REVIEW ARTICLE

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Severe Malaria

ABSTRACT

Tropical infections accounts for 20–30% of ICU admissions in the tropics. *Plasmodium falciparum* is responsible for most of the cases, though recently, *Plasmodium vivax* is increasingly found to be implicated in severe malaria. Cerebral malaria is more common among children, the severe malaria in adults presents with multiorgan failure such as thrombocytopenia, acute respiratory distress syndrome, acute kidney failure, coagulopathy, encephalopathy, and features of liver injury. A secondary bacterial infection in this clinical setting is not uncommon and may contribute to poor outcome. Several metabolic anomalies such as lactic acidosis, hyponatremia, and hypoglycemia may be invariably seen. Aggressive intensive care management, namely, fluid resuscitation, immediate appropriate drug therapy, correction of metabolic irregularities, vasopressors along with blood, and component therapy determines favorable outcomes. Quinine which was the mainstay of therapy over many decades has now been replaced with more effective and safer artesunate or artemisinin-centered combination therapy.

Key words: Artemisinin, Artesunate, Malaria and pregnancy, *Plasmodium falciparum*, *Plasmodium vivax*, Quinine, Severe malaria

INTRODUCTION

Severe malaria is not unusual in India and is by and large seen with *Plasmodium falciparum*, nevertheless of late has been documented with *Plasmodium vivax* too. Malaria is due to a protozoal infection that is spread by the bite of an infested female Anopheles mosquito. Malaria is endemic in Africa, Asia, South America, Central America, and Australasia, and has been registered in 91 countries.[1] In India, the incidence of severe malaria is declining, the large INDICAPS study was conducted in 124 ICUs across India, which recruited 4038 patients, of which 231 (5.7%) patients had tropical infections with only 1.1% due to malarial parasites. There are five types of malaria, *P. falciparum* accounts for 60% of the cases, most of the remaining are due to *P. vivax*. The other form of malaria are caused by *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*, they account for 1% of the cases.[2] The WHO registered over 229 million malaria cases across endemic areas around the world. The likely deaths were about 4 lakhs in the same year. Children under the age of 5 years are clearly the most susceptible group and they were responsible for 67% of deaths globally. The region of sub-Saharan Africa is where 94% of malaria cases and deaths occur. In India, malaria is a public health challenge in several parts of our country. Nearly 95% of the population in India resides in areas that are endemic to malaria and 80% of malaria cases reported here are limited to regions comprising the 20% of the population residing in tribal and rural areas with limited access to medical facilities [Figure 1].

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PARASITOLOGY

Sporozoites enter the human bloodstream following a bite of an infected mosquito. The parasite invades the liver goes through a pre-erythrocytic stage develops into hepatic merozoites over 1–2 weeks following which it enters the circulation. Mature merozoites released into the blood undergo an asexual intraerythrocytic sequence which lasts for 48 h in both *P. falciparum* and *P. vivax*, leading to ring-like schizonts. These infected erythrocytes with schizonts rupture and release several daughter merozoites all of which infect fresh erythrocytes, leading to the clinical manifestation of the disease. A proportion of the parasites develops into female and male gametocytes. These are then transmitted to a fresh mosquito following a bite and ingestion of the infected blood. Male and female gametes subsequently fuse to form a zygote in the midgut of the mosquito, where it becomes an ookinete that penetrates through the wall of the gut. The oocyst then let loses sporozoites which find their way to the salivary glands of

the mosquito, thereby carrying out the lifecycle. In both vivax and ovale, a section of the sporozoites remains quiescent in the liver leading to relapses later on.[3]

PATHOGENESIS

In malaria, the symptoms result when the merozoites are released into the bloodstream with a level above 100 parasites/μL. The incubation period varies between 2 and 3 weeks, usually manifesting sometimes with cyclic periodic febrile spikes.[4] A crucial facet of *P. falciparum* is cytoadherence, where the infected erythrocytes would adhere to the endothelium within the microcirculation. Both the infected erythrocytes and the uninfected cells attach to each other leading to rosetting, this process then leads to a reduction in flexibility of the erythrocytes, which subsequently leads to microvascular stagnation and occlusion of the microcirculation.[5] The parasite metabolism within the erythrocytes leads to systemic lactic acidosis and hypoglycemia. The parasite invading erythrocytes leads to hemolysis, hemoglobinuria, and cytokine activation, this network of changes leads to multiorgan failure and in severe cases death.[6] In the erythrocytic stage, *P. falciparum* adheres to the endothelial cells, in this stage, only ring forms circulate, in the peripheral blood and their concentration may be low even in the presence of severe infection.

CLINICAL FEATURES OF SEVERE MALARIA

Most cases of malaria present with high-grade fever, largely associated with chills and rigors. The fever may be recurrent or even irregular lasting for few hours followed by plenty of perspiration. Severe malaria can present clinically with headache, altered mental status, delirium, seizures disorders, acute renal failure, lactic acidosis, multiple organ failure, hypoglycemia, metabolic changes, severe thrombocytopenia, and hemolysis.[7-9] Severe malaria may lead to bacterial sepsis following translocation of bacteria from the gut, this is possibly due to hypoperfusion of the gut mucosa. The WHO definition of severe malaria is demonstrated in Table 1.

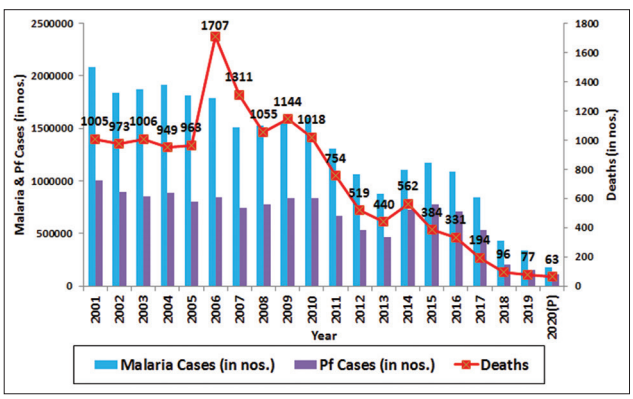

Figure 1: Figure from https://nvbdcp.gov.in/index4.php?lang=1 and level=0 and linkid=420 and lid=3699

Cerebral malaria may present with delirium, altered sensorium, and epileptic seizures from an encephalopathy. Cerebral malaria is usually seen in cases of *P. falciparum* infection resulting in a coma, not necessarily due to metabolic causes or meningeal inflammation or encephalitis or following a post-ictal state with Glasgow Coma Score ≤11. Cerebral malaria typically presents with fever, headache, agitation, vomiting, meningismus, seizures, drowsiness, and coma with papilledema. Autopsies of cerebral malaria demonstrate that cerebral venules and capillaries have sequestrated red blood cells (RBCs) infected with the parasite combined with uninfected RBCs.[10] The sequestration of RBCs with the parasite within the microcirculation is responsible for all the major complications run into with *P. falciparum* which leads to cerebral malaria. The presentation of cerebral malaria is a perfusion defect, leading to microcirculatory failure.

Sepsis leading to multiple organ dysfunction may be seen with severe malaria and can be fatal. This is due to a dysregulated host response to the parasite. Severe malaria with organ failure (defined as qSOFA ≥2) has a high mortality.[11] In *P. falciparum* infection, the presence of shock is called algid malaria syndrome, which is due to adrenal insufficiency,

Table 1: Diagnosis of severe malaria (WHO criteria)[1] to make the diagnosis of severe malaria in *P. falciparum* infection, any one of the below criteria is sufficient to make the diagnosis

Feature	Definition
Impaired consciousness	GCS<11 or Blantyre coma score<3 in children
Prostration	Generalized weakness – person unable to sit, stand or walk without assistance
Multiple convulsions	>2 episodes in 24 h
Acidosis	Base deficit of>8 mEq/L, serum bicarbonate<15 mmol/L, or plasma lactate ≥5 mmol/L
Hypoglycemia	Blood or plasma glucose<2.2 mmol/L or <40 mg/dL
Anemia	Hemoglobin≤5 g/dL or hematocrit≤15% in children and hemoglobin<7 g/dL or hematocrit<20% in adults
Renal impairment	Serum creatinine>265 μmol/L or>3 mg/dL or blood urea>20 mmol/L
Jaundice	Serum bilirubin>50 μmol/L or>3 mg/dL with parasite count (number of infected RBCs) >100,000/μL
Pulmonary edema	Radiological features, hypoxemia, tachypnea, and crackles
Bleeding	Spontaneous bleeding or coagulopathy
Shock	Systolic blood pressure<70 mmHg in children and<80 mmHg in adults, cool peripheries, prolonged capillary refill
Hyperparasitemia	*P. falciparum* parasitemia>10%

P. falciparum: *Plasmodium falciparum*, RBCs: Red blood cells

myocardial dysfunction, metabolic acidosis, sepsis, or hemorrhage due to splenic rupture. In this type of vasodilatory shock, the cardiac output is high as a result of diminished peripheral vascular resistance. If this shock is not treated aggressively with fluids, vasopressors, and blood transfusions, this may lead to increased morbidity or even high mortality.

LABORATORY DIAGNOSIS FOR MALARIA

Light microscopy using thick and thin film is in fact the gold standard for the diagnosis of malaria, it not only confirms the diagnosis of malaria but also furthermore identifies the species. More recently, rapid diagnostic tests (RDTs) are now the dominant initial investigation to confirm malaria.[12] For *P. falciparum,* an RDT test using histidine-rich protein 2 (PfHRP2) antigen which may persist for several weeks even after complete effective therapy [Table 2]. A strip that identifies Pan species using lactate dehydrogenase enzyme causing malaria, while this may be not sensitive for diagnosing *P. knowlesi* species. A nucleic acid amplification test is much more sensitive (identifies one parasite/μL) [Table 2].[12]

TREATMENT OF SEVERE MALARIA

Appropriate fluid resuscitation is an integral component of treating patients with severe malaria, such patients may be severely fluid depleted needing considerable administration of fluid therapy. Severe hypovolemia is often seen in these patients and is capable of intensifying the acidosis and precipitate acute kidney failure both of which increase mortality. Too much of fluid resuscitation increases the risk of pulmonary edema which may potentially be fatal. The optimal quantity and nature of fluid used for resuscitation still continue to remain uncertain. Colloid solutions may be potentially detrimental and should largely be avoided. Crystalloid is usually the preferred infusion, however, the best resuscitative fluid and the possible role of a balanced solution are uncertain.[13] Hypoglycemia which is regularly encountered should be appropriately treated with IV 25% dextrose infusions. As the result of hemoglobin falling below 7 g/dl, blood transfusions must be administered. In the event, of multiorgan failure and severe metabolic acidosis, appropriate organ support should be initiated. This includes mechanical ventilation in acute lung injury, renal replacement therapy in acute renal failure, suitable fluids, vasopressors and inotropes in the presence of hemodynamic instability, and proper component therapy if disseminated intravascular coagulopathy is present. Cerebral malaria may present with seizures, this must be contained with benzodiazepines, if it persists, then long-acting anticonvulsants may be added. Patients will need mechanical ventilation in the event of severe drowsiness, to protect the airway and prevent aspiration, with a nasogastric tube for enteral nutrition support *in situ*.

As soon as severe malaria is diagnosed, parenteral artesunate should be administered to the pediatric, adults, and even pregnant women in any trimester. Over the years, artesunate is notably a cut above quinine in both the larger Asian and African trials, mortality reduced in the Asian adult trial and there was a significant reduction in death in pediatric population from Africa.[14,15] Both parenteral quinine and quinidine are an alternative therapy but are linked with considerable cardiotoxicity. The drug of choice is intravenous artesunate (2.4 mg/kg/dose at 0 h, 12 h, and 24 h; following which every 24 h; in children having their body weight below 20 kg, the dose is 3 mg/kg). Artesunate is available as a powder dissolved in 5% $NaHCO_3$ forming sodium artesunate. This mixture is dissolved in 5 mL of 5% dextrose then administered intravenously (should be freshly prepared and not stored as it is unstable) or can be given intramuscularly. Artesunate swiftly eradicates the ring stage of the parasite, these red blood cells sequestrate in the spleen leading to hemolysis distinctly seen in patients with hyperparasitemia.[16] Alternatively, intravenous quinine infusion preceded by 20 mg/kg of a loading dose administered over 4 h followed by 10 mg/kg given over a 2 h period every 8 h. An intramuscular injection of artemether at a dose of 3.2 mg/kg, followed by 1.6 mg/kg every 24 hour. Once the patient is able to eat and drink oral or enteral therapy with an artemisinin-centered combination therapy (ACT) should be given for 3 days.[4] An efficient oral antimalarial ACT is a combination of artemether + lumefantrine, artesunate + amodiaquine, and dihydroartemisinin + piperaquine. If ACT is unavailable, artesunate + doxycycline, artesunate + clindamycin, quinine + doxycycline, or quinine + clindamycin may be considered.[16] Doxycycline should be avoided in pregnant women and children below 8 years of age. The

Table 2: Adapted from Clin Microbiol Rev. 2002 Jan; 15 (1):66-78 (21)

Parameter	Microscopy	PCR	Fluorescence	Dipstick HRP-2	Dipstick pLDH, ICT Pf/Pv
Sensitivity parasites/μl	50	5	50	>100	>100
Specificity	All species	All species	*P. falciparum* good, others difficult	*P. falciparum* only	P.f and *P* V good, and P.O and P.M only with pLDH
Parasitemia	Yes	No	No	Crude estimation	Crude estimation
Time for result	High	High	Moderate	Low	Low
Costs	Low	High	Moderate/low	Moderate	Moderate

P. falciparum: *Plasmodium falciparum*

ACTs clear out the parasites more swiftly than chloroquine. ACTs that have a longer half-life reduce new infections and relapses.

TREATING UNCOMPLICATED *P. FALCIPARUM* MALARIA

Less complicated *P. falciparum* malaria may be treated with one of the following ACTs: Artesunate + amodiaquine or artesunate + mefloquine or artemether + lumefantrine or artesunate + sulfadoxine-pyrimethamine, or dihydroartemisinin + piperaquine with the exception of first-trimester pregnancy. The artemisinin in the ACTs when given over 3 days includes two of the asexual cycles, which rapidly clears a large number of parasites leaving behind a small proportion of parasites to be cleared by the partner drug. This ensures that the malarial parasites do not develop drug resistance to the ACT combination.

TREATING MALARIA IN PREGNANT AND LACTATING WOMEN

Pregnant women in the first trimester having uncomplicated *P. falciparum* malaria are treated with 7 days of quinine in combination with clindamycin seem to be the safest regimen. In about 700 women with malaria during the first trimester of pregnancy when given artemisinin inadvertently did not affect the fetus or the mother, artemisinin derivatives in the second and third trimesters have been proven safe.[17,18] Tetracyclines and primaquine should never be used in pregnancy. In lactating women, the quantum of antimalarial drugs secreted in breast milk is fairly small. Tetracycline should never be used in lactating mothers, primaquine too should not be used unless G6PD deficiency has been ruled out in the infant.

TREATING UNCOMPLICATED MALARIA CAUSED BY *P. VIVAX, P. OVALE, P. MALARIAE,* OR *P. KNOWLESI*

Where chloroquine-sensitive *P. vivax* orally, an entire dose of 25 mg base/kg body weight is given. Chloroquine is administered on day 1 at 10 mg base/kg body weight, then 10 mg/kg body weight on 2 and 5 mg/kg body weight on day 3. Relapses can occur within 5–7 weeks after therapy to ensure radical cure primaquine needs to be given in patients without G6PD deficiency. ACTs are extremely efficient in treating vivax malaria. ACTs containing piperaquine, mefloquine, or lumefantrine are the recommended therapy in areas where chloroquine-resistant *P. vivax* is present. Drug resistance to *P. malariae*, *P. ovale,* and *P. knowlesi* is not well documented, these parasites are largely sensitive to chloroquine. ACTs clear parasites more effectively and quicker than chloroquine. High rates of ACT failure have now been reported from Cambodia, Thailand, and Vietnam. To prevent relapse in *P. vivax* and *P. ovale* malaria except in pregnant women or patients with G6PD deficiency, primaquine should be given for 14 days.[16] A 14-day course of primaquine reduces the relapse rates considerably. Primaquine can cause hemolysis in patients with G6PD deficiency, hence, it is important to check each patient's G6PD status before initiating primaquine. Giving one single dose of primaquine with ACT to patients with *P. falciparum* reduced gametocytes and hence protects the community.[16]

ADJUNCTIVE THERAPIES FOR SEVERE MALARIA

Adjunctive therapies such as N-acetylcysteine, pentoxifylline, and exchange transfusions have been ineffective whereas mannitol and dexamethasone have been shown to be harmful in cerebral malaria.[19,20]

OUTCOMES

Mortality due to severe malaria varies and is centered around the nature of the illness, geographical location, the kind of parasite, and presence or absence of comorbidities and differs in adults and children. About 30% mortality is reported in children with cerebral malaria and ARDS. However, with the introduction of artemisinin and derivatives, the mortality has reduced considerably.

HOW TO PREVENT MALARIA?

Prevention of malaria is by providing chemoprophylaxis to travelers when visiting endemic areas, this is primarily done by administering drugs such as sulfadoxine-pyrimethamine plus amodiaquine, atovaquone-proguanil, doxycycline, or weekly doses of mefloquine. Vaccination against malaria is undergoing trials, vector control measures such as mosquito nets, antimalarial creams, and spraying with insecticides.

CONCLUSIONS

All over the globe, *P. falciparum* malaria is predominantly to blame for most of the severe malaria cases. *P. vivax* and *P. knowlesi* can also lead to life-threatening infections needing ICU care. There has been considerable improvement in the management of severe malaria, primarily due to the availability of better drugs and significant improvement in organ support in the ICU. The initiation of artemisinin-based therapy and ACTs has changed results in all the endemic zones, but a matter of apprehension is the evolving details of artemisinin resistance. The numerous adjunctive therapies have not shown to be of use, on the contrary, some of them have been harmful. Organ support in the ICU has clearly been shown to reduce both lengths of stay and mortality. A multidisciplinary team approach, with appropriate infection control, plays an important role in improving outcomes.

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