Developments in Malaria Treatment in Bandar Lampung

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INTRODUCTION

Until now, malaria is still an important community health problem in Indonesia. Prior to the use of DDT in the year 1959, it can be said that there is no region in Indonesia that was free from malaria except for the high lands.

Lampung is a region that is endemic for malaria, but at the peak of eradication in the year 1963, Lampung was protected from malaria, even though in the year 1965 there were still malaria foci in Lampung, with an SPR? Of more than 2%.[1] Up to the year 1989, for regions outside of Java and Bali, Lampung has the least prevalence for malaria.[1]

The halt in malaria eradication using DDT was due to a change in the environment due to large developments that resulted in increased vector nesting sites, might have been the cause for the increase in malaria cases lately in Bandar Lampung.

Some community members have a bad habit of freely consuming anti-malaria medications in case of fever, without adequate indication or accurate dosage. In addition, medical and paramedical workers seem to administer anti-malaria medications incorrectly. These conditions could create "multi-drug resistant" malaria that would consequently create a problem for malaria treatment, especially since new alternative malaria medications are still difficult to obtain in Bandar Lampung.

Concern about drug-resistant malaria cases in Bandar Lampung is quite substansialed, since there have been many malaria cases that demonstrated no response towards chloroquine or even sulfadoxine-pyrimetamin. Since 1978, there have been reports of chloroquine or even S/P resistant malaria.[2,3] Thus, there is a need to consider the provision of new alternative medications, especially "life-saving" medications, such as arthemycin derivatives or halofantrine. Administration of beneficial antibiotics for malaria, such as doxycyclin, clindamycin, cyprofloxacin, etc., should be attempted.

ETIOLOGY

There are 4 species from the Plasmodia genus, which are as follow:

1. *Plasmodium falciparum*,
2. *Plasmodium vivax*,
3. *Plasmodium ovale*, and
4. *Plasmodium malariae*.

Plasmodium falciparum and *plasmodium vivax* are the main cause of malaria in Indonesia. *Plasmodium ovale* has only been reported in Irian and Timor, while *plasmodium malariae* has rarely been found.

LIFE CYCLE

The infective form of Plasmodium is called a sporozoite, which enters the human blood through mosquito bites from infected mosquitoes. In 30 minutes, the sporozoite in the blood disappears, mostly destroyed by fagocytic cells, while a large number enters the liver parenchyma cells and begin its asexual phase.

During the exoerythrocyte phase, the sporozoite enters the liver parenchyma multiplies, which is called the pre-erythrocytic schizogony process, resulting in thousands of merozoites. After 6 to 16 days, the schizonts burst, releasing the merozoites into the bloodstream.

Unlike in the case of *Plasmodium falciparum* and *P. malariae*, all of the schizonts ruptures simultaneously, and no schizonts are left in the liver cells, only a portion of the schizonts of *Plasmodium ovale* and *Plasmodium vivax* multiplies and ruptures within 6 to 9 days, while the rest become dormant within the liver cell until several weeks, months or even years, before re-entering the erythrocytic phase. This dormant form is known as

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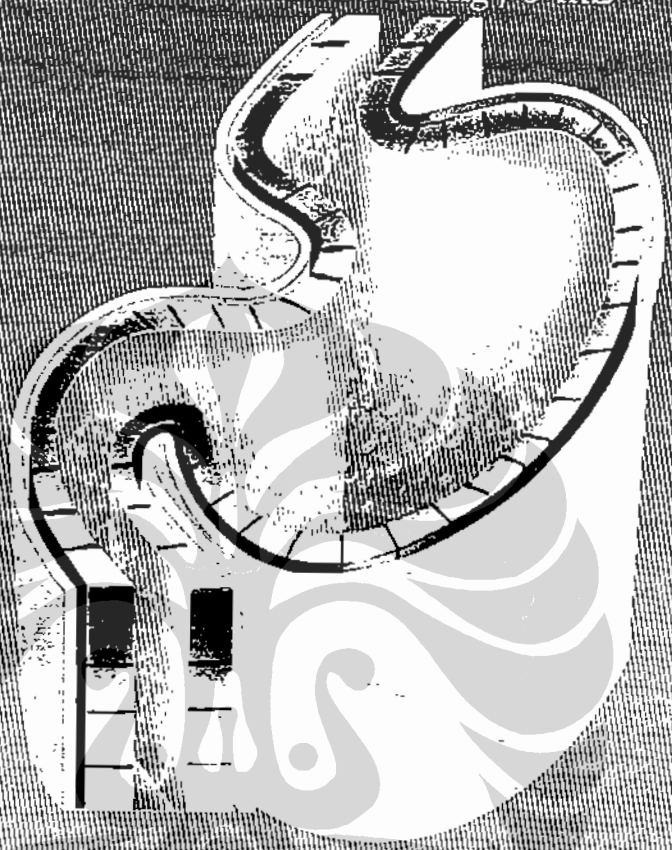

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the hypnozoite.

Plasmodium falciparum and *Plasmodium malariae* do not have a permanent exoerythrocytic phase, so that relapse never occurs in this species. Recurrent paracytemia is due to proliferation of a fixed number of the erythrocytic form, a process known by the term recrudecention.

The erythrocytic phase consists of merozoites that are released by the schizont tissue and would re-infect new erythrocytes and begin a new erythrocytic phase. In the blood, it develops from a ringform trophozoite, which develops into an amuboid trophozoite and then into a schizont. The schizont then ruptures and releases merozoites that are ready to infect new erythrocytes, which is known as the schizogony, erythrocytic phase. This cycle continues where the periodicity of schizogony depends on the species of Plasmodium.

Sexual phase: after 3 to 5 days after the infection, some of the merozoites turn into the sexual gametocyte. The male gametocyte is called the microgametocyte, while the female form is called the macrogametocyte.

The vector phase: if a mosquito bites an infected human whose blood contains the micro and macrogametocyte, sexual reproduction occurs in the stomach of the mosquito.[4]

Transmission of infection:

1. Through mosquito bites,
2. Blood transfusion,
3. Congenital malaria, and
4. Contaminated needle. [4]

IMMUNITY

In general, communities residing in malaria-endemic regions will develop certain immunity against infection. Clinical symptoms, level of paracytemia and formation of gametocyte would be reduced by such immunity. Holloendemic areas and hyperendemic areas have such a high level of gametocyte production in babies and little children with lower immunity, while paracytemia in adults are low due to a high titer of antibody. Other factors that influence immunity are as follows:

- Genetic factors: development of Plasmodium falciparum is impeded by patients with high levels of fetal hemoglobin, sickle cell anemia patients and those with G6PD enzyme deficiency.
- Congenital malaria: rarely found, since babies ages 6 to 12 months receive maternal immunity through the placenta, except in mothers with very low immunity, such as those in areas with low prevalence of malaria.
- Nutritional factors: malnutrition patients would suffer from more severe malaria, while those who receive inadequate intake of para amino benzoic acid in their diet are on the other hand protected from severe and fatal malaria, although they regain susceptibility after nutritional improvement.[4]

PATHOPHYSIOLOGY

Changes in the pathophysiology of malaria begins as an infected erythrocyte which ruptures, releasing merozoites that infect new erythrocytes, while the exoerythrocytic schizon only produces a local reaction, while sporozoites and gametocytes do not produce any reaction. However, the patophysiology of malaria has not been completely understood. Certain processes, as follows, are caused by a number of contributing factors:

- Destruction of erythrocytes: destroyed erythrocytes are not just due to rupture of infected erythrocyte, but also due to phagocytosis of infected and uninfected erythrocyte, causing anemia and tissue anoxia.
- Disseminated intravascular coagulation, often occurring in severe cases with high levels of paracytemia, known as the increase in fibrin degradation products and thrombocytopenia.
- Macrophage endotoxin mediators: during schizogony, infected erythrocytes release a substance that is the same as bacterial endotoxin. Such endotoxin stimulates the macrophage to produce mediators that play an important role in the pathophysiology of malaria.
- Sequestration of erythrocytes inside the capillaries: erythrocytes infected by *Plasmodium falciparum* would then form a knob on its surface. The knobs contain malaria antigens, which then reacts with malaria antibodies. These knobs also help erythrocytes adhere to the capillary endothelium of inner organs, which is why the schizogony process occurs more often in the capillaries of inner organs compared to in the peripheral parts of the body. That is why schizons are rarely found in peripheral blood examinations, except in severe paracytemia. Agglutination that occurs in the capillaries of inner organs cause an obstruction, which results in increased capillary permeability, causing fluid and protein leakage, thus causing tissue anoxia and edema, which could be serious and fatal.

DIAGNOSIS

a. Clinical findings
b. Parasites in the bloodstream
c. Serologic findings.[6]

Clinical Findings

The Patients usually complain of:

a. Fever, most patients with malaria suffer from fever. Classic fever is known by the triage of:
   - Fever
   - Chills
   - Sweats

   After the three phases, some patients are no longer ill and have no significant complaints, while the remaining number continue to suffer complaints. In endemic areas, complaints are relatively mild, or even without complaints. Sometimes the triad is not even present, which leaves the disease undiagnosed. A study in Irian Jaya demonstrated that only 50% of patients with malaria parasites in their bodies suffer from fever.[5]
b. Headache,
c. Fatigue and weakness,
d. Muscle cramps and low backache,
e. Vertigo,
f. Nausea, or even vomiting, sometimes diarrhea and stomach cramps
g. Sometimes cough.[4]

Clinical Signs:

a. Splenomegaly, in approximately 25% of adult cases,
b. Hepatomegaly, in approximately 15%,
c. Liver dysfunction,
d. Renal dysfunction,
e. Pulmonary edema, and
f. Reduced consciousness.[4]

Laboratory Findings:

a. Anemia
b. Leukocytosis in the beginning, continued by leukopenia
c. Haemolytic jaundice
d. Reticulocytosis,
e. Thrombocytopenia in severe cases.[4]

TREATMENT

1. Patients without complications, who suffer from chloroquine sensitive malaria, for all species: phosphate chloroquine with various administration procedures as follows:
   a. 0 (600) 24 (600) 48 (300).[7]
   b. 0 (600) 12 (600) 24 (600) 48 (300).[7]
   c. 0 (600) 6 (600) 24 (600) 48 (300).[8]
   + 14 mg alkaline Primaquine (26.3 mg of saline)
   a. 3 days for *P. falciparum*
   b. 14 days for *P. vivax* and *P. ovale*
2. Severely ill patients with chloroquine sensitive malaria:
   a. 10 mg/kg bodyweight of quinine dyhydrochloride, after improvements, directly switch to oral chloroquine, followed by administration of primaquine as in the first method, or
   b. 250 mg of (saline) chloroquine hydrochloride every 6 hours, after improvements, switch to oral, followed by administration of primaquine as above.
3. For patients with chloroquine resistant malaria:
   a. According to the Department of Health:
   - 500 mg of sulfadoxine – 25 mg pyrimethamine 2 tablets + 45 mg of primaquine
   - 3 x 400 mg of quinine + 45 mg of primaquine.[7]

   b. According to Current Medical Diagnosis and Treatment:
   - 10 mg/kg bodyweight of quinine 3 times daily for 3 to 7 days, plus one of the following:
     - 3 tablets of sulfadoxine-pyrimethamine, or
     - 2 x 25 mg of pyrimethamine, for 3 days, 4 x 500 mg of sulfadiazine, for 5 days, or
     - 4 x 250 – 500 mg of tetracycline, for 7 days, or
     - 100 mg 2 daily doxycycline for 7 days, or
     - 3 x 900 mg of clindamycine for 3 days.
   - 15-25 mg/kg bodyweight of mefloquine, single dose or divided in 2 doses administered after 6 hours
   - 500 mg halofantrine every 6 hours, 3 administrations.[8]

   c. According to Davis TME: one of three regimens:
   - 10 mg/kg bodyweight of sulphate quinine every 8 hours for 7 days, plus 100 mg of doxycycline per day, for 7 days.
   - 4 tablets of malarone (atavaquon 250 mg + 100 mg proguanil) - daily for 3 days.
   - 15 mg/kg bodyweight of mefloquine, in divided doses for the following days.[10]

   d. Antimalaria antibiotics:
   - Tetracycline, dose: 4 mg/kg bodyweight in 4 doses for 7 consecutive days.
   - Doxycycline: 2.5 mg/kg bodyweight once daily for 7 consecutive days.

- Clyndamycine: 2 x 300 mg daily for 5 consecutive days.
- Azytromycine: 250 mg/day.[11]

4. Treatment of advanced malaria

Principle: treat immediately and optimally with parenteral medications.

Advanced malaria includes:

1. Cerebral malaria (coma of minimal ½ hour)
2. Severe anemia (Hb of less than 5 g%)
3. Renal failure (urine output of less than 400 ml/24 hours, serum creatinine of more than 3 mg%)
4. Pulmonary edema
5. Hypoglycemia (blood sugar of less than 40 mg%)
6. Shock or hypotension
7. Spontaneous hemorrhage
8. Recurrent convulsions (more than twice in 24 hours)
9. Acidemia (pH level of less than 7.25 or bicarbonate level of less than 15 mmol/L)
10. Macroscopic hemoglobinuria (black water fever)
11. Hyperparasitemia (of over 10%)
12. Jaundice (serum bilirubin of more than 2.5 mg%)
13. Hyperpyrexia (rectal temperature above 40 degrees Celsius).[12,13]

a. Chloroquine-sensitive malaria:

- Intravenous: starting with 10 mg/kg bodyweight/500 ml of 5% dextrose in 8 hours, followed by 15 mg/kg bodyweight/24 hours.
- Intramuscular/subcutaneous: 3.5 mg of alkaline chloroquine/kgBB every 6 hours, or 2.5 mg of alkaline chloroquine/kg bodyweight every 4 hours.
- Nasogastric: equivalent to oral chloroquine administration

b. Chloroquine-resistant malaria:

- 7 mg of saline HCl quinine/kg bodyweight, followed by 10 mg of alkaline quinine/kg bodyweight in 4 hours, repeat every 8 hours, or
  20 mg/kg bodyweight in 4 hours, followed by 10 mg/kg bodyweight in 2-8 hours, repeat every 8 hours, or 10 mg/kg bodyweight in 5% Dextrose, continuous infusion for 8 hours, seem to be better than administration of an initial dose of 20 mg/kg bodyweight.[14]
- Arthemycine derivatives:
  - Arthesunate: initial dose of 2 mg/kg bodyweight (intravenously), followed by 1 mg/kg bodyweight the following 12 hours, followed by 1 mg/kg bodyweight/day
  - Arthemeter: initial dose of 3.2 mg/kg bodyweight, followed by 1.6 mg/kg bodyweight/day. Studies in North Sulawesi, Eastern Kalimantan,[15] as well as India demonstrate satisfactory results, particularly in the form of more rapid regain of consciousness and decline of fever compared to the use of quinine, even though mortality rates are not significantly different. Arhemeter is a schizontocide as well as gametocide.[16] Thus, this drug should be arranged as an alternative medication in patients with multi-resistant malaria in Bandar Lampung.

TREATMENT OF MALARIA PATIENTS AT THE DEPARTMENT OF INTERNAL MEDICINE, BANDAR LAMPUNG.

1. Uncomplicated cases:
   Chloroquine 0 (600) 6 (300) 24 (300) 48 (300)
   14 mg of alkaline primaquine: 3 days for *P. falciparum*, 14 days for *P. vivax*.
2. Resistant or suspected resistant uncomplicated cases:
   3 x 400-600 mg of quinine for 7 consecutive days, added by one of the following:
   4 x 150 mg of clyndamycine for 5-7 consecutive days, or
   100 mg of doxycycline/ day for 7 consecutive days, or
   3 tablets of sulfadoxine-pyrimethamine
3. Complicated cases:

- 10 mg/kg bodyweight of chloroquine in 500 ml of 5% dextrose, infusion for 8 hours, followed by 5 mg/kg bodyweight in 500 ml of 5% dextrose for 8 hours, repeat every 8 hours (total dose of 25 mg/kg bodyweight in 32 hours)
- If infusion is not possible, administer intramuscular injection of 3.5 mg/kg bodyweight/6 hours, or 2.5 mg/kg bodyweight/4 hours, parentheral administration should be switched to oral once the patient's condition is improved and the patient is able to take the medications orally.
- If HCl quinine is available, administer with a dose of 10 mg/kg bodyweight in 500 ml of 5% dextrose for every 8 hours, switch to oral if conditions are improved, administer for 7 days from initial administration.
- Administration of quinine or chloroquine is accompanied by administration of antibiotics: 4 x 150 mg of clindamycine or 100 mg/day of doxycycline.

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