GUIDELINES

ISCCM Position Statement on the Management of Severe Malaria in Intensive Care Unit

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Abstract

Malaria is a worldwide health concern, but a great majority of cases occur in tropical countries like India. With almost 95% of Indian population living in malaria endemic regions, India contributes to most of the global malaria cases and deaths, outside of African countries. Despite significant advances towards malaria control and eradication, mortality associated with severe malaria remains particularly high. Changing epidemiology, vulnerable patient population, overlapping symptomatology, and limited availability of parenteral preparations of artemisinin derivatives pose significant challenges in management of severe malaria. Further, the dearth of large-scale randomized trials from the developing countries makes it difficult to establish evidence-based guidelines pertaining to their situation. Thus, this position paper aims to provide guidance to critical care physicians across the country on managing patients with severe malaria in intensive care units (ICUs).

Keywords: Antimalarials, India, Intensive care, *Plasmodium falciparum*, Severe malaria.

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Introduction

Malaria is a significant public health issue in India. India accounts for 66% of malaria cases in South East Asia and along with Indonesia, accounts for 94% of all malarial deaths in the region.[1] The majority of cases of malaria admitted to intensive care units (ICUs) are due to *Plasmodium falciparum* but the incidence of severe malaria secondary to *Plasmodium vivax* infection is also steadily increasing. This position statement has been created with a view to help clinicians handle the various aspects of severe malaria.

Methodology

A group of 10 intensivists, who regularly dealt with severe malaria in their clinical practice, were nominated by the Indian Society of Critical Care Medicine (ISCCM) for framing this position statement. Each member was assigned sub-topics by the heads of the committee. Each of the members reviewed the literature dealing with the topics, as assigned to them, and prepared a summary. Clinical practice statements were made based on the level of evidence available. These statements were vetted and edited by the heads of the committee and the final position statement was composed.

Presentation of Severe Malaria

Severe malaria, like other tropical infections usually presents as an acute severe undifferentiated illness. The term "acute undifferentiated febrile illness (AUFI)," implies a fever lasting for more than 14 days with no sign of organ or system specific aetiology.[2] Patients with severe malaria tend to have anemia, normal or low white blood cell (WBC) counts, thrombocytopenia, alteration in liver function tests, and may also have abnormalities in the renal function tests.[3,4]

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Clinical Practice Statement

Malaria should be suspected in every patient admitted to the ICU with a severe undifferentiated febrile illness:

Diagnosis of Malaria

Peripheral Smear Examination

An examination of the peripheral smear, including thin and thick smears, is the standard test for the diagnosis of malaria. The thick smear can detect low levels of parasitemia, detect reappearance of circulating parasites during a relapse or recrudescence, and help in detecting other coexisting hematological diseases or abnormalities. The sensitivity of thick smear is 20–40 more than that of thin smear.[4] However, it cannot differentiate between alive and dead organisms. The overall sensitivity and specificity of microscopic techniques are 42.7 and 99%, respectively.[5] It is estimated that 50–500 parasites/μL of blood can be detected through microscopy.[6] Morphology of the parasites is preserved in thin films and so species identification is easier. The thin film is also better for monitoring the response to treatment. However, an experienced and diligent technician is required to prepare and examine the peripheral blood smears, who may not be easily available.[7–9]

Rapid Diagnostic Tests (RDTs)

These tests may detect either plasmodium genus only or may detect *P. falciparum* or *P. vivax* depending on the target antigen. The common antigens that are detected are either Histidine-rich Protein2 (HRP2) for *P. falciparum* (*Pf* HRP2) or aldolase (for all species) or Plasmodium lactate dehydrogenase (pLDH) for all species or for specific detection of *P. vivax* (PvLDH) or *P. falciparum* (PfLDH).[10] The average sensitivity of *Pf* HRP2-detecting RDTs was 95.0% and the specificity was 95.2% (93.4–99.4%).[11]

The advantages of the RDT are that they can detect multiple species, the results are available very quickly, and they are simple tests which do not need much expertise to perform. However, the sensitivity of these tests may decrease due to a low parasite density. As the critically ill patients with severe malaria are unlikely to have low parasite density, these tests can be effectively applied in these patients.

Both RDT and microscopy must be performed in every patient with suspected malaria. In a patient admitted to the ICU, it is very unlikely that both the RDT and peripheral smear examination will be negative. If, however, both the tests are negative and the clinical suspicion of malaria remains high, both the peripheral smear and RDT (using another antigen) may be repeated. In cases of severe malaria with hyperparasitemia, paradoxically the sensitivity of these tests may decrease because of exhaustion of antibodies (prozone phenomenon).[10] They cannot provide quantitative information regarding parasite density and also cannot differentiate between a new infection or recently treated infection because of persistent antigenemia.[10]

Molecular Tests

Nucleic acid tests like polymerase chain reaction (PCR) can detect 0.02–1 parasite/μL. The PCR tests have the highest sensitivity and specificity compared with all other tests, especially in very early phase and inadequately treated malaria. These tests, however, are more commonly utilized in reference laboratories or for research or epidemiological purposes. The molecular tests should be done in cases of diagnostic difficulties rather than routinely.[8,9]

Table 1: Definition of severe malaria as per the WHO

Presence of one or more of the following:
Impaired consciousness
Prostration
Multiple convulsions
Acidosis
Hypoglycemia
Severe malarial anemia
Renal impairment
Jaundice
Pulmonary edema
Significant bleeding
Shock
Absence of an identified alternative cause
***P. falciparum* asexual parasitemia > 10%**

Clinical Practice Statements

- Both, a peripheral smear examination (including thin and thick smears) and an RDT should be done for confirming the diagnosis of malaria in a suspected case.
- The results of a positive RDT should always be confirmed by a peripheral smear examination.
- RDT should not be used to monitor response to therapy or to diagnose a relapse of malaria.
- Routine use of molecular tests (like PCR) should not be done to diagnose malaria in the ICU.
- Empiric treatment of severe malaria should not be initiated when peripheral smears and RDT are negative for malaria.

Definition of Severe Malaria

The World Health Organization (WHO), defines severe *falciparum* malaria as the presence of one or more clinical signs and symptoms suggestive of malaria, along with documentary evidence of *P. falciparum* asexual parasitemia, with no other identified alternative cause (Table 1).[7] The degree of parasitemia and coexisting organ dysfunction are clinically important. Some cases may have severe organ dysfunction in spite of moderate parasitemia as most of the parasites may get sequestered in the microcirculation. The infestation rate alone might be misleading in such cases.[12]

Clinical Practice Statements

- WHO criteria be used to define severe malaria.
- All patients who meet the criteria for severe malaria should be admitted in ICUs for monitoring and treatment.
- The Infestation Rate alone should not be used as a marker of severity.

Drug Treatment of Severe Malaria

Artesunate remains the treatment of choice for adults (even pregnant women), and children.[8] As compared with quinine, use of artesunate has been associated with a 35 and 22% reduction in case fatality rates in adults and children, respectively.[13]

Sodium bicarbonate is added to artesunic acid powder for preparing artesunate for injection, which is then given by a slow IV push or by the intramuscular (IM) route in the anterior thigh region. As artesunate is unstable after reconstitution, it should not be given as an infusion but given as a slow IV bolus over 1–2 minutes.

Table 2: Dosage and side effects of drugs used in severe malaria

Drug	*Route of administration*	*Dosage*	*Side effects*	*Comments*
Artesunate	Slow IV push or IM	2.4 mg/kg stat, 12, 24 hours, thereafter 2.4 mg/kg daily for a maximum of 7 days	Fever, hemolysis, confusion, seizures, agitation, coma	No dose adjustments required in patients with hepatic or renal impairment
Artemether	IM	Loading dose: 3.2 mg/kg Maintenance dose: 1.6 mg/kg daily. Administer a dose at 0, 8, and 24 hours	Abdominal pain, fever, arrhythmias, headache	No dose adjustments required in patients with hepatic or renal impairment
Quinine	IV/IM	Loading dose: 20 mg/kg Maintenance dose: 10 mg/kg	Blurred vision, blindness, hypoglycemia, confusion, anxiety	Dose adjustment required for patients with renal impairment
Artemether + Lumefantrine	Oral	First-line 3-day schedule; Patients ≥ 35 kg: 4 tablets (artemether 20 mg and lumefantrine 120 mg at 0 and 8 hours on day 1, every 12 hours on days 2 and 3)	Fever, chills, abdominal pain, dizziness, headache, arrhythmias	After parenteral therapy of at least 24 hours, and the patient is stable to tolerate orally
Artesunate + Amodiaquine	Oral	Artesunate 4 mg/kg (range 2–10 mg/kg) and amodiaquine 10 mg/kg (range 7.5–15 mg/kg) once daily for 3 days Patients ≥ 35 kg: 200 mg + 540 mg	Vomiting, fatigue, anorexia, skin rash, itching	
Dihydroartemisinin (DHA) + Piperaquine	Oral	DHA 2 mg/kg and piperaquine 16 mg/kg once daily for 3 days 36 kg–<60 kg: 120 mg = 960 mg 60 kg–<80 kg: ≥80 kg	Headache, dizziness, abdominal pain, diarrhea, fever	

The IV/IM dosage is 2.4 mg/kg stat, to be repeated after 12 and 24 hours, and then 2.4 mg/kg daily. Artesunate is remarkably well tolerated and has no significant cardiovascular toxicity. The IV artesunate should be given for a minimum of 24 hours (Table 2). Once the patient is hemodynamically stable and able to consume oral drugs, the patient may be shifted to an oral Artemisinin Combination Therapy (ACT). The preferred drug is Artemether/Lumefantrine twice daily for 3 days.

For artemether, only IM preparation is available which has to be administered in the anterior thigh, in a dosage of 3.2 mg/kg stat followed by 1.6 mg/kg/d after 24 hours (Table 2). However, its absorption from the IM injection may be erratic.

Quinine should be prescribed only in those rare situations, where both artesunate and artemether are either not available or there is a history of artesunate-induced anaphylaxis.[7] Quinine may be given as a rate controlled IV infusion or an IM injection. However, it should never be given as a bolus injection as it may lead to death due to severe hypotension or ventricular arrhythmias. It may also commonly lead to hypoglycemia; hence blood glucose levels must be closely monitored. The initial dosage of quinine is 20 mg/kg salt, followed by 10 mg/kg salt 8 hourly.

Artesunate clears parasites very quickly. Addition of quinine to artesunate only increases toxicity without increased efficacy.[7] There is no role for IV combinations in the initial management of severe malaria. A second drug is added to artesunate only to prevent relapse and resistance and not for faster clearance of parasitemia. A minimum of 24 hours of parenteral treatment is recommended. Stable patients may be switched to oral therapy after at least 1 day of parenteral therapy. The oral therapy should preferably consist of ACT.[7]

Dose adjustment of artemisinin derivatives is not required in patients with renal or liver dysfunction. On the other hand, in patients with severe organ dysfunction, quinine may accumulate and hence in presence of acute renal or liver dysfunction, quinine dosage has to be reduced by one-third after 48 hours. However, dose reduction may not be required for patients on renal replacement therapy.[14]

Clinical Practice Statements

- IV/IM artesunate be used as the preferred drug for the treatment of severe *falciparum* malaria.
- Weight-based doses, rather than fixed doses, of artesunate be used for the treatment of severe malaria.
- The IV artesunate be administered as a slow IV push rather than as an infusion.
- The IM artemether be used as the drug of second choice, if artesunate cannot be used for any reason.
- Quinine should not be used routinely, either alone or in combination with artesunate, in the management of severe *falciparum* malaria.
- At least 24 hours of parenteral antimalarial therapy should be given before switching to oral therapy.
- Oral therapy should always consist of combination therapy in order to prevent a relapse.

Hemodynamic Monitoring

Patients with severe *falciparum* malaria are vulnerable to both acute kidney injury (AKI) and to pulmonary edema. Careful attention must be paid to fluid balance to avoid both overhydration and underhydration.[15] Aggressive fluid resuscitation must be considered only in hypotensive patients with a clear history of fluid losses secondary to severe vomiting, diarrhea or bleeding. Lactate levels

may be high in severe *falciparum* malaria due to plugging of the microvasculature by the parasitized red blood cells (RBCs). High lactate levels in this situation do not necessarily indicate inadequate resuscitation and it may be misleading to use them as end-point of resuscitation.[15,16]

Clinical Practice Statements

- In patients with severe *falciparum* malaria, a careful consideration of fluid balance and avoidance of both over- and under-hydration should be done.
- In patients with severe *falciparum* malaria, serum lactates must be used cautiously as end point of resuscitation.

Exchange Transfusions in Severe *Falciparum* Malaria

Exchange transfusions (ET) were often used in the past for treating severe *falciparum* malaria. It was thought that ET would rapidly lower the patient's parasite burden and remove infected cells and toxic by-products. This procedure, however, needs aggressive nursing care, and involves transfusion of comparatively large volumes of blood with all inherent risks.[17] Further, there exists no agreement on the indications, benefits, and dangers involved, or the blood volume which must be exchanged. Current evidence does not show any significantly improved outcomes and thus it is not recommended as a routine treatment option.[7,18]

Clinical Practice Statement

- Routine use of ET in patients suffering from severe *falciparum* malaria and hyperparasitemia is not indicated.

Severe *Falciparum* Malaria with Coinfections

Any of the tropical infections like dengue, scrub typhus, leptospirosis, and severe typhoid can present with various combinations of hepatic dysfunction, renal dysfunction, altered sensorium and thrombocytopenia and may mimic severe malaria. Sometimes, these infections may even coexist with malaria.[18] Patients who do not respond to appropriate antimalarial treatment should be tested for coinfections with other organisms causing tropical infections. Serological tests for the diagnosis of tropical infections must, however, be interpreted with caution because these tests may often be falsely positive in patients with malaria.[18]

Bacterial infections may also coexist with malaria. Tissue ischemia in the gastrointestinal tract due to impaired mucosal barrier function and bacterial translocation is deemed to be the most important mechanism of bacterial co-infection.[19,20] Coexisting bacterial infections are more likely in patients with a high degree of parasitemia. Bacterial infection should also be considered in patients with a low infestation rate who have severe organ dysfunction. Procalcitonin levels might not reliably predict the presence of bacterial infections, in patients with severe malaria.[19,20] Hence, blood cultures must be sent in all patients with severe malaria. Patients who present with shock, which does not respond quickly to adequate resuscitation and antimalarial treatment, should be treated with broad spectrum antibiotics pending results of culture.

Clinical Practice Statements

- In patients who do not respond to appropriate antimalarial therapy, we suggest testing for co-infection with other tropical infections.
- Blood cultures should be sent in all patients with severe malaria.
- Procalcitonin should not be used to diagnose bacterial coinfections in patients with severe malaria.
- Empiric broad spectrum antibiotics covering gram-negative infections must be instituted in patients with severe malaria who present with shock which does not respond quickly to adequate resuscitation and prompt antimalarial treatment.

Pulmonary Complications of Severe Malaria

Acute respiratory distress syndrome (ARDS) remains the most significant reason for respiratory distress and hypoxemia in patients with severe *falciparum* malaria. Mild to severe ARDS may present as part of the spectrum of multiorgan dysfunction syndrome (MODS) or might be the primary complication and frequently develop within a few days of initiating treatment when parasite levels are reducing.[21,22]

Parasitized RBCs get sequestered in the pulmonary microcirculation initiating lung damage through direct endothelial activation and recruitment of inflammatory mediators, which can linger even after initiation of antimalarial agents. The development of acute lung injury (ALI) or ARDS in spite of reducing parasitemia or after parasites have been cleared, suggests a post-treatment inflammation as a contributory reason.[22] Though ARDS is the most likely cause of respiratory distress and hypoxia in a patient suffering from severe malaria, true fluid overload, aspiration pneumonia, bacterial pneumonia, severe metabolic acidosis, and anemia-induced cardiac failure must be considered in the differential diagnosis.[22]

The ARDS due to malaria usually resolves quickly, therefore, a closely supervised trial of high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) may be done in patients with mild or moderately severe ARDS. Patients with severe ARDS or patients who have evidence of failing an HFNC/NIV trial should be intubated and ventilated without delay. The principles of mechanical ventilation of a patient with ARDS due to malaria are more or less similar to the principles of management of ARDS of other etiologies. However, permissive hypercapnia may worsen cerebral edema in unconscious patients suffering from cerebral malaria and such patients may need more advanced neuromonitoring.[21,22] Fortunately, the occurrence of cerebral malaria in adults is becoming increasingly rare these days.

Clinical Practice Statements

- A carefully supervised trial of HFNC/NIV may be initiated in patients with mild or moderately severe ARDS due to malaria.
- Patients who have severe ARDS should be intubated and mechanically ventilated.
- Patients who have signs of failing a closely supervised HFNC/NIV trial should undergo intubation and mechanical ventilation without delay.
- All patients who are undergoing mechanical ventilation for ARDS due to severe malaria should be ventilated as per the usual lung protective strategies.

Acute Kidney Injury in Malaria

As per the estimates, AKI with serum creatinine >3 mg/dL occurs as a complication of severe malaria in <1% of patients, but the mortality rate in such cases can be as high as 45%. Further, AKI has been shown to be an independent predictor of a poor outcome.[23]

Table 3: Basic management of malaria-induced acute kidney injury

1. Appropriate antimalarials (parenteral artesunate preferably).
2. Fluid electrolyte management with careful monitoring to prevent both underhydration and overhydration.
3. Use of diuretics should be avoided.
4. Use of acetaminophen in adults with moderate to severe malaria may be renoprotective.
5. Renal replacement therapy should be considered early in AKI treatment, with hemodialysis being more effective modality.

Kidney dysfunction may range from mild proteinuria to severe azotemia along with metabolic acidosis. Renal dysfunction can present as oliguric or non-oliguric renal failure and as a primary complication or as a part of MODS.[23]

The parasite-infested RBC's are inclined to get attached to healthy erythrocytes, platelets, and capillary endothelium, causing development of rosettes and clumps, impairing microcirculation. This may result in renal injury, especially in those patients who are volume depleted or have hemodynamic instability. Activation of endothelial cell causes release of catecholamines, cytokines, thromboxane, endothelin, and other inflammatory mediators which may also contribute to development of malaria-associated AKI.[23] Several other factors may also contribute to the development of such complications, including hypovolemia, vasoconstriction, and hemolysis which may result in hemoglobinuria, parasitemia, deposition of immune complexes in glomeruli, and dysfunctional microcirculation.[23]

It is postulated that acetaminophen may reduce plasma cell-free hemoglobin-mediated oxidative renal damage. Hence, its effect may be more pronounced in patients with severe intravascular hemolysis and high levels of oxidative stress markers and may be useful in preventing development of AKI and reduce the need for RRT.[24]

A recent study showed that 31% malaria-associated AKI cases had normal creatinine levels at the time of presentation. Data suggest that NGAL may be a better biomarker for the diagnosis of malaria-associated AKI.[25] The basic management principles for malaria-induced AKI are given in Table 3.[23,25] Dialysis may be necessary in 46–76% of severe cases, and complete kidney function recovery may occur in up to 64% of patients with *P. falciparum* or *P. vivax* malaria-associated AKI.[26]

Clinical Practice Statements

- Early administration of appropriate doses of artesunate should be initiated to prevent and treat renal dysfunction in patients with severe malaria.
- Dose reduction for artesunate in patients with renal dysfunction is not required.
- Careful monitoring of cases with severe malaria and renal dysfunction should be done to avoid both over- and under-hydration.
- Diuretics should be avoided in severe malaria patients with renal dysfunction.
- Acetaminophen may be used as a renoprotective agent in severe malaria.
- The RRT be instituted early in cases with severe malaria and AKI, if they meet the standard criteria for initiation of RRT.

Coagulopathy in Severe Malaria

Patients with severe malaria often have defects in coagulation. In these patients, bleeding results from a combination of factors including consumptive coagulopathy, thrombocytopenia, and impairment of synthesis of clotting factors.[27] Bleeding is usually a late manifestation of the disease and is usually associated with hyperparasitemia and kidney, lung or liver complications. Disseminated intravascular coagulation (DIC) has been reported in up to 30% of cases of severe *falciparum* malaria and is an indicator of poor prognosis.[28]

Patients with *P. falciparum* infection along with DIC may also develop symmetrical peripheral gangrene (SPG) and purpura fulminans.[29] This is due to activation of coagulation, a decrease in concentrations of protein C, protein S and antithrombin and impaired fibrinolysis. Endothelial cell activation, and a decrease in serum ADAMTS13 function, may contribute to the hypercoagulable state in severe malaria. Eradication of the malarial parasites quickly reverses the hemostatic changes seen in malaria. The most important part of the management of coagulopathy secondary to malaria is, therefore, the initiation of effective antimalarial therapy. Blood products should be administered to patients with severe DIC and spontaneous systemic bleeding.[30,31]

A study in Thailand has shown that ET improved survival in patients who presented with severe parasitemia (>30%) and DIC.[32] However, the usage of exchange transfusion for severe *falciparum* malaria is still controversial and not routinely recommended.[7] Corticosteroids should not be prescribed for thrombocytopenia but heparin may be cautiously used in patients with DIC and, purpura fulminans or acral ischemia.[7]

Clinical Practice Statements

- Prompt commencement of adequate doses of effective antimalarial drugs is the main therapy for severe malaria and coagulopathy.
- In cases of severe malaria and DIC with systemic bleeding, administration of blood products guided by results of laboratory tests of coagulation is advocated.
- Cautious administration of heparin to patients with DIC and purpura fulminans or acral ischemia.
- Exchange transfusion be tried only as a salvage measure in patients with high parasitemia (>30%) and severe DIC.
- Corticosteroids should not be used for the management of thrombocytopenia in severe malaria.

Neurological Manifestations

Severe malaria affecting the brain results in diffuse cerebral edema. This edema is due to hypoxia of the neurons secondary to blocking of the microvasculature by the parasitized RBCs and the neurotoxic effects of the immune host reaction. Several other neurological manifestations have been associated with malaria, including Guillain-Barré syndrome, acute disseminated encephalomyelitis, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, post-malarial neurological syndrome, malarial retinopathy, and cerebellar ataxia.[33] However, neurological involvement in severe malaria is rarely seen in adults nowadays.

There are no drugs specific for the treatment of malaria involving the central nervous system (CNS). Prompt antimalarial

therapy is the most important aspect of therapy. General care of the patient, including airway protection, is otherwise comparable to the general care of any other patient with a depressed sensorium. Benzodiazepines (lorazepam/midazolam) are the agents of choice for the initial management of seizures. Phenytoin is preferably avoided in cases with severe malaria as it may contribute to hemodynamic instability. Prophylactic anticonvulsants should not be used. Mannitol and corticosteroids have not been shown to be beneficial in the management of the cerebral edema in severe malaria with CNS involvement.[33,34]

Clinical Practice Statements

- Rapid IV administration of antimalarial drugs should be initiated for the management of severe malaria with CNS involvement.
- General care of the unconscious patient with severe malaria (including airway management) be no different than the usual general care of an unconscious patient of any other cause.
- Prophylactic antiepileptic drugs should not be initiated in patients with severe malaria and CNS involvement.
- IV benzodiazepines are the first drugs for control of seizures in patients with severe malaria and CNS involvement.
- Steroids and mannitol should not be used for the management of cerebral edema in patients with severe malaria and CNS involvement.

Metabolic Complications

In severe malaria, hypoglycemia and lactic acidosis are important prognostic markers. Hypoglycemia is more common in children and in pregnant patients. It is probably due to an increased glucose turnover. Quinine induces hyperinsulinemia, and therefore, hypoglycemia was much more common in the past when quinine was the primary drug for treatment of severe malaria.[35] Patients with severe malaria (especially, pregnant patients, children, and those receiving quinine) should have their glucose levels monitored and should be managed immediately with intravenous glucose, in case hypoglycemia is detected.

The commonest cause for hyperlactatemia in severe malaria is perhaps the increased anaerobic glucose metabolism, secondary to widespread microvascular sequestration of parasitized RBSs which reduces tissue blood flow. The metabolism of the intraerythrocytic parasites, and impaired lactate clearance by the liver and kidney may also contribute to increased lactate levels. The etiology of increased lactates in severe malaria is, therefore, multifactorial and resuscitation guided by lactate levels might lead to over resuscitation.[17] Except for the prompt administration of antimalarial medication, there is no proven treatment for the management of severe lactic acidosis in malaria. Soda-bicarbonate might be beneficial in patients with severe metabolic acidosis (pH below 7.1 and bicarbonate below 6 mEq/L) or in patients with coexisting AKI.[36]

Clinical Practice Statements

- Closely monitor blood glucose levels in all patients with severe malaria.
- Blood glucose levels of children, pregnant patients, and patients receiving quinine should be monitored even more intensely.
- Serum lactate levels should be used cautiously to guide resuscitation.
- Prompt administration of appropriate doses of antimalarial drugs (preferably IV artesunate), as the primary treatment of severe lactic acidosis in malaria.
- Soda-bicarbonate may be administered to patients with severe malaria and severe lactic acidosis (pH <7.1 and bicarbonate <6 mEq/L).
- Soda-bicarbonate may be administered to patients with severe malaria who have significant lactic acidosis and AKI.

Splenic Rupture in Malaria

Spontaneous splenic rupture is a rare but dreaded complication of severe malaria. It is more common in *vivax* malaria.[37] It usually manifests with severe abdominal pain, tachycardia, and hypotension, while a patient is being treated for malaria. The diagnosis is confirmed on an ultrasound or CT scan. While an emergency splenectomy was advised as the standard treatment for a splenic rupture in the past, a conservative approach, including antimalarials, intravenous fluids and organ support, is now being advocated as splenectomy has several long-term complications, including vulnerability to severe malaria. Splenectomy should, therefore, now be considered as a last resort.[38]

Clinical Practice Statements

- Appropriate investigations should be instituted to diagnose or rule out a splenic rupture in a patient with severe malaria who has severe abdominal pain, tachycardia, and hypotension.
- An initial conservative approach to the management of splenic rupture in a patient with severe malaria.

Severe Malaria and Pregnancy

Malaria during pregnancy can lead to poor birth outcomes like spontaneous abortion, preterm delivery, growth restriction, stillbirth, congenital infection, neonatal mortality, and maternal anemia. Maternal mortality can be as high as 50%.[39]

Erythrocytes infected with the parasite are sequestered in the intervillous space. This erythrocyte adherence reduces the uteroplacental blood flow affecting the oxygen supply, and nutrient supply to the fetus resulting in fetal demise or fetal growth abnormality. The parasitemia of severe malaria can sometimes be less than 2%, because of sequestration of the parasites in the placenta. Pregnant women with higher than 2% parasitized RBCs are at increased risk of developing severe malaria and should be managed as per the severe malaria protocol.[39]

Treatment of Severe Malaria in Pregnant Patients

Parenteral artesunate is the therapy of choice in all trimesters of pregnancy.[40,41] Artemisinin-based therapies have been shown to be safe and effective even in the first trimester of pregnancy with no evidence of embryotoxicity or teratogenicity. They are better tolerated and more efficacious than quinine and hence should be preferred.[36] As per the WHO, quinine may be used as an alternative for managing severe malaria when artesunate or artemether are unavailable or contraindicated.[5] When the patient is able to tolerate oral medications, she can be switched over to a 3-day course of artemether (80 mg) and lumefantrine (480 mg) or alternatively, a 7-day course of quinine and clindamycin (450 mg) three times a day is recommended.[5]

Severe Malaria-related Complications in Pregnancy

Hypoglycemia can be profound and persistent, and in some cases, a life-threatening complication, which should be treated promptly. Hypoglycemia is more likely in patients treated

with quinine. Secondary sepsis should be considered in cases with severe malaria and hypotension despite adequate fluid resuscitation and antimalarial therapy. Women who are severely anemic (Hb <8 gm%) should be transfused packed RBCs slowly and intravenous frusemide 20 mg might be co-administered in order to prevent fluid overload.[42] The ARDS and refractory hypoxemia should be managed as per the usual lung protective strategies.[42]

Clinical Practice Statements

- Parenteral artesunate be used as the agent of first choice for the initial management of severe malaria during all the three trimesters of pregnancy.
- Artemether may be used as an alternative for the initial management of severe malaria during all the three trimesters of pregnancy.
- Quinine must not be prescribed for the management of severe malaria in pregnancy, except in those rare situations where the artemisinin derivatives are not available or are not tolerated.
- A pregnant patient with severe malaria be switched to oral artemether plus lumefantrine once she is stable.
- Close monitoring of glucose levels and prompt treatment of hypoglycemia to be done in a pregnant patient with severe malaria.
- A low threshold for diagnosing secondary bacterial infection to be kept in a pregnant patient suffering from severe malaria who does not respond quickly to antimalarial treatment.

Severe *Vivax* Malaria

Historically, malaria caused by *P. vivax* was considered less severe than that caused by *P. falciparum*. However, recent studies and systematic reviews have challenged this view.[43,44] Severe *vivax* malaria (SVM) is defined in the same way as WHO has defined severe *falciparum* malaria, except for the infestation rate criterion.[7]

A systematic review and meta-analysis revealed a substantial proportion of patients with severe manifestations of *vivax* malaria across various countries, with a notable proportion of cases reported from India.[45] In a trial from a tertiary care center in Mumbai, of the 711 patients admitted with severe malaria 488 (68.53%) patients had severe *vivax*. Thrombocytopenia (89.1%) was reported as the commonest complication. Kidney (32%), liver (19.5%), neurological (8.2%), and lung (1.6%) involvement were also observed. The mortality reported in patients with SVM was 9% (44/488), whereas in patients with *falciparum* malaria it was 16.1% (80/223).[43]

In a review of 162 studies dealing with SVM in India, the pooled proportion of SVM was 29.3%.[44] Severe anemia, jaundice, severe thrombocytopenia and MODS were the main features of severity in this review. Myocarditis was more common in patients with SVM in comparison to *falciparum* malaria. Among the patients hospitalized with SVM, the mortality ranged from 0 to 12.9%.[45] The treatment of SVM and its complications is no different than that of severe *falciparum* malaria.[7]

Clinical Practice Statements

- The WHO criteria for defining severe *falciparum* malaria (excepting Infestation Rate) be applied to define SVM as well.
- The treatment of SVM and its complications is similar to that for severe *falciparum* malaria.
- All patients with SVM be prescribed a course of primaquine after recovery in order to prevent a relapse.

Conclusion

In tropical countries like India, malaria still constitutes a significant health problem. Certain patient populations, including pregnant females, are particularly vulnerable to develop severe disease requiring ICU care. If timely therapeutic interventions are not instituted, severe malaria may be associated with significant morbidity and mortality. Involvement of cardiac, CNS, respiratory or renal systems may further complicate the clinical course of these patients. Management of these complications is largely supportive, along with antimalarial therapy. Intravenous artesunate remains the drug of choice for managing severe malaria, which has been shown to be safe and efficacious, even in pregnant patients.

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