# Malaria diagnosis and treatment guideline

## The Hospital for Tropical Diseases

### Trustwide guideline

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**Owner/ Sponsor**
- Hospital for Tropical Diseases (HTD)

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**Responsible Director**
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  - Divisional Clinical Director, Infection

**Monitoring Committee**
- Hospital for Tropical Diseases Consultants’ Forum

**Target Audience**
- All medical staff at all levels, involved in the care of patients with malaria

**Related Trust Documents/ Policies**

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- 11 pages

**Equalities Impact Assessment**
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1.0 Summary
1.1 These guidelines are for doctors treating patients with malaria.
Advice for healthcare workers on malaria prophylaxis is available via the National Travel Health Network and Centre website: www.nathnac.org.
1.2 Key Points
- Test for malaria in all travellers returning from the tropics with a fever
- Confirm a positive malaria dipstick rapid diagnostic test with a blood film
- If you are not certain of the infecting species then treat as falciparum malaria
- Admit patients with falciparum malaria for a minimum 24 hours observation
- Assess severity based on a parasitaemia >2% and / or complicating clinical features:
  - Conscious level, acidosis, pulmonary oedema, renal failure, anaemia, hypoglycaemia
  - In severe malaria start IV Quinine with loading until IV Artesunate is available
- Patients with severe falciparum malaria can deteriorate rapidly so involve ICU early
- Discuss all cases of severe malaria with HTD
- Read the more detailed notes below

2.0 Introduction
Imported malaria is responsible for approximately 11 000 cases per year in the European Union, of which around 2000 a year are seen in the UK. It is one of the commonest diagnoses in Infectious Diseases units throughout the UK with around 2000 cases a year, and is the principal imported tropical infection causing avoidable deaths every year. Most cases are caused by Plasmodium falciparum with a case fatality rate of 1.2% in the UK. In many non-tropical settings malaria is the commonest identified cause of fever in returned travellers. Over the past two decades, travel to malaria-endemic countries has been rising steadily, and health care providers are increasingly faced with returned travellers.

3.0 Objectives
To provide good practice and consistency in the diagnosis and management of patients with malaria

4.0 Scope
This document applies to all adult patients (18 years and above) who require diagnosis and / or treatment for malaria.

5.0 Duties & Responsibilities
The Hospital for Tropical Diseases at University College Hospital in London provides a 24 hour service to doctors for malaria-related advice. Contact the UCLH switchboard on 020 3456 7890 and ask to speak to the Tropical Medicine Registrar. Alternatively ring the on call mobile: 07908 250924. We may offer to transfer your patient to our intensive care unit, which has extensive experience at managing severe malaria, or provide an out of hours supply of Artesunate after discussion of the case.

During the working day urgent blood films for review should be sent to the Parasitology Department, Hospital for Tropical Diseases, Mortimer Market Centre, Capper Street, London, WC1E 6JB: telephone 020 3456 7890 ext 75414. To review films out of hours and at weekends you should discuss the patient with the Tropical Medicine Registrar and then courier samples to the Nurse in Charge, Ward T8, University College Hospital, 235 Euston Road, London NW1 2PG. S/he will contact the Parasitologist on call when the sample arrives.
6.0 Development & Evidence Base
Locally, there is a need for guidelines that aid clinicians with the diagnosis and management of malaria. These guidelines have been amended from the previous version based on international guidance\(^6\),\(^7\).

7.0 Consultation
- Dr Philip Gothard, Consultant Physician
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8.0 Recognition
Five species of malaria parasite cause clinical disease in humans: \textit{Plasmodium falciparum}, \textit{P vivax}, \textit{P ovale}, \textit{P malariae} and, in specific parts of SE Asia, \textit{P knowlesi}. Falciparum malaria has the potential to cause severe disease and this section concentrates on identifying and treating these patients.

**All travellers returning from the tropics with a fever or recent history of fever should have a blood film for malaria.** This should be done as an emergency and the result followed-up on the same day. Delay in requesting a blood film is a common reason for poor outcome.

Patients with falciparum malaria generally present within a month of returning from the tropics but 10% of cases present up to 3 months after travel. Patients infected with other species of malaria can present many months later and therefore **we recommend that malaria is considered in the differential diagnosis up to one year after returning from the tropics.** Anti-malarial prophylaxis is at best 95% effective but often patients miss doses and a history of prophylaxis should not lower your index of suspicion for malaria.

9.0 Diagnosis
**A thick and thin blood film** examined by an experienced microscopist and correlated with a clinical history is the gold standard for diagnosis. Once the blood arrives in the lab it takes about 45 minutes to prepare the film and a further 15 – 20 minutes to examine and report the slide. The report should include (1) the species, which may be multiple, (2) the parasite density or ‘parasitaemia’ and (3) the parasite stage: trophozoites, (pre)schizonts and gametocytes.

The presence of schizonts may mean that the peripheral parasitaemia is unrepresentative of the degree of sequestration and additionally that a further replication cycle is imminent.

Antigen dip stick tests are simple and reliable alternatives for hospitals where malaria is uncommon and lab technicians may have less experience in microscopy. The tests have three main problems: (1) they are less sensitive than good thick film microscopy by a factor of 10 – 100x, (2) they rely on detecting parasite antigen rather than live parasite and may
therefore be positive in patients who have been recently treated (up to 2 weeks) or come from a malaria endemic area and have a low level of asymptomatic parasitaemia, (3) it is not possible to determine the parasitaemia or stage of parasite. PCR is the most sensitive test but is not used in routine clinical practice. It is available at HTD and other specialist centres for complex cases after discussion with a consultant parasitologist.

We therefore recommend that all positive antigen tests are followed up with microscopy and where there is uncertainty that the film is urgently sent for review to either the Parasitology Laboratory at the Hospital for Tropical Diseases or the Malaria Reference Laboratory at the London School of Hygiene and Tropical Medicine. For rapid clinical advice use the HTD. The HTD provides a 24 hour referral service for clinical advice and emergency review of blood films.

Empirical treatment for malaria is usually not indicated, nor is there a rule for the number of negative blood films that exclude malaria as a diagnosis. If in doubt discuss the case with the tropical medicine registrar on call at HTD.

Patients with falciparum malaria can deteriorate rapidly, even with correct treatment, in part because of the impact of parasitized red cells sequestered in small vessels. We therefore recommend you consider admitting all patients with falciparum malaria. If there is doubt about the species, or there is co-infection on the film, then treat as falciparum malaria until further clarification.

10.0 Assessment of severity

A good clinical assessment of severity can be made in the emergency department using simple signs. Note the following: conscious level, blood pressure, respiratory rate, evidence of prostration, presence of jaundice or pallor, blood glucose, lactate and acid-base balance on ABG and urine output. All patients should have a blood film with parasitaemia plus standard laboratory tests for creatinine and haemoglobin.

A chest radiograph is recommended in breathless patients.

Bacterial co-infection is uncommon in adult travellers but should be considered when a malaria patient presents with shock or with focal signs such as pulmonary consolidation.

10.1 Classification of severity

UNCOMPPLICATED  Parassitaemia <2% and no schizonts and no clinical complications

SEVERE  Parassitaemia >2%
   or Parassitaemia <2% with schizonts reported on blood film
   or Parassitaemia <2% with complications

The above criteria are based on evidence to provide the safe management of people with severe malaria. In exceptional circumstances, where no blood film is available, consider using intravenous treatment after discussion with HTD. The Hospital for Tropical Diseases provides a 24 hour service for emergency review of blood films (details above).

Even patients with low parasitaemias can develop complications.
NB: in malaria-endemic countries the World Health Organisation recommends a parasitaemia of 5% as the cut off for severe disease. This is because frequently infected patients develop partial immunity. However this immunity wanes rapidly when patients stop being infected and we recommend that all patients presenting to UK hospitals are considered ‘non-immune’.

There are 200 to 300 cases of severe malaria a year in the UK with a mortality rate up to 8%. Age is an independent predictor of poor outcome.

10.2 Severe falciparum malaria: complications

1 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

2 Anaemia
- Severe anaemia is uncommon in travellers but common in African children
- It is primarily due to haemolysis
- Correct Hb <8g/dl with packed cells and monitor fluid balance, taking care not to overload

3 Metabolic and lactic acidosis
- is common and predictive of a poor prognosis
- often results from poor peripheral perfusion

4 Renal Failure
Defined as an urine output <0.5 ml/kg body weight/hour, failing to improve after rehydration and serum creatinine >265 micromol/l
- 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
- Most patients eventually regain renal function

5 Pulmonary Oedema
- Correction of hypovolaemia should be carried out with caution
- Earliest sign is a rise in the respiratory rate
- An acute lung injury may develop as the peripheral parasitaemia is resolving, due to increased capillary permeability

6 Hypoglycaemia
- In adults, particularly in pregnancy, this is due to quinine stimulating insulin release
- In children hypoglycaemia is more common and may contribute to impaired consciousness
- Give 1 ml/kg 50% dextrose by IV bolus followed by an infusion of dextrose
7 Hypovolaemia / Shock
- Dehydration requires careful clinical assessment
- Monitor for signs of pulmonary oedema during rehydration – patients can easily be overhydrated; non-cardiogenic pulmonary oedema is much more common in severe malaria than bacterial sepsis
- Children with malaria in Africa are particularly prone to bacterial co-infection. This is less common in healthy adult travellers. If a patient presents with malaria and shock send blood cultures and consider adding in empirical broad spectrum antibiotics

8 Bleeding / DIC
- Thrombocytopenia is almost invariable and is not necessarily an indication of severity although very low platelet counts (<50 x 10^9/l) tend to predict severe disease
- Platelet transfusions are only indicated if there is evidence of bleeding and a very low count
- Beware early DIC and check clotting, fibrinogen and D-dimers in severe malaria

9 Jaundice
- Jaundice is common and defined on clinical grounds or bilirubin > 50 micromol/l
- Jaundice alone is not an indication for parenteral treatment
- Usually pre-hepatic due to RBC destruction causing unconjugated hyperbilirubinaemia
- A cholestatic picture is uncommon

11.0 Treatment
Severe Falciparum Malaria
This is a medical emergency. Start effective anti-malarial drug therapy immediately – either with Quinine or Artesunate. Use parenteral therapy if readily available and if not use oral Quinine until pharmacy can provide an IV preparation – which should be within a few hours.

Exchange transfusion is no longer recommended.

Artesunate is the drug of choice for all patients with severe malaria: it has a rapid effect on parasite clearance and has been shown to reduce mortality compared to Quinine in clinical trials (SEAQUAMAT Lancet 2005; AQUAMAT Lancet 2010). However Artesunate is not yet licensed in the UK and most hospitals do not keep a supply. The HTD may be able to courier a supply to you after discussion with the Tropical Medicine Registrar on call. In the meantime do not delay giving IV Quinine whilst waiting for Artesunate to arrive as this may take 6 – 12 hours.

If the patient has features of severe malaria they should be managed in a High Dependency Unit with frequent medical review and accurate fluid balance. It is not uncommon for patients to develop an acute lung injury if over hydrated or to develop renal failure several days after admission.
**Artesunate**
Artesunate has few side effects and there is no need to adjust for renal impairment or to monitor for cardiac toxicity. It does not promote hypoglycaemia.

The dosing regimen is:
Artesunate is 2.4mg/kg IV bolus at 0 hours, 12 hours, 24 hours, and then 2.4mg/kg IV every 24 hours thereafter

Continue above regimen until patient is improving and can reliably swallow, then switch to an oral antimalarial to complete the course.

Oral options include (all adult doses):
- **Riamet® (Artemether 20mg/Lumefantrine 120mg)**
  >35kg weight: 4 tablets PO initially then a further 4 tablets at 8 hours, 24 hours, 36 hours, 48 hours and 60 hours
  Riamet® should be taken with fatty foods or milk

Usually 3 days of oral Artemisinin containing regimen (ACT) is sufficient treatment for cure. Occasionally, and particularly in patients with reduced ability to clear parasites (e.g. hyposplenism), a longer course of treatment may be required. If in doubt discuss with the HTD consultant on call.

Other oral options include (adult doses):
- Doxycycline 200mg PO every 24 hours for 7 days
- Malarone (Atovaquone 250mg/Proguanil 100mg) 4 tablets PO every 24 hours for 3 days
- Clindamycin 450mg PO every 8 hours for 7 days (safe in pregnancy)

Dihydroartemisinin/Piperaquine is an acceptable alternative ACT to Riamet® and is now licenced in the UK (not formulary at UCLH).

It is good practice to examine daily blood films, particularly in patients presenting with severe malaria.

**Quinine**
The dosage regimen for quinine by IV infusion is:
Loading dose of 20mg/kg (max 1.4g) IV in 250ml of Sodium Chloride infused over 4 hours, then 8 hours after the start of the loading dose,
Maintenance dose of 10mg/kg (max 700mg) IV every 8 hours – in 250ml of Sodium Chloride infused over 4 hours
If the patient has received Mefloquine in the preceding 3 days, a loading dose is NOT required. Start with maintenance dose of 10mg/kg.

Continue above regimen until patient is improving and can reliably swallow to complete a total 7 day course.
Quinine should be given together with or followed by either:
  - Doxycycline 200mg PO every 24 hours for 7 days
  - OR
  - Clindamycin 450mg PO every 8 hours for 7 days

Quinine is a class 1 anti-arrhythmic drug. It interacts with other class 1 agents to lengthen the QT interval, predisposing patients to Torsade de Pointes. Therefore check an ECG before starting IV Quinine and in patients with underlying cardiac disease use cardiac monitoring.
and consider withholding regular anti-arrhythmic medication. IV Quinine also induces endogenous secretion of insulin thereby promoting hypoglycaemia. Monitor a patient’s BM every 2 – 4 hours whilst on IV Quinine. Tinnitus is expected, reversible and not an indication for stopping Quinine.

**Patients do not need both IV Quinine and IV Artesunate. When the Artesunate arrives you should discontinue the Quinine once the patient has received the first dose of Artesunate.**

**12.0 Continuing care**

Manage patients with severe falciparum malaria in a high dependency unit with accurate fluid balance and careful medical review. Consider blood transfusion if the haemoglobin drops below 8g/dL. There is no need for platelet transfusions unless the patient has active bleeding. There is no need for antibiotics unless the patient is shocked or has a clear clinical focus such as unilateral pulmonary consolidation or a significant positive blood culture. Take daily blood for parasitaemia, haemoglobin and renal function.

The decision to discharge a patient is based on a combination of clinical response, declining parasitaemia and home circumstances. Before leaving, offer patients advice on future anti-malarial prophylaxis.

**13.0 Pregnancy**

Falciparum malaria in pregnancy is likely to be more severe than suggested by the peripheral blood film due to marked placental sequestration. The foetus is usually fine but under treatment may lead to placental insufficiency and occasionally still birth. Quinine is safe and effective in all stages of pregnancy and is used in standard doses.

Current WHO guidelines recommend avoiding Artesunate in the first trimester of pregnancy although evidence is accumulating that it is safe and effective (ref 8). In pregnant patients returning from SE Asia, where resistant parasites are more common, Artesunate is the drug of choice for severe malaria in all stages of pregnancy.

**14.0 Uncomplicated Falciparum malaria**

Use oral treatment unless the patient is vomiting, in which case treat as severe falciparum malaria. Do not use a drug for treatment if the patient has been using it for prophylaxis (e.g. Malarone).

Oral Artemisinin Combination Therapy (ACT) is simple, effective and well tolerated. We recommend ACT as first line treatment although recognise this may not be available in all UK hospitals. If there is a delay in sourcing ACT the priority is to start any effective anti-malarial drug.

1st line: **Artemether-lumefantrine (Riamet®)**

4 tablets PO initially, followed by a further 4 tablets at 8 hours, 24 hours, 36 hours, 48 hours and 60 hours. Take with milk or fatty food as this aids absorption. Riamet® should not be used for women in the first trimester of pregnancy without specialist advice.

2nd line: **Quinine plus Doxycycline (option 1)**

Quinine 10 mg/kg (max 700mg) PO every 8 hours (reduce to 12 hourly regimen if patient develops severe cinchonism with tinnitus & deafness)

*plus*

Doxycycline 200mg PO every 24 hours (*do not use in pregnancy or children under 12 years*)

Total duration: 7 days
**Quinine plus Clindamycin (option 2)**
Quinine 10mg/kg (max 700mg) PO every 8 hours (reduce to 12 hourly regimen if patient develops severe cinchonism with tinnitus and deafness)

*plus*
Clindamycin 450mg PO every 8 hours *(NB – this combination is effective and safe in pregnancy)*

Total duration: 7 days

**3rd line:** **Atovaquone / Proguanil (Malarone®)**
4 tablets PO every 24 hours for 3 days. Take with milk or a fatty meal to increase absorption. Do not use if the patient took Malarone prophylaxis. Less evidence exists for the use of Atovaquone / Proguanil in treating malaria and there have been occasional reports of treatment failure in travellers possibly linked to parasite resistance.

**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.

### 15.0 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

#### 15.1 Initial treatment
**Chloroquine (as base)** 25 mg/kg PO in divided doses (total dose) over 2 days
For 40 - 80kg use standard dosing as per table below:

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<td>48</td>
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- 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

#### 15.2 Relapse prevention
**P. vivax:**
The prevalence of both chloroquine and primaquine resistant *P. vivax* is increasing. **Primaquine** 15mg PO every 12 hours (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* 15mg PO every 24 hours for 14 days
- *P. malariae* has no hypnozoite stage and no second drug is required

15.3 **Patient with G6PD deficiency**
Discuss with HTD consultant. Where levels are very low then consider once weekly primaquine for eight weeks.

15.4 **Pregnancy**
- Do not give primaquine in pregnancy or while breast-feeding.
- After treatment with chloroquine, relapse should be prevented by giving weekly Chloroquine 300mg PO every 24 hours or Proguanil 100mg PO every 24 hours until delivery.
- After delivery & breast feeding primaquine can be given as normal

16.0 **Guidance implementation**
- The guidance will be available electronically on Insight and on the Hospital for Tropical Diseases website ([www.thehtd.org](http://www.thehtd.org))
- A paper copy of the guidance will be given to all medical staff working within Infection Division, during their Induction

17.0 **Review, Monitoring & Compliance**

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<td>Adherent to treatment guideline</td>
<td>Audit</td>
<td>Prof D Lockwood, Clinical Audit Lead for Infection</td>
<td>Yearly</td>
<td>HTD Audit Committee</td>
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18.0 References