia as follows: <ul style="list-style-type: none"> • Increased mortality at parasite count >100,000/μl • High mortality at >50,000/μl • >20% parasites identified as pigment containing trophozoites and schizonts. • >5% of neutrophils with visible malarial pigment

TREATMENT:

The effectiveness of early diagnosis and prompt treatment as the principal technical components of the global strategy to control malaria is highly dependent on the efficacy, safety, availability, affordability and acceptability of antimalarial drugs. Severe malaria is a medical emergency and may rapidly progress to death without prompt and appropriate treatment. The main objective of the treatment of severe malaria is to prevent the patient from dying, prevention of recrudescence, transmission, prevent emergence of resistance and prevention of disabilities. The mortality of untreated severe malaria is high but with antimalarial treatment, the overall mortality has fallen to 15–20%. Therefore, appropriate antimalarial chemotherapy is the KEYSTONE of all malaria control efforts.

Anti-malaria Drugs - According to activity:

- Blood schizonticides: Act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These includes artemisinin compounds, chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines etc.
- Gametocytocides: These drugs prevent transmission of the infection to the mosquito, by destroying sexual forms of the parasite in blood. Both artemisinin compounds and primaquine have gametocidal activity against all species.
- Tissue schizonticides: These drugs act on the hypnozoites of *P. vivax* and *P. ovale* in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of *P. vivax* and *P. ovale*). Thus, a combination of blood schizonticides and primaquine is needed in all cases of malaria.

Artemisinin based combination therapy (ACT)

Artemisinin and its derivatives (aresunate, artemether, artemotil, dihydroartemisinin) produce a rapid clearance of parasitemia and a rapid resolution of symptoms. They reduce parasite numbers by a factor of approximately 10,000 in each a sexual cycle, which is more than all other antimalarials (reduce parasite number 100 to 1000 fold per cycle). Courses of ACTs of less than 3 days are not advocated as they are less efficacious, and provide less protection as compared to when co-administered with slowly eliminated partner antimalarials.

Currently, there are four artemisinin compounds that have been recommended by The National Vector Borne Disease Control Program for severe *P. falciparum* malaria. For treatment initiation, any one of the following four can be used:-

1. Artesunate: 2.4 mg/kg i.v. or i.m. given on admission (time=0), then at 12 h and 24 h, then once a day.
2. Artemether: 3.2 mg/kg i.m. given on admission then 1.6 mg/kg per day.

3. Arteether: 150 mg daily i.m for 3 days in adults only (not recommended for children)
4. Quinine: 20 mg quinine salt/kg body weight on admission (IV infusion in 5%-10% Dextrose) followed by maintenance dose of 10 mg/kg 8 hourly; infusion rate not to exceed 5 mg/kg per hour. Loading dose is omitted if the patient has already received quinine.

Once the patient can accept, any one of the following three options can be used by the oral route for 7 days:-

1. Artemisinin Combination Therapy (ACT) specific (ACT+Lumefantrine) for 3 consecutive days. Primaquin single dose given on day 2.
2. ACT-Sulfadoxine Pyramethamine for 3 consecutive days and Primaquin single dose given on day 2. This regimen is not to be given for treatment of malaria in Northeastern states.
3. In those treated with parenteral Quinine, continue with oral Quinine 10mg/Kg every 8 hourly along with either Doxycycline 100 mg daily. Alternatively Clindamycin 10 mg/Kg twice daily can be used in children and pregnant women.

All patients should receive a preferred form of ACT for 3 days as soon as oral treatment is feasible, as artemisinin monotherapy leads to a rapid development of resistance. When injectable treatment cannot be given, artesunate can be administered rectally in children and transferred to a facility for full parenteral treatment. A single dose of rectal artesunate as pre-referral treatment has been shown to reduce the risk of death in children when the time for referral exceeds 6hrs.

Parenteral artesunate, a water soluble artemisinin derivative, administered both by IV and IM route, has shown a better survival as compared to artemether and arteether. Artemether and arteether are oil based formulations given by IM injection and show erratic absorption. The use of quinine has shown a better outcome when compared to quinidine. If quinidine is chosen as the primary agent, then the administration of quinidine must be monitored closely for development of hypotension and dysrhythmias. On the other hand, cardiovascular monitoring is not necessary for quinine, unless the recipient has underlying cardiac disease. All patients on quinine (a pancreatic secretagogue) should receive this drug in a continuous infusion of 5% or 10% dextrose IV. A total plasma level $>8\mu\text{g/ml}$, QT interval $>0.56\text{ s}$, or QRS widening beyond 25% is indication for slowing of infusion rates. The development of arrhythmias or saline unresponsive hypotension, warrants treatment stoppage. A loading dose of quinine should not be used if the patient has received quinine, quinidine and mefloquine in preceding 12 to 24hrs. If patients remains in acute renal failure after 48 hrs of IV quinine therapy, the maintenance dose should be reduced by one-third to half. There are strong recommendations that the initial dose of antimalarial should never be reduced in the presence of renal or hepatic dysfunctions.

Exchange Transfusions: This technique has been proposed as a means to remove infected red blood cells, lower the total parasite burden and promote oxygenation by replacing the deformed and parasitized red cells with non-parasitized red blood cells. Both the CDC-Atlanta and WHO do not recommend this for treatment of hyperparasitemia related to *P.falciparum*

due to lack of sound clinical evidence. However, the American Society of Apheresis favours this technique as an adjunctive therapy in severe *Falciparum* patients with greater than 10% parasitemia.

Supportive care:

Good nursing care of patient with severe malaria is of vital importance. Accurate assessment of blood pressure, respiratory rate and pattern, coma score, and urine output should be recorded as frequently as possible. Fever should be promptly lowered with tepid sponging and acetaminophen. The presence of hyperpyrexia requires the use of cooling blankets, water sprays and cooling fans. Blood glucose should be checked, using rapid stick tests every 4-6 h if possible, careful attention to be given to fluid balance in order to avoid over- or under hydration, particularly in unconscious patients. Assess neck stiffness and examine rash to exclude alternative diagnosis. Fundus should always be examined as papilloedema is contraindication for performing a lumbar puncture.

Comatose patients: Aim is to prevent aspiration, place patient in a semi prone position, elevate the head end of bed to 45°, aspirate contents of stomach through naso-gastric tube as this will reduce the risk for aspiration. Inability to maintain the airway or a Glassgow coma scale <10 mandates endotracheal intubation. Urinary catheterization should be done to monitor the hourly urine output and frequent position changes to prevent bed sores. Always suspect and exclude treatable causes of coma (e.g. hypoglycaemia, electrolyte abnormalities, bacterial meningitis, Leptospirosis and Scrub Typhus) and avoid drugs such as corticosteroids, heparin and adrenaline.

Seizures are common in cerebral malaria, particularly in children. Treatment of seizures is by using intravenous diazepam or lorazepam. If seizure episode persists longer than 10 min after first dose, administer a second dose of benzodiazepine (diazepam, midazolam, or lorazepam). Persistent seizures (status epilepticus) despite use of two doses of benzodiazepine should be treated with propofol infusion or phenobarbitone at a loading dose of 18 mg/kg IV and 15 mg/kg IM or IV respectively followed by maintenance dose of 5mg/kg/day for 48 hrs. High dose of phenobarbitone (20mg/kg) are known to cause respiratory depression so breathing pattern should be monitored closely with capnography. Prophylactic anticonvulsants are not indicated.

Hypoglycemia: If blood glucose is <40mg/dL, treat immediately with 25% dextrose infused over 5-10 minutes. The causation of hypoglycaemia is related to parasite glucose consumption and the impairment of host neoglucogenesis. Other contributory factors are; malnutrition, quinine therapy, adrenal insufficiency and hyperinsulinemia. Hypoglycaemia should be suspected in any patient who has a sudden deterioration in neurological status. The routine monitoring of blood glucose is mandatory for all cases of severe malaria.

Fluid management: Patients with severe malaria are prone for both iatrogenic volume overloading and under-hydration. Children with severe malaria who are unable to retain oral fluids should be managed with 5% dextrose and Ringer's Lactate maintenance fluids (3-4ml/

kg/hour), and adults at 1-2ml/kg/hour, until patient is able to tolerate oral fluids. Enteral feeding should be started as soon as the patients' condition allows. Dehydration should be managed cautiously and ideally guided by the urine output. If the patient becomes oliguric (<0.5 ml of urine/kg/hour) despite adequate rehydration then intravascular volume should be kept at minimum for maintaining systemic perfusion (MAP \geq 65 mmHg). Only fluids to replace insensible losses should be administered. Central venous pressure monitoring if available should be maintained at 8-12 cm of water. If indicated, hemofiltration or SLED should be started early for acute renal failure or severe metabolic acidosis unresponsive to rehydration. Patients with hypotension can be managed with SLED rather than by conventional intermittent hemodialysis.

Pulmonary oedema: Management of this complication includes oxygen therapy. Patients should be nursed in an upright position and filling pressures on the right side of the heart reduced with loop diuretics, opiates, ultrafiltration or dialysis (SLED). Mechanical ventilation (MV) with Non-Invasive Ventilators can eliminate the need for invasive mechanical ventilation. On the other hand, in patients with mental obtundation that have been tracheally intubated, the use of MV with lower tidal volume (4-6 ml/Kg) and positive end-expiratory pressure in life-threatening hypoxaemia improves the clinical outcome.

Metabolic acidosis: This is a common complication leading to death in severe malaria. Early ventilatory support for respiratory abnormalities and early management of renal failure are beneficial.

Anaemia: A threshold of haemoglobin level of greater than 7g/dL (haematocrit >20%) is recommended. This recommendation still need to be tailored to the individual patient. A rapid drop of haematocrit may necessitate blood transfusions much earlier in the course of illness. If necessary, small dose (20mg furosemide) of diuretics can be given before starting blood transfusion to avoid circulatory overload.

Disseminated intravascular coagulation: Less than 5% patients develop this complication. For bleeding patients, fresh blood transfusions and parenteral vitamin K are administered. A non-bleeding patient with platelet level of <20,000/uL or a clinically bleeding patients at counts <50,000/uL merits platelet transfusions. Proton Pump Inhibitors should be given for gastric mucosal protection.

Bacterial infections: Unexplained deterioration during the course of illness may result from a supervening bacterial infection or may be acquired nosocomially. Patients should be given empirical treatment with a third-generation cephalosporin, unless suspicion for aspiration is strong, in which case penicillin or clindamycin is adequate. Urinary tract infections are common in catheterized patients. All antibiotic protocols for nosocomial acquired bacterial infections should take into account the local antibiotic sensitivity patterns.

Treatment of severe falciparum malaria in special clinical situations

Pregnancy:

The antimalarials considered safe in the first trimester of pregnancy are atemisinin compounds, quinine, chloroquine, proguanil, pyrimethamine and sulfadoxine–pyrimethamine. Of these, artesunate and quinine remains the most effective and can be used in all trimesters of pregnancy including the first trimester.

Mefloquine has been associated with an increased risk of stillbirth. Sulfadoxine–pyrimethamine is safe but may be ineffective in many areas because of increasing resistance. Primaquine and tetracyclines should not be used in pregnancy. Amodiaquine, chlorproguanil–dapson, halofantrine, lumefantrine and piperazine have been classified as category C as they have not been evaluated sufficiently to permit positive recommendations.

Lactating women- Tetracycline are contraindicated because of their effect on the infant's bones and teeth.

For travellers returning to non-endemic areas, WHO recommends any of the following regimens:

- Atovaquone–proguanil (15/6 mg/kg; usual adult dose, 4 tablets once a day for 3 days)
- Artemether–lumefantrine (1.5/9mg/kg; usual adult dose, 4 tablets twice a day for 3 days)
- Quinine (10 mg salt/kg bw every 8 h) + doxycycline (3.5 mg/kg bw once a day) or clindamycin (10 mg/kg bw twice a day); all drugs to be given for 7 days

Immunodeficiency state - Patients with HIV infection who develop malaria should receive standard antimalarial treatment regimens. Children with HIV and advanced immunosuppression have more episodes of clinical malaria with higher parasite counts than those that are immunocompetent. In areas of unstable malaria, children with advanced HIV may be more likely to suffer a severe disease or coma.

Associated medical condition/diseases:

Treatment of malaria may have to be modified due to certain associated conditions/ diseases. Therefore, all such should be carefully assessed before starting the patient on anti malarial treatment.

- a. **Epilepsy:** Malaria as well as anti-malarials can trigger convulsions. Mefloquine is better avoided in these patients.
- b. **Cardiac disease:** High-grade fever of malaria can exacerbate left ventricular failure and therefore, in all such patients' energetic management of malaria is called for. Fever should be controlled with anti-pyretics and tepid sponging. Chloroquine, artemisinin, pyrimethamine/ sulphadoxine, tetracyclines and primaquine can be safely used in these patients. Quinine can also be used carefully. Mefloquine and halofantrine are better avoided in patients with known cardiac illness.

- c. **Hepatic insufficiency:** None of the antimalarial drugs have any direct hepatotoxic effect.
- d. **Renal failure:** The initial dose of antimalarial drugs need not be reduced in patients with renal failure. However, if the patient requires parenteral antimalarials even after three days and continues to be sick, then the dose can be reduced by one third to half of usual dose.
- e. **Glucose-6-phosphatase Deficiency:** This sex linked acquired deficiency state affords some protection against *P falciparum* infection but predisposes the host to oxidant related hemolysis. Primaquin is either contraindicated in individuals with severe enzyme defects or in cases of severe *P vivax* malaria the dose is modified in presence of milder forms of this enzyme defect (0.75 mg/Kg every weekly for 8 weeks).

Treatment of Severe vivax malaria

P. vivax malaria causes 40% of malaria worldwide and has been traditionally considered a benign malaria, however, recently it has caused complicated malaria like cerebral malaria, severe anaemia, severe thrombocytopenia and pancytopenia, jaundice, spleen rupture, acute renal failure and acute respiratory distress syndrome. Severe anaemia and acute pulmonary oedema are not uncommon. The underlying mechanisms of severe manifestations are not well understood and differ from that related to *P falciparum*. Management of severe vivax malaria is the same as for complicated falciparum malaria with the exception that inherent resistant to pyrimethamine-sulfadoxine is high in *P vivax*. Tissue schizonticides like primaquin has to be given orally for 2 weeks after completion of the primary antimalarial therapy.

Follow-up:

All cases of *P. falciparum* malaria, particularly in the non-immune and high-risk population, should be monitored for complications. In case of deterioration, treatment for severe malaria should be instituted without any delay.

In all cases of *P. falciparum* malaria, ideally follow-up MP tests should be done on the 6th and 28th days after treatment. The 6th day smear is done to assess clearance of parasitemia. However, gametocytes may be found on the smear and requires treatment with a single dose of primaquine on day 2 after starting anti-malarial therapy. Persistence of ring forms of the parasite indicates incomplete clearance and hence drug resistance. These cases should be re-treated accordingly with a different anti-malarial regimen. RDTs may show a positive test but this does not call for re-treatment, as it remains positive for 4 weeks. The 28th day blood smear is done to identify recrudescence.

References

1. *Management of Severe Malaria: A practical handbook. Third edition. World Health Organization, WHO press, Geneva, Switzerland 2006.*
2. *Mackintosh CL, Beeson JG, Marsh K. Clinical Features and Pathogenesis of Severe Malaria. Trends in Parasitology 2004; 20(12):597-603.*

3. Singh S, Chaudhary D, Varghese GM, et al. *Tropical Fevers: Management Guidelines*. *Indian J Crit Care Med* 2014;18 (2): p 62-9.
4. *National Drug Policy for Malaria 2013*, NVBDCP, MoH & FW, Govt.of India, 2013.
5. *Guidelines for diagnosis and treatment of malaria 2013*, NIMR/TRS/2011/1
6. White NJ, Breman JG. *Malaria*; in *Harrison's Principles of Internal Medicine 18th edition*, MacGraw Hill Publishing 2012, volume 1, p 1688-1705.
7. Tripathi KD. *Antimalarial drugs*. *Essentials of Medical Pharmacology 7th ed*. New Delhi, Jaypee Brothers Medical Publishers Ltd; 2013. p 816 -35
8. Ravinder K Gupta, Asma Saheen, *Malaria Revisited*. *JK Science*, Vol. 16, No. 1, 2014: p 1-3