

Malaria: treatment

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Globally, malaria remains one of the most common and serious infectious diseases. Table 1 lists some points about malaria with which practitioners of acute general medicine should be familiar. This article aims to provide physicians with an update on the current management of malaria in adults and older children, as practised in the UK. Chemoprophylaxis, management of young children, and the treatment of malaria in tropical settings are not covered.

Parasites

Four species of malaria parasite cause disease in man:

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*.

They are all primarily acquired by the bites of female *Anopheles* mosquitoes (Fig 1), but they may also be transmitted in infected blood transfusions, transplacentally and in laboratory inocula-



Figure 1. Female *Anopheles* mosquito feeding.

tion accidents. Physicians need to know something about the geographical distribution, incubation period, pathogenicity, life cycle and prevalence of drug resistance of these four species. The most clinically important information about them is summarised in Table 2.

Clinical manifestations: the diagnosis

Uncomplicated malaria

Symptoms and signs. The predominant symptoms of malaria (due to any

species) are non-specific and include headache, malaise, fever and rigors. This symptom complex is so common, and in non-malarious zones so often due to diseases other than malaria, that the diagnosis may not be considered early. The consequences of such delay may prove fatal, and it is essential that enquiry is made about foreign travel.

There are no specific physical signs. The classical pattern of fever may give a diagnostic clue, but is unreliable as an identifier of the infecting species. *P. vivax* and *P. ovale* infections cause fever every other day, while *P. malariae* causes fever every third day. Fever on alternate days is 'classical' in *P. falciparum* infection but, more usually, this pattern is difficult to spot.

Diagnosis. The diagnosis is best established using thick, rather than thin, blood films because of their greater sensitivity. Interpretation of thick films and identification of parasite species may not be possible in all routine haematology laboratories, and help may be needed from one of the two tropical medicine schools (Liverpool and London) or regional infectious diseases units. In non-immune patients, symptoms can be marked even in the presence of low parasitaemia, making the diagnosis difficult to establish if

Table 1. Important aspects of malaria for doctors in the UK.

- The worldwide prevalence of malaria remains high and may be set to rise further.
- During the 1990s there have been about 2,000 cases of malaria per year, about half of them caused by *Plasmodium falciparum*.
- There is currently no effective vaccination against malaria.
- Malaria may be acquired after just one infected mosquito bite, so transmission may occur during brief visits to transmission zones.
- Malaria chemoprophylaxis does not give 100% protection.
- Repeated exposure to malaria infection often gives rise to a degree of immunity to local strains, which can be lost during pregnancy or by prolonged residence in non-malarious areas.
- Enquiry about foreign travel is an important aspect of the medical history.
- Malaria should be excluded in all febrile patients with a history of recent travel to malarious areas.
- The detection of *P. falciparum* in the blood of a non-immune patient constitutes a medical emergency.

Table 2. Clinically important information about the four most important malarial pathogens.

Plasmodium falciparum:

- Prevalent throughout the tropics (although most cases seen in the UK have originated in Africa).
- Incubation period usually 9–14 days.*
- Highly pathogenic, mainly because of high rate of asexual reproduction and ability to adhere to endothelia ('sequestration').
- No hypnozoite (or 'dormant') stage in the liver, so elimination of parasitaemia is sufficient for cure.
- Resistance to almost all antimalarial drugs has developed, although the 'pattern' of such resistance is geographically variable.

Plasmodium vivax:

- Common in the tropics (except Africa) and in parts of the subtropics.
- Considerably less pathogenic than *P. falciparum*.
- Incubation period usually 12–17 days but can be up to 12 months.*
- Cases of *P. vivax* malaria resistant to chloroquine have been reported.

Plasmodium ovale:

- Encountered throughout the tropics.
- Considerably less pathogenic than *P. falciparum*.
- Incubation period usually 16–18 days.*
- Remains uniformly sensitive to chloroquine.

Both *P. vivax* and *P. ovale* have hypnozoite forms which may remain 'dormant' in the liver causing late relapse after successful elimination of parasitaemia. Hypnozoites are eliminated using primaquine.

Plasmodium malariae:

- Extends throughout tropical and subtropical areas but most common in west and east Africa and parts of India.
- Incubation period usually 18–40 days but can be longer.*
- Considerably less pathogenic than *P. falciparum*.
- No hypnozoite form: hence elimination of blood stages leads to cure.
- Retains sensitivity to chloroquine.

* The incubation periods quoted refer only to transmission by mosquito bite.

reliance is placed on a single blood film. Repetition of the film after six hours may improve diagnostic accuracy. Newer diagnostic techniques have recently joined traditional Giemsa-stained thick films, including fluorescent microscopy techniques based on acridine orange, (such as the quantitative buffy coat (QBC™) method) and enzyme-linked immunosorbent assay of parasite proteins (such as the *Para-Sight™-F* method). These may be available in certain hospitals and are, on the whole, sensitive, specific and probably less operator-dependent than thick films.

Severe falciparum malaria

In non-immune patients, and people who have lost immunity through prolonged residence in non-malarious areas, uncomplicated falciparum malaria (or infections by more than one species including *P. falciparum*) can progress rapidly to life-threatening illness. A full description of the syndromes of severe malaria and discussion of pathogenesis are outside the scope of the present article (see Ref 1). Coma, seizures, hypoglycaemia, lactic acidosis, pulmonary oedema, severe anaemia, renal failure and coagulopathy may occur. The neurological manifestations are not usually accompanied by nuchal rigidity, and the cerebrospinal fluid is usually normal.

Complications of malaria caused by species other than Plasmodium falciparum

Life-threatening illness is considerably less likely with species other than *P. falciparum*, but can occur. All parasite species are potentially dangerous during pregnancy – even women with degrees of immunity tend to lose this during pregnancy – causing maternal anaemia, low birth weight and abortion. Traumatic splenic rupture is an occasional complication of any form of malaria, while chronic *P. malariae* infection can be complicated by nephrotic syndrome.

Key Points

- ▶ About 2,000 cases of malaria are diagnosed in the UK annually
- ▶ About half the cases are caused by *Plasmodium falciparum*
- ▶ Falciparum malaria should be treated as a medical emergency. It has a high mortality rate and deterioration can be both swift and sudden
- ▶ Falciparum malaria may cause hypoglycaemia, especially in pregnant women
- ▶ *P. falciparum* has developed resistance to most antimalarial drugs. Expert guidance on treatment is often needed
- ▶ The other species of human malaria parasites are usually sensitive to chloroquine
- ▶ Severe falciparum malaria should be managed in an intensive care unit. Intravenous quinine is the drug of choice
- ▶ Intravenous quinine should always be diluted and infused slowly

Drug sensitivity and resistance

Although *P. vivax* resistant to chloroquine has been reported, it is predominantly *P. falciparum* that has acquired drug resistance. This is of crucial importance because drug failure may lead to life-threatening illness. The essential points relating to drug sensitivity and resistance for the general physician are summarised in Table 3.

Management

Uncomplicated malaria

In most cases, especially of falciparum malaria, patients should be admitted to hospital to ensure observation and compliance with therapy. Although all cases of falciparum malaria need frequent review to detect deterioration early, care should be possible on general medical wards. The following simple laboratory parameters need to be kept under review, their frequency of estimation depending on the clinical state:

- haemoglobin
- clotting screen
- blood glucose
- renal function.

Parasite counts should ideally be repeated daily to ensure that asexual parasitaemia falls, and is duly eliminated (slides are usually clear of asexual parasites within 5 days). Counts may increase during the first 24 hours after the start of treatment, but should begin to fall thereafter. Gametocytes may well persist, but they are not pathogenic, do not indicate resistant parasites and do not require treatment.

Treatment. The likely geographical origin of falciparum malaria is the major determinant of the drug regimen to be used. Oral medication is usually possible in adults and older children – indeed, inability to give oral drugs is an indicator of disease severity. The main drugs used for the treatment of uncomplicated falciparum malaria are listed in Table 4 (for a more detailed review see Ref 2). Halofantrine, mefloquine, pyrimethamine-sulfadoxine

Table 3. Drug sensitivity and resistance in malarial infections.

- No *in vitro* tests of *Plasmodium falciparum* drug sensitivity are available in a clinical service setting in the UK, so drugs with a high likelihood of reliability should be used (guided by data from the Public Health Laboratory Service Malaria Reference Laboratory; tel: 0171 927 2437).
- In mixed infections which include *P. falciparum*, treatment should primarily address this parasite.

Resistance:

- To chloroquine and amodiaquine: in almost all geographical areas. These drugs should no longer be used routinely in the UK.
- To antifolate combinations, such as pyrimethamine-sulfadoxine (PM-SD): common in both South-East Asia and South America. PM-SD should not be used in cases 'imported' from these areas. PM-SD resistance in Africa is less common, but probably developing rapidly.
- To quinine: uncommon in both Africa and South America, but increasingly recognised in parts of South-East Asia.
- To mefloquine and halofantrine: now encountered in parts of South-East Asia, but uncommon elsewhere.
- To atovaquone-proguanil (Malarone, Glaxo-Wellcome), which has just been released: not an issue at present.

(PM-SD) and atovaquone-proguanil are the drugs of choice. Quinine is listed for completeness, but is difficult to use and unpleasant to take. The artemisinin compounds, although highly effective and widely used throughout the tropics, are not licensed in the UK.

Most cases of vivax malaria and all *P. malariae* and *P. ovale* are sensitive to chloroquine, for which it remains the drug of choice. A dose of 10 mg (of the base)/kg on days 1 and 2 should be followed by 5 mg/kg on day 3. Oral chloroquine is generally well tolerated, but can cause mild central nervous system and gastrointestinal disturbance. Retinopathy, a complication of prolonged use, is not caused by short courses of chloroquine for malaria treatment. *P. vivax* resistant to chloroquine may be treated with mefloquine or halofantrine (in the same doses as for falciparum malaria).

P. falciparum and *P. malariae* have no 'dormant' liver stage and cure depends on killing the asexual blood stages. The hypnozoites of *P. vivax* and *P. ovale* are not eliminated by chloroquine (nor by any of the drugs directed at blood stages), so primaquine is needed in a dose of 15 mg (of the base) daily for 14 days. Primaquine can cause haemolysis and methaemoglobi-

naemia, especially in patients with G6PD deficiency in whom a weekly dose of 30–45 mg is often better tolerated. There are strains of *P. vivax* with acquired resistance to primaquine, and these may need longer courses of treatment. A new primaquine congener (WR238605, etaquine SB) under development promises to have a more acceptable adverse effect profile.

Uncomplicated malaria during pregnancy

Although antimalarial drugs cross the placenta, and some are teratogenic in animal models, the benefits of treatment usually outweigh the risks, especially in falciparum malaria. Chloroquine is probably the drug least likely to be teratogenic, and is first-line therapy for *P. vivax*, *P. ovale* and *P. malariae* infections. Chloroquine should not be used to treat falciparum malaria because of the high risk of encountering drug-resistant parasites. Mefloquine, halofantrine and PM-SD are all acceptable choices for uncomplicated falciparum malaria. There is good evidence that neither mefloquine nor PM-SD is teratogenic in humans, although data on halofantrine are more limited³.

Table 4. Drugs for uncomplicated falciparum malaria.

Drug	Adult dose	Regimen	Precautions	More common serious adverse effects
Mefloquine	15–25 mg/kg	Single dose or as 2 doses 6 h apart	Use alternative in patients with epilepsy	Seizure Dizziness Organic psychosis GI upset Arrhythmias
Halofantrine	500 mg of the salt	6 hourly to a total 3 doses	Use alternative in patients with QT prolongation or history of cardiac arrhythmia	QT prolongation Ventricular arrhythmia GI upset
Atovaquone-proguanil	Atovaquone 1,000 mg Proguanil 400 mg	Daily for 3 days		GI upset
Pyrimethamine-sulfadoxine	Pyrimethamine 75 mg Sulfadoxine 1,500 mg	Single dose	Contraindicated if allergic to sulfonamides Particular caution regarding drug resistance	Life threatening allergy to sulfadoxine Macrocytic anaemia
Quinine	600 mg of the sulphate	8 hourly for 7 days	Omit loading dose if pretreated with mefloquine	GI upset Tinnitus Deafness Vertigo Nystagmus

GI = gastrointestinal

Severe falciparum malaria

Patients with severe malaria should be nursed in an intensive care unit, with access to ventilatory support. The range of observations needed is beyond the scope of this article, but should include blood glucose, arterial pH and fluid balance, with regular checks on parasitaemia (ideally at 6-hourly intervals).

Supportive care^{1,4} is an integral part of management. A full range of intensive therapy unit support may be required, but blood transfusion, correction and maintenance of blood glucose, ventilation and dialysis are often needed.

Antimalarial drugs must be given parenterally, and quinine remains the drug of first choice². Parenteral quinine

is normally continued until the patient is able to take alternative drugs orally. Quinine is both difficult to use and of relatively low potency compared with chloroquine (against chloroquine-sensitive strains), but resistance to quinine is encountered infrequently and it is therefore a reliable treatment for life-threatening disease. Strict adherence to dosing guidelines is

Table 5. Parenteral quinine regimens for severe falciparum malaria.

Loading dose		Maintenance dose			Treatment duration (days)
Dose (mg(salt)/kg)	Infusion duration (hours)	Dose (mg(salt)/kg)	Infusion duration (hours)	Frequency (hourly)	
20	4	10	2	8	7 (or until oral drugs can be taken)
7 followed immediately by 10	0.5* 4	10	2	8	7 (or until oral drugs can be taken)

* The first 7 mg/kg is delivered by syringe-driver over 0.5 h, followed by slow infusion of a further 10 mg/kg over the next 4 h.

mandatory, and the patient should always be weighed to allow the calculation of dose size. The most common salt in use for parenteral treatment is the dihydrochloride, and doses are calculated in terms of this salt, not of the free base. Quinine should always be diluted in crystalloid and infused slowly. A loading dose is empirically sensible and is standard practice, enabling effective drug concentrations to be achieved more rapidly. Much work has been done to simplify and optimise dosing regimens. The two alternative dose regimens given in Table 5 are standard practice. Severe malaria may result in renal failure, but quinine doses are not normally reduced in this setting¹. If parenteral quinine is not immediately available, quinidine may be used instead, although its dose regimen differs slightly². Again, close adherence to the dose schedule is mandatory. When dosing guidelines are strictly followed, quinine is usually safe, but concentration-dependent adverse effects include:

- *Retinal damage*: unusual during treatment of malaria, and more commonly associated with deliberate self-poisoning.
- *Hypoglycaemia*: may be related to the rate of quinine infusion, and tends to be a particular problem during the treatment of pregnant women.
- *Cardiac arrhythmias*:
 - the antimuscarinic properties of quinine may increase the rate of conduction across the atrioventricular node;
 - quinine may prolong the Q-T interval, and may be pro-arrhythmic in patients with pre-existing Q-T prolongation, hyperkalaemia or hypocalcaemia.
- *Hypotension*: the negative inotropic and vasodilator properties of quinine at high concentration may result in hypotension.

Infections that have originated in parts of South-East Asia may be relatively resistant to quinine, and particular care is needed in monitoring such patients. Parasitaemia is often unchanged, or

may rise, during the first 24 hours on quinine, but an unchanged or rising parasite count thereafter should cause concern and expert advice should be sought. In such cases, the artemisinin compounds (including artemether and artesunate), which retain activity against quinine-resistant strains, can be given parenterally. These drugs are not licensed in the UK but supplies can be obtained on compassionate grounds by contacting IDIS World Medicines on 0181 410 0700 (this number is manned 8.00 am to 5.30 pm and is an answerphone at other times).

References

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