MANAGEMENT OF MALARIA IN CHILDREN

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Background

Malaria is the world’s most important parasitic infection\(^1\). The impact of malaria on global health is staggering with an estimated incidence of almost 300 million new cases each year, resulting in more than 1.5 million deaths annually worldwide, malaria remains a major global public health concern\(^2\). Along with tuberculosis and HIV infection, malaria forms a disease triad that accounts for almost half of all infectious disease mortality\(^3\). Most of the 1-3 million who die each year from malaria are children, mainly in Africa, which is hyperendemic for malaria. In older children, malaria has a similar course as in adults. However, in children below the age of 5 years, particularly infants, the disease tends to be atypical and more severe\(^4\).
In the first two months of life, children may not contract malaria or the manifestations may be mild with low-grade parasitemia, due to the passive immunity offered by the maternal antibodies. In endemic and hyperendemic areas, the parasite rate increases with age from 0 to 10% during the first three months of life to 80 to 90% by one year of age and the rate persists at a high level during early childhood. The mortality rate is highest during the first two years of life. By school age, a considerable degree of immunity would have developed and asymptomatic parasitemia can be as high as 75% in primary school children. In Africa, on an average about 1 in 20 children die from malaria, and in worst affected areas, even 1 in 5 or 6 die from malaria and its related diseases (e.g., anemia)\(^4\).
In areas of low endemicity, where the immunity is low, severe infection occurs in all age groups including adults. The morbidity and mortality due to malaria in children tends to be very high in these areas. Malnutrition does not increase susceptibility to severe falciparum malaria. In fact, it has been observed that well-nourished children are more likely to develop severe disease than those with malnutrition. However, when severe malaria does occur, malnourished children have a higher morbidity and mortality⁴.
Vector

The malaria vector is Anopheles sp. Anopheles gambiae contribute to the death of about 1 million people a year. Most of the victims are children in Africa. On that continent, Anopheles gambiae carries the deadliest parasite, plasmodium falciparum, along with three other parasites, plasmodium vivax, plasmodium malariae and plasmodium ovale\(^5\).

**Range:** mosquitoes inhabit almost every corner and climate zone on Earth, from the equator to the Arctic. Anopheles transmit malaria mostly in the tropics and mostly at relatively low elevations, although data suggest that their range is expanding\(^5\).
Transmission: to transmit malaria, a mosquito must bite an infected person and then live long enough -10 to 14 days- to bite an uninfected person. In that period the parasite multiplies and makes its way to the insect’s salivary glands. Whereas some people never seem to get bitten by mosquitoes. Why do mosquitoes feast on some people and leave others alone? Several studies have shown that to mosquitoes, all people really aren’t created equal. Besides factors such as heat and carbon dioxide, mosquitoes use odors to find their victims, and humans appear to exude different ammounts of the volatile compounds the insect love.
Breeding sites: each mosquito has its own preference, but almost any type of water can accommodate some of them: fresh or salt, still or moving, in ponds, lakes, streams, free holes, irrigation ditches, cesspools, used tires, water jugs, sewers, or birds boths.
Anopheles species:

- albimanus
- annularis
- anthropophagus
- aquasalis
- arabiensis
- arabiensis and funestus
- barbirostris
- culicifacies
- darlingi
- dirus
- farauti
- flavirostis
- fluviatilis
- funestus and arabiensis
- funestus and arabiensis and gambiae s.s.
- funestus and gambiae
- gambiae s.s.
- gambiae s.s. and funestus
- maculastus
- marajoara
- melas
- minimus
- nuneztovari
- punctulatus group
- pseudopunctipennis
- sachavori
- sergentil
- sinensis
- sundaicus
- superpictus

Etiology and Clinical Manifestations

Malaria is caused by infection with 1 or more of the 4 *Plasmodium* species that infect humans: (1) P. falciparum, (2) P. vivax, (3) P. Ovale, and (4) P. malariae. Of these infections, falciparum and vivax malaria account for the majority of infections. The likelihood of becoming infected with either of these species depends on the geographic region in which the person became infected. For example, most infections acquired in Africa are attributed to P. falciparum, whereas those acquired in Asia and the Americas are often due to P. vivax.
Transmitted through the bite of an infected female Anopheles mosquito the protozoan parasites cause hemolysis of infected erythrocytes and obstructed in the microcirculation. This disruption results in anoxia, lactic acidosis, and organ failure, most commonly in cases of falciparum malaria, in which severity and mortality correlate with the level of parasitemia. In nonimmune persons, parasitemia that is greater than 5% increases the risk for a fatal outcome.

The incubation period of the disease usually ranges from 9 to 30 days, after which time clinical symptoms appear. With some strains of *P. vivax*, however, the incubation period can last as long as 9 to 12 months. Malaria chemoprophylaxis may also prolong onset of symptoms.
The well-known classic paroxysms of fever are absent at the beginning of the disease, when the presentation may be vague and nonspecific. Mild fever, chills, sweats, headache, and malaise are reported by most patients. Often mistaken for influenza or gastroenteritis, malarial symptoms also can include fatigue, nausea, myalgias, and occasional diarrhea. Uncomplicated malaria may be accompanied by systolic hypotension, jaundice, and hepatosplenomegaly. When severe, infection can result in organ failure (especially the brain, lungs, and kidneys), impaired consciousness, seizures, coma, and death\textsuperscript{10}. A comparison of distinguishing clinical features associated with the different types of malaria is provided in Table 1\textsuperscript{3}. 
Severe Falciparum Malaria in Children

Severe falciparum malaria is the commonest cause of death in infants and children in areas endemic and hyperendemic for malaria. Inadequate immunity results in rapid increase in the parasite count and development of complications. Delay in diagnosis and treatment also contributes to the mortality. Clinical features of severe disease should be given utmost priority. History of travel to malarious area, history of previous antimalarial therapy, history of vomiting, diarrhoea, fluid intake, urine output, convulsions etc. should be obtained from parents. Physical examination should include assessment of hydration and of complications of falciparum malaria. Rectal temperature should be measured in infants and small children. All children should be weighed on admission.
Thick and thin films for malaria, haematocrit and hemoglobin, blood glucose (by finger prick) should be done in all cases. If the report is likely to be delayed, presumptive antimalarial treatment should be started. Parasite count should be done in all positive cases of falciparum malaria and a parasite count of >2% indicates impending problems and >5% should be considered as severe infection. All cases with severe falciparum malaria should be managed as medical emergency⁴ (see Table 2).
Cerebral Malaria

C.N.S. manifestations are common in children and they can be due to the following causes:
1. Severe infection and cerebral malaria.
2. Severe infection and hypoglycemia.
3. Hypoglycemia induced by quinine.
4. Severe anemia.
5. High grade fever.
6. Drug induced behavioural changes.

Therefore C.N.S. dysfunction may not always indicate cerebral malaria and it is very important to differentiate between the various causes⁴.
Clinical Features of Cerebral Malaria

The earliest symptoms of cerebral malaria in children include high-grade fever (37.5-41°C) and failure to eat and drink. Vomiting and cough are common. Febrile convulsions are common in children aged 6 months to five years and it may be difficult to differentiate from cerebral malaria. If coma persists more than 30 minutes after a convolution in a child with falciparum malaria, then cerebral malaria should be suspected. Convulsions can continue after the onset of coma and they are associated with higher morbidity and sequelae. Some children may have noisy and laboured breathing. Deep breathing due to acidosis may be seen in some.
Cold, clammy skin with a core-to-skin temperature difference of >10°C may be seen. Some children may have associated shock, with the systolic pressure below 50 mm Hg. Some children may present with extreme opisthotonus ('bent-like-a-bow') posture, mimicking either tetanus or meningitis.

Neurological signs include features of symmetrical upper motor neuron and brain stem disturbances including disconjugate gaze, decerebrate and decorticate postures. In children with profound coma, corneal reflex and 'Doll's eye' movements may be absent. Retinal haemorrhages and exudates are rarer than in adults.
In all comatose children, C.S.F. examination must be done to rule out other diseases. C.S.F. examination in cerebral malaria is usually normal; however in some, increase in pressure, protein level and cell-count (mostly lymphocytes, 50cells/µl) may be seen. Leukocytosis may be present in severe disease and may not necessarily indicate bacterial infection⁴.
Laboratory Diagnosis

Hemoglobin level and leukocyte count are often within normal limits in persons with uncomplicated malaria. However, thrombocytopenia and elevated levels of liver enzymes and serum lactate dehydrogenase are seen in more than half of infected persons. Three thick blood films should be examined, separated by an interval of 12 to 24 hours\textsuperscript{10}. Alternatively, antigen detection using monoclonal antibodies and examination of acridine dye-stained buffy coat preparations can be used to diagnose falciparum malaria. In cases in which parasite morphology is either uncertain or potentially altered by drug therapy or improper sample handling, molecular diagnostic tests may be helpful. The CDC currently uses nested polymerase chain reaction assays for detections and speciation of \textit{Plasmodium} species\textsuperscript{3}.
Anti Malarial Drugs

Classification. Anti malarial drugs can be classified according to anti malarial activity and structure.

1. According to anti malarial activity:

   a. Tissue schizonticides for causal prophylaxis: These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrimethamine and Primaquine have this activity. However since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.
b. Tissue schizonticides for preventing relapse: These drugs act on the hypnozoites of P. vivax and P. ovale in the liver which cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.

c. Blood schizonticides: These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines etc.
d. Gametocytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocidal activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has anti-gametocidal activity against all plasmodia, including falciparum.

e. Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of P. vivax and P. ovale). A combination of chloroquine and primaquine is thus needed in ALL cases of malaria.
2. According to the structure:

a. Aryl amino alcohols: Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.
b. 4-aminoquinolines: Chloroquine, amodiaquine.
c. Folate synthesis inhibitors:

Type 1 - competitive inhibitors of dihydropteroate synthase - sulphones, sulphonamides.
Type 2 - inhibit dihydrofolate reductase - biguanides like proguanil and chloroprophuanil; diaminopyrimidine like pyrimethamine

d. 8-aminoquinolines: Primaquine, WR238, 605
e. Antimicrobials: Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones
f. Peroxides: Artemisinin (Qinghaosu) derivatives and analogues - artemether, arteether, artesunate, artelinic acid
g. Naphthoquinones: Atovaquone
h. Iron chelating agents: Desferrioxamine
**Chloroquine:** It is the prototype anti malarial drug, most widely used to treat all types of malarial infections. It is also the cheapest, time tested and safe anti malarial agent.

**Mechanism of action:** Unclear. ? by inhibiting nucleic acid synthesis; ? by forming a complex with haemin, it causes damage to the parasite membrane; ? these weak bases increase the pH of acidic vesicles within the parasite thereby causing damage.
Absorption, fate and excretion: 90% of the drug is absorbed from GIT and rapidly absorbed from intra muscular and subcutaneous sites. It has a large distribution volume due to extensive sequestration in tissues of liver, spleen, kidney, lung etc. Hence the need for a larger loading dose. Therapeutic blood levels persist for 6-10 days and elimination half-life is 1-2 months. Half of the drug is excreted unchanged by the kidneys, remaining is converted to active metabolites in the liver.

Anti malarial activity: It is highly effective against erythrocytic forms of P. vivax, ovale and malariae, sensitive strains of P. falciparum and gametocytes of P. vivax. It rapidly controls acute attack of malaria with most patients becoming afebrile within 24-48 hours. It is more effective and safer than quinine for sensitive cases.
Adverse effects: Chloroquine is a relatively safer anti malarial. At therapeutic doses, it can cause dizziness, headache, diplopia, disturbed visual accommodation, dysphagia, nausea, malaise, and pruritus of palms, soles and scalp. It can also cause visual hallucinations, confusion, and occasionally frank psychosis. These side effects do not warrant stoppage of treatment. It can exacerbate epilepsy. When used as prophylactic at 300 mg of the base/week, it can cause retinal toxicity after 3-6 years (i.e. after 50-100 g of chloroquine). Intra muscular injections of chloroquine can cause hypotension and cardiac arrest, particularly in children.
**Contra indications:** Chloroquine should be used with caution in patients with hepatic disease, (even though it is not hepatotoxic per se, it is distributed widely in the liver and is converted to active metabolites there; hence the caution), severe gastro intestinal, neurological or blood disorders. The drug should be discontinued in the event of such problems during therapy. It should not be co-administered with gold salts and phenyl butazone, because all the three can cause dermatitis.
**Availability:** Chloroquine is available as Chloroquine phosphate tablets; each 250-mg tablet contains 150 mg of the base. Chloroquine hydrochloride injection contains 40 mg of the base per ml.

**Dose:** Oral- 10mg/kg stat., then three doses of 5 mg/kg, over 36-48 hours. Intra venous- 10mg of base/kg in 10ml/kg of isotonic saline or 5% dextrose over 8 hours, followed by 15mg/kg in 10ml/kg of isotonic saline or 5% dextrose over 24 hours. Intra muscular: (Avoid in children for fear of fatal hypotension)- 2.5 mg base/kg every 4 hourly OR 3.5 mg/kg every 6 hourly till 25 mg/kg is given.

**Primaquine:** Primaquine is the essential co-drug with chloroquine in treating all cases of malaria.
Treatment of Malaria

Therapy falls into four categories: (1) specific chemotherapy for the attack, whether fresh infection, recrudescence, or relapse; (2) supportive treatment and management of complications; (3) specific chemotherapy to prevent late relapse of vivax or ovale infections; (4) specific chemotherapy to destroy or sterilize gametocytes, and thus to protect the community if mosquitoes are present.
Choice of regimen is based on:\(^7\):

- Local cost and availability of antimalarial drugs.
- Area of malaria acquisition (i.e. drug resistance pattern of *P. falciparum*).
- Prior chemoprophylaxis.
- Known allergies.
- Concomitant illnesses other than malaria.
- Age and pregnancy.
- Likely patient compliance with therapy.
- Risk of re-exposure to malaria after treatment.
Treatment of Uncomplicated Malaria

The treatment of malaria depends on the severity of the infection, the patient's age, the degree of background immunity (if any), the likely pattern of susceptibility to antimalarial drugs, and the cost and availability of such drugs. For this reason, recommendations vary according to geographic region and should be under constant review\(^1\). The three so-called benign malarías, \textit{P. vivax}, \textit{P. malariae}, and \textit{P. ovale}, should all be treated with chloroquine. High-grade resistance to chloroquine in \textit{P. vivax} has been reported from Oceania\(^1\) but elsewhere the parasite remains generally sensitive and responds rapidly.
Chloroquine is usually well tolerated, although it commonly produces pruritus in dark-skinned patients, and in the treatment of acute malaria it may cause nausea, dysphoria, and very rarely, a transient neuropsychiatric syndrome or cerebellar dysfunction. Recent studies have shown that the traditional 3-day course of treatment of 25 mg (base) per kilogram of body weight (10 mg per kilogram initially, 10 mg per kilogram at 24 hours, and 5 mg per kilogram at 48 hours) can be compressed into 36 hours for convenience (Table 2). A two-week course of primaquine is also required to treat infections with P. vivax and P. ovale in order to eradicate forms of the parasite (hypnozoites) that survive in the liver (radical cure).
This prevents relapse in the majority of cases. Primaquine may cause nausea and abdominal pain, particularly if taken on an empty stomach, and more important, oxidant hemolysis with methemoglobinemia, anemia, and sometimes hemoglobinuria. Patients with a deficiency of glucose-6-phosphate dehydrogenase are particularly vulnerable to oxidant hemolysis, and primaquine is contraindicated in patients with severe variants of the deficiency. In places where mild variants of glucose-6-phosphate dehydrogenase deficiency are common, primaquine (0.8 mg of base per kilogram; adult dose, 45 mg) should be given once a week for six weeks for a radical cure. In areas where malaria is endemic and reinfection is common, a radical cure with primaquine is not indicated.
The choice of treatment for P. falciparum depends on the parasite's sensitivity to antimalarial drugs in the area where the infection was acquired. Known sensitive infections (e.g., those from North Africa, Central America north of the Panama Canal, Haiti, or the Middle East) should be treated with chloroquine. Where there is low-grade resistance to chloroquine, amodiaquine (35 mg of base per kilogram over a period of three days) is a more effective alternative. Chloroquine-resistant infections in most of Africa and some parts of Asia and South America usually respond to a single-dose combination of a long-acting sulfonamide (usually sulfadoxine) and pyrimethamine.
Although both amodiaquine and sulfadoxine–pyrimethamine are well tolerated in treatment, neither should be used as a prophylactic drug, because of potential toxicity (amodiaquine can be associated with agranulocytosis and hepatitis, and sulfadoxine–pyrimethamine can be associated with exfoliative dermatitis, hepatitis, and blood dyscrasias). Unfortunately, resistance to sulfadoxine–pyrimethamine has developed rapidly in many areas (particularly in South America and Southeast Asia). For multidrug-resistant P. falciparum, the choice for treatment is mefloquine, halofantrine, or quinine with tetracycline. Clindamycin is used with quinine in some countries; three-day combination regimens have proved effective in areas of endemic disease, but there is insufficient evidence of their effectiveness in nonimmune patients.
Mefloquine is cleared slowly (elimination half-life, two to three weeks), and a course of treatment comprises one or two doses (Table 3). Mefloquine is relatively well tolerated, although nausea, vomiting, giddiness, weakness, dysphoria, feelings of dissociation, clouding of consciousness, and nightmares are all common. More serious self-limiting neuropsychiatric reactions have been reported in 0.5 to 1 percent of Europeans and Africans, but in approximately 0.1 percent of Southeast Asian patients. Although vomiting in the first hour after administration is more common in children, the other adverse effects of mefloquine are more common in adults.
Halofantrine is more active and better tolerated than mefloquine, but its oral bioavailability is poor and variable (although it is increased by the consumption of fat). Halofantrine induces a concentration-dependent delay in atrioventricular conduction and ventricular repolarization that has cast a shadow over its future role. Halofantrine should not be given to patients with an abnormally long corrected QT interval or those taking drugs likely to prolong it (Table 3). Neither halofantrine nor mefloquine should be used to treat early recrudescences (within 28 days of treatment) of malaria after primary mefloquine treatment, because their respective cardiac and central nervous system effects are increased.
Treatment with oral quinine or quinidine is not well tolerated. These venerable compounds are extremely bitter and often induce the complex of cinchonism (nausea, dysphoria, tinnitus, and high-tone deafness). Fortunately, more serious toxic reactions are rare. Although the combination of quinine with tetracycline or doxycycline remains more than 85 percent effective nearly everywhere, compliance with the seven-day courses of treatment required for resistant P. falciparum infections is poor.
The derivatives of artemisinin (qinghaosu) obtained from qinghao, or sweet wormwood (Artemesia annua), and developed as pharmaceutical agents in China, are the most rapidly acting of all antimalarial drugs. These drugs are not registered and therefore not generally available in many countries, but they have been used extensively for the treatment of drug-resistant falciparum malaria in China and Southeast Asia. In both severe and uncomplicated malaria they have given faster relief of fever and considerably faster clearance of parasites than other antimalarial agents, without evident toxicity.
Three compounds have been used: the parent, artemisinin, and two more active derivatives (a water-soluble hemisuccinate, artesunate, and an oil-soluble ether, artemether), both of which are metabolized to a biologically active metabolite, dihydroartemisinin. Indeed, artesunate can be considered a prodrug for dihydroartemisinin. In some parts of Southeast Asia (particularly the eastern and western borders of Thailand) where the failure rates of treatment with high-dose mefloquine alone in falciparum malaria now exceed 40 percent, oral artesunate given for three to five days in combination with mefloquine still remains highly effective. When used alone (for example, for the treatment of recrudescence after treatment with mefloquine), the artemisinin derivatives should be given for seven days.
Children and Pregnant Women

Children tolerate antimalarial drugs relatively well. Mefloquine is not recommended for children who weigh less than 15 kg, but this is a policy of caution based on limited published data. Experience suggests that children are at no additional risk, although infants are more likely to vomit the drug. Primaquine should not be given to pregnant women or newborn babies because of the risk of hemolysis. Chloroquine, sulfadoxine–pyrimethamine, quinine, and quinidine are considered safe in therapeutic doses in all trimesters of pregnancy, although there is a theoretical risk of kernicterus if sulfadoxine is given in the third trimester. There is also evidence that mefloquine is safe in the second and third trimesters.
Although there is little information on the use of the artemisinin derivatives in pregnancy, the general consensus is that they too should be used if they are indicated (i.e., for mefloquine-resistant falciparum malaria), except in early pregnancy, when alternative treatment (quinine) is still preferred. Apart from primaquine and halofantrine (for which there are no data), the other antimalarial agents can all be used in women who are breast-feeding.
There are no pediatric formulations of mefloquine, the artemisinin derivatives, primaquine, or in many countries, quinine or chloroquine. Quinine, and particularly chloroquine, are dangerous in overdoses, and should be stored in childproof containers. When treating children, particular care should be taken to ensure that the correct doses are given and retained. Early vomiting is common, particularly after the administration of mefloquine or quinine to infants, and is more likely in children with high fever. Patients should be cooled with acetaminophen, fanning, and sponging with tepid water before they receive oral antimalarial treatment, and they should then be observed for one hour.
If vomiting occurs within 1 hour, the full dose should be repeated (with mefloquine, we repeat half the initial dose if the child vomits between 30 and 60 minutes after administration). If vomiting occurs after one hour, it is not necessary to readminister the drugs.

Postural hypotension is common in uncomplicated malaria and is exacerbated by the quinoline antimalarial agents. Febrile patients, both adults and children, should be kept in a horizontal position, and great care should be taken if they get up rapidly from their beds. Mothers should be discouraged from carrying febrile babies vertically immediately after parenteral quinine or chloroquine has been given.
Severe P. Falciparum Malaria

Management

Although infections with P. vivax, P. ovale, or P. malariae are very rarely fatal, an infection with P. falciparum may progress rapidly to a lethal multisystem disease. The clinical manifestations of severe malaria depend on age. Hypoglycemia, convulsions, and severe anemia are relatively more common in children acute renal failure, jaundice, and pulmonary edema are more common in adults. Cerebral malaria (with coma), shock, and acidosis, which often terminate in respiratory arrest, may occur at any age.
The state of hydration of patients on admission is quite variable; the dividing line between overhydration and underhydration is thin. Adults in particular may have noncardiogenic pulmonary edema and are vulnerable to fluid overload, yet dehydration and hypovolemia contribute to hypotension and shock (particularly in children) and may hasten acute renal failure arising from acute tubular necrosis (particularly in adults). After rehydration, the central venous pressure should be maintained at approximately 5 cm of water (pulmonary-artery occlusion pressure, less than 15 mm Hg). When hypercatabolic acute renal failure develops with other evidence of vital-organ dysfunction, dialysis or hemofiltration should be started quickly. Renal function (restoration of urine flow to more than 20 ml per kilogram per day) returns after a median of four days, although some patients will require dialysis for more than a week.
Hypoglycemia occurs in approximately 8 percent of adults and 25 percent of children. After rehydration, a maintenance infusion of 5 to 10 percent glucose should be given to all patients, but the blood glucose level should still be checked frequently. Unconscious patients with cerebral malaria should be kept on their sides, and a lumbar puncture should be performed to rule out bacterial meningitis. The incidence of seizure ranges from more than 80 percent in infants to less than 20 percent in adults. Many of these seizures are focal, and the signs may be subtle in an unconscious patient. Seizures should be treated promptly with intravenous benzodiazepines.
Use of prophylactic intramuscular phenobarbital reduces the incidence of seizure, but the optimal dose remains to be determined. Hemolysis is extensive, and anemia develops rapidly. Blood should be transfused if the hematocrit falls below 20 percent. In Africa, where blood free of viral pathogens is in short supply, it has been recommended that the threshold for transfusion be a hemoglobin level of less than 5 g per deciliter if there is respiratory distress, and less than 3 g per deciliter if there is not. A transfusion of fresh blood is preferable, particularly if there is marked bleeding due to disseminated intravascular coagulation (found in approximately 5 percent of adults with severe malaria) or to stress ulceration.
Bacterial infections are common. Pneumonia is likely if the duration of coma exceeds three days; urinary tract infections may complicate the drainage of indwelling catheters; and spontaneous (usually gram-negative) septicemia may occur occasionally. Systemic salmonella infections may develop in patients with otherwise uncomplicated malaria. If the condition of a patient with severe malaria deteriorates suddenly without an evident cause, hypoglycemia should be ruled out; blood cultures should be performed, and empirical treatment with broad-spectrum antimicrobial agents started. Vital signs, including a patient's coma score, urine output, blood glucose level, and if possible, lactate level, arterial pH, and blood gas levels, should be monitored as frequently as possible. The parasite count should be measured at least twice a day in all patients. If the parasite count has not fallen by at least 75 percent 48 hours after the start of treatment, it should be rechecked, and if confirmed, a different antimalarial agent should be used.
Treatment

Chloroquine

In the few remaining places where there is not widespread resistance to the drug, parenteral chloroquine should be given, but if there is any uncertainty about resistance, then quinine or quinidine should be used. Chloroquine should be given by controlled-rate intravenous infusion and never by intravenous injection. Intramuscular or subcutaneous administration is a satisfactory alternative: absorption is rapid; bioavailability exceeds 80 percent, even in severe malaria; and the injections are not painful. Provided it does not enter the circulation too rapidly, either because the intravenous infusion is too fast or because the dose given in an intramuscular or subcutaneous injection is too large (more than 3.5 mg of base per kilogram), hypotension will not occur and parenteral chloroquine is very well tolerated. (See Table 4).
Quinine and Quinidine

The alkaloids from the bark of the cinchona tree still constitute the mainstay of the antimalarial pharmacopeia, as they have for over three centuries. Quinidine, the dextrorotatory diastereoisomer, is more active than quinine, but it is also more cardiotoxic and more expensive. In the United States parenteral quinidine is recommended for severe malaria, because of its wide availability as an antiarrhythmic agent. Elsewhere, quinine is used. The cinchona alkaloids are effective against all species of malaria including chloroquine-resistant strains of P. falciparum. Both quinine and quinidine have narrow therapeutic ratios, although serious cardiovascular or nervous system toxic effects during antimalarial treatment are most unusual.
Quinine and quinidine should be given by intravenous infusion — never by bolus injection, which can lead to fatal hypotension. The principal adverse effect of these drugs in severe malaria is hyperinsulinemic hypoglycemia. Iatrogenic hypoglycemia usually develops after at least 24 hours of treatment and is a particular problem in pregnant women. Quinidine has effects similar to quinine's on insulin secretion but a fourfold greater effect on the heart. Electrocardiographic monitoring is required so that infusion rates can be reduced if the corrected QT interval is prolonged by more than 25 percent of the base-line value. Routine electrocardiographic monitoring is unnecessary when quinine is used in patients with previously normal hearts.
The pharmacokinetic properties of the cinchona alkaloids are altered considerably in malaria, with a contraction in the volume of distribution and a reduction in clearance that is proportional to the severity of disease. Consequently, doses should be reduced by 30 to 50 percent after the third day of treatment to avoid accumulation of the drugs in patients who remain seriously ill. Binding to plasma proteins, principally to 1-acid glycoprotein, is increased in malaria (from approximately 80 percent to 90 percent for quinine).
This explains why plasma quinine levels that have been associated with blindness and deafness after self-poisoning (more than 10 mg per liter), although common during the treatment of severe malaria, do not cause such adverse effects. The therapeutic range for the unbound drug, which depends on the sensitivity of the infecting malaria parasites to the drug, has not been defined precisely but probably lies between 0.8 and 2 mg per liter, corresponding to total plasma concentrations of approximately 4 to 8 mg per liter for quinidine and 8 to 20 mg per liter for quinine.
When intravenous infusions cannot be given, quinine dihydrochloride, diluted to between 60 and 100 mg per milliliter, should be administered by deep intramuscular injection to the anterior thigh; the initial loading dose should be divided, with half injected in each leg. The intramuscular bioavailability of quinine is good (approximately 90 percent) even in severe malaria. Injections of undiluted quinine (300 mg per milliliter) are painful and occasionally produce sterile abscesses.
Artemisinin

Artesunate is unstable in solution and is therefore dispensed as a dry powder of artesunic acid, together with an ampule of 5 percent sodium bicarbonate solution. The powder and liquid are mixed, and the sodium artesunate solution is given by intravenous or intramuscular injection. Artemether is more stable than artesunate. It is formulated in peanut oil and given by intramuscular injection. In recent studies rectal suppositories of artemisinin have proved as effective as the parenteral drugs.
Thus, effective drug treatment for severe malaria can be given in rural settings even if injections cannot. Artemisinin and its derivatives have a broader "window period" of effectiveness than other antimalarial agents during the 48-hour asexual life cycle of the parasite. Antiparasitic effects on the younger ring-form parasites lead to their clearance and prevent development to the more mature pathogenic forms that induce the parasitized erythrocytes to adhere to uninfected cells (rosetting) or to vascular endothelium (cytoadherence).
Artesunate is the most rapidly acting of the available compounds, possibly because it is immediately bioavailable (as dihydroartemisinin) after intravenous injection, and it is absorbed rapidly after oral or intramuscular administration. In two recent, large comparative studies of patients with severe falciparum malaria (which together enrolled over 1000 patients), treatment with intramuscular artemether accelerated parasite clearance but slightly prolonged recovery from coma, and it did not reduce mortality significantly in comparison with quinine.
The results of these trials confirm that artemether is an acceptable and well-tolerated alternative to quinine in severe malaria, but a final assessment with respect to mortality should await a systematic overview of these and other recently completed studies. Over a million patients have been treated with the artemisinin derivatives. No serious toxicity has been reported. However, in experiments with animals, artemether, the closely related compound arteether, and the metabolite dihydroartemisinin have induced a consistent, but unusual, selective pattern of damage to some of the brain-stem nuclei. The relevance of these findings to their use in humans is unresolved but remains a cause of concern.
Ancillary Treatment

Many ancillary treatments have been suggested and tried in severe malaria, but none have been shown unequivocally to affect outcome. Only antipyretics (acetaminophen), anticonvulsants (prophylactic phenobarbital), and exchange transfusion have been supported by sufficient evidence to warrant their use. Exchange transfusion should be performed if there are adequate facilities, the patient is seriously ill, and the parasitemia exceeds 15 percent.
Exchange should still be considered with parasitemia in the range of 5 to 15 percent if there are other signs of poor prognosis. The roles of antibody against tumor necrosis factor, deferoxamine, mannitol, prostacyclin, dextran, pentoxifylline, and acetylcysteine in the treatment of malaria are unclear; aspirin and hyperimmune serum have been shown to confer no benefit, and heparin, cyclosporine, and high-dose corticosteroids are probably harmful.
Malaria Treatment (last updated March 2002)¹

P. falciparum.

This species was originally sensitive to chloroquine, however, strains resistant to this and other antimalarial drugs are now commonplace. Because the parasite is able to multiply very rapidly and sequester within the microvasculature, a life threatening illness may develop in a very short space of time.
Uncomplicated malaria (where patients can take oral therapy) can be treated with one of three regimens:

1. Quinine sulphate 10 mg salt/kg 8 hourly for seven days plus doxycycline 100 mg daily for 7 days. Patients will usually develop 'cinchonism' (tinnitus, high-tone hearing loss, nausea, dysphoria) after 2-3 days but should be encouraged to complete the full course to avoid recrudescence.

2. Malarone™ (atovaquone 250 mg plus proguanil 100 mg) 4 tablets daily for three consecutive days. This combination therapy is relatively new and appears to be very effective but it is also very expensive. Already resistance to this drug combination has been reported in a patient from Nigeria.

3. Mefloquine (Larium™) given as 15 mg/kg in a divided dose followed by 10 mg/kg the following day. Antipyretic and antiemetic agents may need to be given prior to mefloquine administration to reduce the risk of vomiting.
In uncomplicated cases in which nausea and vomiting preclude oral therapy, quinine dyhydrochloride 10 mg salt/kg base can be given I.V. in 5% w/v dextrose or normal saline as a 4-hour infusion 8-hourly until the patient can take medication by mouth.

**Severe malaria.** (where patients have coma, jaundice, renal failure, hypoglycaemia, acidosis, severe anaemia, high parasite count, hyperpyrexia) is ideally treated in an intensive care or high dependency unit where patients can be monitored closely both clinically and biochemically. Intravenous quinine is the treatment of choice but rapid injection can lead to hypotension, dysrhythmias and death.
In patients who have not received quinine in the previous 48 hours, one of two regimens can be used:

1. Quinine dihydrochloride 20 mg salt/kg base given I.V. in 5% w/v dextrose or normal saline as a once-only 4 hour infusion followed, 4 hours later, by quinine dihydrochloride 10 mg salt/kg base 4-hour infusions 8 hourly.

2. Where a syringe pump or other accurate infusion device is available, quinine dihydrochloride 7 mg salt/kg base over 30 minutes followed immediately by quinine dihydrochloride 10 mg salt/kg base over 4 hours then, starting 4 hours later, quinine dihydrochloride 10 mg salt/kg base as 4 hour infusions, 8 hourly.
Electrocardiographic monitoring can be done if available but is not essential unless additional cardiac risks are present. Where patients have received quinine within the previous 24 hours, give quinine dihydrochloride 10 mg salt/kg base I.V. in 5% w/v dextrose or normal saline as 4-hour infusions, 8-hourly. Hypoglycaemia may occur in patients with severe malaria particularly in patients treated with Quinine and careful monitoring is required. Steroids should not be used in patients with severe malaria.
P. vivax.

Most strains of P. vivax are still sensitive to chloroquine although some chloroquine resistant strains have been reported in Papua New Guinea, Indonesia, Thailand and India. This drug will clear the erythrocyte stages of the parasite but it has no effect on the exo-erythrocytic liver stage and a course of primaquine (an 8-amino-quinoline) is required for radical cure. The Chesson strain of P. vivax found in New Guinea shows some resistance to primaquine and an increased dose of primaquine is required. If primaquine is not given, the patient may suffer a relapse which will occur weeks or months after the original attack.
### Adult Treatment

Based on Chloroquine tablets containing 150mg base

<table>
<thead>
<tr>
<th>Day</th>
<th>Dosage Details</th>
</tr>
</thead>
</table>
| Day 1      | 4 tablets (600mg base) or 10 mg/kg first dose.  
               2 tablets (300mg base) or 5 mg/kg 6-8 hours later. |
| Day 2      | 2 tablets (300mg base) or 5 mg/kg.                                  |
| Day 3      | 2 tablets (300mg base) or 5 mg/kg                                   |
| Next 14 days | primaquine 2 tablets (each tablet contains 7.5mg base daily with food). |
The primaquine is preferably started after the chloroquine. When the infection is acquired in New Guinea, 3 tablets of primaquine (22.5mg base) should be given daily for 14 days. In the case of a relapse repeat both chloroquine and primaquine treatment. Up to three relapses may occur before the parasite is finally eliminated. Unfortunately there is no other effective treatment. Etaquine is a newly developed long-acting, potent primaquine-like drug which may be available soon for radical cure.
Patients should have their G6PD status checked before primaquine is prescribed. Those with G6PD deficiency may undergo haemolysis if given a daily dose of primaquine and it is recommended that these patients be given 30-45mg once a week for 8 weeks.

Malarone™ may also be used to treat P. vivax malaria but a course of primaquine will still be required to eliminate liver forms.

P. malariae, P. ovale.

Treatment for the eradication of these two strains of malaria is the same as that for P. vivax except it is not necessary to give primaquine to those patients with P. malariae
Artemisinins.

Artemisinin has been used for many years by the Chinese as a traditional treatment for fever and malaria. It is a sesquiterpene lactone derived from *Artemisia annua*. Because it is being increasingly used in a number of countries and is both cheap and effective it was decided to include treatment schedules here. However, it is not yet licensed for use in Australia, North America or Europe. Its main value at present is in the treatment of multidrug resistant *falciparum* malaria. If artemisinin is used to treat *vivax* malaria it should be accompanied by a course of primaquine. Unless used with a second antimalarial as described below there is likely to be a high recrudescent rate. Side effects have been reported but these are comparatively rare and seldom severe. It is recommended only for treatment not for prophylaxis.
Artemisinin (500mg tablets): give 10-20 mg/kg on day 1 (500-1,000 mg) orally then 500mg for 4 days. Then give mefloquine 15mg base/kg or split dose 25mg base/kg.

Artemisinin (200 mg suppositories): for severe malaria 600-1200mg stat, 400-600mg after 4 hours then 400-800mg twice daily for 3 days. Give mefloquine as above.

Artesunate (50 & 60 mg vials for intravenous use): for severe malaria 120mg I.V. stat. 60 mg at 4, 24 and 48 hours, 50-60 mg on days 3-5. Give mefloquine as above.
Dihydroartemisinin (20 mg tablets): first dose 120mg then 60mg daily for 4-6 days then give mefloquine as above.

Artemeter (vials for intramuscular use): for severe malaria 3.2 mg/kg intramuscularly stat then 1.6mg/kg twice daily for 3-7 days, Give mefloquine as above.
Prevention of Malaria$^{3,11}$

1. Protection against Mosquito Bites
2. Using an insect repellent
3. Prophylactic Agents

The risk for acquiring malaria varies according to geographic area, altitude, season, time of day, specific setting (urban versus rural), duration of stay in an endemic area, type of accommodation, and compliance with preventive measure.
Protection Against Mosquito Bites and Using Insect Repellent\textsuperscript{3,11}

The best way to prevent malaria is to avoid exposure to the Anopheles mosquito that carries the disease. This can be difficult in tropical areas because of the pervasiveness of mosquitoes and the inadequate screening of windows. However, the Anopheles mosquito has several distinguishing characteristics that may be helpful in avoiding exposure. Unlike other mosquito types, it flies silently and, at rest, adopts a head-down rather than a horizontal position. In addition, the Anopheles mosquito feeds from dusk to dawn. Thus, travelers can significantly reduce their risk of malaria by limiting evening exposure to mosquitoes. Travelers who take day trips from a malaria-free city to a malarious countryside are at minimal risk if they return to the city before dusk.
Mosquito bed netting can be useful in reducing nighttime exposure to mosquitoes, especially if the netting is sprayed with permethrin. Wearing long-sleeved, light-colored clothing is also helpful, but the best protection comes from using an insect repellent that contains no more than 35 percent N,N-diethyl-meta-toluamide (deet). Insect repellents with higher percentages of deet carry a small risk of neurotoxicity, particularly if they are used repeatedly on small children.
In addition to assessing and minimizing exposure risk, physician need to be aware of specific medical contraindications to the use of particular anti malarial drug (e.g., pregnancy) : they should also determine patients’ potential exposure to drug-resistant parasites. Moreover, prior to travel, patients should be provided with information regarding acces to medical care if needed during travel.
Prophylactic Agents $^3,^11$

Chloroquine

Chloroquine (Aralen) is a 4-aminoquinoline that inhibits heme polymerase, thus preventing the conversion of heme, a toxic byproduct of hemoglobin digestion by the parasite, into nontoxic malarial pigment. The erythrocytic or blood-feeding phase of the parasite life cycle is therefore interrupted but without affecting the hepatic phase.
For many years, chloroquine was the standard prophylactic agent against malaria, as well as a convenient treatment for acute attacks of the disease. Chloroquine is inexpensive, fast acting and fairly nontoxic at usual dosages. Furthermore, it can be used safely in pregnant women and women who are breast-feeding.
Because of the emergence of drug-resistant P. falciparum strains, however, chloroquine has become ineffective in most parts of the world. With a few exceptions, chloroquine is now used as malaria prophylaxis only in the Middle East, Central America and Hispaniola (the island nations of Haiti and the Dominican Republic). The antimalarial dosage for a traveler to these areas is one 500-mg tablet (300-mg base) per week beginning one week before departure, one 500-mg tablet per week during exposure and one tablet per week for four weeks after the traveler returns home.
Side effects of chloroquine include mild nausea, blurred vision, headache and psoriasis flare-ups. In addition, itching may occur in dark-skinned (black) persons. In dosages higher than 500 mg per week, chloroquine has been associated with retinal degenerative disorders and therefore probably should not be used in persons with such disorders. In the typical prophylactic dosage, however, the drug is not harmful to the retina. Very rare reactions to chloroquine include agranulocytosis, photosensitivity and neuropsychiatric effects.
Because of the bitter taste of chloroquine, pediatric dosing is very difficult. Chloroquine syrups are not commercially available in the United States. However, weekly doses of powdered chloroquine can be prepared in advance by a pharmacist and administered in food to disguise the taste. Child-proof containers are very important because chloroquine is extremely toxic in accidental overdose and has provoked fatal arrhythmias in small children.
Mefloquine

Mefloquine (Lariam), a quinolone methanol derivative, has supplanted chloroquine as the standard prophylactic agent against malaria. The Centers for Disease Control and Prevention (CDC) now recommends the prophylactic use of mefloquine in travelers to most malarious regions. Although mefloquine provides the best current protection against chloroquine-resistant P. falciparum malaria, resistant strains have developed in Cambodia and along Thailand's borders with Cambodia and Myanmar (the former Burma).
Because mefloquine has a long half-life (21 days), the dosing regimen is similar to that for chloroquine. The traveler begins by taking a 250-mg tablet once a week for one to two weeks before departure, then takes a 250-mg dose once a week during travel and takes a 250-mg tablet once a week for four weeks after returning home. Mefloquine tablets are scored to facilitate pediatric dosing.
Despite its effectiveness, mefloquine prophylaxis has some serious drawbacks. The drug is expensive, and there are relative contraindications to its use in pregnant women (at least in the first trimester), small children (those weighing less than 15 kg [33 lb]) and airline pilots (because the drug may possibly decrease spatial discrimination ability). Some exceptions to these relative contraindications are made because of increasing evidence that the risk of malaria far outweighs the risk of prophylaxis in persons traveling to destinations such as Africa. For example, pilots at high risk for malaria may be candidates for malaria prophylaxis using mefloquine, but only if they successfully adapt to prophylactic doses before flying. In special high-risk circumstances, use of this agent may also be warranted in pregnant women and children weighing 10 to 15 kg (22 to 33 lb).
Mefloquine should be used with caution in patients with seizure disorders, cardiac conduction defects or a history of psychosis. Therapy with beta blockers or calcium channel blockers is no longer considered a contraindication to the use of mefloquine unless a traveler has an underlying cardiac conduction problem or arrhythmia.
The neuropsychiatric side effects of mefloquine have led to a public controversy about this drug, particularly in Europe. Numerous anecdotal reports have been made of insomnia, nightmares, paranoid delusions, hallucinations, depression and even frank psychoses occurring in persons who received mefloquine, even in those without a significant psychiatric history. An estimated 70 percent of such problems occur within receipt of the first three doses. This may justify the use of a longer trial of mefloquine before travelers leave their home country. Most psychiatric problems have resolved on cessation of therapy. It is reasonable to caution patients about the possibility of psychiatric reactions to mefloquine and to provide an alternative therapy if they are unable to take the drug.
The mefloquine drug scare has received attention in the U.S. lay press. Consequently, some travelers have become reluctant to take mefloquine, even when no good alternatives are available. The fact remains, however, that most travelers tolerate the weekly dosage of mefloquine quite well. If anything, they have only a few mild gastrointestinal side effects, some slight dizziness and an occasional vivid dream. In multiple clinical trials, rates of serious neuropsychiatric problems have not been found to be significantly higher with prophylactic dosages of mefloquine than with alternative agents. Thus, despite some problems, mefloquine remains more convenient and effective than other available therapies suitable for use in areas where Plasmodium species are resistant to chloroquine.
Proguanil

Proguanil, or chloroguanide hydrochloride, is an effective antimalarial agent that is manufactured in Great Britain, where its brand name is Paludrine. This drug inhibits dihydrofolate reductase, thereby disrupting the ability of Plasmodium parasites to synthesize nucleic acids in the preerythrocytic phase. Proguanil best serves as a less effective alternative to mefloquine in sub-Saharan Africa, but it must be taken daily (200 mg after food) in conjunction with the weekly chloroquine regimen. The traveler should start taking proguanil several days before departure and continue taking the drug (in addition to the weekly chloroquine dose) for four weeks after returning to the home country.
Proguanil is usually well tolerated, although it may cause gastrointestinal distress and aphthous ulcers. The dosage must be reduced in patients with renal insufficiency. The combined regimen of proguanil and chloroquine is safe in pregnant women and infants. If this regimen is used with folate supplementation, it is a reasonable prophylactic option in pregnant women who travel to Africa.

Proguanil is not commercially available in the United States, but it may be readily obtained in Canada and overseas. Widespread resistance to proguanil limits its use to Africa. Even in Africa, however, the proguanil-chloroquine regimen is significantly less effective than a mefloquine or doxycycline regimen. Therefore, most U.S. physicians consider proguanil the third choice for malaria prophylaxis in travelers.
Doxycycline

Doxycycline (Vibramycin) attacks both the preerythrocytic phase (occurring in the liver) and the erythrocytic phase of the Plasmodium life cycle through ribosomal inhibition. As an antibiotic, doxycycline has also been used to prevent or treat traveler's diarrhea, although it has become less useful for either purpose because of bacterial resistance.
Fortunately, doxycycline remains an effective option for the multidrug-resistant P. falciparum malaria occurring in areas along Thailand's borders. It is often the best alternative when mefloquine is contraindicated. The drug is taken in a dosage of 100 mg per day during exposure and continued for four weeks after the traveler returns home.

Side effects of doxycycline therapy include photosensitivity (which necessitates the wearing of hats and sunscreen preparations), nausea, esophagitis and monilial vaginitis. With care, most of these side effects can be minimized. Consequently, the daily doxycycline regimen, although cumbersome, is still feasible. Doxycycline therapy is contraindicated in pregnant women and children less than nine years old.
Primaquine

Travelers exposed to malaria may use primaquine, in a dosage of one 26.3-mg tablet per day for 14 days, as terminal prophylaxis or for the elimination of Plasmodium vivax or Plasmodium ovale hypnozoites from the liver. Malaria prophylaxis using primaquine is reserved for use in persons who travel for relatively long periods (more than two months) in areas in which the probability of contracting malaria is high even with the use of reasonable prophylaxis. Before primaquine therapy is initiated, the possibility of glucose-6-phosphate dehydrogenase deficiency must be excluded. If present, this deficiency can result in severe hemolytic anemia in persons taking primaquine (Table 5).
Vaccines

Many travel-related diseases can be prevented by vaccines. Unfortunately, a malaria vaccine is unlikely to be available in the near future. Although immunity to malaria does occur, it is often incomplete and short-lived, and frequent rechallenging with malarial antigen is required. Residents of malarious areas eventually develop some immunity, but they appear to lose this immunity after they spend several years in a nonmalarious area.
One of the most promising vaccines was Spf66. This vaccine was developed by Dr. Manuel Patarroyo of Colombia, who subsequently donated it to the World Health Organization. Initial trials showed that the vaccine was capable of producing 30 percent or greater immunity; however, the results of more recent trials of Spf66 have been disappointing. Several other experimental vaccines are currently undergoing field trials in Africa. A successful vaccine will probably need to contain sporozoite, merozoite and gametocyte antigens.
The Future

Mother Nature gave us the cinchona alkaloids and qinghaosu. World War II led to the introduction of chloroquine, chloroguanide (proguanil), and eventually, amodiaquine and pyrimethamine. The war in Vietnam brought mefloquine and halofantrine. These drugs are all we have available now to treat malaria. It is difficult to see where the next generation of antimalarial drugs will come from. Even though malaria now affects about 250 million people and kills between 1 million and 2 million children each year, there is little pharmaceutical-industry interest in developing new antimalarial drugs; the risks are great, but the returns on investment are low. Much of the world's malaria occurs in countries with an annual per capita expenditure on health of less than $10. If drug resistance in \textit{P. falciparum} continues to increase at the current rate, malaria may become untreatable in parts of Southeast Asia by the beginning of the next millennium.
Table 1: Distinguishing Clinical Characteristics of Malaria by Infectious Plasmodium Species

<table>
<thead>
<tr>
<th></th>
<th><em>P. falciparum</em></th>
<th><em>P. vivax</em></th>
<th><em>P. ovale</em></th>
<th><em>P. malariae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average incubation period (days)</td>
<td>10–14</td>
<td>10–14</td>
<td>10–14</td>
<td>27–40</td>
</tr>
<tr>
<td>Severity of paroxysms</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Duration of paroxysms (hours)</td>
<td>36 (maximum)</td>
<td>Fewer than 12</td>
<td>Fewer than 12</td>
<td>Fewer than 12</td>
</tr>
<tr>
<td>Duration of untreated primary attack (weeks)</td>
<td>2 to 3</td>
<td>3 to 8</td>
<td>2 to 3</td>
<td>3 to 4*</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>++++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>++++</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Complications</td>
<td>Seizures, coma, hypoglycemia, acidosis, pulmonary edema, disseminated intra-vascular coagulation, circulatory collapse</td>
<td>Splenic rupture (2–3 months after initial infection)</td>
<td>Immune complex glomerulonephritis/ nephrotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

*Low-grade parasitemia may persist for many years.

### Table 2: Severe Malaria: Differences between Adults and Children

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of illness prior to complications</td>
<td>5-7 days</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Common</td>
<td>Very common; can be due to severe infection, hypoglycemia, febrile seizures, severe anemia etc.</td>
</tr>
<tr>
<td>Abnormal brain stem reflexes (oculovestibular, oculocervical)</td>
<td>Rare</td>
<td>More common</td>
</tr>
<tr>
<td>C.S.F. pressure</td>
<td>Usually normal</td>
<td>Variable, often raised</td>
</tr>
<tr>
<td>Resolution of coma</td>
<td>2-4 days</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Neurological sequelae</td>
<td>&lt; 5%</td>
<td>&gt; 10%</td>
</tr>
<tr>
<td>Cough</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Anemia</td>
<td>Common</td>
<td>More common and more severe; may be the presenting feature</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pre-treatment hypoglycemia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding/clotting disturbances</td>
<td>Up to 10%</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Table 3: Recommended Doses of Antimalarial Drugs For The Treatment of Malaria in Adults and Children *

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Treatment for Uncomplicated Malaria</th>
<th>Parenteral Treatment For Severe Malaria†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-sensitive malaria Chloroquine ‡</td>
<td>10 mg base/kg followed either by 10 mg base/kg at 24 hr and 5 mg base/kg at 48 hr or by 5 mg base/kg at 12, 24, and 36 hr (total dose, 25 mg base/kg). For P.vivax or P.Ovale, add primaquine (0.25 mg base/kg daily) § for 14 days for radical cure.</td>
<td>10 mg base/kg by constant-rate infusion over 8 hr followed by 15 mg base/kg over 24 hr, or 3.5 mg base/kg by intramuscular or subcutaneous injection every 6 hr (total dose, 25 mg base/kg).</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine ¶</td>
<td>20 mg sulfadoxine and 1 mg of pyrimethamine/kg in a single oral dose (usual adult dose, 3 tablets; 1 tablet=500 mg sulfadoxine and 25 mg pyrimethamine).</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Oral Treatment for Uncomplicated Malaria</td>
<td>Parenteral Treatment For Severe Malaria†</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Drug-resistant malaria</td>
<td>For people with some background immunity, 15 mg base/kg in a single dose. For people without immunity or in areas of mefloquine resistance, give second dose (10 mg base/kg 8-24 hr later. In U.S., 1 tablet = 228 mg base; elsewhere, 1 tablet = 250 mg base</td>
<td>20 mg of dihydrochloride salt/kg by intravenous infusion over 4 hr followed by 10 mg/kg infused over 2-8 hr every hr **</td>
</tr>
<tr>
<td>Mefloquine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>10 mg salt/kg every 8 hr for 7 days, combined with tetracycline (4 mg/kg four times daily) or doxycycline (3 mg/kg once daily) for 7 days.</td>
<td></td>
</tr>
<tr>
<td>Clindamycin (10 mg/kg twice daily for 3-7 days) is an alternative to tetracycline.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>10 mg base/kg infused at constant rate over 1 hr followed by 0.02 mg/kg/min, with electrocardiographic monitoring</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Oral Treatment for Uncomplicated Malaria</td>
<td>Parenteral Treatment For Severe Malaria†</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Halofantrine ††</td>
<td>8 mg/kg repeated at 6 and 12 hr. Repeat the regimen 1 wk later in people without immunity.</td>
<td></td>
</tr>
<tr>
<td>Artesunate ‡‡</td>
<td>In combination with a total of 25 mg of mefloquine/kg, give a total of 10-12 mg/kg in divided doses over 3-5 days (e.g., 4 mg/kg daily for 3 days or 4 mg/kg followed by 1.5 mg/kg/day for 4 days). If used alone, the same total dose is given over 7 days (usually 4 mg/kg initially followed by 2 mg/kg on days 2 and 3 and 1 mg/kg on days 4-7). 1 tablet = 50 mg.</td>
<td>2.4 mg/kg intravenously or intramuscularly initially, followed by 1.2 mg/kg at 12 and 24 hr, then 1.2 mg/kg daily. Artesunic acid (60mg) is dissolved in 0.6 ml of 5% sodium bicarbonate, diluted to 3-5 ml with 5% dextrose, and given by intravenous bolus or intramuscular injection. 1 ampule = 60 mg.</td>
</tr>
<tr>
<td>Artemether ‡‡</td>
<td>Same regimen as for artesunate. 1 capsule = 40 mg</td>
<td>3.2 mg/kg intramuscularly initially, followed by 1.6 mg/kg daily. Not to be given intravenously. 1 ampule = 80 mg</td>
</tr>
</tbody>
</table>
* If there is any doubt concerning the drug sensitivity of the parasite, the infection should be considered to be resistant. Antimalarial doses are generally recommended in terms of the base form of the drug, but the drugs are often dispensed in salt form. This gives rise to confusion; prescribers should make clear to nurses and pharmacists which they mean.

† Oral treatment should be substituted as soon as the patient can take tablets by mouth.
‡ Either chloroquine phosphate (250 mg of the salt equals 156 mg of the base) or chloroquine sulfate (200 mg of the salt equals 147 mg of the base) may be used. If neither is available, then hydroxychloroquine 200 mg of the salt equals 155 mg of the base) may be substituted.
§ For primaquine phosphate, 26.3 mg of the salt equals 15 mg of the base. In Ocenia and Southeast Asia the dose should be 0.33 mg of base per kilogram.

¶ The combination is currently recommended in the United States only for self-treatment of presumptive malaria (not prophylaxis) by travelers.

||Neither tetracycline nor doxycycline should be given to pregnant woman or children less than eight years old.

**Alternatively, 7 mg of salt per kilogram can be infused over a period of 30 minutes, followed by 10 mg of salt per kilogram over a period of 4 hours.⁷

Quinine, dihydrochloride is not available in the United States.
†† Halofantrine should not be taken with fatty foods and should not be given to patients with preexisting cardiac-conduction defects, those who have a long QT interval, those who have received mefloquine within the previous 28 days, or those who are taking drugs known to prolong the QT interval (i.e., quinine, quinidine, chloroquine, tricyclic antidepressants, neuroleptic drugs, terfenadine, or astemizole). Halofantrine is not available in the United States.

‡‡ This drug is not available in the United States.
Table 4: Malaria Chemosuppressive Regimens to Zones of Drug Resistance

<table>
<thead>
<tr>
<th>Zone</th>
<th>Drug of Choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chloroquine resistance</td>
<td>Chloroquine phosphate 300 mg base (500 mg salt) orally once weekly</td>
<td>Doxycycline 100 mg orally once daily</td>
</tr>
<tr>
<td>Chloroquine resistance</td>
<td>Mefloquine 228 mg base (250 mg salt) orally once weekly</td>
<td>Primaquine 15 mg base (26.3 mg salt) orally once daily for 14 days after departure from malaria-endemic area</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg orally once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloroquine phosphate 300 mg base (500 mg salt) orally once weekly plus either pyrimethamine-sulfadoxine 3 tablets (75 mg pyrimethamine/1500 mg sulfadoxine) orally as a single dose for presumptive treatment or proguanil (Paludrine)*</td>
<td></td>
</tr>
<tr>
<td>Chloroquine and mefloquine resistance</td>
<td>Atovaquone-proguanil 1 tablet (250 mg atovaquone/100 mg proguanil) daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg orally once daily</td>
<td>Primaquine 15 mg base (26.3 mg salt) orally once daily for 14 days after departure from malaria-endemic area</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atovaquone-proguanil 1 tablet (250 mg atovaquone/100 mg proguanil) daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloroquine phosphate 300 mg base (500 mg salt) orally once weekly plus either pyrimethamine-sulfadoxine 3 tablets (75 mg pyrimethamine/1500 mg sulfadoxine) orally as a single dose for presumptive treatment or proguanil (Paludrine)*</td>
<td></td>
</tr>
</tbody>
</table>

*Proguanil (Paludrine) is not available in the United States but is widely available in Canada and overseas. It is recommended mainly for use in Africa, south of the Sahara desert. Prophylaxis is recommended during exposure and for 4 weeks afterwards. Proguanil has been used in pregnancy without evidence of toxicity.
### Table 5: Drugs for Malaria Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Areas of effective use</th>
<th>Adult dosage</th>
<th>Pediatric dosage</th>
<th>Use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine (Aralen)</td>
<td>Middle East, Central America (west of Panama Canal) and Hispaniola (especially Haiti)</td>
<td>300-mg base (500-mg salt) orally once a week starting one week before travel, once weekly during exposure and once weekly for four weeks after return home</td>
<td>Same weekly regimen as for adults but dosage is as follows: 5 mg per kg base (8.3 mg per kg salt), to a maximum of 300-mg base</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug</td>
<td>Areas of effective use</td>
<td>Adult dosage</td>
<td>Pediatric dosage</td>
<td>Use in pregnancy</td>
</tr>
<tr>
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<td>------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Mefloquine (Lariam) | Areas of chloroquine-resistant malaria (South America, Asia, Africa, India and Oceania [Pacific islands and New Guinea]) | 250-mg salt using the same regimen as for chloroquine | Same weekly regimen as for adults but dosages are as follows:  
Less than 15 kg (33 lb): 5 mg per kg salt  
15 to 19 kg (33 to 42 lb): one fourth of a 250-mg salt tablet per week  
20 to 30 kg (44 to 66 lb): one half of a 250-mg salt tablet per week  
31 to 45 kg (68 to 99 lb): three fourths of a 250-mg salt tablet per week  
More than 45 kg (99 lb): one 500-mg salt tablet per week | Usually not in first trimester  
May be used in second and third trimesters if use is warranted based on risk and the pregnant woman is unable to postpone travel plans |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Areas of effective use</th>
<th>Adult dosage</th>
<th>Pediatric dosage</th>
<th>Use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proguanil (Paludrine; not available in the United States)</td>
<td>Less effective alternative to mefloquine in sub-Saharan Africa; used with weekly chloroquine dose</td>
<td>200 mg per day after food</td>
<td>Less than two years: 50 mg per day Two to six years: 100 mg per day Seven to 10 years: 150 mg per day Older than 10 years: 200 mg per day</td>
<td>Yes, with folate supplementation</td>
</tr>
<tr>
<td>Drug</td>
<td>Areas of effective use</td>
<td>Adult dosage</td>
<td>Pediatric dosage</td>
<td>Use in pregnancy</td>
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<tr>
<td>Doxycycline (Vibramycin)</td>
<td>Reasonable alternative to mefloquine in areas with mefloquine-resistant Plasmodium strains or when mefloquine is contraindicated</td>
<td>100 mg per day during exposure and for four weeks after return home</td>
<td>Contraindicated in children less than nine years old Otherwise, regimen is the same as for adults</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Areas of effective use</strong></td>
<td><strong>Adult dosage</strong></td>
<td><strong>Pediatric dosage</strong></td>
<td><strong>Use in pregnancy</strong></td>
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<tr>
<td>Primaquine</td>
<td>Terminal prophylaxis if at risk for relapsing type of malaria or for elimination of Plasmodium species in persons who travel for more than two months in a high-risk area</td>
<td>15-mg base (26.3-mg salt) per day for 14 days before return home</td>
<td>0.3 mg per kg base (0.5 mg per kg salt) per day for 14 days</td>
<td>No</td>
</tr>
</tbody>
</table>
| Pyrimethamine-sulfadoxine (Fansidar) | No longer used for prophylaxis  
Self-treatment if in remote setting or if on inadequate prophylaxis | Three tablets as a single dose  
5 to 10 kg (11 to 22 lb): one-half tablet (single dose)  
11 to 20 kg (24 to 44 lb): one tablet (single dose)  
21 to 30 kg (46 to 66 lb): one and one-half tablets (single dose)  
31 to 45 kg (68 to 99 lb): two tablets (single dose)  
More than 45 kg (99 lb): three tablets (single dose) | Not in first or third trimesters |

Adapted from Health information for international travel, 1996-97. Atlanta: Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Quarantine, 1997. HHS publication no. 95-8280.
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