

Chapter 12 **THE TREATMENT OF MALARIA**

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Malaria is the most important parasitic infection of man. Although eradicated from temperate zones, increasing numbers of travellers return each year from tropical countries, where the disease remains a major cause of morbidity and mortality. In these areas malaria is currently thought to affect approximately 250,000,000 people. Antimalarial drugs and antipyretics are the most commonly used drugs in the tropics. The drugs are consumed on a vast scale, and much of this use is unregulated. In many parts of Africa the majority of the population has chloroquine in the blood at any time. The treatment of malaria has changed over the past two decades in response to declining drug sensitivity in Plasmodium falciparum, and a resurgence of the disease in tropical areas. Chloroquine resistance is now widespread in three continents, and resistance to sulphadoxine-pyrimethamine has developed rapidly in many countries. Mefloquine resistance has become a problem in S.E.Asia. This review concentrates on practical aspects of treatment.

DIAGNOSIS

The treatment of malaria should be based on a parasitological diagnosis where possible. Of course this is often not possible and treatment is given on suspicion, in febrile illnesses. When microscopic diagnosis is not available many non-malarial fevers are ascribed to malaria, severe malaria is often diagnosed incorrectly, drug resistance is usually underestimated, and the drug pressure to resistance is greater because of the widespread incorrect use of antimalarial drugs. The net cost to the community may be greater than the provision of a diagnostic service.

Malaria usually presents with non-specific and irregular fever, chills, headache and malaise. Abdominal discomfort and vomiting occur in approximately 20% and mild diarrhoea in 10% of cases. As the disease progresses the spleen enlarges and the patient becomes anemic. Malaria is so common that any patient who has been in a malarious area within the previous two months (usual incubation period two weeks) should be considered to have malaria until proved otherwise. The diagnosis is confirmed by microscopy under oil immersion of stained thick and thin blood films. The parasites should be speciated (if in doubt consider as P. falciparum) and counted. In severe malaria the stage of parasite development, and the percentage of neutrophils containing malaria pigment should be noted also. The prognosis worsens with increasing counts, more mature parasites, and more neutrophils containing pigment (Table 1). A negative blood smear makes the diagnosis very unlikely, but if there is still diagnostic uncertainty the smear should be repeated after 24 hours. A simple stick test based on a monoclonal antibody to

Plasmodium falciparum histidine rich protein 2 has a diagnostic sensitivity similar to that of microscopy.

THE MANAGEMENT OF UNCOMPLICATED MALARIA

The treatment of malaria depends on the severity of the infection, the age and degree of background immunity (if any), the likely pattern of antimalarial susceptibility, and the cost and availability of antimalarial drugs. For these reasons recommendations vary geographically, and should be under constant review.

The three "benign" malarial parasites P. vivax, P. malariae and P. ovale should all be treated with chloroquine. Although there is significant chloroquine resistance in P. vivax on the island of New Guinea (Papua New Guinea, Irian Jaya) [2,3] and possibly some parts of the Solomon Islands, elsewhere it remains sensitive and responds rapidly. Other reports of chloroquine resistance are either unconvincing, or have confused recrudescence of the infection with relapse.

Chloroquine is generally well tolerated, although it commonly produces pruritus in dark skinned patients, and may cause nausea, dysphoria and, very rarely, a transient neuropsychiatric syndrome or cerebellar dysfunction. Children often object to the taste of chloroquine, particularly in tablet form. Recent studies have shown that the traditional 3 day 25 mg (10, 10, 5) base/kg regimen can be compressed into 36 hours for convenience [4] (Table 2). "Radical cure" with *Primaquine* 0.25mg base/kg/ (0.33 mg/kg in Oceania and S.E. Asia) daily for 14 days is also required in P. vivax or P. ovale infections to eradicate persisting liver forms (hypnozoites) and prevent relapse. Primaquine may cause nausea and abdominal pain, particularly if taken on an empty stomach and, more importantly, oxidant hemolysis with methemoglobinemia, anemia, and sometimes hemoglobinuria. Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency are particularly vulnerable to oxidant hemolysis, and primaquine is contraindicated in severe variants of G6PD deficiency. Where mild variants of G6PD deficiency are common, primaquine (0.8 mg base/kg: adult dose 45 mg) should be given once weekly for six weeks for radical cure [5].

In endemic areas where reinfection is common, radical cure with primaquine is not indicated.

Chloroquine resistant P. vivax responds to mefloquine and primaquine (which also possesses asexual stage activity) The choice of treatment for P. falciparum depends on the antimalarial sensitivity in the area where the infection was acquired. Known sensitive infections (e.g. from North Africa, Central America or the Middle East) should be treated with *chloroquine*. Where there is low-grade chloroquine resistance, *amodiaquine* (Total dose 35mg base/kg/day over 3 days) is an alternative. Amodiaquine is well tolerated. Children prefer the taste to chloroquine. The risks of life-threatening adverse effects (agranulocytosis, hepatitis) which occurred in approximately 1:2000 people who took amodiaquine for prophylaxis, are considered much lower in treatment, although firm data are lacking. Chloroquine-resistant infections from most of Africa and some parts of Asia and S. America usually respond to the combination of a long acting *sulphonamide* (usually sulphadoxine) and *pyrimethamine*. This is a well tolerated single dose treatment. Serious sulphonamide toxicity (Severe skin reactions, cytopenias, haemolytic anaemia, neuropathy, hepatitis) which was estimated to have occurred in 1:7000 people who took the combination for prophylaxis is considered rare in treatment, although again firm data are lacking. In practice chloroquine is still extensively used even in areas with established resistance, because the alternatives are too expensive. At the time of writing only Malawi of the African countries has changed its National Policy to treatment with sulphadoxine-pyrimethamine, although chloroquine resistance has spread from the east to the west coast of the

continent. The therapeutic response to chloroquine, or any other antimalarial drug, is always better in semi-immune subjects compared to non-immunes so chloroquine is still useful in these resistant areas, but the incidence of severe anaemia in infants and young children inevitably increases as drug susceptibility declines. Thus the full impact of chloroquine resistance in areas of high transmission may not be fully appreciated unless there are longitudinal data on the incidence of severe anaemia in young children.

Unfortunately resistance to sulphadoxine-pyrimethamine has developed rapidly in some areas (particularly S. America and S.E.Asia). For multi-drug resistant strains of *P. falciparum* the choice of treatment lies between mefloquine, halofantrine, or quinine plus tetracycline (clindamycin is used in some countries).

Mefloquine is cleared slowly ($t_{1/2}$ 2 - 3 weeks) and either a single or split dose is sufficient for cure [6]. An initial 15 mg base/kg dose should be followed 8 - 24 hours later by 10 mg/kg. Most data on dosage refer to the formulation Lariam^R (Roche). As oral bioavailability varies considerably with mefloquine, more information is required on other formulations. Mefloquine treatment is relatively well tolerated although nausea, vomiting, giddiness, weakness, dysphoria, feelings of dissociation, mental clouding, and nightmares are all common. Rarely (1:1700 with 15 mg/kg, 1:1200 with 25mg/kg) more serious self-limiting neuropsychiatric reactions may occur [7,8]. Although early (< 1 hour) vomiting is more common in children, the other adverse effects of mefloquine are more common in adults [9], and interestingly are complained of more frequently by women than men..

Halofantrine is more active and better tolerated than mefloquine, but it has poor and variable bioavailability (improved by fats). Halofantrine induces a significant concentration dependent delay in atrioventricular conduction and ventricular repolarisation [11], that has cast a shadow over its future role. Halofantrine should not be given to patients with a long QT_c interval or those taking drugs likely to delay repolarisation. Neither halofantrine nor mefloquine should be used to treat early recrudescences of malaria (< 28 days) following high dose mefloquine as their respective cardiac and central nervous system effects are increased.

Oral treatment with the Cinchona alkaloids *quinine* or *quinidine* is not well tolerated. These venerable compounds are extremely bitter and reliably induce the symptom complex of cinchonism (nausea, dysphoria, tinnitus and high tone deafness). Fortunately more serious toxicity is rare. Although the quinine plus tetracycline or doxycycline combination remains >85% effective nearly everywhere [12], compliance with the five to seven day courses of treatment required in resistant areas is poor. In areas where the *P.falciparum* parasite is more sensitive than a three day course of quinine can be combined with seven days of tetracycline. Unfortunately in most of these areas the brunt of malaria is in children who cannot take tetracyclines. Short courses of quinine (<5 days) are not effective, and even if compliance is good, courses of 5 days treatment have significant failure rates.

The derivatives of *artemisinin* (qinghaosu) obtained from qinghao or sweet wormwood (*Artemisia annua*) and developed in China, are the most rapidly acting of all antimalarial drugs. In both severe and uncomplicated malaria they have given consistently faster fever and parasite clearance than other antimalarials without evident toxicity [13,14]. 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 metabolised to a common biologically active metabolite dihydroartemisinin (DHA). Indeed artesunate can be considered a

pro-drug for DHA. In some parts of S.E. Asia (particularly the Eastern and Western borders of Thailand) treatment failure rates with high dose mefloquine alone in falciparum malaria now exceed 40%. In these circumstances oral artesunate given for 3 - 5 days in combination with mefloquine (25 mg/kg) still remains highly effective [15,16]. If the artemisinin derivatives are used alone (e.g. for the treatment of recrudescence following mefloquine) then they should be given for seven days. The main concerns surrounding these extraordinary drugs are the unresolved issue over neurotoxicity, and the difficulty in regulating drugs which are relatively cheap, very well tolerated, and highly effective. Already these compounds are available in the market place. This is a prescription for abuse, and the development of resistance. The development of resistance to the artemisinin compounds would be a disaster, as these drugs are still effective against multi-drug resistant falciparum malaria, and also offer the potential to reduce the mortality of severe malaria. In animal models these drugs, particularly the oil-soluble ethers artemether and arteether, have produced an unusual, selective pattern of damage to brain stem nuclei. There is no evidence of this to date in man despite extensive use of the drugs, but studies are ongoing and the possibility remains that they may be neurotoxic.

Children and Pregnant Women

Children tolerate antimalarial drugs relatively well. Mefloquine is not recommended for children < 15 kg, but this is a policy of caution because of limited published experience. Our own experience suggests there are no additional risks, although infants are more likely to vomit the drug. In resistant areas it has been recommended that quinine should be given in an eight day course to young children, increasing the dose in the last four days to 15mg/kg three times daily. Primaquine should not be given to newborns or pregnant women. 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 used in the third trimester. There is increasing evidence that mefloquine is safe in the second and third trimesters. Although there is very 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 where alternative treatment (quinine) is still preferred. Apart from primaquine and halofantrine (where there are no data), the other antimalarials can all be used in women who are breast-feeding.

Practical considerations

There are no pediatric formulations of mefloquine, the artemisinin derivatives, primaquine or, in many countries, quinine or chloroquine. When treating children, particular care should be taken to ensure the correct doses are given and retained. Early vomiting is common, particularly following the administration of mefloquine or quinine to infants, and is more likely with high fever. Patients should be cooled (acetaminophen, fanning and tepid sponging) before receiving oral antimalarial treatment and then observed for one hour. If vomiting occurs within one hour the full dose should be repeated (for mefloquine we give half the dose for vomiting between 30 and 60 minutes). If vomiting occurs after one hour, it is not necessary to re-administer the drugs. Postural hypotension is common in uncomplicated malaria, and is exacerbated by the quinoline antimalarials. Febrile patients should be nursed horizontally, and should take great care 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 FALCIPARUM MALARIA

Management

Whereas *P. vivax*, *P. ovale* or *P. malariae* are very rarely fatal, *P. falciparum* infections may progress rapidly to a lethal multi-system disease. The clinical manifestations of severe malaria depend on age [17]. Hypoglycemia, commonly accompanied by lactic acidosis, convulsions, and severe anemia are relatively more common in children [18], whereas acute renal failure, jaundice and pulmonary edema are more common in adults. Cerebral malaria (coma), shock and respiratory distress leading to respiratory arrest occur at all ages. The state of hydration on admission is very variable. The physician must tread a thin dividing line between over and under-hydration. Adults in particular may develop non-cardiogenic pulmonary edema and are vulnerable to fluid overload, yet dehydration and hypovolemia contribute to hypotension and shock, and may hasten the development of acute renal failure from acute tubular necrosis [19]. After rehydration the central venous pressure should be maintained at approximately 5 cm of water (pulmonary artery occlusion pressure <15 mm Hg). When hypercatabolic acute renal failure develops with other evidence of vital organ dysfunction, dialysis or hemofiltration should be started early. Renal function returns with a median time to restoration of urine flow (> 20 ml/kg/day) of 4 days, although some patients will require dialysis for more than a week. Hypoglycemia occurs in approximately 8% of adults and 25% of children [18,20]. After rehydration a maintenance 10% glucose infusion should be given to all patients but the blood glucose should still be checked frequently. Unconscious patients (cerebral malaria) should be nursed on their side, and a lumbar puncture performed to exclude bacterial meningitis. Convulsions should be treated promptly with intravenous benzodiazepines. Use of prophylactic intramuscular phenobarbital reduces the incidence of seizures, but the optimum dose remains to be determined. Hemolysis is extensive and anemia develops rapidly. Blood transfusion should be given if the hematocrit falls below 20%. Fresh blood transfusion is preferable, particularly if there is significant bleeding secondary to disseminated intravascular coagulation (□ 5% of patients with severe malaria) or stress ulceration. Bacterial infections are common; pneumonia is particularly likely if the duration of coma exceeds three days, urinary tract infections complicate indwelling catheter drainage, and spontaneous (usually gram negative) septicemias may occur occasionally. In Africa non-typhoidal systemic *Salmonella* infections may develop in otherwise uncomplicated malaria [21]. If a patient with severe malaria deteriorates suddenly without an evident cause, hypoglycaemia should be excluded, blood cultures drawn, and empirical broad spectrum antimicrobial treatment started. Vital signs including coma score, urine output, blood glucose and, if possible, lactate, and arterial pH and gases should be monitored as frequently as possible. After starting antimalarial treatment, the parasite count should be measured at least twice daily in all patients. If the parasite count has not fallen by 75% at 48 hours, it should be re-checked, and if confirmed, then the antimalarial should be changed.

Antimalarial Treatment

Chloroquine

In those few remaining places where there is not significant resistance, then parenteral chloroquine should be given as it is intrinsically superior to quinine [22]. If there is any doubt, then quinine or quinidine should be used. Chloroquine should be given by controlled-rate intravenous infusion (never injection). Intramuscular or subcutaneous administration is a satisfactory alternative as absorption is rapid, bioavailability exceeds 80% even in severe

malaria, and the injections are not painful [23]. Provided it does not enter the circulation too rapidly, either because the rate of intravenous administration is too fast, or the individual intramuscular or subcutaneous injection dose is too large (> 3.5 mg base/kg), then hypotension will not occur, and parenteral chloroquine is very well tolerated.

Quinine and Quinidine

The alkaloids derived from the bark of the Cinchona tree constitute the mainstay of the antimalarial pharmacopoeia, as they have for over three hundred years. Quinidine, the dextrorotatory diastereomer, 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, as it is available widely (as an antiarrhythmic) [24]. Elsewhere quinine is used. The cinchona alkaloids are effective against all species of malaria including chloroquine - resistant strains of *P. falciparum* [17]. Both drugs have narrow therapeutic ratios, although serious cardiovascular or nervous system toxicity during antimalarial treatment is most unusual. Quinine and quinidine should be given by intravenous infusion, never by bolus injection, otherwise fatal hypotension may ensue. The principal adverse effect in severe malaria is hyperinsulinemic hypoglycemia [25]. Iatrogenic hypoglycemia usually develops after at least 24 hours of treatment, and is a particular problem in pregnant women [27]. Quinidine has similar effects on insulin secretion but a four-fold greater effect on the heart [28]. Electrocardiographic monitoring is required so that infusion rates can be stopped if the rate corrected QT interval is prolonged by $> 25\%$ of the baseline value. Routine EKG monitoring is not necessary when quinine is used.

The pharmacokinetic properties of the cinchona alkaloids are altered considerably in malaria, with a contraction in V_d and a reduction in systemic clearance that is proportional to disease severity [29]. In severe malaria doses should be reduced by 30 - 50% after the third day of treatment to avoid accumulation in patients who remain seriously ill. The therapeutic range for *free* drug depends on the sensitivity of the infecting malaria parasites. This has not been defined precisely, but is probably in the range of 1 - 2 mg/L (South East Asian parasites tend to be more resistant), which corresponds to total plasma concentrations of approximately 4 - 8 mg/L for quinidine, and 8 - 20 mg/L for quinine. Binding, principally to α_1 -acid glycoprotein is increased in malaria (from approximately 80% to 90% for quinine) [30]. This probably explains why total plasma concentrations of quinine (> 10 mg/L) that have been associated with blindness and deafness following self-poisoning, are usual in the treatment of severe malaria and do not cause these adverse effects.

Where intravenous infusions cannot be given, quinine dihydrochloride, diluted to of 60 - 100 mg/ml, should be administered by deep intramuscular injection to the anterior thigh. The initial loading dose should be split and given to both legs. Intramuscular bioavailability is good ($\approx 90\%$) even in severe malaria [31,32]. Quinine injections are painful and, if undiluted, occasionally produce sterile abscesses.

Artemisinin (Qinghaosu)

Artesunate is unstable in solution and is therefore dispensed as a dry powder of artesunic acid together with an ampoule of 5% sodium bicarbonate. The two are mixed and the solution is given by intravenous or intramuscular injection. Artemether is more stable. It is formulated in groundnut oil, and is given by intramuscular injection. In recent studies [33] artemisinin rectal suppositories have proved as effective as the parenteral drugs. Thus effective antimalarial

treatment can be given for severe malaria in rural settings where injections cannot. Artemisinin and its derivatives appear to have a broader "time-window" of effect than other antimalarials during the 48 hour asexual life cycle. Antiparasitic effects on the younger "ring-form" parasites lead to their clearance and prevent development to the more mature pathogenic forms that induce the parasitised 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 DHA following intravenous injection, and is absorbed rapidly following oral or intramuscular administration. Over a million patients have been treated with the artemisinin derivatives. No significant toxicity has been reported [13]. However, in experimental animals, artemether, arteether, and the metabolite DHA have induced an unusual and selective pattern of damage to some of the brain stem nuclei [34]. The relevance of these findings to their use in man is unresolved, but remains an area of concern.

Ancillary Treatments

Many ancillary treatments have been suggested and tried in severe malaria, but only antipyretics (acetaminophen) and anticonvulsants (prophylactic phenobarbital), and exchange transfusion have been supported by sufficient evidence to warrant their use [24,35]. The role of anti-TNF antibody, desferrioxamine, mannitol, prostacyclin, dextran, oxpentifylline, and N-acetylcysteine is uncertain, aspirin and hyperimmune serum have been shown to confer no benefit, and heparin, cyclosporine, and high dose corticosteroids are probably harmful. Exchange transfusion should be performed if there are adequate facilities, and the parasitemia exceeds 15%, and should still be considered with parasitemias in the 5-15% range, particularly if there are other signs of poor prognosis (Table 1).

The future

Mother nature gave us the cinchona alkaloids and qinghaosu, the Second World War led to the introduction of chloroquine, proguanil (chloroguanide), and started the research that led to amodiaquine and pyrimethamine. The conflict in Viet Nam 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 one and two million children each year, there is little pharmaceutical industry interest in developing new antimalarial drugs as the risks are significant, but the returns on investment are so low; much of the world's malaria occurs in countries with an annual per-capita expenditure on health of less than \$10. However, if drug resistance in P. falciparum continues to develop at the current rate, then we may be confronting untreatable malaria in parts of South East Asia by the beginning of the next millenium.

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Table 1: Severe malaria: Poor prognostic features

Deep coma
Repeated convulsions
Respiratory distress (rapid, deep, laboured, stertorous, breathing often with intercostal recession)
Significant bleeding
Renal impairment¹ (serum creatinine >250 µmol/L)
Hyperlactatemia (venous lactate >5 mmol/µL)
Hypoglycemia (blood glucose <2.2 mmol/L)
Elevated transaminases (> 3 times normal)
Parasitemia >500,000/µL or
>10,000 mature trophozoites² + schizonts/µL
≥ 5% of neutrophils contain malaria pigment

¹ The combination of deep jaundice and renal failure is particularly grave.

² Mature parasites in which pigment is visible under light microscopy.

Table 2: Antimalarial Drugs: Recommended doses for treatment

	Uncomplicated malaria (Oral)	Severe malaria* (Parenteral)
Chloroquine	10mg <u>base</u> /kg followed either by 10mg/kg at 24 hrs and 5mg/kg at 48 hrs <u>or</u> 5mg/kg at 6, 12 and 18 hrs. Total dose 25mg base/kg. For <i>P. vivax</i> or <i>P. ovale</i> add primaquine 0.25 mg base/kg daily for 14 days** for radical cure.	10mg <u>base</u> /kg by constant rate infusion over 8 hrs followed by 15mg/kg over 24 hrs <u>or</u> 3.5mg <u>base</u> /kg by intramuscular or subcutaneous injection every 6 hrs. Total dose 25mg base/kg
Sulfadoxine - pyrimethamine	20/1mg/kg single oral dose (3 tablets for an adult).	
Mefloquine	In mefloquine resistant areas or for non-immunes give second 10mg/kg dose 12 - 24 hrs later. For semi-immunes 15mg <u>base</u> /kg single dose.	
Quinine	10mg <u>salt</u> /kg 8 hourly for 7 days combined with tetracycline † (4mg/kg) four times daily <u>or</u> doxycycline 2.5mg/kg once daily for 7 days.	20mg <u>salt</u> /kg by intravenous infusion over 4 hrs ‡ followed by 10mg/kg infused over 2 - 8 hrs every 8 hrs.
Quinidine		10mg <u>base</u> /kg infused at constant rate over 1 hr followed by 0.02mg/kg/min, with electrocardiographic monitoring.
Artesunate	In combination with 25mg/kg mefloquine, 10-12mg/kg is given in divided doses over 3-5 days (e.g. 4mg/kg for 3 days or 4mg/kg followed by 1.5mg/kg/day for 4 days). If used alone, the same dose is divided over 7 days (usually 4mg/kg initially followed by 2mg/kg on days 2 and 3 followed by 1mg/kg on days 4- 7).	2.4mg/kg i.v. or i.m. stat followed by 1.2mg/kg at 12 and 24 hrs and then daily.
Artemether	Same dose regimen as artesunate.	3.2mg/kg i.m. stat followed by 1.6mg/kg daily.

N.B. In severe malaria quinine or quinidine should be used if there is any doubt about the chloroquine - sensitivity of the infection

* Oral treatment should be substituted as soon as the patient can take tablets by mouth

** In Oceania and S.E. Asia the dose should be 0.33 mg base/kg.

† Tetracycline should not be given to pregnant women or children < 8 years old
‡ Alternatively 7 mg salt/kg can be infused over 30 minutes followed by 10 mg salt/kg over 4 hours [35].

8 June 1994