Severe *Plasmodium falciparum* malaria

Malária grave por Plasmodium falciparum

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ABSTRACT

Malaria is one of the world's leading parasitic diseases and affects a considerably large number of people. Considering the epidemiological reach of *Plasmodium falciparum*, which is almost always responsible for the most severe cases of malaria, a discussion of the clinical features and therapeutic interventions is important. In the cases of patients with severe malaria, admission to an intensive care unit is mandatory to reduce complications. To have an impact on survival rates, treatment with antimalarial drugs and supportive measures should be initiated as quickly as possible. The aim of this article is to discuss the components of severe malaria, with an emphasis on its clinical features and treatment.

Keywords: Malaria/therapy; Malaria/diagnosis; Malaria/pathology; *Plasmodium falciparum*.

INTRODUCTION

Malaria is the world's leading parasitic disease and affects approximately 40% of the world's population (approximately 2.4 billion people) in more than 100 countries.[1] The disease, that is caused for *Plamodium* spp., particularly affects populations in tropical and subtropical areas, especially in developing and underdeveloped countries. Brazil has the largest number of cases on the American continent with an estimated 300,000 yearly cases.[2] Reporting this disease is mandatory in Brazil.

Malaria is mostly seen in Africa, the South American Amazon Region and Southeast Asia. The highest incidence of the disease is in the South Saharan region of Africa.[3] In Brazil, malaria is predominantly seen in the Legal Amazon Region, which includes the Brazilian states of Acre, Amapá, Amazon, Maranhão, Mato Grosso, Pará, Rondônia, Roraima and Tocantins.[4]

Tourists from malaria-free regions who visit areas with a high prevalence of malaria are highly vulnerable to infection for *Plasmodium* spp. when exposed to the disease. If they are not appropriately treated, they may have their diagnosis delayed upon return home. Malaria is the most frequent cause of post-travel fever and is the most common and preventable cause of infectious death among travelers.[5]

Severe malaria is caused by *Plasmodium falciparum*, a protozoan belonging to the *Sporozoa* class of the *Plasmodiidae* family whose genus

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is *Plasmodium* and whose species is *Plasmodium falciparum.* Its complex lifecycle depends on specialized protein expression within the host that determine the intra- and/or extra-cellular parasite survival, the invasion of several types of cells and the ability to bypass the host's immune response. The codification in 2002 of the *Plasmodium falciparum* genome provided the basis for comparative proteomics trials. Several studies have presented data and explored the pathophysiology of this disease along with the potential therapeutic implications.[6-11]

This disease remains an important cause of morbidity and mortality in many areas, and the severe forms of the disease require treatment in intensive care units.[12] This article is focused on the clinical and pathophysiological aspects of severe malaria with the aim of providing information concerning diagnosis and therapy.

METHODS

This article was based on a literature review. The DeCS (health sciences key words) search strategy included the keywords malaria and intensive care. The search for articles was conducted through the SciELO (Scientific Electronic Library Online) and PubMed (U. S. National Library of Medicine) databases. Textbooks were also consulted.

Seventy-nine references were selected based on their focus on the intensive care of malaria patients. The extracted information was categorized as 1) host/parasite interaction: the pathophysiological aspects; 2) clinical-pathological features; 3) diagnosis; and 4) therapy.

HOST/*Plasmodium* INTERACTION*:* THE PATHOPHYSIOLOGICAL ASPECTS

The severity of malaria depends on the interaction between the host (vulnerability and immune status) and *Plasmodium* spp. (infecting species and parasitic density). Pregnant women, children and individuals who have been infected for the first time are more vulnerable to the disease.[13]

The majority of the cases of severe malaria and deaths from malaria are caused by *P. falciparum,* although there has also been an increase in the number of reported cases of severe *Plasmodium vivax* infections.[14] However, the focus of this article is on *P. falciparum*. *P. falciparum* infections begin with the introduction of the parasite into the human body's blood stream from the bite of the female *Anopheles* mosquito. This parasite is introduced through the mosquito's saliva in the form of sporozoites (the infecting form). Some sporozoites are destroyed by phagocytes while others successfully enter the hepatocytes.[15] The sporozoites then multiply in a reproductive process called schizogony where they develop into hepatocyte schizonts.[16] After 5 to 16 days (depending on the species), each schizont will generate 10,000-40,000 merozoites that then gain access to the intrahepatic capillary vessels[17] and invade the erythrocytes.[18] Once inside the erythrocytes, the parasites are transformed into trophozoites. The trophozoites develop, undergo nuclear division and turn into blood schizonts. The divisions of the blood schizonts (schizogony) develop into 8 to 32 merozoites, depending on the species.[19,20] The infected cells are then disrupted, liberating the merozoites, which then restart the cycle and cause fever paroxysms. The blood schizogony periodicity, which varies between the species, is 36 to 48 hours for *P. falciparum.*[21]

Due to its shorter tissue cycle, higher merozoites production during tissue and erythrocyte schizogony and the ability to infect any age of red blood cells, *P. falciparum* has the potential to cause hyperparasitemia, a condition that closely correlates with the severity of the infection.[13] Additionally, *P. falciparum* is the only species that causes microcirculatory changes, which are known to contribute to worse patient outcomes.[12] The invasion of red blood cells by the protozoa progressively effects the cell membranes by changes involving the transportation properties, the exposure of surface antigens and the insertion of microorganism proteins. The surface of infected red blood cells have electrodense protrusions that easily adhere to the post-capillary venulae and capillary vessels of several organs,[22] such as the brain, lungs and kidneys. These adhesions, along with knob-like protrusions, increase the severity of the disease through the phenomenon known as cytoadherence.[23]

In addition to cytoadherence, rosettes are formed through a process known as rosetting. In this process, infected cells adhere to non-infected cells and form conglomerates that block microcirculatory flow. Both infected and noninfected red blood cells also become rigid in cases of severe malaria, which additionally affects blood flow.[24] Cytoadherence explains why only young trophozoites are visible in peripheral

blood samples. The mature trophozoites are not visible due to their microcirculatory sequestration.

The capacity of infected cells to bind to endothelial cells depends on host cells receptors, such as ELAM-1, ICAM-1, VCAM-1 and CD36. The expression of these receptors may vary according to the concentration of cytokines, such as tumor necrosis factor (TNF-alpha), which is produced and released from activated macrophages in the presence of material from the disrupted infected cells. In addition to TNF-alpha, other substances are released into the circulation, such as interleukins IL1, IL6 and IL8. These substances cause fever and other malarial symptoms.[25]

Severe *P. falciparum* parasitemia, defined as the infection of more than 5% of the red blood cells, has been correlated with an increase in microcirculatory effects and with harmful metabolic effects, such as hypoglycemia and lactic acidosis. These effects are part of an infective systemic inflammatory response syndrome (SIRS). Severe malaria, then, may be categorized as a severe *Plasmodium* sepsis. The progression into multiple organ dysfunction syndrome (MODS) is one of the leading causes of death in the intensive care units of several regions around the world.[26,27]

P. vivax malaria can also present as severe sepsis that progresses into MODS. The potential severity *of P. vivax* has been ascribed to its dissemination and its resistance to chloroquine and sulfamethoxazole/trimethoprim, both of which contribute to increased rates of morbidity and mortality.[14]

The immune response to *P. falciparum* is complex and consists of two central mechanisms. At the cellular level, activated phagocytic cells release nitric oxide and toxic oxygen derivatives that induce the destruction of infected red blood cells in the spleen. In the humoral mechanism, antibodies activate the macrophage and monocyte receptors on the surface of the infected red blood cells, which causes an increase in parasitemia. During acute infections, there is a poor antigen-specific response that then slows the systemic immune response. In regions where malaria is endemic, individuals who are continuously exposed to malaria gradually develop specific antibodies that increase in number and stabilize by the third decade of life.[13] The immune response provides protection against the most severe presentations of malaria. However, the activation of the immune system itself is involved in some clinical features that are responsible for the severity of infection because both responses involve the release of TNF-alpha.[13]

Other factors may protect individuals from severe malaria, such as glucose-6-dehydrogenase deficiency, sickle cell syndrome and thalassemia.

Recent studies have shown the relevance of the interactions between *P. falciparum* and the human host in relation to the severity of the clinical presentation. These studies have shown that there is an association between parasitemia and the controlling effects of the inflammatory cytokines TNF-alpha, IL-1, IL-6, IL-12 and IFN-gamma.[28,29] Ongoing studies have aimed to increase our understanding of this interaction and the innate role of the immune system, especially in relation to the effects of the dendritic cells (DC) and the Toll-like receptors (TLRs) on the pathophysiology and immunity of this agent.[30] Experimental data have shown the role of hemozoin as a TRL-9 ligand that leads to IL-6, IL-12 and TNF-alpha secretion.[30,31] Glycophosphatidylinositol (GPI) is also an acknowledged pathogen-associated molecular particle (PAMP)[32] that mediates cytokine production by binding to TRL-2.[33] GPI has a role in the genesis of symptoms, such as fever, chills, headache, asthenia and shock, but it is also involved in the development of hypoglycemia and the expression of adhesion molecules.

CLINICAL AND PATHOLOGICAL FEATURES

The clinical features and laboratory results vary widely among cases of severe malaria and affect multiple organs and organ system disorders (see Table 1). In general, for the sake of consistency in patient care, *P. falciparum* malaria should always be considered severe or potentially severe, even when the classic symptoms of severity noted by the WHO are not initially seen.

The main clinical-pathological features of severe malaria will be discussed below and include central nervous system (CNS) involvement, severe anemia, renal failure, pulmonary dysfunction, shock, disseminated intravascular coagulation, hypoglycemia, metabolic acidosis and liver dysfunction.

CNS involvement (cerebral malaria)

The frequency of cerebral malaria varies widely and is noted to occur in 0.01% to 16% of the patients.[35] It is relatively common in severe malaria and is the main cause of death, with a mortality rate of 10% to 50%.[36]

Table 1 – Indicators of a worse severe malaria prognosis

Feature	Characteristics
World Health Organization 1990 criteria (WHO, 1990)	
Cerebral malaria	Coma not ascribed to other causes, Glasgow ≤ 9
Severe anemia	Hemoglobin < 7 g/dl or hematocrit < 20% with parasitemia >10,000/µl
Acute renal failure	Urinary output < 400 mL/24 hours in adult patients (< 12 mL/kg/24 hours in children) and serum creatinine > 3.0 mg/dL
Pulmonary edema	Radiographic changes and severe hypoxemia
Severe hypoglycemia	Blood glucose < 40 mg/dL
Shock	Systolic blood pressure < 70 mmHg in patients over 5 years of age (< 50 mmHg in children)
Abnormal bleeding and/or disseminated intravascular coagulation	Spontaneous nasal bleeding from the gastrointestinal tract or laboratory evidence of disseminated intravascular coagulation
Repeated generalized seizures	≥ 3 episodes within 24 hours
Metabolic acidosis	Arterial pH < 7.25 or HCO_3 < 15 mmol/L
Macroscopic hemoglobinuria	Non-secondary to glucose-6-phosphate deficiency hemolysis
Additional criteria published in 2000 (WHO, 2000)	
Consciousness status impairment	Altered consciousness level
Prostration or weakness	
Hyperparasitemia	>5% erythrocytes infected or > 250,000 parasites/µl in non-immune subjects
Hyperpyrexia	Body temperature > 40ºC
Hyperbilirubinemia	Total bilirubin > 2.5 mg/dL

Source: Trampuz A, Jereb M, Muzlovic I, Prabhu RM. Clinical review: Severe malaria. Crit Care. 2003;7(4):315-23. Review.[34]

Cerebral malaria is defined as the coma or seizures that accompany patients infected with *P. falciparum* who have no other cause for encephalopathy.[13]

The pathogenesis of cerebral malaria is complex and not fully understood. There are two major theories concerning the pathogenesis of the disease: mechanical and inflammatory.[37] The mechanical theory suggests that erythrocyte sequestration, and the consequent impairment of cerebral blood flow and hypoxia, directly affects the brain in patients with severe malaria.[38] The inflammatory theory suggests that cerebral malaria is initiated by the intensive immune response characterized by Th1 cytokine release.[39] Cerebral malaria was also studied in *Plasmodium berghei* infection models in mice and was found to be associated with the innate dependent pathway responses of TLR-2, TLR-9 and MyD88, along with the local inflammatory response of T CD_8+ lymphocytes and natural killer (NK) cell infiltration.[40]

The development of cerebral malaria progresses from symptoms, such as headaches, behavioral changes and confusion, to seizures and coma. Bruxism may be present.[41] The neurological examination may show hyperreflexia and bilateral Babinski's sign, along with symptoms that indicate intracranial hypertension, especially in children.[41,42] Other concomitant causes for neurological changes should be ruled out, such as hypoglycemia and stroke.[13,36]

Severe anemia

Severe anemia is a frequently noted symptom that occurs early in the course of malaria. The anemia is due to several factors including erythrocyte sequestration, erythropoietic changes and blood loss from the eventual coagulopathy.[42] Severe malarial anemia is defined as a hematocrit below 15% or a hemoglobin concentration below 5 g/dL.[1,43] However, these parameters are not applicable outside of Africa, where malarial anemia is defined as a hemoglobin or hematocrit that decreases below the age, gender and contextually appropriate levels for the patient, along with the presence of *Plasmodium* spp.[13]

Recently, some cytokine expression polymorphisms have been associated with the susceptibility of patients to severe anemia: 1) IL-6 inducing hepcidin expression is the central regulator of iron homeostasis and leads to less iron availability for erythropoiesis; 2) transforming growth factor (TGF) inhibits erythroblasts proliferation; 3) TNF-alpha leads to increased erythroid transcription factor cleavage; 4) INF-gamma induces the macrophage production of the TNF-related ligand inducer, which inhibits

erythroblast differentiation.[43]

Studies have shown that viral infections (such as HIV) and bacterial and parasitic infections (such as helminths) increase the likelihood of severe anemia in patients with *P. falciparum* malaria.[44] Genetic disorders, such those associated with diseases that affect hemoglobin, and nutritional deficiencies also affect the likelihood of the occurrence of severe anemia.[43] Pregnant women with TLR-4 polymorphisms may have anemia.[45] The risk to the child may also increase and is associated with TLR-4 mutations.[45] Studies have therefore established that changes involving TLR are associated with an individual's susceptibility to malaria.[46]

Renal failure

Renal tubular changes are more prominent than glomerular changes during *P. falciparum* infections and may range from minor changes to acute tubular necrosis and acute renal failure (ARF) accompanied by frequent oliguria and hypercatabolism.[43] A diagnosis of ARF should be considered in the presence of oliguria (urinary output less than 400 mL/24 hours) and an increased serum creatinine and blood urea nitrogen.[1]

The effects of infected red blood cells on the microcirculation of the patient are the main cause of ARF. Additionally, changes in the hemodynamic and immunological status, increased creatinine and blood urea nitrogen levels, and metabolic changes also cause ARF.[47] Cytoadherence and microcirculation emboli, in addition to reduced red blood cell flexibility and reduced systemic blood flow, lead to renal ischemia.[24,47] Changes in the hemodynamic status of the patient are not limited to the effects of microemboli. Endothelial activation mediated by the massive release of vasoactive cytokines leads to hypovolemia and a reduced blood viscosity,[47] which is similar to sepsis.[48]

The inflammatory mediators released by the immune response induce vasoconstriction and the release of catecholamines, which then additionally increase vasoconstriction. The consequent renal injury is directly related to direct catecholamine toxicity of the renal parenchyma, as well as with the hemodynamic implications that result in ischemia. Other mechanisms, such as immunocomplex deposition and immunomediated glomerulopathy, also contribute to kidney injury.[49]

ARF is a frequent and serious complication of *P. falciparum* in children and non-immune adults.[50]

Pulmonary dysfunction

The incidence of pulmonary dysfunction is 3% to 10% in patients with *P. falciparum* infections, and the mortality rate is approximately 70%.[51] The first sign of pulmonary dysfunction is an increase in the respiratory rate that precedes radiographic changes.[1] The most severe presentation of pulmonary dysfunction is acute respiratory distress syndrome (ARDS), which is characterized by diffuse endothelial injury with increased capillary permeability[42] that manifests itself early in the course of the disease.[52] Pulmonary edema may occur after the initiation of treatment. In some cases, edema is associated with the infusion of an excessive amount of fluids.[13] Fluid replacement therapy should be judiciously administered.

Endothelial injury is likely to play a central role in lung injury due to the adherence of the infected red blood cells, cytokine release and leukocyte adhesion.[53] In the post-mortem studies of patients with *P. falciparum* and respiratory failure, endothelial cell cytoplasmic edema was detected, along with pulmonary interstitial edema, and infected red blood cells adhered to the inner capillary layers.[54]

Because of the potential fatal pulmonary complications and the progression into acute respiratory failure, mechanical ventilation should be considered for patients with severe malaria, depending on the patient's clinical context and considering the potential risks of nosocomial pneumonia, pneumothorax and a prolonged length of stay in the intensive care unit (ICU).[55]

Hypotension and shock

Circulatory collapse, which may occur early in the disease process, is characterized by a supine systolic blood pressure below 90 mmHg in patients more than 5 years old and is generally associated with pulmonary edema, metabolic acidosis, sepsis and/or massive bleeding due to gastrointestinal hemorrhage or spleen rupture.[34] In most cases, the shock is characterized by a reduction in peripheral vascular resistance and preserved heart function: a hyperdynamic shock.[36]

Shock in *Plasmodium falciparum* infected patients is known as algid malaria syndrome, which may be associated with acute adrenal insufficiency, myocardial failure, acute pulmonary edema and profuse bleeding caused by either disseminated intravascular coagulation or the rupture of a subcapsular hematoma of the spleen.[56] This is a rare complication that is triggered by several mechanisms, including concomitant bacterial

infection,[1] dehydration and glucocorticoid deficit due to acute adrenal insufficiency.[56]

Disseminated intravascular coagulation

Although *P. falciparum* infection is generally associated with a procoagulant status that is characterized by thrombocytopenia as well as coagulation cascade and fibrinolytic system activation, bleeding events are uncommon.[23]

Hypoglycemia

Hypoglycemia is common in patients with severe malaria and may lead to seizures and coma. The pathophysiology of adult hypoglycemia is usually associated with hyperinsulinemia, which may result from pancreatic cell stimulation and *Plasmodium* spp-derived factors. Hypoglycemia is difficult to detect. Its clinical features are similar to other changes observed in severe malaria, such as anxiety, dyspnea, tachycardia, diaphoresis, coma and generalized seizures.[34] In some patients, a deterioration in consciousness may be the only sign.[1]

Metabolic acidosis (lactic)

Metabolic acidosis is related to an increase in the anaerobic metabolism of glucose. In addition to a reduction in liver lactate clearance due to the reduced flow of blood to the liver, metabolic acidosis in patients with severe malaria may be related to the tissue hypoxia associated with anemia (reduced oxygen transport), to an increase in muscle activity during seizures, to an increase in nutritional requirements due to the infected erythrocytes and to the inhibition of mitochondrial glucose oxidation and the subsequent increase in cytokines.[57] A combination of factors shifts the metabolism from aerobic to anaerobic, which then leads to increased levels of lactate.[13]

Hypovolemia, once considered an important factor in cases of metabolic acidosis in patients with severe malaria, does not contribute to increases in serum lactate.[58]

Attempts to compensate for metabolic acidosis may include hyperventilation, as has been seen with Kussmaul breathing.

Liver dysfunction

Liver involvement is common in severe malaria. The main symptoms include jaundice (increased direct bilirubin), hepatomegaly and a mild increase in serum aminotransferase. Liver dysfunction has a distinctive histopathology that may result in a reduction in the synthesis of coagulation factors, in the impaired metabolism of certain antimalarial drugs and in changes to glycogenesis, all of which contribute to hypoglycemia and lactic acidosis. These changes may eventually progress into acute liver failure.[59]

The most frequent pathological findings include the proliferation of reticuloendothelial cells, congestion, periportal infiltration, sinusoid infiltration and dilation and cholestasis.[59]

DIAGNOSIS

Clinical

The strategy recommended by the Brazilian Health Ministry consists of early diagnosis and timely and appropriate therapy.[60] Recent studies indicate that delayed diagnosis is responsible for the worsening of malaria in patients, especially those with malaria caused by *P. falciparum*.[36,61,62,63]

Malaria should be suspected in any subject who has a fever of unknown origin, who has a history of visiting regions where malaria is endemic or who has visited the Atlantic Forest.[61] In addition to natural transmission (*Anopheles* spp. mosquito bites), individuals may also contract malaria from blood transfusions, organ transplantation or penetrating wounds.

When intensive care physicians are asked to evaluate a case of fever of unknown origin, malaria should be suspected as a differential diagnosis along with other infections, such as meningitis, typhoid fever, sepsis, influenza, dengue, hepatitis, leptospirosis and viral encephalitis.

Laboratory

The diagnosis of malaria is confirmed through the microscopic identification of *Plasmodium* spp. in the Giemsa or Walker-stained thick blood smear. Thin blood smear can identify the species, but shows less sensitivity than thick blood smear. Although microscopic identification is the gold-standard for the diagnosis and follow-up of malaria, this technique requires trained personnel.[60] Therefore, the Brazilian Health Ministry recommends the following tests:

1) **Thick blood smear** is considered the gold standard in malaria diagnosis. Parasitemia can be quantified, which may assist in both the prediction of *P. falciparum* infection severity and in the therapeutic monitoring of the infection.

2) **Thin blood smear** assess the form of the parasite and can differentiate between infecting species, which is important for choosing the appropriate therapy.

Blood for the thick blood smear can be obtained from any peripheral vein or by digital pulp puncture.

For the thin blood smear assessment, the different species characteristics should be considered in reference to the differential diagnosis of *P. falciparum* malaria. Due to its cytoadherence properties, *P. falciparum* trophozoites can only be observed in the peripheral blood.

In addition to hematoscopy, other methods are in development for the diagnosis of malaria, such as the capillary method for parasite identification (using acridine orange staining) and ParaSight®. This test uses monoclonal antibodies that are directed against *P. falciparum* antigens. Some studies have shown that this method has a sensitivity and specificity of greater than 95%.[60] However, this test is not useful for cure control.

In recent years, several studies have used polymerase chain reaction (PCR) for *Plasmodium* spp. DNA detection.[64-66] However, due to the cost, this technique has not been routinely used for diagnosis and is restricted to research sites.

THERAPY

General care

P. falciparum malaria is a medical emergency.[67] Considering the severity of the clinical condition, patients should be admitted to an ICU.[34] Upon admission, the patency of the airway should be secured, and respiratory and cardiovascular indicators should be assessed. The patients should be weighed to calculate the treatment doses. Venous access should be established. Blood samples should be drawn for the following laboratory tests: blood glucose, complete blood count, parasite counting, arterial blood gas and both renal and hepatic function parameters. The fluid and electrolytic balance should be strictly monitored. A detailed neurological examination is recommended, especially with the use of the Glasgow scale for the assessment of consciousness.

Specific treatment

Because the level of parasitemia determines the severity of the infection, it must be controlled. Fast-acting erythrocytary schizonticides, such as artemisinin derivatives, should be prescribed. The medications should be given intravenously. Oral drugs, such as mefloquine, chloroquine and halofantrine, should not be used.

Artemisinin derivatives, such as artesunate and artemether, are commonly used. Artesunate can be administered intravenously, intramuscularly or rectally. Artemether is only available in an intramuscular form. These drugs are extracted from the Chinese herb *Artemisia annua.* Pharmacologically, these fast-acting schizonticides are also effective against *P. vivax* gametocytes and are indicated for severe malarial therapy, especially for cerebral malaria because of how rapidly they affect parasitemia. These drugs are well tolerated with only a few adverse effects, such as diarrhea, abdominal pain and nausea.

Quinine is the oldest antimalarial drug. This fast-acting erythrocyte schizonticide is effective against *P. vivax, P. ovale* and *P. malariae* gametocytes. It is not effective against *P. falciparum* gametocytes. Quinine is quickly absorbed following oral or intravenous dosage. Quinine, with a half-life of approximately 12 hours, can be found in measurable concentrations in all organ fluids and tissues, including the inside of erythrocytes at approximately 1/3 to 1/2 of the plasma concentrations.[68] The main adverse effects of quinine, in addition to the occurrence of hypoglycemia at higher dosages, include cinchonism (tinnitus, transient hearing impairment, trembling and visual disorders), upper abdominal pain, nausea and vomiting. These adverse effects are reversible upon the discontinuation of treatment. The intravenous infusion of this medication can lead to thrombosis, arterial hypertension and changes in heart rhythm. Quinine should be diluted and infused slowly. Currently, it is recommended that clindamycin should be prescribed along with quinine, as is shown in table 2.

Although age is an important factor, the patient's weight should be considered the most important factor for maximal effectiveness and minimal toxicity when adjusting the dosage of these drugs.[67] The Brazilian Health Ministry provides antimalarial therapy free of charge across the country.

Therapy may be complicated by drug resistance and disease severity. Parasitemia assessment after 24 hours of treatment is important to detect treatment failures, especially in patients with an unchanged or worsening status.

Supportive measures

In addition to antimalarial drugs, general supportive measures, as shown on Table 3, should be considered.

Table 2 – Therapeutic schedules for severe and complicated *Plasmodium falciparum* malaria

Artesunate: 2.4 mg/kg intravenous loading dose followed by 1.2 mg/kg 12 and 24 hours after the initial dose. Maintain the 1.2 mg/kg daily dose for 6 days. If the patient can swallow, daily doses may be given as tablets.	+	**Clindamycin:** 20 mg/kg/day, intravenous in 5% glucose (1.5 mL/kg), infused within 1 hour for 7 days. If the patient can swallow, daily doses may be given as tablets.
Should not be given to pregnant women during the 1st trimester.		
Or		
Artemether: 3.2 mg/kg intramuscular loading dose. After 24 hours, give the patients 1.6 mg/kg/day for an additional 4 days for a total of 5 treatment days. If the patient can swallow, daily doses can be given as tablets.	+	**Clindamycin:** 20 mg/kg/day, intravenous in 5% glucose (1.5 mL/kg), infused within 1 hour for 7 days. If the patient can swallow, daily doses may be given as tablets.
Should not be given to pregnant women during the 1st trimester.		
Or		
Quinine: 20 mg/kg intravenous quinine dihydrochloride diluted in 10 mg/kg 5% glucose (maximum 500 mL) infused over 4 hours. 8 hours after the start of therapy, give the patient a maintenance dose of quinine 10 mg/kg in 10 mL 5% glucose for each kg, with a maximum dose of 500 mL over 4 hours. This maintenance dose should be repeated every 8 hours from the beginning of the previous infusion until the patient is able to swallow, and then quinine 10 mg/kg every 8 hours should be given as tablets for a total of 7 days of treatment.	+	**Clindamycin:** 20 mg/kg/day, intravenous in 5% glucose (1.5 ml/kg), infused within 1 hour for 7 days. If the patient can swallow, daily doses can be given as tablets.
This dosing schedule is appropriate for pregnant women during the 1st trimester and for children less than 6 months old.		

Source: Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica.Guia prático de tratamento da malária no Brasil. Brasília: Ministério da Saúde; 2010. 36p. (Série A. Normas e Manuais Técnicos).[67]

Table 3 – Maintenance therapy of severe malaria complication

Complication	Approach
Hypotension and shock	Careful volume replacement, risk of ARDS and acute lung edema. Start sympathomimetic amines, such as dobutamine and/or noradrenalin, for the recovery of adequate pressure levels. Broad spectrum antibiotic therapy should be considered if concomitant bacterial infection.[56]
Acute kidney injury	Early dialysis therapy. Intermittent hemodialysis is better than peritoneal dialysis. Continuous dialysis is better than intermittent dialysis.[69-71] Central venous pressure and mean blood pressure should be monitored, in addition to serum creatinine and blood urea nitrogen.[72] Withhold nephrotoxic drugs.[73]
Anemia	Assess for hemodynamic repercussions, renal perfusion and actual blood transfusion requirements, which should be based on the clinical evidence of risk for cerebral oxygenation due to the risk of increased parasitemia following the transfusion.[72] If packed red blood cells transfusion is required, the infused volume should be included in the fluid balance calculation.[1]
Hypoglycemia	Strict blood glucose control and 50% regular glucose bolus injection as necessary. Continuous 10% glucose infusion is preferred.[1]
Disseminated intravascular coagulation	Fresh plasma replacement and coagulation factors.[23]
Respiratory failure	Orotracheal intubation and mechanical ventilation as required.[71] Use of protective ventilation by high-frequency oscillatory ventilation as an alternative for malaria-related acute respiratory distress syndrome patients has been shown to have good results with the addition of low tidal volumes and positive end-expiratory pressure (PEEP).[74] Non-invasive mechanical ventilation was successfully used in *P. vivax* malaria with patients in respiratory distress.[74-76]

CLOSING REMARKS

Severe malaria is a medical emergency. The infection should be promptly diagnosed and treated. Admission into intensive care units should be considered for the management of these patients. The prognosis for this infectious process is closely related to the initiation of early therapy, the appropriate supportive measures and the management of complications. There are scales that provide guidance for the stratification of severe malaria patients. The Malaria Prognosis Score (MPS) is simple to use and has an excellent level of sensitivity.[77] The Model Severity Prognostic Score (MSPS) has demonstrated an 88.8% sensitivity and an 88.4% specificity for predicting the outcomes of severe malaria patients, but additional studies are required before the MSPS can be widely used.[78] The Coma Acidosis Malaria scale (CAM) is an easy monitoring method based on renal function.[79]

Appropriate follow-up, advanced support and early diagnosis can impact the disease-related mortality. However, measures to control the disease worldwide should not be neglected.

RESUMO

A malária é uma das principais doenças parasitárias do mundo, acometendo importante contingente de pessoas. Por seu alcance epidemiológico e pela possibilidade de desenvolvimento de quadros graves – quase sempre devidos ao *Plasmodium fqalciparum* –, se faz necessário o conhecimento adequado de suas manifestações clínicas e da terapêutica, para otimização da conduta. Na malária grave a internação em unidade de terapia intensiva é mandatória para redução das complicações decorrentes da infecção. O início do tratamento deve ser o mais precoce possível, o qual tem impacto na sobrevida do paciente, e é baseado na combinação de drogas antimaláricas e medidas de suporte. Neste âmbito, o presente artigo destina-se à discussão da forma grave da malária por *P. falciparum*, com ênfase no quadro clínico e no tratamento.

Descritores: Malária/terapia; Malária/diagnóstico; Malária/patologia; *Plasmodium falciparum*

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