

Medical Treatment of Malaria in Thailand

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Malaria is the most important parasitic infection in people, accounting for more than one million deaths a year¹. Malaria has become a priority for the international health community, and it is now the focus of several new initiatives. Prevention and treatment of malaria could be greatly improved with existing methods if increased financial and labour resources were available. However, new approaches for prevention and treatment are needed. Several new drugs are under development, which are likely to be used in combinations to show the spread of resistance, but the high cost of treatments would make sustainability difficult.

Malaria infection is caused by coccidian protozoan parasites of the genus *Plasmodium* carried by female *Anopheles* spp. mosquitoes. The clinical disease in humans may vary widely according to the species of the parasites -- *Plasmodium falciparum*, *P. vivax*, *P. ovale* or *P. malariae* -- and the genetics, immune status and the age of the host. These variables have a major influence on all aspects of the disease, including epidemiology, pathogenesis, clinical features and management.

DIAGNOSIS

In 95% of malarial cases, people develop symptoms and signs of malaria within six weeks of exposures, with the majority of cases presenting within two weeks of exposures.² However, in some cases, particularly *P. vivax* infection, the symptoms may not appear until two to three years after exposure and occasion even later in case of *P. malariae*. Thus, healthcare providers should suspect malaria in every patient with febrile illness, the hallmark of malaria, those who have been to a malaria-endemic region two to three years prior to presentation. Malaria can also be transmitted by blood transfusion, by sharing of contaminated needles, and by transplacental stage of the transmitted parasite. Patients generally present with non-specific symptoms consistent with a viral illness such as malaise, headache, myalgia, fatigue, abdominal discomfort, dry cough, nausea, vomiting and diarrhea can occur and irregular fever, misleading the diagnosis. Lack of fever periodicity is common and does not rule out the diagnosis of malaria. The classic fever pattern does not generally occur during the acute phase of the infection and does not often occur in *P. falciparum* infection. Periodicity may develop after a week of infection with *P. vivax*, *P. ovale*, and *P. malariae*. Malaria does not cause lymph node enlargement. In uncomplicated malaria, leukopenia and thrombocytopenia and other abnormalities of routine laboratory tests are usual. The patient who has malaria parasitemia plus any one of the followings in Table 1 is considered to have severe malaria.

A definitive diagnosis of malaria is made by prompt microscopic examination of thick and thin blood films. There is no need to wait for a fever peak before carrying out a blood film as parasites are often present throughout the red cell cycle. Malarial chemoprophylaxis should be withheld during investigation for malaria as antimalarial can suppress peripheral parasitemia. The most common abnormality on full blood count is thrombocytopenia, especially in the nonimmune. This is thought to be largely splenic pooling of platelets but also platelet activation. The total white count is usually in the normal range but there is often lymphopenia on presentation due to lymphocyte redistribution. More recently, apoptosis of lymphocytes has been identified in falciparum malaria.

Identification of *Plasmodia* on stained blood films provides a definitive diagnosis of malaria. Microscopy performed by an experienced operator is a very sensitive, rapid, and inexpensive; and, it still remains the gold standard. Thin and thick blood smears can be examined with Giemsa, Wright's, or Field's staining. Giemsa stain provides the greatest detail and will allow the detection of Schüffner's dots, whereas the application of Field's stain is much more rapid. Although thick films provide a higher degree of sensitivity for making the diagnosis, identification of species generally predicts the degree of clinical severity and should be determined promptly. An adequate amount of time must be spent to analyze multiple forms and to determine whether there is a mixed infection. A feature suggestive of a poor prognosis includes the following: 5-10% of erythrocyte parasitized, account of peripheral pigment-containing neutrophils of >5%, and finding of mature cells in the periphery with 10,000 mature trophozoites and/or schizonts per microliter of blood. If malaria is suspected and the first smear is negative, examinations should be repeated three times a day, if the diagnosis is suspected (because in synchronous falciparum malaria the mature forms are sequestered from the circulation), until they either become positive or another diagnosis is established. If *Plasmodium* parasites cannot be identified to a particular species, it should be treated immediately as *P. falciparum*. If an experienced microscopist is not available there are, nevertheless, a number of rapid diagnostic devices available. Rapid tests include ICT Malaria Pf (ICT Diagnostics, Sydney, Australia); ICT Malaria P.f/P.v. (ICT Diagnostics); and PATH Falciparum Malaria IC Strip (Program for Appropriate Technology, Seattle, Washington).³ OptiMAL and ICpLDH (Flow, Inc, Portland, Oregon) detect parasite lactate dehydrogenase enzyme and can distinguish *P. falciparum* from the other species. Unfortunately, the most rapid diagnostic tests do not detect vivax

TABLE 1. Manifestation of severe malaria

Abnormal level of consciousness (cerebral malaria)
Severe anemia (Hct < 15% or Hb 5 g/dl)
Renal failure
Pulmonary edema or adult respiratory distress syndrome (ARDS)
Hypoglycemia
Circulatory collapse or shock
Spontaneous bleeding from gums, nose, gastrointestinal tract and/or DIC
Repeated generalized convulsion- more than 2 observed within 24 hours despite cooling
Acidemia (arterial or capillary pH < 7.35) or acidosis (plasma bicarbonate < 15 mmol/l or base excess > 10)
Macroscopic hemoglobinuria
Prostration in children
Hyperparasitemia

infections, and those that do are expensive. Rapid and inexpensive polymerase chain reaction assay, which is often the most sensitive technology, is being developed for detection of malaria. It is important to know the limitation of the test being used, and it is imperative to repeat the test if the result is negative in order to enhance the sensitivity.

UNCOMPLICATED MALARIA

Treatment

Malaria due to *P. vivax*, *P. ovale* or *P. malariae* requires a standard course of treatment with chloroquine, which usually leads to defervescence. Chloroquine-resistant forms of *P. vivax* have recently been documented and may require quinine treatment. In case of *P. vivax* and *P. ovale* malaria treatment with primaquine is given to eradicate the exoerythrocytic forms, especially the hypnozoites which are responsible for relapses. Levels of G6PD should be measured in all patients before they are given primaquine, an oxidant drug which can lead to major hemolysis in G6PD and /or breastfeeding in pregnant women⁴. Primaquine-resistant vivax hypnozoites have been identified which required more prolonged (often three weeks) and higher dose (22.5 mg/day or more preferable 30 mg/day) therapy.

For the treatment of chloroquine-resistant *P. falciparum* in Thailand, the choice of therapy according to the National Antimalarial Policy of Thailand are shown in Table 2.

However, in general practice artemisinin-based combined therapy (ACT) is preferred to be given in combination with artesunate (4 mg/kg/day) plus mefloquine (8 mg/kg/day) once daily for three days. This simultaneous combination is now being packed in a pre-packed blister and will be formulated as a fixed combination tablet in the near future.

Primaquine 30 mg base may be given at the end of treatment for gametocide eradication of *P. falciparum* malaria. Primaquine, however, should be avoided in pregnant women and newborn babies due to the risk of hemolysis. Doxycycline should not be given in children below eight years of age, and pregnant women. Clindamycin (10 mg/kg bid for 3-7 days) is an alternative to doxycycline.

ACT for uncomplicated malaria

Artemisinin derivatives are highly active against asexual forms of the four species of *Plasmodium* that

TABLE 2. Standard treatment of uncomplicated *P. falciparum* in the field at Malaria Clinics in Thailand to suit patients' compliance

In mefloquine less sensitive area*: artesunate (a total dose of 10-12 mg/kg) plus mefloquine (25 mg/kg) over 2 days or quinine (10 mg salt/kg every 8 hours) plus doxycycline (3 mg/kg/day bid) over 7 days.
In mefloquine sensitive area**: artesunate (a total dose of 10-12 mg/kg) plus mefloquine (15 mg/kg) over 2 days or quinine (10 mg salt/kg every 8 hours) plus doxycycline (3 mg/kg/day bid) over 7 days.

* Chiang Rai, Chiang Mai, Mae Hong Son, Tak, Kanchanaburi, Phetchaburi, Ratchaburi, Prachuap Khiri Khan, Chumphon, Ranong, Sa Kaeo, Nakhon Nayok, Chantaburi, Trat

** The other 62 provinces in Thailand

infect humans. Its initial reduction of parasitemia is the most rapid of all available antimalarial drugs.⁵ Their half-lives are short, relative to the duration of their effect on parasite clearance. This suggests the equivalent of a "post-antibiotic effect" where there is persistent suppression of bacterial overgrowth following limited exposure to an antimicrobial agent. The derivatives of artemisinin are also active against the sexual form of the parasites (gametocytes) taken up by the mosquito and can therefore reduce the transmission rates. The World Health Organization has endorsed ACT as the first-line treatment where the potentially life-threatening parasite *P. falciparum* is the predominant infecting species. ACTs combine the rapid schizontocidal activity of an artemisinin derivative (artesunate, artemether or dihydroartemisinin) with a longer-half-life partner drug. Currently available alternative partner drugs include mefloquine, lumefantrine and piperazine. Artesunate-mefloquine is highly effective but expensive. Artemether-lumefantrine appears less effective than artesunate-mefloquine and needs to be administered with food to ensure adequate bioavailability. Dihydroartemisinin-piperazine is highly effective, well tolerated and relatively inexpensive. The goal of potent, safe, easy-to-administer and inexpensive ACTs may see trioxolanes in place of artemisinin derivatives, as well as novel partner drugs such as pyronaridine or naphthoquine, in the future. Table 3 shows new antimalarial drug trials at the Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Thailand.

Malaria in pregnant women and children

Women are more vulnerable to severe malaria during their 2nd and 3rd trimesters of pregnancy. It is often complicated by pulmonary edema and hypoglycemia. Sequestration of infected erythrocytes in placenta leads to maternal anemia and placental insufficiency, leading to retarded fetal growth and stillbirth. Congenital malaria is rare, however, it has been found to occur in up to 0.3% of the immunized mothers and up to 7.4% of the nonimmunized³. Treatment options are becoming more limited because the malaria parasites are developing resistance to existing drugs and due to the concerns that the drugs may harm the baby. The susceptibility to malaria is highest during the second and the third trimesters of pregnancy and early postpartum period (up to 60 days after delivery).¹⁵ Data from two trials in Thailand have shown that artesunate plus mefloquine (given in two

TABLE 3. Combination therapy clinical trails in uncomplicated malaria

Malarone ⁶ (atovaquone-proguanil)	- combination tablet of atovaquone 250 mg plus proguanil 100 mg - adult dose: 4 tab OD given in 3 days - cure rate 100%
Coartem ^{7,8} (artemether-lumefantrine)	- combination tablet of artemether 20 mg plus lumefantrine 120 mg - adult dose: 4 tab bid given over 3 days - cure rate 97%
Artequin ⁹ (artesunate-mefloquine)	- blister- prepacked of combination tablet of artesunate 200 mg plus mefloquine 250 mg - dose: artesunate 4-5 mg/kg plus mefloquine 25 mg/kg (~ 8.5mg/kg/day) OD given over 3 days - cure rate 100%
Artesunate-mefloquine ¹⁰ (2 day - regimen)	- adult dose: artesunate 200 mg plus mefloquine 312.5 mg bid given over 2 days - cure rate 99%
Artecom ¹¹ (dihydroartemisinin- piperazine-trimethoprim)	- combination tablet of dihydroartemisinin 32 mg plus piperazine 320 mg plus trimethoprim 90 mg - adult dose: 2 tab at 0, 6, 24, 32 hours plus primaquine 26.4 mg at 0 hour - cure rate 97%
Artekin ¹² (dihydroartemisinin- piperazine)	- combination tablet of dihydroartemisinin 40 mg plus piperazine 320 mg - dose: dihydroartemisinin 6.4 mg/kg + piperazine 51.2 mg/kg - adult dose: 2 tab at 0, 8, 24, 48 hours - cure rate 96.1%
DNP ¹³ (dihydroartemisinin-naphthoquine-trimethoprim)	- combination tablet of dihydroartemisinin 160 mg plus naphthoquine 400 mg plus trimethoprim 200 mg - adult dose: 1 tab bid given over 1 day - cure rate 99%
Artesunate -azithromycin ¹⁴	Regimen 1. - adult dose: artesunate 100 mg bid + azithromycin 750 mg OD given over 3 days - cure rate 100% Regimen 2. - adult dose: artesunate 200 mg OD + azithromycin 1,000 mg bid given over 3 days - cure rate 100%
Quinine-azithromycin ¹⁴	- adult dose: quinine 10 mg/kg tid + azithromycin 500 mg tid given over 3 days - cure rate 91.7%

different regimens) appears to be better than quinine-clindamycin in terms of clearing parasites and fever in uncomplicated malaria.¹⁶ However, doxycycline, primaquine, tafenoquine and halofantrine should not be used. Although artemisinin derivatives have been used with apparent safety in the 2nd and 3rd trimesters of pregnancy, they can cause resorption of embryos in animal studies. Consequently, these agents should not be used during the first trimester.

HIV

HIV 1 infection is associated with an increased frequency of clinical malaria and parasitemia.¹⁷⁻¹⁸ Lower CD4⁺ counts are associated with higher parasite densities. Maternal HIV infection predisposes pregnant women to a higher prevalence of malaria and parasite density, more fever and predisposes their newborns to congenital malarial infection and low birth weight. Placental malarial infection and maternal HIV infection increase post-neonatal mortality beyond the independent risk associated with exposure to either of them.

Treatment of recrudescence and relapse

Patients who have been treated for *P. vivax* or *P. ovale* infection but have not had appropriate radical

cure may have a reappearance of asexual parasitemia, known as relapse. The patients will require radical cure with primaquine along with retreatment with the appropriate blood schizontocide drug. In patient with recrudescence, reappearance of detectable asexual parasitemia due to persistence of the asexual erythrocytic stage at an undetectable level, a treatment with the appropriate blood schizontocide drugs is required.

SEVERE FALCIPARUM MALARIA

Management

The management of severe falciparum malaria constitutes medical emergency. The diagnosis needs to be confirmed microscopically and intravenous access should be secured as soon as possible. Severe manifestation may occur independently or in combination with other symptoms on the admission day or later. Hypoglycemia, anemia and convulsion are more common in children, whereas jaundice, pulmonary edema and renal failure are more common in adults. Patients with severe malaria should be transferred to the highest possible level of clinical care. Advanced life support techniques are advised initially to stabilize the patient:

- Assess airway, breathing and circulation and intervene where necessary.

TABLE 4. Indications for exchange blood transfusion for hyperparasitemia in presumed non-immune patients with *P. falciparum* malaria.²⁰

Parasitemia > 30% in the absence of clinical complications
Parasitemia > 10% in the presence of severe disease, especially cerebral malaria, acute renal failure, adult respiratory distress syndrome, jaundice and severe anemia
Parasitemia > 10% and failure to respond to optimal chemotherapy after 12-24 hour
Parasitemia > 10% and poor prognostic factors (eg. elderly patients, shizonts in peripheral blood)

- Draw blood for emergency investigations for parasite count, glucose level, complete hemogram, blood group and cross match, blood gas analysis (if metabolic acidosis is suspected), serum electrolyte, blood urea and creatinine level, blood culture, coagulation indices, serum liver enzymes.
- Treat hypoglycemia.
- Coma with parasitemia should consider cerebral malaria until proved otherwise.
- Assess the level of consciousness by the Glasgow coma score (GCS) in adult or the Blantyre coma score (BCS) in children.
- Treat seizures promptly with intravenous benzodiazepines. Other anticonvulsants e.g. paraldehyde has less deleterious effects on respiration. With repeated or prolonged seizures, phenytoin, phenobarbitone, fosphenytoin, chlormethiazole and thiopentone have been used.¹⁹ These longer-acting anticonvulsants require continued monitoring of vital signs for at least four hours after administration.
- Convulsions are common, particularly in children, but prophylactic phenobarbitone may cause respiratory arrest. Patients requiring repeated anticonvulsants should be swiftly intubated by experienced operator and ventilated.
- At present, prophylactic anticonvulsant is not indicated in adult. A nasogastric tube should be inserted in all unconscious patients and the stomach contents should be emptied to prevent aspiration.
- Record vital signs: temperature, pulse, blood pressure, respiratory rate.
- Weigh the patient to calculate the dose of antimalarial drugs.
- Assess hydration status, consider urinary bladder catheterization and restoration of urine flow to more than 20 ml/kg/day. Central venous line (if evaluation of hydration status is difficult) with central venous pressure of approximately 5 cm of water.
- Adequate fluid replacement avoiding fluid overload is essential.
- Transfusion is indicated for well-hydrated adult patients with hematocrit below 20%. In malaria endemic areas, it is given to children with hemoglobin concentration less than 4 g/dl or having respiratory distress or parasitemia greater than 10%, with hemoglobin concentration between 4 and 5 g/dl.
- Plan the first eight hours of intravenous fluid administration.
- Early dialysis or hemofiltration in oliguric acute renal failure or severe metabolic acidosis. Non-oliguric renal failure may be managed conservatively.
- Bacterial superinfection is common in malaria and must be suspected, particularly if the fever remains high despite antimalarial treatment, or when there is an evidence of septicemia or focal infection (e.g. pneumonia or urinary tract infection).
- Blood cultures have detected bacteremia in 7-14% of

patients admitted with severe malaria. Non-typhoid *Salmonella* septicemia is the most common co-infection in children with severe malaria.

- Chest x-ray to detect pulmonary edema or infection.
- Prompt endotracheal intubation if indicated.
- Early detection of adult respiratory distress syndrome (ARDS) and use positive-end expiratory ventilator support.
- Unconsciousness may be due to hypoglycemia, cerebral malaria, prolonged hypoxia, shock, sepsis, severe metabolic acidosis and rarely concomitant traumatic cerebral hematoma during transferral.
- In cerebral malaria there may be some passive resistance to neck flexion but this is easily distinguished from true meningism. For inexperienced physicians the distinction may be uncertain, and a lumbar puncture should be performed in most cases to exclude any possible cause of bacterial or viral meningoencephalitis.
- Inotropic support may be required after correction of hypovolemia. Dopamine appears to provide better inotropic effect than adrenaline in adults with shock.
- Detect pregnancy due to high morbidity and mortality particularly during the 2nd and 3rd trimesters. They are prone to hypoglycemia, pulmonary edema and anemia.

Treatment

Early diagnosis and prompt treatment is key to successful treatment of severe malaria. In Thailand, artesunate is the potent antimalarial drug of choice in the treatment of severe malaria. If parenteral artesunate is not available, parenteral quinine is its alternative.

Artesunate

In hospital

Artesunate 2.4 mg/kg iv given on admission (time = 0), then at 12 and 24 hours, then once daily for seven days. If artesunate treatment duration is five days, mefloquine 25 mg/kg in divided doses should be added on day 5.

In a clinic where iv administration is not possible

Artesunate may be given by im (less preferred).

Quinine

In hospital

Initial dose: quinine dihydrochloride 20 mg salt/kg (diluted in 5% D/NSS/2 4 ml/kg) infused over four hours. Maintenance dose: 10 mg salt/kg (diluted in 5% D/NSS/2 2 ml/kg) infused over two hours every eight hours.

In a clinic where iv administration is not possible

Quinine dihydrochloride 20 mg salt/kg diluted 1:2 with sterile water given by split injection into both anterior thighs. Maintenance dose: 10 mg/mg 8-hourly (less preferred).

When the patients can swallow reliably and safely, oral treatment of the same parenteral drug may be substituted. However, this will depend on local antimalarial treatment policies. A seven-day course of either artesunate-mefloquine or quinine-doxycycline (or clindamycin in children and pregnant women) is useful in Thailand and gives over 90% cure rates. Mefloquine administered by the nasogastric route in patients with cerebral malaria showed rapid but incomplete absorption. This suggests that the route is unreliable in patients with severe malaria; however, it may be used in later stages of the management of severe malaria to reduce the period of parenteral treatment, improve compliance and cure, and prevent the development of resistance to the parenteral antimalarials.

Ancillary treatment

Unfortunately, none adjuvant therapy (heparin, low molecular weight dextran, mannitol, urea, corticosteroid, aspirin, prostacyclin, pentoxifylline, desferrioxamine, anti-TNF antibody, cyclosporin and hyperimmune serum) has been proved beneficial. Although here is no unanimous opinion on exchange transfusion (Table 4), partial exchange (2-3 L in adult) may be sufficient.

PROSPECTIVE

Multidrug resistance in parasites has forced the use of combined antimalarial regimens. However, we are still far from the discovery of an ideal regimen. The best available option now includes artesunate-mefloquine, which works well in Thailand. Dihydroartemisinin-piperazine and fosmidomycin-clindamycin²¹ are promising treatment candidates. Although effective new drugs are available, there are too few examples, and they are too expensive. To hold our ground against malaria, it is essential to have continued collaboration between scientists, the pharmaceutical industry, and malaria-control program personnel.²²

SUMMARY

Multidrug resistance has rendered monotherapy for malaria useless in most parts of the world, and has also compromised the usefulness of many of the available combination therapies. New antimalarial regimens are, therefore, urgently needed and have been studied in Thailand. However, according to the National Antimalarial Policy of Thailand, artesunate-mefloquine or quinine-doxycycline are drugs of choice in the treatment of uncomplicated falciparum malaria. Whereas intravenous artesunate or quinine is recommended for severe falciparum malaria. Chloroquine is still sensitive for the treatment of *P. vivax*, *P. ovale*, and *P. malariae*. Primaquine 15 mg for 14 days is given to eradicate hypnozoites in *P. vivax* and *P. ovale*. In primaquine-resistant *P. vivax*, higher dose of primaquine is required.

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