INVITED ARTICLE

Malaria in the Intensive Care Unit

Ashit Hegde

Abstract

Most cases of severe malaria are caused by *Plasmodium falciparum*. Severe malaria is characterized by severe organ dysfunction. Both peripheral smear examination and rapid diagnostic test have a role in the diagnosis. Parenteral artesunate is clearly the drug of choice for the management of severe malaria. Parenteral artesunate should always be followed up with ACT.

Most of the complications of severe malaria require supportive care only. The role of exchange transfusions in the management of severe malaria is questionable in the postartesunate era. Malaria in pregnancy can be quite severe and artesunate is now the drug of choice for all three trimesters. Vivax malaria is being increasingly recognized as a cause of severe malaria. The cause for this increased virulence is still not clear. Management of severe vivax malaria is similar to that of severe falciparum malaria.

Keywords: Falciparum malaria, Malaria in pregnancy, Malaria intensive care, Severe malaria, Severe vivax malaria.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23871

A majority of the cases of severe malaria warranting care in the ICU are caused by *Plasmodium falciparum*.

Pathophysiology of Severe Falciparum Malaria[1]

Severe falciparum malaria causes profound organ dysfunction. The RBCs infected by the schizonts of *P. falciparum* form knobs on the cell surfaces. These knobs express an adhesive protein—*P. falciparum* erythrocyte membrane protein—by virtue of which the infected cells attach to receptors on capillary and venular endothelium (sequestration). This protein also allows the infected cell to adhere to other uninfected cells forming "rosettes." The microvasculature is blocked as a result of this phenomenon of sequestration and rosetting (which is unique to *P. falciparum*) and this contributes to organ dysfunction. Also, the spleen is not able to efficiently clear the infected RBCs because of sequestration. The parasite index may therefore be misleadingly low in patients with severe malaria because most of the parasites are sequestered. Previously cerebral malaria was the predominant presentation of severe malaria. The incidence of acute kidney injury (AKI) and multiorgan dysfunction is now increasing.

Clinical Features of Severe Falciparum Malaria (As Per WHO)[2]

Severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitemia.

- *Impaired consciousness:* A Glasgow coma score <11 in adults.
- *Prostration:* Generalized weakness so that the person is unable to sit, stand, or walk without assistance.
- *Multiple convulsions:* More than two episodes within 24 hours.
- *Acidosis:* A plasma bicarbonate level of <15 mmol/L or venous plasma lactate ≥5 mmol/L.
- *Hypoglycemia:* Blood or plasma glucose <40 mg/dL.
- *Severe malarial anemia:* Hemoglobin concentration and hematocrit of <7 gm/dL and <20%, respectively, in adults with a parasite count >10,000/μL.
- *Renal impairment:* Plasma or serum creatinine >3 mg/dL.
- *Jaundice:* Plasma or serum bilirubin >3 mg/dL with a parasite count >100,000/μL.
- *Pulmonary edema:* Radiologically confirmed or oxygen saturation <92% on room air with a respiratory rate >30/minute, often with chest indrawing and crepitations on auscultation.
- *Significant bleeding:* Including recurrent or prolonged bleeding from the nose, gums, or venepuncture sites; hematemesis or melena.
- *Shock:* Compensated shock is defined as capillary refill ≥3 seconds or temperature gradient on the leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- *Hyperparasitemia: P. falciparum* parasitemia >10%.

Both, the degree of parasitemia and evidence of organ dysfunction are therefore important. As has already been mentioned, some patients might have moderate parasitemia but severe organ dysfunction because most of the parasites are bound to the endothelium.

Better Test for Diagnosing Malaria

A well-performed peripheral smear (both thick and thin smears) examination is ideal. Detection of the malarial parasite is easier on a thick smear, whereas the thin smear enables identification of

Department of Critical Care Medicine, PD Hinduja National Hospital and Medical Research Centre Hospital, Mumbai, Maharashtra, India

Corresponding Author: Ashit Hegde, Department of Critical Care Medicine, PD Hinduja National Hospital and Medical Research Centre Hospital, Mumbai, Maharashtra, India, Phone: +91-22-24462250, e-mail: ahegde1957@gmail.com

How to cite this article: Hegde A. Malaria in the Intensive Care Unit. Indian J Crit Care Med 2021;25(Suppl 2):S127–S129.

Source of support: Nil

Conflict of interest: None

the species and estimation of the parasite index. Unfortunately, technicians who examine peripheral smears well are hard to find. The rapid diagnostic test may therefore be useful in the ICU because it is unlikely to be negative in a patient with severe falciparum malaria. There is therefore almost no role for empiric antimalarial therapy in the ICU.

Differential Diagnosis of Severe Malaria

Any of the severe tropical infections (dengue, leptospirosis, rickettsial infections) may resemble severe malaria and vice versa.

Some Points in the Differential Diagnosis of These Infections

Cerebral malaria is becoming less frequent nowadays. Altered sensorium at onset, therefore, is more likely with leptospiral and rickettsial infections.

Significant anemia is more likely in severe malaria.

WBC: In malaria, the WBC count is usually normal or decreased however if there is severe hemolysis or secondary infection, the counts may be raised. WBC counts are usually increased in leptospirosis and rickettsial infections and are decreased in dengue.

Platelets: Whereas all of the tropical infections can cause thrombocytopenia. Platelet counts below 40,000 are usually seen in malaria and dengue.

Jaundice: It suggest malaria or leptospirosis. Jaundice is unusual in dengue unless the patient has severe hepatic damage.

Of course, community-acquired bacterial infections can also mimic severe malaria and should always form part of the differential diagnosis.

Specific Antimalarial Treatment[2,3]

Two classes of medicines are available for the parenteral treatment of severe malaria: cinchona alkaloids (quinine and quinidine) and artemisinin derivatives (artesunate and artemether).

Randomized trials from Southeast Asia which compared artesunate and quinine showed clear evidence of benefit with artesunate. The SEAQUAMAT study, which was the largest multicentre trial enrolled 1,461 patients. In this study, mortality was reduced by 34.7% (RRR) in the artesunate group.

Artesunate is therefore the treatment of choice for adults with severe malaria artesunate 2.4 mg/kg body weight IV or IM given on admission (time = 0), then at 12 and 24 hours, then once a day is the recommended treatment. The reconstituted solution of artesunate is unstable and should be administered immediately after reconstitution as a bolus.

Artemether: About 3.2 mg/kg is often used but it is not recommended because it needs to be given intramuscularly and the absorption is erratic.

Artesunate is a very safe drug and serious side effects are very rare. Delayed hemolysis is sometimes observed, especially in patients from non-endemic regions.

Quinine may be used as an alternative to artesunate in the treatment of severe falciparum malaria but there is no role for combining quinine with artesunate.

A loading dose of quinine (20 mg salt/kg body weight—twice the maintenance dose) reduces the time needed to reach therapeutic plasma concentrations. The maintenance dose of quinine (10 mg salt/kg body weight) is administered at 8-hour intervals, starting 8 hours after the first dose. Quinine must be administered as a slow, infusion (usually diluted in 5% dextrose and infused over 4 hours). The infusion rate should not exceed 5 mg salt/kg body weight per hour. Patients receiving quinine should have their QTc monitored regularly in order to prevent polymorphic tachycardia which is a serious side effect of quinine. Patients receiving quinine (especially in pregnancy) are also prone to develop hypoglycemia and need monitoring of blood glucose levels.

Follow-up Treatment

At least 1 day of parenteral treatment is recommended. Whenever possible the patient should then be switched to oral therapy (Artemesinin Combination Therapy (ACT) or quinine plus doxycycline or clindamycin).

Dosage in Organ Failure

Artemisinin derivatives do not need adjustment. Quinine levels may accumulate in severe vital organ dysfunction. If the patient has Acute Renal Failure (ARF) or has hepatic dysfunction, dose should be reduced by one-third after 48 hours. Dosage adjustments are not necessary if patients are receiving either hemodialysis or Continuous Renal Replacement Therapy (CRRT).

Supportive Care[4,5]

Patients with severe falciparum malaria may develop several complications:

- Coma
- Hyperpyrexia
- Convulsions
- Hypoglycemia
- Severe anemia
- Acute pulmonary edema/acute respiratory distress syndrome (ARDS)
- Acute renal failure
- Spontaneous bleeding and coagulopathy
- Metabolic acidosis
- Shock
- Splenic rupture

Most of these complications require only supportive care.

Fluids should be administered cautiously to patients with severe malaria. A liberal fluid strategy may increase the risk of pulmonary edema. Cardiac dysfunction caused by severe malaria may also contribute to cardiogenic pulmonary edema.

ARDS is a potentially serious complication of falciparum malaria. It is probably caused by an immune response to the infected RBCs which are sequestered in the pulmonary circulation. An immune response to the plasmodium antigen even after the parasitemia has been cleared can also occur. ARDS may therefore occur as a late complication even in patients in whom the parasite load has decreased. Management of ARDS in falciparum malaria is no different from the management of routine ARDS. ARDS in falciparum malaria usually tends to be short-lived and patients with falciparum malaria and ARDS can often be successfully managed with a closely supervised trial of Non Invasive Ventilation (NIV).

AKI is a relatively common complication of severe falciparum malaria. The patients need supportive care only with special attention to fluid balance. Some patients may need renal

replacement therapy temporarily. The prognosis of AKI is usually good.

Patients who present with shock should be treated with broad-spectrum antibiotics (after blood cultures are sent) because they may have gram-negative bacteremia from gut translocation.

There is no role for prophylactic anticonvulsants in cerebral malaria. There is also no role for dexamethasone or mannitol in the management of cerebral malaria.

Splenic rupture is more commonly seen with vivax malaria but can occur with falciparum malaria as well. Traditionally splenectomy was the treatment for splenic rupture but the modern view is that conservative management should be tried first.

Pregnant patients and patients receiving Quinine are vulnerable to Hypoglycemia. Blood glucose monitoring should therefore be routinely performed in such patients.

Delayed hemolysis following artesunate therapy may be observed especially in nonimmune patients who have recovered from severe malaria.

Exchange Blood Transfusion[2,6]

The role of exchange transfusion in falciparum malaria is controversial.

The rationale for exchange transfusion is that it decreases parasite load, decreases antigen and toxin load, and improves the deformability of RBCs. However, it requires intensive nursing care and requires a relatively large volume of blood, and the procedure carries significant risks. There is therefore no consensus recommendation regarding the use of exchange blood transfusion (EBT). The Artemisinin derivatives decrease the parasitemia quite rapidly, the role of EBT is therefore likely to be even more limited in patients who are receiving artesunate.

Severe Malaria in Pregnancy

Malaria in pregnancy tends to be more severe. Pregnant women with severe falciparum malaria are also more prone to hypoglycemia and pulmonary edema. Postpartum bacterial infection is quite common.

Artesunate is now the drug of choice in all trimesters. These drugs should be combined with clindamycin in order to prevent relapse/resistance.

Severe Vivax Malaria[7]

Vivax malaria which was thought to be a benign infection is now reportedly causing severe complications, commonly—ARDS, cerebral malaria, severe anemia, severe thrombocytopenia and pancytopenia, jaundice, splenic rupture, acute renal failure.

The definition of severe vivax malaria is the same as that for severe falciparum malaria except that there are no parasite density thresholds.

The reasons why vivax malaria has changed its behavior are not fully clear. Management of severe vivax malaria should be the same as for complicated falciparum malaria. The patient can be switched to oral chloroquine once stable and should be prescribed primaquine later (after checking G6PD levels).

Orcid

Ashit Hegde https://orcid.org/0000-0003-4342-122X

References

1. Pasvol G. Management of severe malaria: interventions and controversies. Infect Dis Clin North Am 2005;19(1):211–240. DOI: 10.1016/j.idc.2004.10.007.
2. WHO Guidelines for malaria. Geneva: World Health Organization; 2021.
3. Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366(9487):717–725. DOI: 10.1016/S0140-6736(05)67176-0.
4. Cheng MP, Yansouni CP. Management of severe malaria in the intensive care unit. Crit Care Clin 2013;29(4):865–885. DOI: 10.1016/j.ccc.2013.06.008.
5. Marks M, Gupta-Wright A, Doherty J, Singer M, Walker D. Managing malaria in the intensive care unit. Br J Anaesthesia 2014;113(6):910–921. DOI: 10.1093/bja/aeu157.
6. Riddle MS, Jackson JL, Sanders JW, Blazes DL. Exchange transfusion as an adjunct therapy in severe *Plasmodium falciparum* malaria: a meta-analysis. Clin Infect Dis 2002;34(9):1192–1198. DOI: 10.1086/339810.
7. Rahimi BA, Thakkinstian A, White NJ, Sirivichayakul C, Dondorp AM, Chokejindachai W. Severe vivax malaria: a systematic review and meta-analysis of clinical studies since 1900. Malar J 2014;13:481. DOI: 10.1186/1475-2875-13-481.