



Guidelines for Doctors

**“Guidelines are guidelines
- not tablets of stone”**

November 2007

6 HTD Malaria Guidelines



If consulted about a case of severe malaria, please inform Specialist Registrar or Consultant. These guidelines refer to malaria diagnosed with a positive blood film. If this is not the case, refer the call / decision to SpR or Consultant. Empirical treatment is usually not indicated.

Many hospitals lack expertise in malarial speciation. If the species is in doubt the safest course is to treat as *P. falciparum* with quinine, while clarification awaited.

Similarly, many hospitals do not expect their staff to provide accurate parasitaemia percentages. HTD will gladly review films and check species and parasitaemia, but to be of benefit to the patient these must be sent urgently by courier or cab.

Some hospitals are using rapid diagnostic tests for malaria overnight. A positive test makes *falciparum* malaria almost certain, but the tests are not quite as sensitive as expert microscopy. They are less good at detecting vivax and other non-*falciparum* species. We therefore recommend that all rapid tests are confirmed with a slide.

Urgent films can be sent to: HOSPITAL FOR TROPICAL DISEASES, Department of Parasitology, Mortimer Market Centre, Capper St. WC1E 6AU

GPs or hospitals requiring this service should please phone first, 0845 1555 000 x5414/5418

After 17.00 or at weekends the sample should be addressed to: SHO on call, T8, University College Hospital, 235 Euston Road, London NW1 2BU . 0845 155 5000 bleep 5840

6.1 *P. falciparum* malaria

We advise that all patients with *P. falciparum* malaria should be admitted to hospital in view of the complications that can develop even at low parasitaemia. We are willing to receive any adult patients from anywhere with malaria, particularly if complicated / severe disease. Our ICU colleagues have a great deal of experience in the management of severe malaria. They have their own ambulance in which they have travelled as far as Hereford to collect patients.

6.1.1 Assessment of Severity

Mild: Parasitaemia <2% and patient ambulant, and no complications*

Severe or potentially complicated: Parasitaemia >2% or schizonts[#] or patient non-ambulant, or complications*

*Complications = cerebral involvement, severe anaemia, renal failure, pulmonary oedema, hypoglycaemia, hypovolaemia, bleeding, DIC, acidosis, (see 6.1.5)

[#]The presence of schizonts or pre-schizonts may mean that:

- The peripheral parasitaemia is unrepresentative of the total parasite burden due to sequestration
- A further cycle of replication is imminent

For ALL cases, whether mild or severe, there must be no delay in starting antimalarial drug therapy

6.1.2 Treatment of Mild Disease

- Oral treatment unless patient is vomiting, in which case treat as in 6.1.3

Quinine 10 mg salt/kg (max 700 mg) 8 hourly

- Reduce to a 12 hourly regimen if develops severe cinchonism (tinnitus & deafness)

When the patient is better and the asexual parasitaemia has cleared, give **ONE** of the following as a **SECOND** drug:

Fansidar 3 tablets stat (1 tablet per 20kg)

- Avoid if there is a history of sensitivity to sulphonamides.

OR

Doxycycline 100 mg od for 7 days (not in pregnancy)

OR

Clindamycin 5 mg/kg tds for 7 days.

Alternatives to quinine-based treatment are:

Atovaquone + proguanil (Malarone) 4 tablets OD for 3 days

Artemether-lumefantrine (Riamet) 4 tablets initially, followed by further doses of 4 tablets to be given at 8, 24, 36, 48 and 60 hours. This should not be used for women in the first trimester of pregnancy without specialist advice.

Atovaquone-proguanil and artemether-lumefantrine are particularly appropriate for patients from SouthEast Asia.

NB: Gametocytes, the sexual forms of the parasite, are unaffected by virtually all anti-malarial drugs and are of no clinical significance

- Patients who have received halofantrine in the last 48 hours should not be given quinine without Consultant approval because of the potential risks of cardiac arrhythmias.

6.1.3 Treatment of Severe Disease. These guidelines refer to managing severe malaria in adults; different complications occur in children, and those treating children should refer to specialist paediatric advice.

Severe disease from Asia or Papua New Guinea should be treated with artesunate (see 6.1.7) but if this is not immediately available then intravenous quinine should be given without delay

Severe disease from elsewhere should normally be treated with either quinine or artesunate, provided a reliable source of artesunate is available. HTD holds stocks of the drug. We will send artesunate to other hospitals dealing with severe cases if there is going to be a delay in transferring the patient to HTD. **Never delay starting treatment.**

Quinine dihydrochloride IV 10 mg/kg (max 700 mg) in 250 ml of normal saline over 4 hours

- A *loading dose* of IV quinine 20 mg/kg (maximum of 1400mg) over 4 hours should be given if the patient fulfils any of the criteria for severe disease
- Patients who have received a treatment dose of mefloquine within 3 days should not have a loading dose of quinine, and quinine should be used with caution because of the risk of arrhythmia
- 12 hourly IV quinine is usually sufficient, but IV quinine can be given at the same dose 8 hourly at the discretion of the Consultant
- Monitor BM stix 2 hourly during the infusion, 4 hourly otherwise
- Check an ECG before starting IV Quinine
- Convert to oral quinine 8 hourly when patient is better and can reliably take oral medication (often this may be after only 1 or 2 doses of IV quinine)
- Stop quinine and give second drug once asexual parasitaemia has cleared as in 6.1.2

Artesunate. Note that currently this is not licensed in the UK and no GMP manufacturers are making it. There is trial evidence it lowers mortality in severe malaria from Asia, especially those with high parasite counts. This may be true for malaria from Africa.

Artesunate should be considered especially in patients with severe malaria from Asia (where there is evidence of relative quinine resistance), patients with hyperparasitaemia (>10% red cells parasitised) and those with a history of cardiac arrhythmia, or risks of arrhythmia.

Artesunate intravenous 2.4 mg/kg bodyweight given as a bolus (n=730) at 0, 12, and 24 h, and then daily until patients recover or parasites clear.

6.1.4 Complications

The key to managing severe malaria is getting an effective parenteral antimalarial (artesunate or quinine) in to the patient at adequate doses, fast. All secondary treatment is supportive and of much less prognostic importance, except correct fluid management, which is essential.

- All patients with severe *P. falciparum* malaria require management in the highest care environment available

- Haemofiltration, ventilation with PEEP and exchange transfusion may become necessary
- Consider transfer to ICU or the renal high-care unit at the Middlesex
- Discuss with ICU Registrar at an early stage bp4520

Cerebral involvement

- May manifest as drowsiness, confusion, stupor, fits or coma - even mild drowsiness or confusion should be regarded as showing possible cerebral involvement
- Exclude hypoglycaemia, maintain airway, consider ventilation
- Convulsions should be controlled with **diazepam**
- Status epilepticus should be managed with anti-convulsants, but beware of potential interactions with quinine

Anaemia

- Common in severe malaria due to haemolysis
- If Hb <8.0g/dl or PCV <0.20, parenteral therapy is indicated and transfusion should be considered
- Correct with packed cell transfusion. Monitor fluid balance, taking care not to overload

Acidosis

- is common and predictive of a poor prognosis
- often results from poor peripheral perfusion

Renal Failure

- Defined as a urine output <0.5 ml/kg body weight/hour, failing to improve after rehydration and serum creatinine >265 μ mol/l
- Largely confined to adults, the mechanism is usually an acute tubular necrosis, manifest by rising plasma urea and creatinine, oliguria, and finally anuria. (Hyponatraemia is common in malaria and does not usually require correction)
- Consider early haemofiltration or dialysis (creatinine >500, or any evidence of hyperkalaemia).

Pulmonary Oedema and ARDS/ALI

- Correction of hypovolaemia should be carried out with caution. Adult patients with severe malaria may be dehydrated, but they almost never die of shock, and they may have difficulty excreting fluids. Vigorous rehydration is often not indicated.
- Earliest sign is a rise in the respiratory rate
- An ARDS-type picture, due to abnormal capillary permeability, may develop as the peripheral parasitaemia is resolving
- The outcome of pulmonary oedema is good. The outcome of ARDS is poor with substantial mortality even in ITU settings. This complication can occur even after all parasites have cleared.

Hypoglycaemia

- In adults, particularly pregnant women, arises as a consequence of quinine stimulating insulin release
- In children hypoglycaemia is more common and may contribute to impairment of consciousness at presentation
- Give 1 ml/kg 50% dextrose by IV bolus followed by infusion of dextrose

Hypovolaemia / Shock

- Dehydration requires careful assessment (skin turgor, postural hypotension etc.)
- Monitor for signs of pulmonary oedema during rehydration
- Patients with malaria, especially children, are particularly prone to sepsis with bacteria, which must be considered if they develop, or present in, a state of hypotension and circulatory collapse. If there is any evidence of septicaemia, consider empirical broad-spectrum antibiotics

Bleeding / DIC

- Thrombocytopenia is almost invariable in malaria, and is not necessarily an indication of severity
- If platelet count <20 x 10⁹/l, and evidence of bleeding, liaise with haematologists, consider platelet support
- Beware early DIC; check clotting, fibrinogen and D-dimers

6.1.5 Exchange Transfusion

There is no data to support the use of exchange transfusion if parenteral artesunate or parenteral artemether are being used; we do not advise it unless quinine is being used.

Evidence for the benefit of exchange transfusion is controversial. It is a mechanical means of removing parasitised red cells from the circulation. It is recommended you seek specialist advice prior to undertaking it. Patients who may benefit are:

- ✓ Parasitaemia > 30% in the absence of organ failure
- ✓ Parasitaemia > 10% in the presence of organ failure

- ✓ Parasitaemia > 10% and failure to respond to optimal chemotherapy after 12-24 hours
 - ✓ Parasitaemia > 10% and poor prognostic factors such as elderly, peripheral pre-schizonts and /or schizonts
- Exchanges should take place on the ICU / HDU
 - Insert a double lumen catheter (vascath or similar), usually into the femoral vein.
 - Cross match 6 units of red cells
 - The exchange should be isovolumetric- do not remove more than you put in.
 - Remove and replace a unit (or less, as tolerated) at a time over 30-60 mins
 - Obtain the necessary blood bags from Haematology
 - Use a spring balance to monitor the weight of each bag (1g=1ml)
 - Give 2 units FFP to replace clotting factors
 - Exchange between doses of quinine if possible, but DO NOT delay or adjust quinine dose
 - Save and send to Parasitology the exchanged blood in *acid citrate* bags numbered sequentially

An alternative in some centres is erythrocytapheresis.

6.1.7 Quinine Resistance

Decreased efficacy of quinine has been documented in some parts of the world, notably SouthEast Asia

Mild disease

Discuss with SpR or Consultant. There are several possibilities, and one of these should be used first line in patients from areas with high risk of quinine resistance:

- **Malarone** 4 tabs od for three days
- **Artemether** 200 mg/day oral for three days, then **Mefloquine** 500 mg x two doses

Severe disease

Artesunate is preferred to artemether

Artesunate 2.4 mg/kg IV as a bolus at 0, 12, and 24 hours, then daily, changing to oral artesunate 2mg salt per kg per day as soon as clinically safe to do so, to complete a total of 7 days therapy (including parenteral).

- **Artemether** - this is generally not recommended if artesunate or quinine are available.

Artesunate or artemether should be followed by **mefloquine** or **doxycycline** or **clindamycin** (see 6.1.2)

6.1.8 Recrudescence infections:

- Seek specialist advice
- Malarone (atovaquone + proguanil) 4 tablets od for three days

6.1.9 Pregnancy

- Quinine and Fansidar in standard doses should be first line treatment unless from SE Asia
- Pregnant women are at increased risk of severe malaria
- There is an association between high fever and premature labour. There is no convincing evidence that quinine increases this risk
- Hypoglycaemia is common and may be asymptomatic
- Fansidar is safe in the second and third trimesters
- There is no evidence that either quinine or artemisinin derivatives are teratogenic in humans, but animal studies indicate artesunate should currently not be used in the first trimester unless there are good reasons to do so.
- Pregnant women with malaria should be warned at the outset that loss of the pregnancy is a real risk.

6.1.10 Advice on Discharge

- Give all patients a Travel Clinic card for future advice
- Possibility of recrudescence: the patient should re-attend promptly if febrile

- Outpatient Follow-up: only if complicated

6.2 Non-falciparum malaria

- Patients should be offered admission if unwell
- If spleen enlarged, advise avoiding strenuous activity/trauma to rib cage
- Generally patients with non-falciparum malaria can be managed as outpatients

6.2.1 Initial Treatment

Chloroquine 25 mg/kg body weight given over 3 days. For 40-80kg:

Time (Hrs)	Dose (mg)	Tablets (No)
0	600	4
6	300	2
24	300	2
48	300	2

- Many patients of African origin report itching with chloroquine. This should not necessarily be considered as a contraindication to its use. It does not generally respond to anti-histamines and if troublesome an alternative such as quinine should be offered
- Patients with epilepsy should not be prescribed chloroquine without Consultant approval

6.2.2 Relapse Prevention

P. vivax:

The prevalence of both chloroquine and primaquine resistant *P. vivax* is increasing. **Primaquine** 15mg bd (0.25mg/kg in children) for 14 days [Unlicensed drug] should be given to patients with *P. vivax*. Quinine should be used if chloroquine resistance is suspected (recrudescence with 28 days)

- **First** check G6PD level (heparin tube) - normal range 5.9 - 11.7 U/g Hb. If there is G6PD deficiency seek advice; there is a real risk of haemolysis.

P. ovale:

- *P. ovale* remains fully sensitive to chloroquine and primaquine. Therefore give a lower dose of **primaquine** 15 mg od x 14 days
- *P. malariae* has no hypnozoite stage and no second drug is required

6.2.3 Pregnancy

- Do not give primaquine in pregnancy or while breast-feeding.
- After treatment with chloroquine, relapse should be prevented by giving weekly chloroquine 300mg or daily proguanil 100mg until delivery.
- After delivery & breast feeding primaquine can be given as normal

6.2.5. Malaria Antigen Tests:

- Dip-stix testing should be done in parallel with a blood film out-of-hours
- Antigen testing may help in speciation of parasites
- Antigen testing should **not** replace microscopy as the tests are less sensitive than microscopy performed by an experienced microscopist