

MALARIA TREATMENT GUIDANCE

GP Referrals:

- ID team will review febrile returned travellers on an urgent outpatient basis; bleep 5075 or email tay.id@nhs.scot
- At weekends discussion with AMU would be required.
- All patients with malaria should be reviewed by ID team and all with falciparum malaria will be admitted

Key Points

- Test using blood films for malaria in all travellers returning from the tropics with a fever
- Thick and thin blood films are the gold standard investigation for malaria
- 3 negative diagnostic samples, with 12-24 hours between samples, are necessary to exclude malaria
- The haematology laboratory will routinely process an antigen dipstick test when a malaria blood film is requested
- Any uncertainty over infecting species should be treated as falciparum malaria
- Admit all patients with falciparum malaria for a minimum of 24 hours observation
- Assess severity based on:
 - **parasitaemia >2%**
and/or
 - **complicating clinical features: conscious level, acidosis, pulmonary oedema, renal failure, anaemia, hypoglycaemia**
- In severe malaria IV artesunate is the treatment of choice (if necessary start IV quinine until IV artesunate is available)
- Patients with severe falciparum malaria can deteriorate rapidly so involve ICU early
- 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.
- Uncomplicated falciparum malaria and non-falciparum malaria should be treated with Riamet®
- All doses in this document are for adults and assume normal renal and hepatic function
- All patients should be referred to ID team

1. Diagnosis

A thick and thin blood film examined by an experienced microscopist and correlated with a clinical history is the gold standard for diagnosis

Antigen dipstick tests are simple but have three main problems:

- (1) they are less sensitive than microscopy
- (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

2. Assessment of severity

- 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

Classification of severity

UNCOMPLICATED Parasitaemia $\leq 2\%$ and no schizonts (on blood film) and no clinical complications

SEVERE Parasitaemia $>2\%$

or Parasitaemia $\leq 2\%$ with schizonts reported on blood film
or Parasitaemia $\leq 2\%$ with complications (see list above)

Even patients with low parasitaemias can develop complications. Immunity wanes rapidly when patients move from endemic areas and we recommend that all patients presenting to UK hospitals are considered 'non-immune'. Age is an independent predictor of poor outcome.

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
- Convulsions should be controlled with benzodiazepines
- Status epilepticus should be managed with anti-convulsants, but beware of potential interactions if using quinine

2. Anaemia

- Severe anaemia is uncommon in travellers but common in African children
- It is primarily due to haemolysis
- Correct Hb $\leq 80\text{g/L}$ with packed cells and monitor fluid balance, taking care not to overload

3. Metabolic and lactic acidosis ($\text{pH} < 7.3$)

- Acidosis is common and predictive of a poor prognosis

4. Renal Failure

- Defined as an urine output $< 0.4\text{ ml/kg body weight/hour}$, failing to improve after rehydration or serum creatinine $> 265\text{ micromol/l}$
- Hyponatraemia is common in malaria and does not usually require correction
- Consider early haemofiltration or dialysis

5. Pulmonary Oedema

- Correction of hypovolaemia should be carried out with caution

6. Hypoglycaemia ($< 2.2\text{mmol/L}$)

- In adults, particularly in pregnancy, this is due to quinine stimulating insulin release

7. Hypovolaemia/Shock

- Dehydration requires careful clinical assessment
- Secondary bacterial infection is possible

8. Bleeding / DIC

- Thrombocytopenia is almost invariable and is not necessarily an indication of severity although very low platelet counts ($< 50 \times 10^9/\text{L}$) 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-dimer in severe malaria

9. Jaundice

- Jaundice alone is not an indication for parenteral treatment

3. Treatment

Severe Falciparum Malaria – Initial IV treatment followed by oral therapy

This is a medical emergency. **Artesunate** is the drug of choice for all patients with severe malaria. 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. Start effective anti-malarial drug therapy immediately – ideally with IV artesunate but if not available start IV quinine.

If neither parenteral therapy is available use oral Riamet® until pharmacy can provide an IV preparation.

Artesunate (Kept in NW Night Emergency Drug Cupboard)

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
- See appendix 1 for administration details
- Continue above regimen until patient is improving (minimum 24 hours/maximum 5 days) and can reliably swallow, then switch to complete a full course of oral ACT – see treatment of uncomplicated falciparum malaria below
- Check Hb approximately 14 days after completion of IV artesunate – delayed haemolysis can occur in 10-15% of patients

Quinine Dihydrochloride (Kept in NW Night Emergency Drug Cupboard and NW 42)

The dosage regimen for quinine by IV infusion is:

- **LOADING DOSE**
 - 20mg/kg (max 1.4g) IV in 250ml of 5% glucose infused over 4 hours.
 - NO loading dose is required if the patient has received quinine or mefloquine in the preceding 12 hours (consider antimalarial prophylaxis)
- Then 8 hours after the start of the loading dose:
- **MAINTENANCE DOSE**
 - Started 8 hours after start of loading dose infusion
 - 10mg/kg (max 700mg) IV every 8 hours
 - In 250ml of glucose 5% infused over 4 hours
 - If given for > 48 hours (or patients with renal failure or severe liver dysfunction) reduce frequency to 12 hourly

- Continue above regimen until patient is improving and can reliably swallow then switch to complete a total 7 day course of quinine (+either doxycycline or clindamycin) – see treatment of uncomplicated falciparum malaria below
- **Monitoring**
 - 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 older patients and 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 patient's BM routinely every 4 hours or every 2 hours during quinine infusion
 - Tinnitus is expected, reversible and not an indication for stopping Quinine.

Oral options – to complete treatment after IV therapy

See treatment of uncomplicated falciparum malaria below

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. Severe malaria in any trimester of pregnancy should be treated as for any other patient with artesunate preferred over quinine. Quinine is safe and effective in all stages of pregnancy and is used in standard doses.

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. ACT is recommended first line treatment. If there is a delay in sourcing ACT the priority is to start any effective anti-malarial drug.

1st line: Artemether-lumefantrine (Riamet®) Kept in NW 42

4 tablets PO initially, followed by a further 4 tablets at 8 hours, 24 hours, 36 hours, 48 hours and 60 hours. It must always be given with fatty food or milk to maximise absorption.

Riamet® should not be used for patients in the first trimester of pregnancy without specialist advice. Occasionally, and particularly in patients with reduced ability to clear parasites (e.g. hyposplenism), a longer course of treatment may be required.

2nd line: Quinine plus Doxycycline (option 1)

Quinine sulphate 600mg PO every 8 hours (reduce to 12 hourly regimen if patient develops severe cinchonism with tinnitus and deafness)

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

Total duration: 7 days

2nd line: Quinine plus Clindamycin (option 2)

Quinine sulphate 600mg 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. GI side effects likely.

Non-Falciparum malaria

Patients should be offered admission if unwell. If evidence of hepatosplenomegaly advise avoidance of contact sports for 6/52.

Initial treatment

First line: 1st line: Artemether-lumefantrine (Riamet®) Kept in NW 42

4 tablets PO initially, followed by a further 4 tablets at 8 hours, 24 hours, 36 hours, 48 hours and 60 hours. It must always be given with fatty food or milk to maximise absorption. Can be used in 2nd and 3rd trimesters of pregnancy.

2nd line: Chloroquine (as base) 25 mg/kg PO in divided doses (total dose) over 2 days (safe in pregnancy)

For all adult patients use the dosing table below

Time (Hrs)	Dose (mg)	Tablets (Number)
0	620	4
6	310	2
24	310	2
48	310	2

Chloroquine (Alvoclor®) tablets kept in NHS Tayside contain 250mg of chloroquine sulphate and each tablet contains 155mg of chloroquine base.

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 Riamet should be offered. Patients with epilepsy should not be prescribed chloroquine without Consultant approval

Relapse prevention (to eradicate dormant parasites (hypnozoite) stage in liver)

- ideally, should overlap with initial treatment
- required for all *P.vivax* and *P.ovale* infections
- check G6PD levels at baseline as Primaquine can induce haemolysis in G6PD deficient individuals

P. vivax

Primaquine 30mg PO daily for 14 days

P. ovale

Primaquine 15mg daily for 14 days

Advice in G6PD deficiency

Normal range 5.9 - 11.7 U/g Hb. If there is G6PD deficiency seek advice; there is a real risk of haemolysis. Where G6PD levels are very low then discuss with ID consultant and consider primaquine 45mg once weekly for eight weeks.

Pregnancy

Do not give primaquine in pregnancy or while breast-feeding.

After treatment with chloroquine, relapse should be prevented by giving chloroquine 500mg PO once weekly. After delivery and completion of breast feeding primaquine can be given as normal.

References:

BIA [UK Malaria treatment guidelines 2016](#)
UCLH malaria treatment guidelines 2013
WHO Guidelines for Malaria 2021

Adapted for NHS Tayside
Dr M Evans, ID Consultant
K Hill, Antimicrobial Pharmacist
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