Current Review in Malaria Pathogenesis and Host Immune Response

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ABSTRACT

Indonesia is one of the countries in the Southeast Asian region that contributes the largest malaria cases after India. In 2022, there has been the highest increase in cases in the last 3 years. Various molecular findings and malaria genomization projects are now increasingly being researched in a number of research centers around the world. However, only a few systematic reviews are available regarding malaria in Indonesia. This article aims to explore the latest update of malaria pathogenesis, so that it is expected to be a reference in establishing proper diagnosis and deciding on therapy, as well as contributing to the development of tropical infection science in Indonesia. As one of parasite causing Malaria, *P. falciparum* has ability to carry out an unlimited antigen variation by altering gene expression on the surface of infected red blood cells. When infected, the morphology of red blood cells changes significantly compared to uninfected ones. One indicator of the severity of malaria is a significant reduction in the flexibility of red blood cells. Plasmodium products trigger host release of a number of cytokines that aggravate clinical manifestations. For this reason, treatment with anti-cytokines is thought to be able to overcome the clinical manifestations of severe malaria. Malaria toxin is an immunogen produced by parasites. This toxin will induce the host so that it releases molecules bound to the serum. The Pf155 antigen, also called *ring-stage erythrocyte surface antigen* (RESA), can also trigger TNF-. Thrombospondin, CD36, ICAM-1, and VCAM-1 which are receptors located on infected erythrocytes. The degree of parasitemia may change over time in malaria infection. Repeated infections followed by the appearance of other antigens are a way for plasmodium to trick the immune system.

INTRODUCTION

Globally, WHO reported 249 million cases of malaria in 2022, with clinical cases have increased each year since 2016. [1] There are five species of parasites known to affect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi*. The highest mortality was reported in 76% of cases affecting children under 5 years of age, caused by *Plasmodium falciparum*. This species causes the most complications in humans in Southeast Asia. *Plasmodium vivax* also causes severe morbidity whereas *P. ovale* and *P. malariae* rarely cause severe clinical manifestations. [2]

Indonesia is one of the countries in the Southeast Asian region that contributes the largest malaria cases after India. In 2022, there has been the highest increase in cases in the last 3 years. According to data from the Ministry of Health, there are still 11 percent of the population in malaria-endemic areas spread across 142 regencies/cities. This increase in the number of cases was followed by an increasing trend in mortality from malaria. In the period 2018-2022, the death rate from malaria reached 71 people. Almost 80 percent of the incidence of death is contributed by children under the age of 5 years who are the most vulnerable group to malaria [3].

Malaria infection begins with the bite of a female Anopheles mosquito and *Plasmodium spp* species in the form of sporozoites which then enter the bloodstream. The parasite will replicate and invade erythrocytes. [4] The course of malaria is divided into two clinical manifestations: without and with complications. [5] Uncomplicated malaria is generally characterized by fever, chills, headache, anorexia, nausea and emesis and other non-specific symptoms. [6–7] Signs and symptoms such as splenomegaly, anemia, kidney dysfunction, altered consciousness to coma are manifestations found in severe malaria, which is commonly caused by *P. falciparum*. This is associated with the ability of parasites to infect mature and immature erythrocytes, the speed of asexual reproduction, and other pathological processes in capillary veins, specifically in the nervous system. [8]

Understanding pathogenesis is a complex review involving the interaction of host, agents and environmental factors.

This article focuses on the importance of the infectious pathogenesis of malaria species *P. falciparum* and *P. vivax* regarding severe malaria cases and death. A deeper understanding of pathogenesis can assist clinicians in identifying interventions to improve patient clinical outcomes.

MALARIA PATHOGENESIS

Plasmodium falciparum

In malaria caused by *P. falciparum,* proliferation of parasites occur in erythrocytes. As a result, erythrocytes will attach to the endothelial layer (*cytoadherence)* and attach to fellow uninfected erythrocytes (*rosetting)*. This attachment causes clusters of infected red blood cells in the post-capillary venules in the microvascular, then clogging blood flow, resulting in decreased oxygen supply. [9] In order to survive in the host body, *P. falciparum* modulates the human immune response to escape from anti-malarial agents. This manipulation aims to maintain parasites in the host's body in order to expand parasitization, resulting death in infected patient. [10]

P. falciparum has the ability to carry out unlimited antigen variation by altering gene expression on the surface of infected red blood cells. A number of these antigens will be ligands attached to endothelial receptors in postcapillary venules. With the sequestration mechanism, *P. falciparum* can avoid *clearance* in the spleen. This mechanism also supports parasites to further proliferate and reinvade hosts. [11] Recent research has shown that the *var* gene has been identified as the gene encoding *P. falciparum erythrocyte membrane protein 1* (PfEMP1). The *var* gene also encodes riffin and rosettin on the surface of infected red blood cell membranes. [12]

When infected, the morphology of red blood cells changes significantly compared to uninfected ones. The membrane of red blood cells becomes inflexible, making it difficult to pass through the bloodstream in the microvascular. *P. falciparum* deliberately creates special pores or canals in the erythrocyte membrane so that it can transport the nutrients it needs, such as purine bases, amino acids, and glucose. [13] *P. falciparum* then digests red blood cell membrane proteins and proteoglycans in them. Furthermore, the parasite secretes several polypeptides, such as rifin/rosettin and PfEMP1 to be presented outside the red blood cell membrane. [14]

The term *knobs* refers to ultrastructural changes in the form of protrusion with a diameter of 100 um. *Knobs* can only form on the membrane of infected red blood cells, where one of the constituents of the polypeptide composition is PfEMP1. A study showed that transmission of PfEMP1 into infected red blood cells is a major factor in the attachment of *knobs* to the surface of other red blood cells, even if they are normal. [15] These *knobs* are also thought to be the place of attachment of erythrocytes with endothelium in the brains of patients who died of severe falsiparum malaria. (Fig. 1) However, infected erythrocytes that do not have *knobs* are still very adesive, because there are a number of adesine molecules that contribute to the attachment of erythrocytes, such as rosettin, rifin, and various other proteins expressed on the surface of red blood cells. [16]

One indicator of the severity of malaria is a significant reduction in the flexibility of red blood cells. Erythrocyte deformability in severe malaria tends to decrease compared to erythrocytes in moderate malaria. Sequestration of the microvascular internal organs affected by rigid erythrocytes will distract blood flow, resulting in fatal consequences. [9] Severe acidosis caused by anaerobic glycolysis by plasmodium and parasite antigens absorbed by erythrocyte membranes will affect normal erythrocyte deformability in severe malaria. This condition ensures that lipid antigens produced by plasmodium will cause the membrane of normal erythrocytes to become stiff. It is this decrease in deformability that supports the severity of the disease. [17]
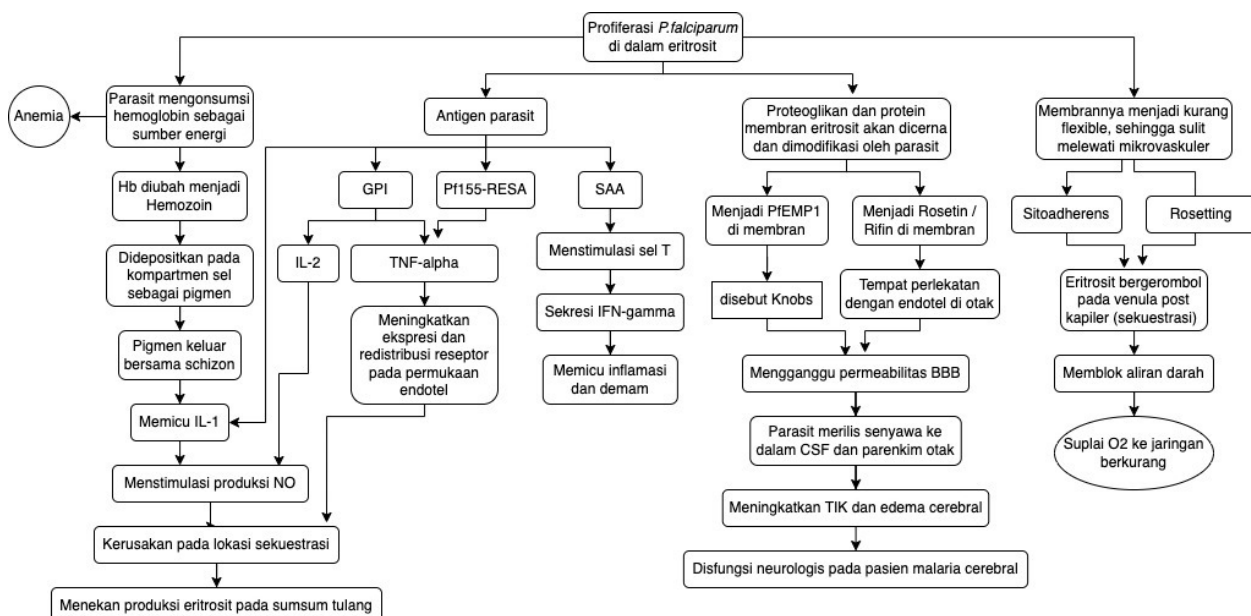
Figure 1. Proliferation of P. falciparum Inside Erythrocytes

Plasmodium products trigger host release of a number of cytokines that aggravate clinical manifestations. Cytokines that have high levels in patients with severe malaria include IFN- and TNF-. Deposits of IL-1 and these two cytokines in severe sequestration events such as in the brain are most often found in patients who die of cerebral malaria. [18] Cytokines play a role in severe malaria by triggering redistribution and expression of receptors on the endothelial surface, as well as causing physiological disturbances in the host in the form of high fever. Cytokines also trigger the production of nitric oxide (NO) which results in massive injury at the sequestration point and suppresses reticulocyte production in the bone marrow. [19]

For this reason, treatment with anti-cytokines is thought to be able to overcome the clinical manifestations of severe malaria. Giving anti-TNF- monoclonal antibodies to children with severe malaria will be able to reduce fever, although it does not improve the manifestation entirely. Exploring more about plasmodium antigens that trigger cytokine storms is critical in studying pathogenesis and designing up-to-date preventive strategies. [20]
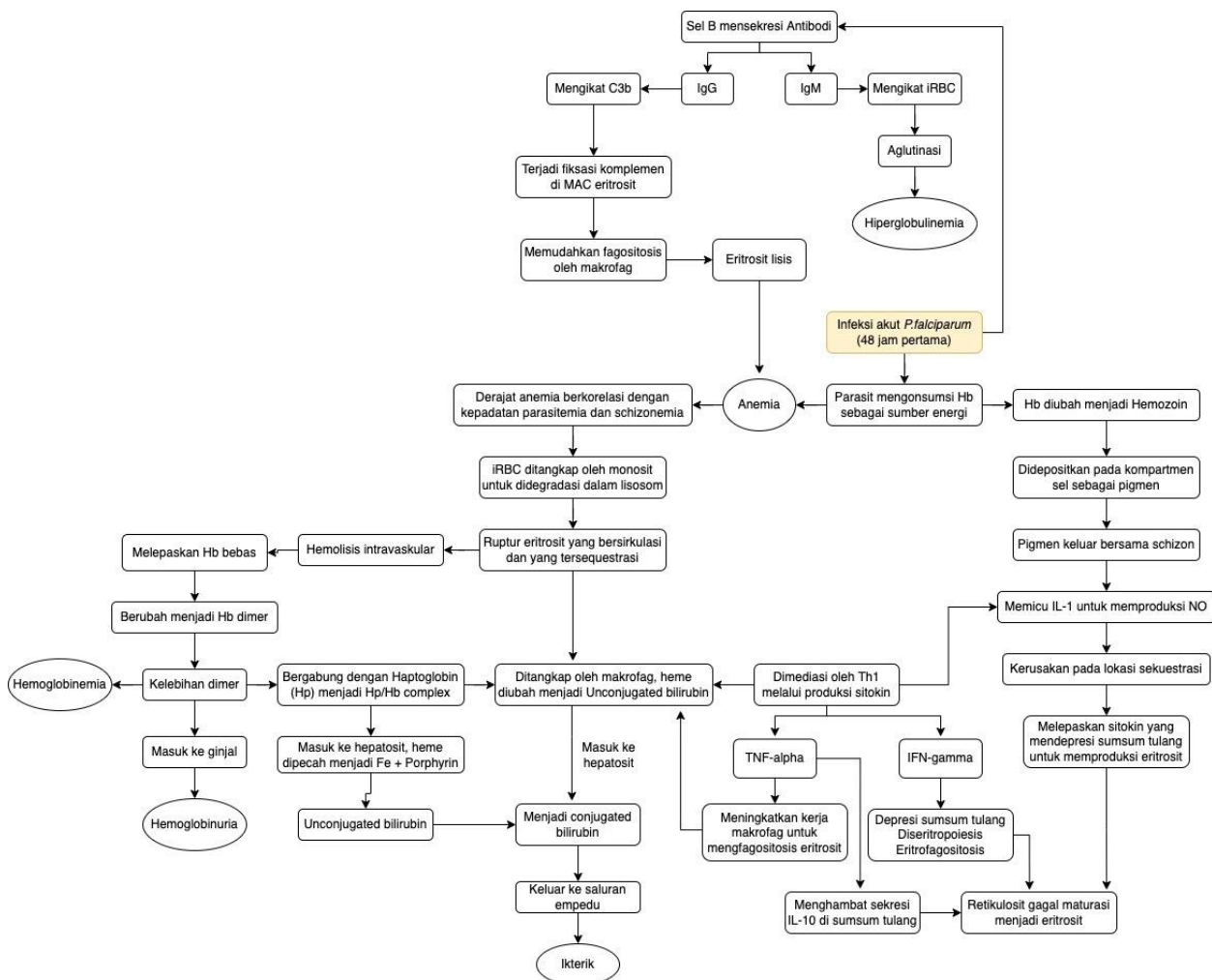

Figure 2. Host immune response to P. falciparum

Malaria toxin is an immunogen produced by parasites. This toxin will induce the host so that it releases molecules bound to the serum. Supernatants from plasmodium contain antigens that trigger the secretion of IL-1, TNF-, and a number of other cytokines in host cells. (Fig. 2) Immunity to these antigens plays a role in the pathophysiology of fever, increased expression of receptors in the endothelium, and in disease resistance. [21]

The protein *glycosyl phosphatidyl inositol* (GPI) plays a role in transmembrane protozoa in the body of mammalian cells. The protein is bound to the terminal end of the carboxyl group which plays a role in the process of signal transduction, maturation, and intracellular protein transport. GPI is also referred to as malaria toxin resistant to protease therapy. Immunogens with GPI content, such as MSP-1 and MSP-2 have been shown to be able to induce IL-1 and TNF-. [22]

The Pf155 antigen, also called *ring-stage erythrocyte surface antigen* (RESA), can also trigger TNF-. As Pα. *falciparum* merozoites invade erythrocytes, MSP precursors are digested by enzymes produced by roptri. Recent research has concluded that immunogenes that have GPI are contained in plasmodium and often undergo glycosylation. GPI functions in the survival of plasmodium, inducing the formation of NO and the release of proinflammatory cytokines. This process will aggravate sequestration of internal organ capillaries and result in the course of malaria.

Schizon protein has a toxic effect because it triggers the release of TNF- massively, resulting in high fever. α*Schizont associated antigen* (SAA) can stimulate T cells to produce IFN-, aided by IL-12 and IL-10. SAA has resistance to proteases, pH changes and heating, and contains phosphate groups that are believed to amplify its toxicity effects. [24] Plasmodium metabolite products are also toxins, such as heme which contains iron. Throughout the asexual phase, parasites feed on hemoglobin as an energy source. This process produces hemozoin as a byproduct deposited as pigment in the cell compartment. When the schizon ruptures, this pigment will escape and induce IL-1. [25]γ

Thrombospondin, CD36, ICAM-1, and VCAM-1 are receptors located on infected erythrocytes. ICAM-1 has a low affinity and plays a role in stabilizing the position of red blood cells along the endothelium, as well as strengthening their binding with CD36. Other polypeptides such as PECAM-1 or CD31 with a mass of 130kDa will be glycosylated in the endothelial circle to assist plasmodium receptors. Negatively charged glycosaminoglycans (GAGs) such as chondroitin sulfate A (CSA) and heparin sulfate (HS) are evenly distributed on the endothelial wall. GAGs play a role throughout the invasion of merozoites forming rosettes. CSA plays a role in placental sequestration of pregnant women, so malaria can be transmitted maternally. [26]

The degree of parasitemia may change over time in malaria infection. Repeated infections followed by the appearance of other antigens are a way for plasmodium to trick the immune system. Both the schizont stage, trophozoites, and merozoites, form antigen variations, so the host's immune response is less efficient. This condition results in infection occurring for quite a long time. Plasmodium modulates the host's immune system through two mechanisms: it forms genetic recombination in the mosquito's body, resulting in extensive genomic changes. The parasite then forms antigenic variations against the gene family, including Pf60, rosettin, and var genes in the parasite's genome. This variation prevents the parasite from being cleared by an immune response. [27]

Plasmodium vivax

P. vivax is a malaria parasite that can be found in tropical and sub-tropical regions other than Africa. It is well known, this type of plasmodium can cause severe disease although it can appear as an asymptomatic infection and mild symptoms. Unlike *P. falciparum* which can invade all erythrocyte subtypes, P. vivax is known to only invade a specific predilection, reticulocytes. [28] Invasion of erythrocytes by binding to transferrin receptor 1 (CD71) and Duffy antigen receptor for chemokines (DARC) present on the surface of reticulocytes. P. vivax merozoites target more reticukocytes expressing immature reticulocyte markers that have recently undergone enucleation and express CD 71. [29] Research conducted by Kanjee, et al. 2020 states that antibodies to CD71 cannot prevent the invasion of merozoites. [30]

Other membrane proteins such as CD98 are reportedly also involved in the invasion of *P. vivax* into reticulocytes. About 70% of barriers to P. vivax invasion of reticulocytes with anti-CD98 antibodies suggest additional new pathways of attack against reticulocytes that could be targets for intervention. [31] During malaria infection, the spleen attempts to eliminate plasmodium by enhancing the immune response. However, the parasite has the ability to evade clearance of the spleen through cytoadherence to infected erythrocytes and create cryptic sites in the tissues of the spleen and bone marrow. [32] Natural immune cells will phagocyte pathogens and attempt to eliminate them by increasing the production of reactive oxidative stress (ROS) in phagosomes as a mechanism called oxidative explosion. ROS production is also released extracellularly thereby increasing oxidative levels in the host body. Oxidative stress can induce inflammation because it produces an inflammatory response through NF-kB activation resulting in the secretion of inflammatory cytokines. The severity of *P. vivax* and *P. falciparum* is associated with oxidative stress levels that indicate oxidation also plays a role in malaria complications. [33]

CLINICAL MANIFESTATION

The time between sporozoites invading humans and onset of febrile symptoms occurs on average within 8-37 days, depending on the infecting species, host immunity degree, or previous treatment history. In addition, it can also be caused by certain modes of transmission, such as mosquito puncture and induction, such as in blood transfusions containing asexual stages. This condition is called the intrinsic budding period which ends with the appearance of the first attack (*first attack*). The next condition is the prepatent period that occurs from when sporozoite invaded until plasmodium was found in a blood smear for the first time, because the parasite count had reached the *microscopic threshold*. The intrinsic budding period of falciparum malaria ranges from 12 days, vivax and ovale malaria 13-17 days, and quaternary malaria (malariae) 28-30 days. [34]

The pathogenesis of malaria differs between people who are non-immune (living outside endemic areas) and those who are semi-immune (living in endemic areas). In non-immune people, the average fever occurs approximately 2 weeks after returning from malaria-endemic areas. A history of fever with a temperature of >38 C is often found in malaria patients. At the beginning of the illness, fever is usually aperiodic, so it is not typical and may be felt every day. Fever can be continuous (continuous febrile), or remitted. It can also be followed by other less specific symptoms, such as diarrhea, nausea, vomiting, cough, muscle pain, dizziness, weakness, headache, and chills. Fever must be distinguished from fever in other diagnoses, such as hepatitis, ARI, dengue fever, typhoid fever, etc.[35]

After 1-2 weeks of fever attacks, there will be interspersed with other symptoms and disease-free periods. Furthermore, fever will be periodic typical for malaria, namely intermittent febris. However, in a number of semi-immune people living in endemic areas, the clinical manifestations of malaria are usually milder than in non-immune patients. In endemic areas, we can find Most patients with parasitemia, although without symptoms. Meanwhile, in pediatric patients, clinical symptoms are often found in the form of joint pain, body chills, dizziness, and headaches. Other conditions that accompany malaria include hepatomegaly, splenomegaly, and anemia. [36]

The periodicity of fever is related to the duration of rupture of mature schizons and sporulation of merozoite that invades blood circulation. In malaria ovale and vivaks, schizon will mature within 48 hours, so the periodicity of fever is reduced. While in quaternary malaria, it occurs with a span of 72 hours. The appearance of fever also depends on the *pyrogenic level and fever threshold* due to the number of parasites in the blood. The shivering stage begins with a feeling of extreme coldness, even to the point of shivering. His pulse was quick but weak, his skin was dry pale, and his lips and fingers turned blue. In adult patients it is sometimes accompanied by vomiting. While in children often followed seizures. This stage occurs for 15 minutes to 1 hour. [37]

The peak phase of fever begins after a sudden chill turns into high body temperature. The patient's face is red, pulse full and throbbing, nausea vomiting, headaches getting heavier, dry skin and feeling hot like burning. The patient then feels very thirsty when his body temperature reaches 41 °C or more. This phase occurs for 2-6 hours. The sweating phase is characterized by temperatures that suddenly drop significantly, sometimes even below the normal threshold. The patient begins to sleep soundly, but upon waking up feels weak. This condition occurs within 2-4 hours. [38]

Typical fever symptoms usually begin during the day and occur over 8-12 hours. Furthermore, the patient will experience apirexia. The longer, the fever will go down because the body begins to adapt to the presence of parasites in the blood vessels and the human immune response that works. Clinical manifestations that appear again after the first attack are called reducency. This happens because parasites in red blood cells increase again in number. Such conditions are usually due to inadequate doses of drugs or due to parasite resistance to the drugs given. This recruitment appears at any time in 4-6 weeks. [39]

DIAGNOSIS

The exact diagnosis of malaria can be made by obtaining the parasite in a blood smear observed under a microscope. Blood preparations with Giemsa reviews are the basis for examination with a light microscope and are still used today as the gold standard for routine diagnosis. Malaria blood preparations can be used in identifying species and calculating parasite density. Examination of thick blood preparations is done by observing 100 microscope fields of view with a magnification of 1000x or equivalent to 0.2 uL of blood. We can calculate the number of plasmodium per microscope field of view. [40]

Quantitative calculation of parasites can be done by calculating the number of parasites per 200 leukocytes in thick blood preparations and the average leukocyte count is 8000 per uL of blood. In thin blood preparations, the number of erythrocytes per microscope field of view is calculated. In addition, it is also important to know the total number of erythrocytes. Furthermore, the number of asexual stage parasites is calculated at least in 25 microscope fields of view. [41]

A number of innovations have been found to optimize the sensitivity of conventional microscopic techniques, one of which is the *quantitative buffy coat* (QBC) technique. The QBC technique is based on *acridine orange*'s ability to daub nucleic acids residing in cells. Blood from the patient's fingertips is collected in a microhematocrit tube containing orange dye and anticoagulants. Then the tube was centrifuged at 12,000 xg for 5 minutes. Plasmodium fluorescence with fluorosense microscopy examination is one of the results of this examination. However, this technique has not been widely utilized like a thick blood smear on conventional examination. This QBC technique can be modified with the use of halogen lamps, also called the Kawamoto technique. [42]

Various findings in the detection of malaria without a microscope are also widely developed with the aim of facilitating the diagnosis. The method detects nucleic acids or proteins derived from plasmodium, one of which is the *rapid antigen detection test (*RDT) based on nitrocellulose paper. In this way, a specific amount of plasmodium protein can be detected in the blood from the patient's fingertips. *Histidine rich protein II* specific *P. falciparum* is used as a marker of infection. The lactate *dehydrogenase* enzyme produced by a number of plasmodium species can be used to diagnose non-falciparum infections, such as *P. vivax* and *P. malariae.* [43]

Recent research has developed many markers for *P. ovale* from the same enzyme. Another enzyme studied is aldolase. *This malaria rapid test* is already available in a number of malaria-endemic areas in the world, including in Indonesia. This test is simple and fast, because the results can be read within 15 minutes. In addition, this test can be done by poorly trained staff and requires little habituation. The material is simple, small, and does not need electricity. Generally, *rapid tests* have specificity and sensitivity values of more than 90%. [44]

The disadvantages of *rapid tests* include: less sensitive if the number of parasites in the blood is low (<100 parasites / uL of blood), unable to quantitatively measure parasite density, the cost is quite expensive, unstable at room temperature >30 C, immature gametocytes may still be detected, and may have antigens still circulating in circulation

several weeks after the parasite is gone, thus giving a false positive reaction. False *positive* results caused by residual antigens and young gametocytes in circulation are generally obtained in asymptomatic patients. It can also occur in patients who have rheumatoid factor. Ideally, this test does not cause *overtreatment* if used to support clinical diagnosis in symptomatic patients. [45]

MANAGEMENT

Chloroquine (CQ) has a blood schizontoside effect on all infections caused by *P. malariae, P. ovale, and P. vivax* as well as *chloroquine-sensitive P. falciparum* . The use of chloroquine as a first-line drug in falciparum malaria is currently limited. In a number of locations, the use of chloroquine is combined with sulfadoxin-pyrimethamine (SP), because it has anti-inflammatory, antipyretic, and effective effects against vivax malaria. The combination SP_CQ is still used as the first choice in Papua New Guinea, Ethiopia, and East Timor because of its better efficacy than SP monotherapy. [46]

Amoadnine includes drugs that have activity and structure similar to chloroquine, as well as anti-inflammatory and antipyretic effects. Amoadline is classified as potent in areas resistant to minimal degrees of chloroquine. The debate over increasing the dose of amoaded more than 25 mg/kg is still ongoing regarding whether to increase the efficacy of the drug or actually cause drug toxicity. In the mid-1990s, harmful adverse effects of amoadline were reported on its consumption as a prophylactic. In 2000, amoadline was no longer recommended as a prophylactic. However, until now amoadan is still used for treatment and is safe in pregnant women. [47]

Antifolate drugs specifically work on dihydropteroate synthase and dihydrofolate reductase which are plasmodium enzymes. Antifolate is no longer recommended as a prophylactic. Sulfadoxine-pyrimethamine has blood schizontoside activity only against falciparum malaria, but no gametocytoside effect. It does not cross-react with artemisinin, halofantrine, quinine, mefloquine, amodiakui and chloroquine derivatives. Folic acid administration in patients receiving sulfadoxine-pyrimethamine is not recommended because it will inhibit the work of sulfadoxine. [48]

Quinine is a powerful malaria drug against sulfadoxine-pyrimethamine and chloroquine resistant *P. falciparum*. In patients infected with uncomplicated falsiparum, quinine is often prescribed with a combination of clindamycin, tetracycline and doxycycline. If the patient is unable to tolerate quinine (continuous vomiting), intramuscular quinine injections may be given. If you are not vomiting, quinine should be given orally again. In patients with severe malaria or malaria with complications, quinine is administered intravenously in 5% dextrose. Now it is a safe drug for pregnant women because it does not cause fetal distress and uterine contractions. [49]

Artemisinin is an antimalarial extracted from the Artemisia *annua plant*. It belongs to the *sesquiterpene group of lactones* with peroxide bonds. Artemisinin has the most rapid blood schizontocide effect compared to other antimalarials. It can be utilized in severe malaria patients and uncomplicated malaria patients. The drug does not have a hypnozoiticidal effect, although it exhibits a gametocytoside effect. On average, malaria patients who obtain artemisinin will show clinical improvement within 1-3 days after ingestion. [50]

Primaquine is a group 8 aminoquinolone that has gametocide activity against all plasmodium species and hypnozoitide against *P. ovale and P. vivax*. This drug is the only option on the market that can be used to prevent recurrence. Other derivatives such as tafenoquine and bulakuin are still in clinical trials. Before prescribing primaquine, G6PD enzyme should be measured in patients to prevent hemolytic anemia. The use of primaquine as a prophylactic is still under research. This drug is contraindicated in pregnant women, because it causes hemolysis in the fetus which is generally G6PD deficiency. [51]

COMPLICATION

Cerebral malaria is a complicator resulting in the highest mortality (81%) when compared to other severe malaria. The clinical manifestations may begin slowly or suddenly after the initial symptoms. Drowsiness, dizziness, and headache followed by focal or generalized seizures, nervous disorders, to decreased consciousness. There may be bleeding in the retina, but few papil edema findings. Neurological manifestations that occur are identical to *heat stroke,* intoxication, acute delirium, epilepsy or meningitis. In adult patients, coma may appear several days after the onset of fever, even sooner in immunocompromised individuals. While in children, coma will occur 2 days after fever which begins seizures and loss of consciousness. [52]

Severe anemia can occur in malaria patients characterized by a sudden decrease in Ht (hematocrit) (<16%) or Hb (hemoglobin) levels of <5g/dL. Anemia is a complicator that is often experienced by children. This condition may worsen when the patient begins treatment, especially if the quantity of parasites in the blood is too high. Anemia is often normochrome normocytic, but reticulocytes are rare. However, microcytic-hypochrome anemia can occur either due to hemoglobin abnormalities or iron deficiency. The pathogenesis of severe anemia can be seen in Figure 1. Anemia may result from massive destruction of red blood cells or depletion of red blood cell production by the bone marrow. In addition, the age of normal erythrocytes also shortens due to the presence of immunoglobulins and complement that modify their surface. [53]

Kidney failure usually occurs in adult patients. Initially blood creatinine and urea increased, followed by oliguria

(urine output <400 ml / 24 hours in adults and 12 ml / kg body weight / 24 hours in children. In more severe conditions, anuria can occur due to acute tubular necrosis. However, there are some cases that are precisely polyuria. Serum creatinine will increase >3 mg/dl. Sometimes kidney failure is followed by pulmonary edema. Mortality can occur >50%, although some acute kidney failure can be reversible. Infusion of physiological solutions in dehydrated patients needs to be done carefully. Peritoneal dialysis or hemodialysis is indicated if oligouria persists after dehydration or if blood creatinine and urea rise significantly. [54]

Pulmonary edema is one of the dangerous complicators with mortality up to 80%. Pulmonary edema will appear a few days after being given antimalarials or precisely when the general condition of the patient improves and the parasitemia gradually disappears. A number of cases show a picture similar to *acute respiratory distress syndrome* (ARDS) which is an indication of increased pulmonary permeability. This complication may also be iatrogenic due to excessive fluid administration. These two conditions overlap and may occur together in one patient. An early sign of pulmonary edema is an increase in breathing frequency accompanied by a decrease in arterial pO2 pressure. Hypoxia experienced will trigger seizures and impaired consciousness, so that the patient is not helped. If pulmonary edema is found in infected pregnant women, then we give diuretics and oxygen with high concentrations. [55]

Hypoglycemia becomes a frequent manifestation of malaria. The patient will feel anxious, sweating, lightheadedness (floating), tachycardia, chills, oligouria, shortness of breath, and pupil dilation. This condition may worsen resulting in rowdy tingling, shock, seizures, and coma. Blood sugar concentrations drop to <40 mg/dL. Patients can be given 50 cc of 50% dextrose in physiological fluids, then administered within 5 minutes. This is followed by an intravenous infusion of 5% or 10% dextrose. Next, monitor blood sugar periodically. [56]

PREVENTION

Environmental conditions have a significant influence on the incidence of malaria in a region. Climate conditions also affect malaria cases. In cold climates, malaria transmission may only occur in summer. The incubation period is also influenced by climate. In areas less favorable to vector biology, malaria prevalence may be smaller. The hilly mountainous regions are usually free of malaria. Conditions that result in changes in the location of vector parents greatly affect the incidence of malaria and have a good or bad impact on malaria cases in the region. Humidity, air temperature, and rainfall are also risk factors for the spread of malaria. [57]

Population/vector density and rainfall in Indonesia have different influences between regions. In Central Java rainfall has no effect on mosquito density, while in West Java it is the opposite. High rainfall will affect the increase in water storage locations suitable for mosquito breeding points. The El Niño cycle was also reported to correlate with an increased risk of malaria prevalence. Milkfish ponds for example, this is a *man made breeding place* for *Anopheles sundaicus.* While the processing of rice fields that do not stop becomes breeding *places* for *Anopheles aconitus.* Development activities can also result in the formation of *breeding places* for vectors, so that the incidence of malaria worsens with the development. [58]

The goal of prevention is to reduce morbidity and mortality, so that it is no longer a public health problem. Prevention begins by breaking the parasite's life cycle, namely by eradicating plasmodium in the host's body through treatment or by eradicating mosquitoes through a number of strategies. Ideally, eradication is done through both methods at once, namely curing parasite carriers and eliminating mosquito breeding sites or exterminating mosquitoes using various insecticides. International citizens are committed to preventing malaria with a *roll-back malaria* (RBM) approach through strategies: early detection and appropriate treatment; the active role of citizens in malaria eradication; improving the quality of malaria eradication and treatment through increasing the capacity of health workers involved. [59]

The Malaria Eradication Movement (Gebrak Malaria) in 2001 is still an operational form of RBM. To prevent malaria, there are 2 efforts, namely control *and eradication.* Malaria eradication programs in Indonesia carried out so far such as: initial diagnosis and treatment; insecticide-treated mosquito net program; spraying; passive and active detection surveillance; fever surveys and migrant surveillance; early detection and epidemic control; *larvaciding;* improvement of the expertise of Health workers. [60].

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