Pathogenesis and Clinical Features of Malaria

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Abstract

Understanding the pathogenesis of malaria requires a detailed investigation of the mechanisms of *Plasmodium* invasion, *Plasmodium* biology, and host defense, and by understanding the life history of *Plasmodium*, the impact of *Plasmodium* and host interactions on each other can be elucidated. *Plasmodium falciparum* infection causes the most severe clinical manifestations, and its pathogenesis is the best studied. The clinical presentation of patients with malaria is closely related to the malaria parasites and varies according to local malaria epidemiology, the patient's immune status and age. Populations at high risk of malaria include infants and young children (6–59 months), where severe malaria can occur, and pregnant women, where anemia and low birth weight neonates may occur. In areas where malaria is transmitted year-round, older children and adults develop partial immunity after repeated infections and are therefore at relatively low risk of severe malaria. Treatment of malaria includes antimalarial treatment and symptomatic management, which is difficult given the pathophysiological changes in multiple organ systems involved in severe malaria. This topic will discuss in detail the pathogenesis and clinical features of malaria.

Keywords

Malaria · *Plasmodium* · Pathogenesis · Clinical manifestations · Treatment

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5.1 Pathogenesis

5.1.1 Pathophysiology

All species of human *Plasmodium* that cause human infection may adhere to the surface of human cells at some point in their life history, but this period is short for all but *Plasmodium falciparum*: more than half of the 48-hour intraerythrocytic phase of *Plasmodium falciparum* is in adhere to the surface of human cells. Adherence to the surface of human cells is an important mechanism in the pathogenesis of *P. falciparum*. As *P. falciparum* matures from ring form to large trophozoites in erythrocytes, they induce the formation of adhesive bumps on the surface of erythrocytes (Newbold et al., 1999; Oh et al., 1997). These bumps consist of a combination of proteins produced by *Plasmodium falciparum* and human-derived proteins. These include *P. falciparum* erythrocyte membrane protein-1 (PFEMP-1; it is the product of *Var* gene expression and is currently considered to be the major cell adhesion factor), KAHRP, PFEMP-2, and PFEMP-3; human-derived proteins include hemosiderin, actin, and band 4.1 proteins (Sharma, 1991; Aikawa, 1988; Sharma, 1997). Each *P. falciparum* has more than 60 different *Var* genes, and the protein product of only one of these genes is present in a single *P.* falciparum (Chookajorn et al., 2008). This bump binds receptors on a variety of cells in the capillaries, including endothelial cells. Common receptors include the intercellular adhesion molecule (ICAM-1) located in the vascular endothelium and the endothelial protein c receptor (ePCR), CD36 on endothelium and platelets, and chondroitin sulfate A (CSA) on placenta (Maubert et al., 2000; Rogerson et al., 1999; Maubert et al., 1997; Chaiyaroj et al., 1996). Binding to the endothelium results in the isolation of *P. falciparum*-infected RBCs (iRBCs) from these small vessels, thus allowing *P. falciparum* to remain absent for a long period of life. The iRBCs are not present in the peripheral circulation for a long period of their life history, thus effectively preventing them from entering the spleen and being phagocytosed. When iRBCs adhere to uninfected red blood cells and form rose node-like masses, a rose node reaction, the masses block the microcirculation and contribute to microvascular disease (Chen et al., 2000). Isolation of iRBCs leads to partial blockage of blood flow, disruption of the endothelial barrier, inflammation, and abnormalities in coagulation. This pathology can occur in vital organs such as the brain, lungs, and kidneys, with the most severe clinical manifestations leading to cerebral malaria (Ponsford et al., 2012). The intravascular lysis of large numbers of *Plasmodium*-infected erythrocytes can lead to hyperhemoglobinemia with back pain, soy sauce-colored urine and, in severe cases, acute renal failure owing to mechanical obstruction of the renal vasculature caused by massive lysis of infected erythrocytes, and, of course, immune-mediated glomerulopathy and alterations in the renal microcirculation are likely to promote the development of renal failure as well (Das, 2008).

Solation of a vascular bed with *Plasmodium* allows for the accumulation of high levels of *Plasmodium* biomass in the host. HRP-2 is a secreted *Plasmodium falciparum* antigen expressed on the erythrocyte membrane, and its expression

indirectly reflects the amount of *Plasmodium* biomass in the circulation and isolated in microvascular structures. Studies suggest that plasma HRP-2 concentrations correlate with the severity of malaria (Dondorp, 2008).

5.1.2 Cytokines

The role of cytokines in the pathogenesis of malaria is extensive and complex. The cytokines TNF-a, IL-6, IL-10, IL-12, IL-18, and macrophage inflammatory protein-1 (MIP-1) are all expressed at elevated levels in malaria infection. However, the role of these cytokines in malaria is not fully understood. The "cytokine storm" hypothesis suggests that in severe malaria, damaging cytokines and small molecules become unregulated, leading to a systemic inflammatory response syndrome (SIRS)-like state with multiorgan and multisystem dysfunction (Fried et al., 2017). However, there is limited evidence of a direct association between severe malaria and SIRS.

Plasmodium infection of hepatocytes activates interferon regulatory factors (IRFs) and induces the secretion of type I interferons (IFNs), which increase the expression and secretion of chemokines by autocrine means, such as CXCL9 and CXCL10. CXCL9 and CXCL10 in turn chemotactically recruit immune cells expressing the chemokine receptor CXCR3, including NK cells, T cells, and NKT cells, to the liver, and these cells in turn inhibit intracellular *Plasmodium* expansion by secreting IFN-γ (Liehl et al., 2014).

Rupture of the exoerythrocytic schizonts releases thousands of merozoites into the bloodstream and invades red blood cells within seconds, with an extremely short exposure to immune cells. Intrinsic immunity is the body's first line of elimination and defense against *Plasmodium* infection, and iRBC rupture stimulates the release of proinflammatory cytokines, including TNF-α. Macrophages that have engulfed iRBCs do not secrete proinflammatory cytokines because of phagosomal acidification (Wu et al., 2015). iRBC rupture releases pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), including microvesicles, hemozoin, and glycosylphosphatidylinositols (GPIs). Dendritic cells (DCs) recognize these PAMPs and DAMPs through pattern recognition receptors (PRRs) and secrete IL-6, TNF-a, and IL-12, and DC-derived IL-12 in turn activates the secretion of IFN-γ by NK cells to activate the clearance of iRBCs (Wu et al., 2015; Stevenson & Riley, 2004). In addition to immune cells, TNF-α can also induce endothelial cell activation, promote chemokine secretion by endothelial cells, recruit inflammatory cells to locally damaged endothelial cells, and cause endothelial barrier damage (Viebig et al., 2005; Rénia et al., 2012).

5.1.3 Hemoglobin and Red Blood Cell Antigen

Hemoglobin and erythrocyte antigens can affect the body's ability to defend itself against malaria to varying degrees. In many parts of the world, the disease burden of malaria has been selected for a range of medically significant traits, including alleles

encoding hemoglobin (Hb), erythrocyte enzymes, and membrane proteins. The following hemoglobinopathies have been identified to defend against malaria infection: hemoglobin S (sickle cell hemoglobin) (Gong et al., 2012; Bunn, 2013); hemoglobin C (Travassos et al., 2015; Kreuels et al., 2010); hemoglobin SC disease (Lin et al., 1989); hemoglobin E (Nagel et al., 1981); hemoglobin F (fetal hemoglobin) (Pasvol et al., 1977); and α and β thalassaemia (Allen et al., 1997; Willcox et al., 1983). The defense mechanism for intraerythrocytic phase *P. falciparum* may involve one or more of the following mechanisms: (1) blocking the entry of merozoites into erythrocytes (Tiffert et al., 2005); (2) inhibition of the intracellular growth of *Plasmodium*; (3) prevention of erythrocyte lysis at the end of *Plasmodium* maturation, thereby preventing the release of merozoites into the circulation; (4) enhanced phagocytosis of iRBCs (Ayi et al., 2004; Bunyaratvej et al., 1986); (5) reduced adhesion of iRBCs to endothelial cells, uninfected erythrocytes, platelets or antigen-presenting cells; and (6) enhanced immune response to malaria infection. A number of potential mechanisms have been identified for hemoglobinopathy resistance to malaria, but it remains unclear which mechanisms play an important role in vivo. Genetic abnormalities in erythrocyte surface antigens and cytoskeletal proteins may also have a defensive role against malaria infection.

5.1.4 Immunity After Infection

Patients living in endemic areas appear to be partially immune to clinical episodes of malaria after repeated infections; the degree of protective immunity appears to be proportional to the intensity of transmission and increases with age (Dondorp et al., 2008). In areas where malaria is highly endemic (e.g., sub-Saharan Africa), near-complete clinical disease resistance is acquired by early adulthood. In low-transmission areas (e.g., Southeast Asia), however, individuals remain at risk of fatal malaria in adulthood and are referred to as “semi-immune.” Individuals infected with malaria in nonendemic areas (e.g., travelers) have a detectable antibody response; however, this response does not protect against initial malaria infection and is only a marker of previous infection (Doolan et al., 2009).

5.1.4.1 Humoral Immune Response

The humoral immune response to malaria appears to be slow, with gradual refinement in the presence of continuous stimulation by different *Plasmodium* species antigens. IgG4, IgE, and IgM are more markedly elevated in patients with severe malaria, while IgG (IgG, IgG1, IgG2, and IgG3) is more markedly elevated in individuals with mild malaria and asymptomatic infections (Leoratti et al., 2008). In addition, individuals who leave endemic areas appear to lose some humoral immune protection; these individuals are "semi-immune," and their protection is diminished when they return to endemic areas after prolonged periods without *Plasmodium* antigenic stimulation.

5.1.4.2 Cellular Immune Response

The body can defend against hyperplasmodiumemia through the ability to generate a strong IFN-γ response (mainly via CD56+γ T cells). (D'Ombrain et al., 2008) Phagocytosis of *Plasmodium* pigments and trophozoites impairs the ability of monocytes and macrophages to mount oxidative bursts, kill ingested pathogens, properly present antigens, and mature into functional dendritic cells. These cells produce TNF-α and other proinflammatory cytokines to mediate and amplify the immune response.

5.2 Clinical Manifestations

5.2.1 Incubation Period

The incubation period is the time between the entry of *Plasmodium* into the human body and the appearance of clinical symptoms and includes the time for the development of the exoerythrocytic phase and the proliferation of several generations of *Plasmodium* in the erythrocytic phase to reach a certain number. The length of the incubation period is related to *Plasmodium* species, the number of sporozoites entering the human body, and the immunity of the body. The incubation period was 7–27 days for *P. falciparum*, 11–25 days for *P. vivax*, 11–16 days for *P. ovale*, and 21–25 days for *P. malariae*. iRBCs release merozoites when they rupture, which can lead to chills, fever, and other clinical manifestations of malaria. Most people infected by *P. falciparum* develop clinical manifestations within 1 month, but longer incubation periods may occur in individuals with partial immunity. *P. vivax* and *P. ovale* are recurring types of *Plasmodium*, which also have an incubation period of approximately 2 weeks but can develop several months after the initial infection owing to activation of residual dormant substrates in the liver (Schwartz et al., 2003). Recurrence usually occurs 3–6 months after recovery. The incubation period for asymptomatic infection of *P. malariae* has been reported to persist for several years on an extremely rare basis. *P. falciparum* and *P. malariae* do not have a dormant period and therefore do not recur. *P. knowlesi* and *P. simium* are among the malaria parasites that infect nonhuman primates, but human infections have been reported in Southeast Asia and Brazil; microscopy and PCR show that *P. knowlesi* is similar to *P. malariae*, and *P. simium* is similar to *P.* vivax (Grigg & Snounou, 2017).

5.2.2 Clinical Manifestations

5.2.2.1 Uncomplicated Malaria

Patients with a positive pathogenic test and mild malaria symptoms are considered to have uncomplicated malaria if they do not show signs of severe malaria (Olliaro et al., 1996). The initial symptoms of malaria are usually nonspecific, including a variety of discomforts, such as fever, chills, malaise, sweating, headache, cough,

anorexia, nausea, vomiting, abdominal pain, diarrhea, arthralgia, and myalgia (Svenson et al., 1995). All *Plasmodium* parasites, including *P. falciparum*, can cause uncomplicated malaria. Early malaria infection usually presents with intermittent fever, typically with sudden onset of chills, high fever, and profuse sweating. In the later stages of infection, the infected red blood cells rupture, with simultaneous rupture of the schizonts and release of merozoites from the red blood cells. The interval is 48 h for *P. vivax* and *P. ovale*, 36–48 h for *P. falciparum* and approximately 72 h for *P. malariae*. *P. malariae* is considered to have more regular intervals than other *Plasmodium* species. With improvements in early diagnosis and treatment, the usual periodic fever is now rare. On examination, signs of anemia and an enlarged spleen that could be palpated under the ribs could be seen. Mild jaundice can occur in patients with falciparum malaria without other complications. Splenomegaly is common in usually healthy patients in high malaria areas and may be the result of repeated malaria infections or other infections. After multiple malaria infections, the spleen often atrophies due to infarction to the point where it is not palpable.

5.2.2.2 Severe Malaria

Clinical manifestations of severe malaria include impaired consciousness with or without seizures, acute respiratory distress syndrome (ARDS), circulatory failure, renal failure, hemoglobinuria, hepatic failure, circulatory failure, and coagulation disorders with or without disseminated intravascular coagulation, acidosis, and hypoglycemia (Trop Med Int Health, 2014; White, 1996).

Although most severe malaria with complications is caused by *P. falciparum*, *P. vivax* infection can also have serious complications. It has been reported that severe vivax malaria may also cause pulmonary complications and ARDS (McGready et al., 2014). High-risk groups of severe malaria include individuals without immunity, patients with impaired immune function (including those without spleen), children aged 6–59 months, and pregnant women (Steketee et al., 2001). The increase in the number of *Plasmodium* is related to the aggravation of the disease. Patients with partial immunity may have obvious parasitemia, but there is almost no obvious clinical manifestation.

Physical examination may include pale skin (severe anemia appearance), ecchymosis, jaundice, and hepatosplenomegaly. Laboratory examination results may include parasitemia (parasitized red blood cells $\geq$ 4%–10%), anemia, thrombocytopenia, coagulation dysfunction, elevated transaminase, elevated creatinine, acidosis, and hypoglycemia. (McGready et al., 2014; Devarbhavi et al., 2005) Thrombocytopenia and severe anemia often suggest a poor prognosis. (Lampah et al., 2015)

Cerebral malaria is characterized by impaired consciousness, delirium, and seizures. The symptoms of patients may develop slowly or suddenly after convulsions. Its severity depends on a variety of factors, including the species and pathogenicity of *Plasmodium*, host immune response and timely treatment. Risk factors for cerebral malaria include age (children and the elderly), pregnancy, malnutrition, HIV infection, previous history of splenectomy, and host genetic susceptibility. Cerebral malaria is more common in adults without immunization

than in residents in malaria-endemic areas, while cerebral malaria is more common in children in malaria-endemic areas (Hochman et al., 2015; Idro et al., 2007; Ranque et al., 2005; Reyburn et al., 2005). The mortality rate of cerebral malaria is 15%–20%. If treatment is not timely, cerebral malaria can quickly progress to coma or even death. There are more cerebral sequelae in children (approximately 15%) than in adult patients (approximately 3%). Residual defects may include hemiplegia, deafness, epilepsy, language defects, and cognitive impairment. (Mung'Ala-Odera et al., 2004) These sequelae are more common when accompanied by other complications, including severe anemia, hypoglycemia, and acidosis. Postmalarial nervous system syndrome is an autoimmune encephalitis that occurs within 2 months after treatment, and remission of cerebral malaria often manifests as seizures.

ARDS may occur in adults with severe falciparum malaria, and its mechanism is not completely clear. However, it may be related to the isolation of parasitic red blood cells and cytokine-induced alveolar capillary leakage (Taylor et al., 2012). ARDS can even be seen days after antimalarial treatment. In addition to falciparum malaria, ARDS can also be seen in patients with vivax malaria without other complications.

Acute renal injury and even renal failure often occur in severe *P. falciparum* malaria in adults and are less common in children (Conroy et al., 2016). The pathogenesis of renal failure is not completely determined, but it may be closely related to the interference of red blood cell isolation with renal microcirculation blood flow and metabolism. Other possible pathophysiological mechanisms include low blood volume and mechanical obstruction caused by hemolysis. When intravascular hemolysis occurs, a large amount of hemoglobin and malarial pigments may appear in urine, and its mortality is high.

Acidosis is an important cause of death in patients with severe malaria, which can be caused by a variety of factors, including *Plasmodium* isolation interfering with microcirculatory blood flow, causing anaerobic fermentation of host tissue; *Plasmodium* producing lactate; low blood volume; and severe acidosis, often suggesting poor prognosis.

Hypoglycemia is a common complication of severe malaria. The mechanism of hypoglycemia involves the reduction of hepatic gluconeogenesis, the depletion of hepatic glycogen reserve, and the increase of host glucose consumption. Hypoglycemia can lead to poor prognosis, especially for children and pregnant women.

New onset malaria infection is often accompanied by a sudden decrease in hemoglobin concentration, which is related to increased hemolysis and bone marrow suppression. Children with multiple episodes of malaria infection may develop chronic severe anemia in malaria-endemic areas. The mechanisms of anemia in malaria patients include the following: hemolysis of parasitic red blood cells; the isolation and clearance of red blood cells increased in spleen; cytokines inhibit hematopoiesis; red blood cell life shortened; repeated infection and ineffective treatment (Boele van Hensbroek et al., 2010). Anemia caused by falciparum malaria is usually characterized by anemia of positive cells and positive pigments, but reticulocytes are significantly reduced (Roberts et al., 2005). Mild falciparum

malaria often causes mild thrombocytopenia and coagulation disorders. Some patients with severe malaria will have bleeding and even disseminated intravascular coagulation (DIC) (Angchaisuksiri, 2014).

Malaria patients often have mild jaundice due to hemolysis. Severe jaundice can occur in falciparum malaria infection. The causes are hemolysis, hepatocyte injury, and cholestasis. The incidence in adults is higher than that in children. If liver dysfunction is combined with renal injury and other organ dysfunction, it indicates a poor prognosis (Woodford et al., 2018).

5.2.2.3 Malaria Infection During Pregnancy

Compared with nonpregnant women, patients during pregnancy are more prone to severe malaria, such as hypoglycemia and respiratory complications (pulmonary edema and ARDS) (Trans R Soc Trop Med Hyg, 1990). Anemia is a common complication of malaria during pregnancy, and approximately 60% of pregnant women infected with malaria have anemia (Espinoza et al., 2005). Pregnant women are particularly susceptible to *P. falciparum* infection. Infected red blood cells can stay in the placenta, resulting in adverse effects on the fetus, which may be prone to adverse pregnancy outcomes, including spontaneous abortion, premature birth, fetal growth restriction/low birth weight (LBW), stillbirth, congenital infection, and neonatal death. In addition, during treatment, if the antimalarial drugs in the placenta cannot reach the treatment level, the *Plasmodium* retained here may be intermittently released into the peripheral blood, resulting in maternal recurrent infection (Cohee et al., 2016).

5.2.2.4 Recurrent Malaria Infection

The causes of malaria recurrence are treatment failure (resurgence) or reinfection, which are difficult to identify. Both resurgence and relapse showed that the disease recurred after recovery. Resurgence most often occurs in a few days or weeks, and relapse often occurs after months. Resurgence is caused by ineffective treatment, and some *Plasmodium* will remain in the bloodstream. At the time of relapse, the dormants are resuscitated in hepatocytes, causing *Plasmodium* parasitemia again. *P. falciparum* infection is a common cause of resurgence, and *P. vivax* and *P. ovale* can reonset a few months after the initial infection is cured (usually 3–6 months) because they have dormants.

5.3 Treatment

The most important thing in the treatment of malaria is the killing of *Plasmodium* in red blood cells. The choice of antimalarial drugs is based on whether the block is falciparum malaria, the density of *Plasmodium* in the blood, the severity of the disease, whether it comes from a drug-resistant endemic area, the local type of *Plasmodium* resistance, and the availability of local drugs. The World Health Organization (WHO) recommends the use of a combination of an artemisinin derivative and another effective antimalarial drug as the most effective and currently

available method to avoid the development of *Plasmodium* resistance. In addition to antimalarial treatment, symptomatic supportive treatment is critical, especially for severe malaria with severe complications. The basic treatment includes the following aspects: bed rest during the attack and 24 h after the fever subsides, pay attention to vomiting and diarrhea patients by appropriate rehydration, pay attention to warmth when chills are present, physical cooling can be used when fever is present, patients with high fever can be treated with nonsteroidal anti-inflammatory drugs such as ibuprofen and acetaminophen to reduce temperature or glucocorticoids to reduce fever, and patients with serious conditions should be closely monitored for vital signs and water intake and output should be accurately recorded. The patient should be isolated according to insect-borne infectious diseases.

5.3.1 Treatment of Uncomplicated Falciparum Malaria

Uncomplicated falciparum malaria is defined as *P. falciparum* infection with less than 4% parasitemia and no symptoms associated with severe malaria. Hospitalization allows for observation of patient tolerance of antimalarial therapy, monitoring of remission of parasitemia, and further treatment of patients who progress to severe malaria. The following groups may deteriorate rapidly and require consideration of hospitalization, including infants and young children; those with compromised immune function; those without acquired immunity to *Plasmodium*; and those with hyperplasmodemia (4%–10%) without severe manifestations who are vulnerable to the development of severe malaria and may be at risk of treatment failure (World Health Organization, 2015). Therefore, antimalarial treatment should be initiated as soon as possible.

5.3.2 Treatment of Severe Malaria

Severe cases of falciparum malaria are defined by the WHO as the presence of *Plasmodium falciparum* parasitemia in a patient with at least 1 of the following:

I. Impaired consciousness: Adult Glasgow Coma Score (GCS) <11 or Child–Pugh Coma Score <3.
II. Poor general condition: General weakness, having to rely on assistance to sit, stand or walk.
III. Multiple convulsions (>2 episodes in 24 h).
IV. Acidosis: Alkali surplus >8 mEq/L, plasma bicarbonate level <15 mmol/L or venous plasma lactate ≥ 5 mmol/L.
V. Hypoglycemia: Blood or plasma glucose <2.2 mmol/L (<40 mg/dL).
VI. Severe anemia: Hemoglobin ≤ 5 g/dL or hematocrit $\leq 15\%$ in children under 12 years (<7 g/dL or $< 20\%$ in adults, respectively) with a *Plasmodium* count $>10{,}000/\mu L$.

VII. Renal impairment: Plasma or serum creatinine >265 μmol/L (3 mg/dL) or blood urea >20 mmol/L.
VIII. Jaundice: Plasma or serum bilirubin >50 μmol/L (3 mg/dL) and *Plasmodium* count >100,000/μL (parasitism rate approximately 2%).
IX. Pulmonary edema: This may be determined by imaging examination, or oxygen saturation <92% on breathing room air and a respiratory rate >30 breaths/min, often with chest depression and auscultatory twanging.
X. Significant bleeding: Including repeated or prolonged bleeding from the nose, gums, or venipuncture sites; vomiting blood or black stools.
XI. Shock: Compensated shock defined as capillary refill time ≥3 seconds or presence of a temperature gradient in the leg (mid to proximal) without hypotension. Decompensated shock is defined as a systolic blood pressure <70 mmHg in children or <80 mmHg in adults with evidence of impaired perfusion (syncope of the extremities or prolonged capillary reperfusion time).
XII. Hyperplasmodiumemia: Parasitism rate>10% (or *P. falciparum* density 500,000/μL).

To reduce the morbidity and mortality of cerebral or severe malaria, a comprehensive treatment approach is needed. Therefore, in addition to the timely initiation of antimalarial treatment for severe malaria, other treatments, including supportive care, symptomatic management, treatment of complications, and enhanced care and prevention of coinfection treatment, are particularly critical for patients with severe malaria.

5.3.2.1 Antimalarial Treatment

The treatment of patients with severe malaria, particularly cerebral malaria, requires the use of rapidly insecticidal antimalarials, administered intramuscularly or intravenously. The choice of antimalarial regimen can be found in Chap. 10.

5.3.2.2 Supporting Treatment

Fluids should be given in appropriate amounts to provide adequate energy, correct metabolic acidosis, and maintain water–electrolyte balance. Give a liquid or semi-liquid diet to those with poor appetite and gradually transition to a high-protein diet during the recovery period and iron supplements to those with anemia.

5.3.2.3 Symptomatic Management and Management of Complications

I. Fever: Physical cooling (cold towels or ice packs), acetaminophen, or small doses of glucocorticoids may be used to reduce fever in patients with high fever, and ice blankets may be considered to reduce fever if it persists. Attention should be given to rehydration during fever reduction to prevent hypotensive shock due to excessive sweating during fever reduction.
II. Cerebral edema: Cerebral edema and coma often occur in cerebral malaria and should be treated promptly with dehydration and commonly used clinical dehydrating agents, including mannitol and glycerol fructose.

III. Epilepsy: Seizures can occur in up to 70% of children with severe malaria. Seizures may be generalized or focal, and clinical manifestations may be subtle, such as nystagmus and irregular breathing. In addition to cerebral malaria, other causes of seizures (e.g., hypoglycemia and fever) need to be assessed and managed accordingly. Benzodiazepines are useful first-line drugs for the treatment of seizures, and commonly used drugs include diazepam and lorazepam. If benzodiazepines do not control the seizures, phenobarbital may be given for maintenance.

IV. Hypoglycemia: Hypoglycemia is a common complication of malaria and is a hallmark of severe malaria; it should be suspected in any patient who is comatose or whose condition suddenly deteriorates. Clinical signs of hypoglycemia include seizures and altered consciousness, so blood glucose concentrations should be routinely assessed, preferably with bedside blood glucose monitoring. Intravenous access should be established rapidly in hypoglycemic patients, followed by rapid administration of glucose (10% dextrose). For recurrent hypoglycemia, continuous infusion of 50% high glucose solution by bedside infusion micropump may be considered.

V. Hemolytic anemia: Glucocorticoids are recommended; pay attention to hydration and diuresis, and alkalinize the urine with an appropriate amount of sodium bicarbonate infusion; exclude other causes of hemolysis other than the primary disease, such as stopping the use of drugs that may cause hemolysis, such as quinine, primaquine, and other antimalarial drugs; consider transfusion if appropriate for severe anemia, use calcium gluconate or glucocorticoids before transfusion. For patients with severe jaundice, liver protection, and anti-yellowness drugs may be used as appropriate.

VI. Shock: Patients with severe malaria are often hypovolemic. When low peripheral perfusion occurs, including hypotension and cold extremities, a high alert should be given for infectious shock and fluid resuscitation, supplementation of crystalloids and colloids, and the use of vasoactive drugs such as norepinephrine and dopamine should be used as appropriate.

VII. Metabolic acidosis: Consider supplementation with 5% sodium bicarbonate solution for mild metabolic acidosis and continuous renal replacement therapy (CRRT) for severe metabolic acidosis.

VIII. Renal injury: Patients with severe malaria should be closely monitored for urine output, renal function, and urinary routine. Mild kidney injury may be treated with renal protection medication as appropriate. If renal failure is diagnosed, fluid intake should be strictly limited, and if necessary, dialysis should be administered promptly.

IX. ARDS: Patients with severe malaria can also have ARDS. Oxygen therapy can be administered, and noninvasive mechanical ventilation or even invasive mechanical ventilation should be considered if nasal cannula oxygenation fails to correct hypoxemia.

X. Coinfection: Coinfection with bacteria is an important contributor to complications and death in patients with severe malaria. When there is a high clinical suspicion of bacterial infection, empirical antibiotic therapy

should be available, and blood bacterial cultures should be performed promptly.

5.3.3 Treatment of Malaria in Pregnancy

Malaria in pregnancy is an important cause of maternal complications worldwide and can also lead to adverse birth outcomes. Pregnant women are more likely than nonpregnant women to develop complications from malaria infection. Malaria in pregnancy can have serious consequences for both the mother and fetus; therefore, pregnant women with malaria infection should be treated immediately with effective antimalarial drugs to rapidly eliminate the malaria parasite. There are limited data on safety and efficacy to guide treatment and even fewer data on safety in the fetus. Treatment decisions, therefore, need to take into account the clinical severity of the infection, epidemiological resistance patterns, and available information on the safety of a drug or class of drugs used during pregnancy. Amniotic fluid volume, fetal size, and general fetal health should be closely monitored during acute clinical malaria episodes.

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