

Severe Vivax Malaria Infection in Infants : A Case Report

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Abstract

Plasmodium vivax presents a significant challenge to malaria elimination efforts, as a single primary infection may result in multiple relapses over months to years. This is due to the ability of parasite to form dormant liver stages (hypnozoites), which can reactivate following the initial acute episode. Recurrent infections substantially increase the risk of severe anemia, facilitate ongoing transmission to other individuals, and in some cases may lead to death. Although *Plasmodium vivax* is associated with lower mortality compared to other *Plasmodium* species, the global burden of morbidity attributable to this parasite remains considerable.

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INTRODUCTION

Malaria is a parasitic infectious disease caused by *Plasmodium* species and transmitted to humans through the bite of an infected female *Anopheles* mosquito.¹ In 2023, an estimated 263 million malaria cases were reported across 83 endemic countries worldwide. Within the World Health Organization (WHO) South-East Asia Region, eight countries remain malaria endemic, contributing approximately 4 million cases or 1.5% of the global malaria burden. Indonesia accounts for nearly one-

third of these cases, with *Plasmodium vivax* responsible for more than 48% of the estimated infections.² The misconception that *P. vivax* infection results only in mild clinical manifestations has contributed to slower progress in controlling this parasite compared to *P. falciparum*. However, increasing evidence demonstrates that *P. vivax* can cause severe malaria and life-threatening complications, particularly among children in endemic regions such as India, Brazil, and Indonesia.^{3,4} Severe malaria is a critical condition and a leading cause of blood transfusions in areas with

high transmission intensity.^{5,6} Delayed recognition and management can be fatal. Therefore, early detection and timely intervention are essential, particularly in cases caused by *Plasmodium vivax* infection.¹

CASE PRESENTATION

An 11-month-old female infant was admitted with a history of fever persisting for the past four weeks. The fever occurred daily, with a maximum temperature of 40°C, and was not associated with afebrile intervals except following the administration of antipyretic medication. Although the fever subsided temporarily after antipyretic use, it recurred within a few hours. The febrile episodes were often preceded by chills and were accompanied by profuse sweating.

Two weeks prior to admission, the patient experienced a single seizure episode lasting approximately three minutes. The seizure was generalized, characterized by tonic-clonic jerking movements of the entire body, and occurred during a febrile episode when the patient's temperature reached 40 °C. Post-ictally, the patient regained full consciousness and no further seizures were reported.

Over the past two weeks, the child was noted to appear pale. There was no history of bleeding manifestations (e.g., epistaxis, gum bleeding, melena, or hematochezia), jaundice, nausea, vomiting, cough, or respiratory distress. Urination was normal, with clear yellow urine output. There was no history of recent travel to malaria-endemic areas.

On physical examination, pallor was observed in the extremities. There were no signs of respiratory distress, nasal flaring, rhonchi, wheezing, or palpable hepatosplenomegaly. Laboratory investigations revealed microcytic hypochromic anemia, thrombocytopenia, and impaired renal function. Rapid diagnostic testing (RDT) was positive for *Plasmodium vivax*. Microscopic examination of thick blood smears demonstrated *Plasmodium* species positivity, while thin smears confirmed *Plasmodium vivax*. The parasite distribution showed 81% asexual stages (trophozoites, schizonts, and ring forms) and 19% sexual stages (gametocytes), with a parasite density of 1,896 parasites/μL.

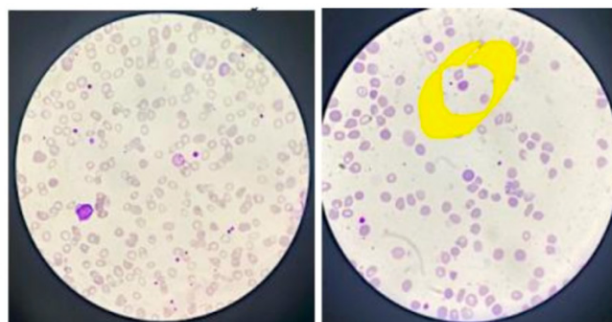


Figure 1. Blood Smear Test

DISCUSSION

Malaria is a life-threatening disease caused by the infection of red blood cells by protozoan parasites of the genus *Plasmodium*, transmitted to humans through the bite of infected female *Anopheles* mosquitoes. Five species of *Plasmodium* are known to infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*. *P. falciparum* remains the leading cause of malaria in endemic regions, followed by *P. vivax*. Severe malaria is most commonly associated with *P. falciparum* infection, but can also result from *P. vivax* and *P. knowlesi*.⁷⁻⁹

According to data from the Ministry of Health of the Republic of Indonesia, in 2024 there were 418,546 confirmed malaria cases, with *P. vivax* accounting for 34% of the total. Children aged 1–14 years represented 34% of these cases, while infants under 1 year accounted for 1.8%. Currently, 401 districts/cities in Indonesia are considered malaria-free. In areas with moderate to low transmission where population immunity is limited, all age groups are at risk of *P. vivax* infection. In contrast, in regions of high endemicity with mixed transmission (*P. falciparum* and *P. vivax*), partial immunity develops gradually through repeated exposure. Infants and young children, who lack prior exposure, remain the most vulnerable to infection and to severe or recurrent disease. Consequently, children and adolescents contribute significantly to the global burden of malaria. In endemic areas, population immunity to *P. vivax* develops gradually, but children continue to bear

the heaviest burden because of their limited clinical immunity. Repeated relapses contribute to anemia and may adversely affect growth and development. Besides age-related lack of immunity, proximity to vector breeding sites further increases the risk of infection in children. Socioeconomic factors, including maternal education and rural residence or travel, are also linked to higher disease burden.¹⁰

In this case, an 11-month-old girl presented with intermittent fever for one month. The fever occurred daily, reaching up to 40 °C, without fever-free intervals except after antipyretic administration. Febrile episodes were often preceded by chills and followed by profuse sweating. The patient resided in North Sumatra and had no history of travel to malaria-endemic areas prior to symptom onset. Physical examination revealed anemic palpebral conjunctiva, with other findings within normal limits. Acute *Plasmodium vivax* malaria without complications typically presents with similar features in both children and adults, ranging from asymptomatic infection to fever of unknown origin. Asymptomatic cases are less frequent in children under one year. Fever is the hallmark symptom of malaria, resulting from the rupture of mature schizonts. In *P. vivax* infection, schizonts mature every 48 hours, producing a tertian fever pattern. However, this classical periodicity is often absent in the early stages of illness, and its absence cannot exclude the diagnosis.^{9,11}

With progression, some patients develop classic malaria paroxysms, consisting of three phases: (1) a cold stage (15–60 minutes) with chills and rigors, (2) a hot stage (2–6 hours) with high fever (up to 41 °C), flushed and dry skin, headache, nausea, and vomiting, and (3) a sweating stage (2–4 hours), during which temperature declines rapidly with profuse sweating.¹²

Laboratory findings in this patient showed severe anemia (hemoglobin 5.8 g/dL) and thrombocytopenia (94,000/mm³). Malaria testing was positive for *P. vivax*, with peripheral smear demonstrating a parasitemia index of 1,896 parasites/μL. Based on these findings, a diagnosis of *P. vivax* malaria was established. Given the hemoglobin level <7 g/dL and the patient's residence in a non-endemic area, this

case was classified as severe malaria.

Severe malaria is defined as the presence of asexual stages of *Plasmodium falciparum*, *Plasmodium vivax*, or *Plasmodium knowlesi* in peripheral blood with at least one of the following clinical manifestations according to WHO criteria^{2,5}:

- Altered consciousness (GCS <11 or Blantyre <3 for children unable to speak)
- Muscle weakness (inability to sit or walk)
- Recurrent seizures (more than two episodes within 24 hours)
- Metabolic acidosis (plasma bicarbonate <15 mmol/L)
- Pulmonary edema (radiological evidence or oxygen saturation <92% and respiratory rate >30 breaths/min)
- Circulatory failure or shock (capillary refill time >3 seconds, systolic blood pressure <80 mmHg; in children <70 mmHg)
- Jaundice (bilirubin >3 mg/dL with parasite density >100,000/μL in falciparum malaria; >20,000/μL in knowlesi malaria)
- Abnormal spontaneous bleeding
- Hypoglycemia (blood glucose <40 mg%)
- Severe anemia (in children in endemic areas <12 years: hemoglobin <5 g/dL and hematocrit <15%; in moderate-to-low endemicity areas: hemoglobin <7 g/dL, hematocrit <21%)
- Hyperparasitemia (parasites >2% of erythrocytes or >100,000/μL in low-endemic areas; >5% of erythrocytes or >250,000/μL in high-endemic areas)
- Hyperlactatemia (lactic acid >5 mmol/L)
- Renal dysfunction (serum creatinine >3 mg% or blood urea >20 mmol/L)

Blood smear and microscopic examination are considered the gold standard for laboratory confirmation of malaria. Blood smear examination should include both thick and thin smears. Staining is ideally performed using Giemsa. Thick smears are used to detect the presence of parasites, while

thin smears provide greater resolution for observing the morphology of red blood cells and parasites, allowing for *Plasmodium* species identification and quantification of parasite density. This information is essential for determining treatment strategies and patient monitoring.⁸

In severe *Plasmodium vivax* infection, common clinical manifestations include anemia, thrombocytopenia, jaundice, and acute respiratory distress syndrome. Severe anemia is the most frequent manifestation in children. Its incidence is higher in *Plasmodium vivax* malaria than in *Plasmodium falciparum*, with infants and children under five years of age being the most vulnerable group. In areas with high endemicity such as Papua, Indonesia, up to one third of infants hospitalized with *Plasmodium vivax* infection develop severe anemia.¹⁰ This condition often develops rapidly following infection with high parasitemia and tends to occur earlier and with greater severity compared to cases with low parasite density.⁹

A study by Castelino et al. reported anemia in 23 percent of patients infected with *Plasmodium vivax*. In children with recurrent infections, limited recovery time contributes to progressive anemia, while in some patients a single episode can cause a drastic decline in hemoglobin.¹³

This is partly due to the strong preference of *Plasmodium vivax* for infecting reticulocytes, red blood cells that have exited the bone marrow within the preceding 14 days. The natural cycle of erythrocytes infected by *Plasmodium vivax* or *Plasmodium falciparum* involves parasite replication for approximately 48 hours before rupture and release of merozoites. Peripheral parasitemia in *Plasmodium vivax* infection is generally lower than in *Plasmodium falciparum*, and parasitemia exceeding 2 percent is rare. However, the premature destruction of *Plasmodium vivax* infected reticulocytes is sufficient to cause severe anemia within a few months by disrupting the supply of mature erythrocytes. Although parasitemia levels are usually lower in *Plasmodium vivax* than in *Plasmodium falciparum*, the absolute number of red blood cells removed from circulation,

and therefore the degree of anemia, is often similar. This is explained by the fact that in *Plasmodium vivax* malaria, approximately 34 non infected erythrocytes are cleared for every one infected cell, compared with a ratio of about 8 to 1 in *Plasmodium falciparum*. Similar to *Plasmodium falciparum*, *Plasmodium vivax* can bind to uninfected erythrocytes in a process known as rosetting, but unlike *Plasmodium falciparum*, *Plasmodium vivax* infected erythrocytes have a limited ability to adhere to endothelial cells, and sequestration in the microvasculature is not a major factor in its pathogenesis.¹⁴

Thrombocytopenia is frequently observed in malaria and has a strong association with severe disease progression that may require rapid and aggressive management. It contributes to complications such as an increased risk of haemorrhage, including spontaneous bleeding. The precise mechanism of thrombocytopenia in malaria is not fully understood, but proposed explanations include increased platelet consumption or destruction, reduced platelet production, or a combination of coagulation abnormalities, oxidative stress, splenomegaly, and bone marrow suppression. Platelets may also act as cofactors in the pathogenesis of severe malaria. In addition, antibody mediated platelet destruction, in which antibodies bind to platelets and accelerate their depletion, has been suggested as a contributing factor. Thrombocytopenia is more frequently associated with *Plasmodium falciparum* than with *Plasmodium vivax*.¹⁵

The primary goal of treating severe malaria is to prevent death, while secondary goals include preventing morbidity and recurrence of infection. It is therefore essential to achieve effective therapeutic concentrations of antimalarial drugs as quickly as possible. Although *Plasmodium vivax* malaria is generally considered mild with a low case fatality rate, it may still cause debilitating fever with progressive anemia. In some cases, *P. vivax* can also present as severe disease similar to *P. falciparum* malaria.

Parenteral artesunate is the treatment of choice for all cases of severe malaria. Current recommendations advise administering parenteral antimalarial drugs for at least 24 hours, regardless

of the patient's ability to tolerate oral medication, before continuing with oral therapy. The recommended artesunate dose for both children and adults is 2.4 mg/kg body weight per dose. However, for children weighing <20 kg, a higher dose of 3 mg/kg body weight per dose is required because younger children exhibit faster metabolism and clearance, resulting in lower plasma concentrations. Intravenous artesunate is administered at hours 0, 12, and 24.^{2,13,16} potentially obviating the need for G6PD testing. Hemizygous G6PDd healthy adult Thai and Burmese male volunteers were admitted to the Hospital for Tropical Diseases in Bangkok. In Part 1, volunteers were given ascending dose primaquine regimens whereby daily doses were increased from 7.5 mg up to 45 mg over 15-20 days. In Part 2 conducted at least 6 months later, a single primaquine 45 mg dose was given. RESULTS: 24 volunteers were enrolled in Part 1, and 16 in Part 2 (13 participated in both studies Following initial parenteral therapy, treatment must be continued and completed with a full dose of artemisinin-based combination therapy (ACT). Several ACT regimens are available, including artesunate plus amodiaquine, artemether plus lumefantrine, or dihydroartemisinin plus piperaquine (DHP).⁵

In Indonesia, the most widely used regimen is DHP, a fixed-dose combination containing 40 mg dihydroartemisinin and 320 mg piperaquine phosphate. According to WHO recommendations, the dihydroartemisinin dose for *P. vivax* malaria is 2–4 mg/kg body weight/day and the piperaquine dose is 16–32 mg/kg body weight/day, administered once daily for three days. Current treatment of *P. vivax* malaria requires DHP combined with primaquine. Primaquine is given for 14 days at 0.25 mg/kg body weight per day. It is contraindicated in infants under six months, pregnant women, and breastfeeding mothers of infants under six months.^{2,5}

The artemisinin component rapidly clears blood-stage parasites, reducing parasitemia by approximately 10,000-fold in each 48-hour asexual cycle. Artemisinin also has activity against sexual gametocytes, which are essential for malaria transmission. The partner drug with a longer half-

life clears residual parasites and provides protection against resistance to artemisinin derivatives. The three-day ACT regimen covers two asexual cycles, ensuring that only a small number of parasites remain for clearance by the partner drug. This strategy reduces the risk of resistance development. Shorter regimens of one to two days are not recommended, as they are less effective, have weaker impact on gametocytes, and offer insufficient protection for the slowly eliminated partner drug.^{2,7}

Control of *P. vivax* malaria remains challenging due to the dormant liver stage (hypnozoites) and the early appearance of gametocytes. Without hypnozoitocidal treatment, relapse accounts for up to 80% of *P. vivax* cases. Primaquine is the only available hypnozoitocidal drug, essential for eliminating dormant liver forms and gametocytes, making it a cornerstone of *P. vivax* control and elimination. Its efficacy is influenced by dose, number of activated hypnozoites, host immunity, and cytochrome P450 genetic polymorphisms.¹⁷ WHO recommends a 14-day primaquine course at 0.25–0.5 mg/kg/day for eradication of liver stages and prevention of relapse. Primaquine acts by generating toxic radicals effective against non-replicating forms, including both hypnozoites and gametocytes.^{2,17}

The main obstacles to the use of primaquine are the risk of hemolytic toxicity in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and poor adherence to the prolonged treatment regimen. The strategy of administering primaquine in lower doses over a longer duration is intended to minimize toxicity, which is typically associated with higher doses given over shorter periods. If the patient's G6PD status is unknown and testing is unavailable, hemoglobinuria can be monitored using the Hillmen urine color chart, where values above 5.20 are considered indicative of hemolysis.¹⁶ potentially obviating the need for G6PD testing. Hemizygous G6PDd healthy adult Thai and Burmese male volunteers were admitted to the Hospital for Tropical Diseases in Bangkok. In Part 1, volunteers were given ascending dose primaquine regimens whereby daily doses were increased from 7.5 mg up to 45 mg over 15-20 days. In Part 2

conducted at least 6 months later, a single primaquine 45 mg dose was given. RESULTS: 24 volunteers were enrolled in Part 1, and 16 in Part 2 (13 participated in both studies

In addition to antimalarial therapy, comprehensive supportive management plays a critical role in addressing complications and improving prognosis. Severe malaria is often associated with rapid-onset anemia. In high-transmission settings, blood transfusion is generally recommended for children with hemoglobin levels below 5 g/100 mL (hematocrit <15%), whereas in low-transmission areas the threshold is higher, at hemoglobin 7 g/100 mL (hematocrit 20%). Nevertheless, transfusion decisions must always be individualized based on the patient's clinical status.^{2,7}

In this case, the child received parenteral artesunate for 24 hours, with three doses administered at 0, 12, and 24 hours, totaling 27 mg (3 mg/kg). Therapy was then continued with DHP at ½ tablet daily (dihydroartemisinin 20 mg + piperazine 160 mg) for 3 days. Primaquine was prescribed at ¼ tablet daily for 14 days, with urine color monitoring to detect potential hemolysis. The patient was closely monitored through clinical assessment and serial blood smears. Following the first dose of artesunate, the fever subsided, and by the second day of treatment, the parasite density decreased markedly from 1,896/μL at admission to 184.5/μL. On the third day, no parasites were detected on blood smear, demonstrating a favorable therapeutic response.

CONCLUSION

If a child presents with persistent fever lasting for one month, accompanied by a decline in hemoglobin levels and confirmed *Plasmodium vivax* infection on thick and thin blood smears, prompt initiation of appropriate treatment is essential. Early therapy facilitates clinical recovery and improves prognosis, as reflected by symptomatic improvement and clearance of parasites on subsequent blood smear examinations.

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