Guideline for the Treatment Of Malaria In Adults

University Hospitals of Leicester NHS
NHS Trust

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1 Introduction

Malaria should be considered in any unwell or febrile person who has visited an endemic area (tropics and most subtropical areas of Africa, Asia, Americas, and Oceania; detailed information at https://www.cdc.gov/malaria/travelers/country_table). Malaria should also be considered in any patient with unexplained fever and thrombocytopenia, regardless of travel history.

Most cases of severe malaria present within 3 months of return from the endemic area, but may present later. Malaria is a medical emergency and should be investigated and treated as such.

Malaria is a notifiable disease under the Health Protection (Notification) Regulations 2010

2 Guideline Standards and Procedures

2. 1 Suspicion of malaria in adults

- **Admit to a sideroom, until a diagnosis is made.** All cases of falciparum malaria should be admitted. All febrile returning travellers should be isolated.
- **Take travel and general history.** Fever and other symptoms are nonspecific and may include malaise, rigors, drowsiness, headache, diarrhoea and cramps.
- **Send EDTA (FBC) blood urgently to Haematology for malaria film +/- rapid diagnostic tests.** Stop any antimalarial prophylaxis; repeat daily up to 3 times if negative. **Take blood cultures in all unwell travellers and perform other investigations according to clinical indications** - FBC, clotting, U&E, LFT, Bone, CRP, glucose, G6PD (EDTA bottle), urine dipstick, stool MC&S, CXR, hepatitis/HIV serology, lactate.
- **Clinical suspicion of malaria should always be supported by laboratory confirmation: empiric treatment is seldom, if ever, justifiable.**

2.2 Assessing severity

In a patient with malaria and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features indicates severe malaria:

- Impaired consciousness (GCS <11)
- Prostration (i.e. generalized weakness so that the patient is unable to walk or sit up without assistance)
- Multiple convulsions – more than two episodes in 24 h
- Shock (SBP < 80 mm Hg or capillary refill ≥ 3 s)
- Abnormal spontaneous bleeding
- Hypoglycaemia (blood glucose < 2.2 mmol/l)
- Metabolic acidosis (plasma bicarbonate < 15 mmol/l or base deficit of >8 mEq/l or venous plasma lactate ≥ 5 mmol/l). Severe acidosis manifests clinically as rapid, deep, laboured breathing
- Severe malarial anaemia (Hb < 70g/l or haematocrit <20%)
- Haemoglobinuria
- Hyperparasitaemia (> 2% of red cells parasitised)
- Acute kidney injury (serum creatinine > 265 µmol/l)
- Pulmonary oedema (radiological) **or** oxygen saturation < 92% on room air **or** respiratory rate > 30
- Jaundice - bilirubin > 50umol/L **and** *Plasmodium knowlesi* or *vivax* parasitaemia >0.5%

2.3 Treatment of malaria in adults

ONCE MALARIA IS CONFIRMED, START TREATMENT IMMEDIATELY

In pregnancy or lactation, obtain specialist advice, and discuss with a pharmacist if the patient wishes to continue breastfeeding during treatment

2.3.1 Initial treatment of severe malaria (any species)

Artesunate is the drug of choice for treatment of severe malaria. If artesunate is unavailable, commence treatment with IV quinine and **notify the on call pharmacist** to arrange urgent supply of artesunate. Once artesunate is available, stop quinine and start artesunate.

Artesunate is unlicensed: all cases of severe malaria should be discussed with Infectious Disease on call at the point of diagnosis.

IMPORTANT
In cases of severe *P falciparum* malaria acquired in Cambodia, Lao PDR, Myanmar, Thailand or Viet Nam, treat with IV artesunate AND IV quinine initially.

1st line	2nd Line
Artesunate IV IV bolus of 2.4 mg/kg at 0 hours, 12 hours, 24 hours, then once daily thereafter until parasitaemia is <1%, markers of severity have gone, and the patient is able to take oral medication **THEN** follow treatment guidance for uncomplicated malaria in the following sections according to *Plasmodium* species (always follow with artemether with lumefantrine in *Plasmodium falciparum* malaria)	**Quinine IV** Loading dose of 20 mg/kg (max 1400 mg) quinine, in 250 ml 5% glucose by slow infusion over 4 hours, followed with maintenance doses of 10 mg/kg (max 700 mg) by slow infusion over 4 hours every 8 hours until parasitaemia is <1%, markers of severity have gone, and the patient is able to take oral medication **THEN** follow treatment guidance for uncomplicated malaria in the following sections according to *Plasmodium* species

Notes: A minimum of 24h treatment duration must be given before switch to oral medication This medicine is not licensed in the UK but is stocked at UHL pharmacy. **Notify the on call pharmacist when this medicine is prescribed.**	**Notes**: All doses given in 250ml 5% glucose Dose is applicable for quinine dihydrochloride, hydrochloride, or sulfate Adverse effects include • Arrhythmias (monitor ECG, HR, and BP) • Hypoglycaemia (monitor BM 2-4 hourly) • cinchonism (vertigo, tinnitus, hearing problems, no urgent action required) In hepatic or renal impairment, or if intravenous quinine is needed for more than 48 hours, frequency of dosing should be reduced to 12 hourly. Consider quinine levels Omit loading dose if mefloquine or quinine was taken in preceding 12 hours; go straight to maintenance dose Quinine should not be used in lactating women if the infant has G6PD deficiency

Monitoring and follow up

- Repeat blood film daily
- Late onset haemolysis is described in patients with severe hyperparasitaemic malaria, with onset >1 week after artesunate treatment; follow such patients carefully

Adjunctive management

- In the case of shock, after taking blood cultures, add meropenem 1g every 8 hours to cover bacterial sepsis
- Avoid fluid overload, which can precipitate fatal pulmonary oedema **(DO NOT FOLLOW SEPSIS GUIDELINES)**
- Transfuse if Hb < 70 g/L taking care not to overload
- Support clotting if bleeding, avoid drugs which may cause GI bleeding
- If severe complications (metabolic acidosis, oliguric renal failure, pulmonary oedema or adult respiratory distress) manage in ITU setting

2.3.2 Treatment of uncomplicated malaria due to infection with *Plasmodium falciparum*

Artemisinin based combination therapies (ACTs) are the drugs of choice for treatment of uncomplicated malaria due to infection with *P falciparum*. Artemether with lumefantrine (Riamet®) is the recommended licensed ACT in the UK.

1st line	2nd line	Alternative 2nd line

Riamet® tablets (artemether 20 mg with lumefantrine 120 mg) orally Four tablets immediately then four tablets given at 8, 24, 36, 48 and 60 hours	**Quinine orally** Quinine base 600 mg every 8 hours for 7 days or until parasites have cleared Followed by • doxycycline 200 mg once daily for 7 days • **OR** clindamycin 450 mg every 8 hours for 7 days	**Malarone® tablets (atovaquone 250 mg with proguanil 100 mg) orally** Four tablets once daily for 3 days
Notes: Give with milk or fatty food to increase absorption Riamet® should not be used in the first trimester of pregnancy without specialist advice No dose adjustment needed in renal or hepatic impairment but consider enhanced monitoring for ADRs Women taking Riamet should not breastfeed during their treatment and for at least one week after the last dose	**Notes**: Seek pharmacist advice on quinine base equivalent of available quinine salt preparation Do not give doxycycline in pregnancy or lactation Clindamycin is the preferred agent in pregnancy Quinine should not be used in lactating women if the infant has G6PD deficiency	**Notes**: Give with milk or fatty food to increase absorption Do not use if the patient took Malarone prophylaxis Proguanil should not be used in pregnancy

Adjunctive management

- Repeat blood film daily until asexual parasites have cleared. If blood film remains positive for asexual forms of *P falciparum* after 72 hours treatment with ACT, consider partial resistance, extend treatment course to 6 days and seek expert advice
- If the patient intends to return to a malaria endemic region within 120 days, administer a single dose of primaquine 0.25mg/kg up to maximum 15mg (G6PD measurement is not required for this single dose; contraindicated in pregnancy and lactation)
- It is recommended to obtain a blood film 28 days after start of treatment to classify treatment response.

2.3.3 Treatment of uncomplicated malaria due to infection with presumed chloroquine resistant *Plasmodium vivax*

Chloroquine resistance is likely in *P vivax* infections from Papua New Guinea & Indonesia, but occurs to a lesser extent in almost all countries where *P vivax* is endemic. Treat *P vivax* infections from New Guinea from the outset, and infections from other countries if asexual forms have not disappeared from the blood film after 72h treatment, as chloroquine resistant.

ACTs are the drugs of choice for treatment of uncomplicated malaria due to infection with chloroquine resistant *Plasmodium vivax*. Artemether with lumefantrine (Riamet®) is the recommended licensed ACT in the UK.

1st line	2nd line

Riamet® tablets (artemether 20 mg with lumefantrine 120 mg) Four tablets immediately then four tablets given at 8, 24, 36, 48 and 60 hours. Follow with primaquine 30 mg once daily for 14 days.	**Quinine orally** Quinine base 600 mg every 8 hours for 7 days or until parasites have cleared Follow with primaquine 30 mg once daily for 14 days.
Notes: Give Riamet® with milk or fatty food to increase absorption. Riamet® should not be used in the first trimester of pregnancy without specialist advice. Rule out G6PD deficiency before prescribing primaquine • In mild G6PD deficiency, primaquine can be given weekly (45 mg weekly for 8 weeks) unless haemolysis develops • In severe G6PD deficiency primaquine is contraindicated Primaquine is contraindicated in pregnancy, use weekly chloroquine 310mg base (i.e. two chloroquine phosphate 250 mg tablets) to prevent relapse, until primaquine can be given. In lactating women, test both mother and infant for G6PD deficiency is advisable before primaquine is given to the mother	**Notes**: Seek pharmacist advice on quinine base equivalent of available quinine salt preparation Rule out G6PD deficiency before prescribing primaquine • In mild G6PD deficiency, primaquine can be given weekly (45 mg weekly for 8 weeks) unless haemolysis develops • In severe G6PD deficiency primaquine is contraindicated Primaquine is contraindicated in pregnancy, use weekly chloroquine 310mg base (i.e. two chloroquine phosphate 250 mg tablets) to prevent relapse, until primaquine can be given. In lactating women, test both mother and infant for G6PD deficiency is advisable before primaquine is given to the mother

2.3.4 Treatment of uncomplicated malaria due to infection with chloroquine sensitive *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae* or other non-falciparum species

Treat with either Riamet® or chloroquine, followed with primaquine.

Admission may not always be required

EITHER	OR
Chloroquine Chloroquine base 620 mg orally (equivalent to four chloroquine phosphate 250 mg tablets) on days 1 & 2 Then 310 mg base (i.e. two chloroquine phosphate 250 mg tablets) on day 3 Give additional doses of 310 mg base daily if required to achieve a total dose of 25mg/kg of chloroquine base	**Riamet® tablets (artemether 20 mg with lumefantrine 120 mg)** Four tablets immediately then four tablets given at 8, 24, 36, 48 and 60 hours.

In *P. vivax* follow with primaquine 30 mg once daily for 14 days In *P. ovale* follow with primaquine 15 mg once daily for 14 days	In *P. vivax* follow with primaquine 30 mg once daily for 14 days In *P. ovale* follow with primaquine 15 mg once daily for 14 days
Notes: Rule out G6PD deficiency before prescribing repeated primaquine doses • In mild G6PD deficiency, primaquine can be given weekly (45 mg weekly for 8 weeks) unless haemolysis develops • In severe G6PD deficiency primaquine is contraindicated • In lactating women, testing the infant for G6PD deficiency is advisable before primaquine is given to the mother Primaquine is contraindicated in pregnancy, use weekly chloroquine 310mg base (i.e. two chloroquine phosphate 250 mg tablets) to prevent relapse, until primaquine can be given	**Notes**: Give Riamet® with milk or fatty food to increase absorption Riamet® should not be used in the first trimester of pregnancy without specialist advice Rule out G6PD deficiency before prescribing repeated primaquine doses • In mild G6PD deficiency, primaquine can be given weekly (45 mg weekly for 8 weeks) unless haemolysis develops • In severe G6PD deficiency primaquine is contraindicated • In lactating women, testing the infant for G6PD deficiency is advisable before primaquine is given to the mother Primaquine is contraindicated in pregnancy, use weekly chloroquine 310mg base (i.e. two chloroquine phosphate 250 mg tablets) to prevent relapse, until primaquine can be given

2.3.5 Uncomplicated malaria due to mixed infection, or when the species cannot be determined

Treat as for uncomplicated malaria due to infection with presumed chloroquine resistant *Plasmodium vivax* (section 2.2.3) with Riamet®, followed with primaquine.

3 Education and Training

No additional education or training is required.

4 Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Proportion of patients having the required investigations for malaria completed	Case review	ID	Ad hoc	Internally and Datix
Proportion of drug regimens in line with guidelines	Case review/annual Trust wide antimicrobial prescribing audit	ID/Antimicrobial pharmacists	Ad hoc Annually	Internally and Datix / To ESM CMG Board

5 Supporting References

1. UK malaria treatment guidelines 2016 http://dx.doi.org/10.1016/j.jinf.2016.02.001
2. WHO Guidelines for Malaria (2023). WHO, Geneva https://www.who.int/publications/i/item/guidelines-for-malaria
3. Malaria (in: British National Formulary), Pharmaceutical Press, London, UK [also available online: https://bnf.nice.org.uk/treatment-summaries/malaria-treatment/

6 Key Words

Malaria, Plasmodium, falciparum, malariae, vivax, ovale

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Dr David Bell (Consultant ID Physician)	**Executive Lead** Andrew Furlong
Reviewer(s) Dr David Bell (Consultant ID Physician)	**Ratified by** Antimicrobial Working Party 11th November 2020 Reference: AWP69
Details of Changes made during review: • updated with current WHO recommendations	

Review Record			
Date	**Issue No.**	**Reviewed By**	**Description of change if any**
July 2009	2	I Stephenson	No changes
July 2011	3	I Stephenson	Improved description of chloroquine dosage
April 2013	4	D Bell	Addition of Artesunate and Artemether with lumefantrine (Riamet ®) as treatment option
May 2017	5.1	D Bell O Ahmed R Hamilton	• Reformatted as per Trust requirements • Additional information given regarding assessment and drug treatment • Advice regarding re-screening after 28-days' treatment for P. falciparum given
June 2018	5.2	R Hamilton	• IV quinine dosing and monitoring updated in line with BNF update, renal drug database, and WHO. • Linked to UHL sepsis guideline
November 2020	6	D Bell S Hackney	• ACT first line for P falciparum • Chloroquine resistant P vivax • Primaquine after P falciparum treatment if returning to endemic area
March 2021	6.1	D Bell S Hackney	• Guidance on lactation
November 2023	7	D Bell	• Updated with current WHO advice
Octo 2024	7.1	D Bell, J Veater	• Clarified that on call pharmacist to be contacted to arrange supply of artesunate (approved CPGC 21.11.24)