Malaria treatment is guided by the species of parasite infecting the patient. Combination therapy is required to help eradicate the parasite and prevent the development of resistance to antimalarials.

### Malaria treatment

**By Orla Geoghegan, DipClinPharm, MRPharmS, and Imogen Clarke, DTM&H, MRCP**

**Treatment of patients with malaria is guided by the causative parasite and the severity of the disease.** *Plasmodium falciparum* infection requires patients to be admitted to hospital, whereas *non-falciparum* malaria can generally be managed on an outpatient basis. Patients who have mixed infection that includes *P. falciparum* parasites and those in whom the causative species cannot be determined should be treated for *P. falciparum* infection.

The treatment of malaria during pregnancy and in children varies slightly (see Box 1, p65).

### P falciparum malaria

All patients with confirmed *P. falciparum* malaria should be admitted to hospital for treatment because rapid deterioration is possible, especially in the early stages of treatment. Furthermore, for some patients — children in particular — oral treatment can be poorly tolerated at the beginning of therapy. Severely sick patients should be assessed at the time of admission to hospital. Malaria is considered to be severe if:

- More than 2% of the blood is parasitised (termed parasitaemia)
- Parasitaemia is less than 2% and schizonts (see accompanying article, p57) are detected on blood film
- Parasitaemia is less than 2% and there are other complications (see Box 2, p66)

Clinicians treating patients with severe or complicated malaria should seek advice from a specialist infectious diseases or tropical medicine unit and consider admitting the patient to a high dependency or intensive care unit. Antimalarials should be started immediately.

Combination therapy is necessary to ensure all parasites are eradicated. There are three regimens that can be used for the treatment of patients with uncomplicated *P. falciparum* malaria.

- Oral quinine prescribed at a dose of 600mg every eight hours in combination with doxycycline 200mg once daily or chloroquine 48mg every eight hours; the recommended duration for this regimen is seven days
- Malerone (propazin and atovaquone) at a dose of four 100mg/25mg tablets daily for three days
- Riamet (atovaquone and lumefantrine) may be prescribed at a dose of four 200mg/120mg tablets at eight, 24, 36, 48 and 60 hours after an initial dose.

Although all three of these regimens have been demonstrated to be equally effective, clinical experience

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**REFERENCES**


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**SUMMARY**

Patients who have malaria are treated according to the causative parasite. Generally, those with *Plasmodium falciparum* infection experience more severe illness and should receive treatment in hospital where they can be monitored closely. Patients with non-*falciparum* infection can be treated as outpatients.

Oral quinine in combination with doxycycline or chloroquine, Malerone or Riamet can be used for the treatment of non-*falciparum* infection, with chloroquine and artemether being reserved for severe and complicated illness. Non-*falciparum* infection can be treated easily with chloroquine and riamet prevent using primaquine.
with the latter two regimens is still relatively limited in the UK.

Quinine is a cinchona alkaloid. Although its mechanism of action in malaria is not fully understood, it is thought to penetrate affected red blood cells and exert a schizonticidal action against malaria parasites. P. vivax and P. malariæ gametocytes are also susceptible to quinine, whereas P. falciparum gametocytes are not. Quinine has a low therapeutic index and patients are susceptible to substantial adverse effects, including tinnitus, hearing impairment and vertigo (collectively known as cinchonism), vomiting, abdominal pain, hypoglycaemia and diarrhoea.6

Malariene prevents the development of parasitic liver schizonts and also affects the red blood cell stages of the parasite life cycle. It has no action on hypnozoites (dormant parasites).7

The artemether component in Riamet acts on the ring forms of the parasite (see accompanying article, p57), reducing parasitic burdens and preventing sequestration of peripheral young ring forms.8 The mechanism of action of homeflaquine is not fully understood, but it is thought to inhibit the formation of beta-haematin, nucleic acids and protein synthesis during the erythrocytic cycle. Riamet should be taken with fats, food or milk.

Malariene and Riamet require shorter treatment courses and, unlike quinine, are not associated with cinchonism, which can result in poorer adherence to therapy.

Although mefloquine is effective, it is no longer recommended for the treatment of P. falciparum malaria in the UK, because of its poor side effect profile and subsequent high rates of non-adherence. Chloroquine resistance is high and this medicine should not be used for the treatment of P. falciparum malaria.9

Severe illness

Patients with severe or complicated P. falciparum malaria should be managed in a high-dependency unit where they can be monitored closely. Patients should be treated intravenously with quinine or artesunate until they are well enough to be switched to oral therapy.

Quinine Treatment with IV quinine dihydrochloride is started using a loading dose of 200mg/kg (maximum 1.4g) followed by a dose of 100mg/kg (maximum 700mg) every eight hours — reducing the frequency to once every 12 hours if IV therapy is needed for more than 48 hours. Doses are diluted in 250mls of normal saline 0.9% and infused over four hours.10 Dose reduction is also recommended for patients with renal failure or severe hepatic impairment. Loading doses should not be administered to patients who have had a dose of quinine or mefloquine in the previous 12 hours. Quinine can cause arrhythmias and should be used with caution in the elderly and in patients with heart disease.11 For such patients, treatment with artesunate is preferred.

As soon as the patient is well enough to swallow tablets, he or she should be switched to oral quinine 600mg three times a day to complete a seven-day course. Doxycycline 200mg daily or clindamycin 450mg three times a day should also be started at this point and continued for seven days.

Box 1: Special patient groups

Pregnancy

Pregnant women are more likely to suffer from severe or complicated malaria and there is an increased risk of miscarriage and stillbirth in affected women. Prompt treatment and collaboration with obstetricians is vital. Hypoglycaemia and pulmonary oedema can complicate the treatment of malaria in pregnancy and these should be managed accordingly. Close observation, including uterine and fetal heart monitoring, is essential to monitor for the development of complications. In some cases, early delivery of a near-term infant may be needed.12

The treatment options for Plasmodium falciparum malaria in pregnant women are quinine or artesunate (labeled as per normal adult) with intravenous or oral clindamycin 450mg every eight hours. Although the World Health Organization recommends avoiding artesunate in the first trimester,13 there is growing evidence that it is safe and effective during this time. Artesunate is recommended in all stages of pregnancy in patients returning from South East Asia, where resistant parasites are common.8 Doxycycline and malariene are contraindicated in pregnancy.14

Chloroquine is recommended for the treatment of non-falciparum malaria. Because primaquine is contraindicated during pregnancy, pregnant women with P. vivax or P. ovale infection should be prescribed chloroquine 300mg once weekly after completing the treatment course as prophylaxis against relapse. Pyrimethamine should continue until after delivery, at which point eradication of hypnozoites with primaquine should be considered.15

Paediatrics

Children are treated using the same regimens as adults, but at lower doses. Quinine can be used for the treatment of P. falciparum malaria. However, doxycycline should only be used in children aged over 12 years due to the risk of dental hypoplasia and discoloration of teeth. Clindamycin can be used instead for children who are aged 12 years or younger.

Experience with Malariene and Riamet for the treatment of malaria in children in the UK is limited, with the latter only licensed for children over 12 years of age.16,17

There is limited evidence for the paediatric use of artesunate. However, use is increasing in the UK and there are some large multicentre trials under way in Africa that aim to investigate its use in this population.18 Supportive management for children with malaria is similar to that for adults. Blood transfusion may be required for children with severe anaemia, but there is evidence that this does not significantly reduce mortality rates and can lead to increased rates of adverse events.19

Artesunate Artesunate has been shown to reduce high parasitic loads faster and is associated with lower mortality rates than quinine.20 Upon expert advice only, it can be considered for use in adults with severe malaria or if quinine treatment fails or is not tolerated. Artesunate can also be used for patients who have acquired P. falciparum malaria in South East Asia, where the rate of quinine resistance is high.

Artesunate should be administered IV (usually by slow IV injection) or a dose of 2-4mg/kg, with the first dose being repeated after 12 and 24 hours and then continued daily thereafter.

Artesunate is not licensed in the UK and is available on a named patient basis only. If artesunate is not available, treatment should not be delayed and patients should be started on IV quinine until artesunate can be obtained.

When the condition has improved and the patient is able to tolerate oral medication, artesunate should be stopped.
and a complete course of Biamet prescribed with doxycycline or clindamycin used in combination at the doses described above.

Supportive therapy  Patients with severe malaria may present with severe acidosis, acute respiratory distress syndrome, pulmonary oedema and renal impairment. Four-hourly observations (blood pressure, respiratory rate, pulse, temperature, oxygen saturations, urine output and Glasgow coma score) should be performed until the patient is stable. Full blood count, clotting, urea and electrolytes and liver function tests should be monitored daily; paracetamol should also be measured daily. The paracetamol count may rise in the first 24-36 hours of treatment, but this does not indicate treatment failure. Blood glucose should be monitored regularly because hyperglycaemia can occur in severe malaria and this can be exacerbated by treatment with IV quinine. Regular electrocardiogram monitoring is recommended, especially during treatment with IV quinine.

Ventilatory support may be required in the management of acute respiratory distress syndrome. Fluid balance is important for patients who are acidic to avoid hypovolaemia and over-hydration (which can induce pulmonary oedema). If renal replacement therapy is indicated, haemofiltration is the method of choice because this appears to be superior to peritoneal dialysis in the management of infection-associated acute kidney injury. Quinine and antimalarials are not affected by haemofiltration.

Some patients may develop bacteraemia, leading to septic shock. Blood cultures should be taken, but false-negatives are possible and white blood cell counts are not always raised. Septic patients should be treated empirically to cover for a gram-negative bacteraemia if they do not respond to initial fluid resuscitation.

Although the removal of parasitised red blood cells might theoretically sound, exchange transfusion is not used routinely in the management of severe malaria. There is a lack of evidence supporting its use, and patients treated with amonucleate have not been shown to benefit from this approach.

**Box 2: Complicated malaria**

Complicated malaria is diagnosed when a patient has one or more of the following signs and symptoms:

- Impaired consciousness
- Seizures
- Haemoglobin <80 g/L
- Spontaneous bleeding/disseminated intravascular coagulation
- Haemoglobinuria (in the absence of glucose-6-phosphate dehydrogenase deficiency)
- Hypoglycaemia
- Purulent sputum or adult respiratory distress syndrome
- Renal impairment
- Electrolyte/acid-base disturbance (pH <7.3)
- Shock

**Non-falciparum malaria**

In the absence of complications, non-falciparum malaria can generally be managed in an outpatient setting. The treatment of choice is a three-day course of chloroquine, starting with a dose of 600 mg followed by 300 mg after 8 h, 24 and 48 h. Rates of resistance to chloroquine are low, with only a small proportion of resistant P. vivax strains identified so far.

Relapse occurs in more than 25% of patients with P. vivax and P. malariae infection after treatment with chloroquine. This is due to the presence of hypnozoites in the liver. Primaquine is used to eradicate hypnozoites after treatment of the acute infection. It is best prescribed for 14 days at a dose of 30 mg (base) daily for P. vivax malaria and 15 mg (base) daily for P. malariae. The higher dose is used to eradicate P. vivax hypnozoites, because certain strains of P. vivax are known to possess innate resistance to primaquine. In the UK, relapse can occur in more than 10% of patients despite treatment with primaquine. If relapse does occur, chloroquine can be prescribed again.

In the presence of glucose-6-phosphate dehydrogenase deficiency, haemolysis may occur on administration of primaquine. Therefore, it should be avoided or used with caution under expert supervision in patients who have G6PD deficiency.

**Drug resistance**

Drug resistance can develop in a relatively short space of time. P. falciparum resistance to chloroquine has spread rapidly, and complicates global malaria control severely. The World Health Organization is now attempting to combat the development of resistance to artemisinins-based (ie, artemether and arteether) combination therapies by monitoring antimarial drug efficacy (allowing for early detection of changes in P. falciparum sensitivity to artemisinins so that timely changes can be made to treatment guidelines) and recommending the withdrawal of oral artemisinin-only products from the market.7 Limiting resistance to artemisinin-based products is crucial to the ongoing successful treatment of malaria; no other antimalarial provides the same level of efficacy and tolerability, and there are few promising alternatives in development.

**Future travel**

Infection with malaria does not confer immunity. Therefore, patients who have been diagnosed with malaria should be informed that they will need to use malaria prophylaxis and effective precautions to prevent mosquito bites if they are planning any future travel to malaria-endemic areas.

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**Questions**

This month’s questions are based on the CLINICAL FOCUS articles on malaria, which were commissioned from independent authors.

**Answers from the January/February module**

**Overactive bladder**

1. (a) T, (b) F, (c) F, (d) F, (e) F, (f) T

2. (a) T, (b) F, (c) T, (d) F, (e) T

3. (a) F, (b) F, (c) F, (d) T, (e) T

4. (a) F, (b) T, (c) T, (d) F, (e) F

5. (a) T, (b) F, (c) T, (d) T, (e) F

6. (a) T, (b) F, (c) T, (d) F, (e) T

7. (a) T, (b) F, (c) T, (d) T

8. (a) T, (b) F, (c) T, (d) T

9. (a) F, (b) T, (c) F, (d) F, (e) F

10. (a) F, (b) T, (c) F, (d) F, (e) T

Information in the Box (adjacent) is there to help you identify knowledge gaps and undertake continuing professional development. This module will close on 5 June 2014.

**Answers**

Once you have completed the module, your answers will be submitted for marking and Clinical Pharmacist will send you a certificate and your results by email within two weeks of the module closing.

**Correction**

In marking the December Lifelong Learning module on anxiety disorders, the answer to question 7c (imipramine is recommended for people with social anxiety disorder who do not respond to an SSRI or a serotonin and noradrenaline reuptake inhibitor (SNRI) was erroneously designated as ‘true’. The correct answer is ‘false’. This did not impact on any learner’s eligibility to receive a certificate.

**How to undertake CPD**

Our CLINICAL FOCUS articles and the online Lifelong Learning modules can help you plan your CPD and record the benefits of the activity at www.updatejog.org.uk.

**Reflect on your gaps in knowledge**

How is malaria contracted and what are the clinical features?

What can people who travel to malaria-endemic regions do to avoid catching the disease?

What options are available for treating malaria?

**Act to enhance your practice**

Read the CLINICAL FOCUS articles in this issue (pp57-67)

Test your knowledge by completing the questions at www.clinicalpharmacist.com

**Evaluate the activity**

What have you learnt?

How has it added value to your practice?

What will you do now and how will this be achieved?

The questions in this Lifelong Learning module have been approved by an independent reviewer for quality assurance.

Consider making this activity one of your nine CPD entries this year.