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UK malaria treatment guidelines 2016



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Summary 1. Malaria is the tropical disease most commonly imported into the UK, with 1300–1800 cases reported each year, and 2–11 deaths.

2. Approximately three quarters of reported malaria cases in the UK are caused by *Plasmodium falciparum*, which is capable of invading a high proportion of red blood cells and rapidly leading to severe or life-threatening multi-organ disease.

3. Most non-falciparum malaria cases are caused by *Plasmodium vivax*; a few cases are caused by the other species of plasmodium: *Plasmodium ovale*, *Plasmodium malariae* or *Plasmodium knowlesi*.

4. Mixed infections with more than one species of parasite can occur; they commonly involve *P. falciparum* with the attendant risks of severe malaria.

5. There are no typical clinical features of malaria; even fever is not invariably present. Malaria in children (and sometimes in adults) may present with misleading symptoms such as gastrointestinal features, sore throat or lower respiratory complaints.

6. A diagnosis of malaria must always be sought in a feverish or sick child or adult who has visited malaria-endemic areas. Specific country information on malaria can be found at <http://travelhealthpro.org.uk/>. *P. falciparum* infection rarely presents more than six months after exposure but presentation of other species can occur more than a year after exposure.

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7. Management of malaria depends on awareness of the diagnosis and on performing the correct diagnostic tests: the diagnosis cannot be excluded until more than one blood specimen has been examined. Other travel related infections, especially viral haemorrhagic fevers, should also be considered.

8. The optimum diagnostic procedure is examination of thick and thin blood films by an expert to detect and speciate the malarial parasites. *P. falciparum* and *P. vivax* (depending upon the product) malaria can be diagnosed almost as accurately using rapid diagnostic tests (RDTs) which detect plasmodial antigens. RDTs for other *Plasmodium* species are not as reliable.

9. Most patients treated for *P. falciparum* malaria should be admitted to hospital for at least 24 h as patients can deteriorate suddenly, especially early in the course of treatment. In specialised units seeing large numbers of patients, outpatient treatment may be considered if specific protocols for patient selection and follow up are in place.

10. Uncomplicated *P. falciparum* malaria should be treated with an artemisinin combination therapy (Grade 1A). Artemether–lumefantrine (Riamet[®]) is the drug of choice (Grade 2C) and dihydroartemisinin-piperaquine (Eurartesim[®]) is an alternative. Quinine or atovaquone–proguanil (Malarone[®]) can be used if an ACT is not available. Quinine is highly effective but poorly-tolerated in prolonged treatment and should be used in combination with an additional drug, usually oral doxycycline.

11. Severe falciparum malaria, or infections complicated by a relatively high parasite count (more than 2% of red blood cells parasitized) should be treated with intravenous therapy until the patient is well enough to continue with oral treatment. Severe malaria is a rare complication of *P. vivax* or *P. knowlesi* infection and also requires parenteral therapy.

12. The treatment of choice for severe or complicated malaria in adults and children is intravenous artesunate (Grade 1A). Intravenous artesunate is unlicensed in the EU but is available in many centres. The alternative is intravenous quinine, which should be started immediately if artesunate is not available (Grade 1A). Patients treated with intravenous quinine require careful monitoring for hypoglycemia.

13. Patients with severe or complicated malaria should be managed in a high-dependency or intensive care environment. They may require haemodynamic support and management of: acute respiratory distress syndrome, disseminated intravascular coagulation, acute kidney injury, seizures, and severe intercurrent infections including Gram-negative bacteraemia/septicaemia.

14. Children with severe malaria should also be treated with empirical broad spectrum antibiotics until bacterial infection can be excluded (Grade 1B).

15. Haemolysis occurs in approximately 10–15% patients following intravenous artesunate treatment. Haemoglobin concentrations should be checked approximately 14 days following treatment in those treated with IV artemisinins (Grade 2C).

16. Falciparum malaria in pregnancy is more likely to be complicated: the placenta contains high levels of parasites, stillbirth or early delivery may occur and diagnosis can be difficult if parasites are concentrated in the placenta and scanty in the blood.

17. Uncomplicated falciparum malaria in the second and third trimester of pregnancy should be treated with artemether–lumefantrine (Grade 2B). Uncomplicated falciparum malaria in the first trimester of pregnancy should usually be treated with quinine and clindamycin but specialist advice should be sought. Severe malaria in any trimester of pregnancy should be treated as for any other patient with artesunate preferred over quinine (Grade 1C).

18. Children with uncomplicated malaria should be treated with an ACT (artemether–lumefantrine or dihydroartemisinin-piperaquine) as first line treatment (Grade 1A). Quinine with doxycycline or clindamycin, or atovaquone–proguanil at appropriate doses for weight can also be used. Doxycycline should not be given to children under 12 years.

19. Either an oral ACT or chloroquine can be used for the treatment of non-falciparum malaria. An oral ACT is preferred for a mixed infection, if there is uncertainty about the infecting species, or for *P. vivax* infection from areas where chloroquine resistance is common (Grade 1B).

20. Dormant parasites (hypnozoites) persist in the liver after treatment of *P. vivax* or *P. ovale* infection: the only currently effective drug for eradication of hypnozoites is primaquine (1A). Primaquine is more effective at preventing relapse if taken at the same time as chloroquine (Grade 1C).

21. Primaquine should be avoided or given with caution under expert supervision in patients with Glucose-6-phosphate dehydrogenase deficiency (G6PD), in whom it may cause severe haemolysis.

22. Primaquine (for eradication of *P. vivax* or *P. ovale* hypnozoites) is contraindicated in pregnancy and when breastfeeding (until the G6PD status of child is known); after initial treatment for these infections a pregnant woman should take weekly chloroquine prophylaxis until after delivery or cessation of breastfeeding when hypnozoite eradication can be considered.

23. An acute attack of malaria does not confer protection from future attacks: individuals who have had malaria should take effective anti-mosquito precautions and chemoprophylaxis during future visits to endemic areas.

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Background

Malaria remains one of the most common imported infections in the United Kingdom (UK). Between 1300 and 1800 malaria cases are reported each year in the UK, although reviews of reporting suggest that this may represent about 65% of all cases that occur.¹ Approximately three-quarters of reported infections are due to *Plasmodium falciparum* and there are between 2 and 11 deaths annually. Children under 16 account for around 10% of cases.² Two thirds of cases occur in people of African or South Asian ethnic origin and over half of the cases occur in those who had been visiting friends and family in endemic areas.³ Most patients with falciparum malaria acquire infection in Africa and malaria accounts for about 20% of travellers from Africa presenting to hospital with fever; West Africa is the commonest geographical source. Most *Plasmodium vivax* infections are acquired in South Asia.^{2,4}

This document offers guidance for the management of both uncomplicated and complicated malaria in the UK. It complements existing Public Health England (PHE) guidelines on the prevention of malaria in UK travellers. <https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk>. It has been based on a review of the available evidence by the PHE Advisory Committee on Malaria Prevention (ACMP), with input from other experts and expert bodies, and incorporates international guidance including WHO guidelines on treatment and definitions of severe malaria.^{5,6} These guidelines will specifically present a UK perspective on management. Other non-endemic countries including the USA, Canada and Europe have also developed their own guidelines.^{7–9} These UK guidelines have been developed specifically for use in a non-endemic setting, but necessarily depend heavily upon evidence obtained from studies in endemic areas. More detailed information about individual drug regimens and contra-indications can be found in the British National Formulary (<http://www.bnf.org/>). A short summary of key points in the initial assessment and management, for use in emergency departments, is available from the British Infection Association website (<http://www.britishtinfection.org/>).

Major recommendations have been graded using a modified GRADE approach which grades both the strength of the recommendation and the level of evidence for the recommendations.

A **Grade 1** recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most patients.

A **Grade 2** recommendation is a conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain.

Grade A evidence means high-quality evidence that comes from consistent results from high quality randomised controlled trials (RCTs).

Grade B evidence means moderate-quality evidence from randomised trials that suffers from flaws in conduct or design OR methodologically strong observational studies with consistent effects and exclusion of most sources of bias.

Grade C evidence is low-quality evidence from controlled trials with serious limitations or inconsistent results, or observational studies with limited evidence on effects.

Grade D evidence is based only on case studies or expert judgement or poor quality observational studies.

Assessment of the patient with suspected malaria (Boxes 1 and 2)

History and examination

The crucial issue in the management of malaria is consideration of the possibility of this diagnosis. Malaria should be suspected in anyone with a fever or a history of fever who has returned from or previously visited a malaria endemic area, regardless of whether they have taken prophylaxis. The minimum incubation period for naturally acquired infection is six days. Most patients with falciparum infection present in the first month or months after exposure; almost all present within six months of exposure. *Vivax* or *ovale* infections commonly present later than six months after exposure and presentation may be delayed for years. There are no specific symptoms of malaria: most patients complain of fever, headache and general malaise.¹⁰ Gastrointestinal disturbances, jaundice or respiratory symptoms occasionally occur and are often responsible for misdiagnosis. Most missed malaria infections are erroneously diagnosed as non-specific viral infections, influenza, gastroenteritis or hepatitis. Children are less likely than adults to complain of chills, arthralgia/myalgia or headaches and more likely to present with non-specific symptoms (fever, lethargy, malaise, somnolence): gastrointestinal symptoms (nausea, abdominal pain, vomiting, diarrhoea) are particularly common.^{11,12}

The physical examination of patients with uncomplicated malaria is often unremarkable apart from a fever which is not invariably present. Most patients have no

Box 1. Important considerations in the assessment of a patient with possible malaria.

- Malaria is a medical emergency and patients with suspected malaria should be evaluated immediately.
- Symptoms of malaria are often non-specific: fever/sweats/chills, malaise, myalgia, headache, diarrhoea, and cough.
- Falciparum malaria is most likely to occur within 3 months of return from an endemic area. The incubation period for malaria is at least 6 days.
- Malaria caused by other species may present more than a year after return from an endemic area.
- A careful exposure history is necessary: country and area of travel, including stopovers, and date of return.
- Consider what malaria prophylaxis was taken (i.e. drug, dose & adherence, premature cessation); appropriate prophylaxis with full adherence does not exclude malaria.
- Consider other travel-related infections: e.g. typhoid, hepatitis, dengue or other arboviruses, avian influenza, MERS-CoV, HIV, meningitis/encephalitis and viral haemorrhagic fevers (VHF).¹⁸
- Three negative diagnostic samples over a period of 24–48 h are necessary to exclude malaria.

specific fever pattern. Children are more likely to have hepatomegaly, splenomegaly and somnolence than adults.^{11,12} If the diagnosis of falciparum malaria has been delayed, severely ill patients may present with jaundice, confusion or seizures.

Investigation

If malaria is suspected, a blood test for malaria without delay is mandatory. Unless rapid malaria testing can be achieved in primary care, the patient should be referred to hospital for testing. Results should be communicated the same day: all positive tests should be telephoned back to the requesting doctor as soon as practicable and ideally within 4 h of the test reaching the laboratory. The most important test is examination of thick and thin blood smears by microscopy. This is highly sensitive and specific in expert hands. However, because of a lack of expertise in many UK labs, particularly out of hours, rapid diagnostic tests (RDTs) based upon detection of parasite antigens, are now commonly used in addition to blood slides. Although slightly less sensitive than good quality blood films examined by experienced microscopists, they are easier for the non-expert to use to detect falciparum infections and are useful as an initial screen if expertise in reading slides is not immediately available. RDTs are generally not as specific and sensitive for the detection of non-falciparum infections, although newer generation RDTs perform well in diagnosing vivax infection.^{13,14} RDTs may be used in addition to, but not as a replacement for blood films and all patients with suspected malaria should have blood films prepared and examined as recommended in the British Committee for Standards in Haematology guidelines.¹⁵ If falciparum or knowlesi malaria is diagnosed, the percentage of red blood cells that are parasitized should be estimated.

If there is clinical suspicion of malaria, but initial blood films are negative, repeat films, with or without RDT, should be examined after 12–24 h and again after a further 24 h. RDT use alone should be discouraged where good microscopy is available. Thrombocytopenia is suggestive of malaria in non-immune adults and children, both in non-falciparum malarias and in *P. falciparum*,^{16,17} although it can also occur in a number of other imported infections.

Malaria is unlikely if three negative specimens have been examined by a competent microscopist. Empirical therapy for malaria should not be given unless a patient with a convincing exposure history demonstrates features of severe malaria and expert advice has been taken. In pregnancy, thick films can be negative, despite the presence of parasites in the placenta. Expert advice should be sought if malaria is suspected. PCR techniques are used in reference laboratories to determine the species of malaria, but are not sufficiently standardised or validated to use for routine clinical diagnosis.

Cases of malaria should be notified to public health authorities. In England and Wales, thick and thin films and a blood aliquot should be sent to the Malaria Reference Laboratory for confirmation (which is performed free of charge). The Scottish Parasite and Diagnostic Reference Laboratory provides a reference service for Scotland. If malaria is diagnosed in a returned traveller, other members of the family or travelling group should be warned that they may have shared the same exposure risk and that they should seek medical attention if they develop symptoms.

Assessment and management of confirmed malaria

Malaria, particularly severe malaria, should always be managed in consultation with someone experienced in managing the disease.

General management and assessment

Non-falciparum malaria

The distinction between falciparum malaria and other species of malaria is important. Malaria caused by *Plasmodium ovale*, *P. vivax*, and *Plasmodium malariae* rarely causes life-threatening disease and can usually be managed on an outpatient basis, unless the patient has other comorbidities or cannot tolerate oral medication. However, severe presentations of *Plasmodium knowlesi* infection and *P. vivax* are well recognised and severe *P. ovale* can occur in exceptional circumstances and clinicians should look out for these rare cases.^{20–23}

Box 2. Common errors in diagnosis or management of malaria (adapted from Beeching NJ et al.¹⁹ with permission).

- Delayed patient presentation.
- Failure of health care worker to take a travel history or consider diagnosis of malaria.
- Belief that chemoprophylaxis prevents all malaria.
- Belief that malaria is unlikely if patient does not remember being bitten by mosquitoes.
- Belief that malaria presents with a classical fever pattern.
- Failure to recognise nonspecific clinical presentations of malaria.
- Failure to obtain immediate blood films or RDT.
- Failure to repeat diagnostic tests if first tests are negative.
- Failure to prescribe adequate and appropriate chemotherapy immediately.
- Failure to anticipate or treat complications.

Estimation of the haemoglobin concentration should be done, and in malaria caused by *P. vivax* or *P. ovale*, glucose-6-phosphate dehydrogenase (G6PD) activity should be measured, as concomitant primaquine therapy will be necessary to eliminate hypnozoites (dormant forms) from the liver. Primaquine can cause haemolysis in patients with G6PD deficiency. Patients with a mixed infection that includes falciparum parasites or with an infection with an unidentified species should be treated as though they had falciparum infection in the first instance.

Falciparum malaria

Patients with falciparum malaria should usually be admitted to hospital initially because of the risk of deterioration even after effective treatment has been initiated. There is limited evidence that some patients with falciparum malaria can be managed safely as outpatients in units that see large numbers of patients and use well defined protocols for assessment and follow up.^{24–27} Certain factors such as age, ethnicity and parasite count can predict the likelihood of severe malaria, but even patients who might be expected to be semi-immune may deteriorate rapidly and require intensive care treatment.^{28–31} Outpatient management of malaria in adults should only be undertaken by clinicians experienced in managing malaria with clear protocols and systems for assessing the likely risk of severe malaria and for rapidly reassessing patients. Children with falciparum malaria should be observed in hospital initially for at least 24 h, because of the possibility of rapid progression and also to ensure that

they are tolerating oral therapies; treatment in children may be complicated by vomiting.^{32,33} Patients should be observed closely; certain categories such as pregnant women, infants and the elderly are more likely to develop severe disease or to deteriorate rapidly.^{29,34,35} The management of patients with falciparum malaria, especially if severe, should always be discussed with a specialist; mortality is higher in regions of the UK where malaria is less commonly managed.²⁹ 26% of UK malaria cases are seen in centres with less than 10 cases a year.³⁶

Patients with falciparum malaria (or a mixed infection which includes falciparum parasites) can be divided into those with uncomplicated and those with severe or complicated disease (Box 3). Assessment of the patient should include careful clinical evaluation and review of investigations for the features of severe malaria detailed below. A full blood count, urea, creatinine and electrolytes, liver function tests and blood glucose should be done routinely. Thrombocytopenia is common and in isolation does not reflect severe disease. In ill patients, blood gases, blood culture, lactate and clotting studies should be also performed. Urine dipstick and culture, stool culture and chest X-ray may be appropriate. Lumbar puncture to exclude meningitis should be considered in febrile patients with impaired consciousness or repeated seizures.

The initial parasite count is helpful in estimating the potential future severity of disease. Although highly dependent upon the stage of the infection, if more than 2% of red blood cells are parasitized, there is an increased chance of developing severe disease even if the patient initially

Box 3. Major features of severe or complicated falciparum malaria in adults.

- Impaired consciousness or seizures.
- Renal impairment (oliguria <0.4 ml/kg bodyweight per hour or creatinine >265 µmol/l).
- Acidosis (pH < 7.3).
- Hypoglycemia (<2.2 mmol/l).
- Pulmonary oedema or acute respiratory distress syndrome (ARDS).
- Haemoglobin ≤80 g/L.
- Spontaneous bleeding/disseminated intravascular coagulation.
- Shock (algid malaria – BP < 90/60 mmHg).
- Haemoglobinuria (without G6PD deficiency).
- Parasitaemia >10%.

appears well, and a 10% parasitaemia is considered to represent severe disease. Other important poor prognostic factors are: the presence of peripheral blood schizonts of *P. falciparum*, pigment deposits in peripheral polymorphonuclear leucocytes on the blood film,^{37,38} metabolic acidosis or an elevated lactate level,^{39–41} older age, coma and renal impairment.^{42,43}

Treatment of uncomplicated falciparum malaria in adults

There are now three main therapeutic options for the treatment of uncomplicated falciparum malaria in adults in the UK: artemisinin combination therapy (ACT), oral atovaquone–proguanil or quinine plus doxycycline (or quinine plus clindamycin in certain circumstances) (see [Box 4](#) for details of doses). Two ACTs are licenced for use in the UK; artemether–lumefantrine or dihydroartemisinin–piperaquine. Although mefloquine is an effective treatment, the side effects and high rate of non-completion of courses⁴⁴ means that we do not recommend this as therapy in the UK.

ACTs are highly effective and clear parasites more rapidly than other options because they are effective throughout a broader range of the parasite life cycle.⁴⁵ For this reason, they are now considered to be the drugs of choice in uncomplicated malaria (Grade 1A). Studies comparing ACTs with oral quinine in Africa have demonstrated greater efficacy using ACTs, driven partly by poor compliance with quinine.⁴⁶ There has been most experience with artemether–lumefantrine in a Western setting and this seems to be well tolerated.^{47,48} Artemether–lumefantrine is ideally taken with a high fat meal to maximise absorption and is considered the ACT of choice (Grade 2C). Both ACTs need to be given for only three days. Although DHA piperazine (DHA-PPQ) has the advantage of only needing single daily dosing, there has been concern about the potential for QTc prolongation with DHA-PPQ. Until further data become available, it is recommended that DHA-PPQ is taken more than 3 h after food and that patients should not eat for 3 h after doses of DHA-piperazine to prevent excessive peak piperazine levels. DHA-PPQ should not currently be used in patients with previous arrhythmias, cardiac conditions that predispose to arrhythmia, or those taking drugs that prolong the QT interval. ECGs should be obtained early in the course of treatment with DHA-PPQ and before and after the last daily dose of DHA-PPQ; more frequent monitoring may be indicated in those taking drugs which inhibit CYP3A4 and potentially increase piperazine levels, such as clarithromycin.

Atovaquone–proguanil (Malarone[®]) has been used extensively in some Western settings with high levels of efficacy, although parasite clearance is relatively slow (66% at three days).^{47,49} Almost a quarter of patients experienced gastro-intestinal side-effects and patients should be warned about these to ensure full adherence.

In contrast to the three day regimens for ACTs and atovaquone–proguanil, quinine needs to be taken for five to seven days, or until parasites have cleared, which requires daily monitoring. Quinine is often associated with “cinchonism” (nausea, deafness and ringing in the ears), which may result in poor adherence. Although international recommendations suggest that quinine should be taken for seven days in endemic areas,⁵ UK experience suggests that five days treatment is adequate for the vast majority of cases when combined with a second drug (doxycycline for adults or clindamycin in pregnant women and young children) to ensure complete eradication of parasites. The second drug can be taken either simultaneously with quinine or sequentially after the quinine. In view of increasing failure rates of anti-folate drugs in most part of the world, sulfadoxine-pyrimethamine (Fansidar[®]) should not be used routinely as a second drug to accompany quinine, except on specialist advice. Chloroquine should NOT be used for the treatment of falciparum malaria. Antibiotics, including tetracyclines, sulfa drugs, macrolides and clindamycin, should only be used in combination therapies and not used alone for the treatment of malaria. There is insufficient evidence to support the use of azithromycin either alone or in combination with other drugs for the treatment of malaria.⁵⁰

Treatment of severe or complicated falciparum malaria

Antimalarial therapy

Urgent appropriate parenteral therapy with antimalarials has the greatest impact on prognosis in severe malaria. Treatment should not be delayed in patients with proven or strongly suspected malaria. Parenteral treatment is indicated in all patients with severe or complicated malaria, those at high risk of developing severe disease ([Box 5](#)) or if the patient is vomiting and unable to take oral antimalarials.

Artesunate

There is now substantial evidence for the superiority of intravenous artesunate over intravenous quinine with two

Box 4. Treatment regimens for uncomplicated falciparum malaria in adults.

- Artemether–lumefantrine: If weight >35 kg, 4 tablets then 4 tablets at 8, 24, 36, 48 and 60 h (Recommended).
- DHA-piperazine: 36–60 kg 3 tablets daily for three days >60 kg 4 tablets daily for three days.
- Atovaquone–proguanil: 4 ‘standard’ tablets daily for 3 days.
- Oral quinine sulphate 600 mg 8 hourly for 5–7 days plus doxycycline 200 mg daily (or clindamycin 450 mg 8 hourly for pregnant women) for 7 days.

Box 5. Other indications for parenteral therapy in adults.

- Parasitaemia >2% red blood cells parasitized.
- Pregnant women following specialist advice.
- Patients unable to swallow/retain tablets.

large trials and a meta-analysis combining with other smaller trials demonstrating a mortality benefit in adults and children^{51–53} for all patients with severe malaria. Intravenous artesunate is therefore considered the treatment of choice for severe malaria. (Grade 1A).

The manufacturers of intravenous artesunate have not achieved good manufacturing practice (GMP) certification and artesunate is not licenced in the European Union (2015). However, the factory manufacturing artesunate has achieved WHO prequalification standards and some importers of artesunate also carry out quality checks on imported batches. Intravenous artesunate is now stocked by many infectious diseases units in the UK and can also be obtained from specialist tropical disease centres in London and Liverpool (see below for contact details). We recommend that any centre regularly seeing patients with severe malaria should stock artesunate. However, treatment should never be delayed whilst obtaining artesunate: every patient with severe malaria should start quinine initially if artesunate is not immediately available as delay is very dangerous (Grade 1A). There is no additional benefit from using artesunate in combination with quinine but it is safe to do so.⁵⁴

Following a minimum of 24 h of intravenous artesunate, and once patients have improved and are able to take oral medication, a full course of an ACT (artemether–lumefantrine or DHA-PPQ) should be given. Alternatively, a full course of quinine and doxycycline (clindamycin in children/pregnant women) or atovaquone–proguanil could be used. Clearance of parasites should be checked by daily thick blood films.

There has been increasing experience with the use of intravenous artesunate in Western non-immune travellers, demonstrating rapid effectiveness and generally low adverse event rates compared to quinine.^{55,56} However, there is clear emerging evidence of delayed haemolysis

(7–21 days post treatment) following intravenous artesunate in approximately 10–15% of adults or children, especially those with high parasite counts.^{57–59} This appears to be self-limiting but patients should be warned to be aware of potential symptoms of anaemia and their haemoglobin level should be routinely checked approximately 14 days after completing artesunate (Grade 2C).

The emerging evidence of reduced susceptibility to artemisinin derivatives in SE Asia⁶⁰ does not alter our current recommendations for the use of artesunate as first line therapy for this region (Grade 2C). However, as with all cases of severe malaria, monitoring of clearance of parasites and for recurrence of symptoms is recommended.

Artemether is an oil-based intramuscular artemisinin preparation, which is produced to GMP standards. However, despite generally favourable trends, several studies and meta-analyses have not shown a clear advantage of artemether over quinine in the management of severe malaria in either adults or children^{61–63} and we do not recommend its use (Grade 1B).

Quinine

Intravenous quinine dihydrochloride is an alternative if artesunate is not immediately available. It should be given as an intravenous infusion with an initial loading dose of 20 mg/kg in 5% dextrose or dextrose/saline over 4 h to achieve high blood levels rapidly⁶⁴ (see Box 6). This should be followed by 10 mg/kg infused over 4 h every 8 h. A loading dose should not be given if quinine or mefloquine therapy has been taken within the previous 12 h (Grade 2C).⁶ Caution should be exercised in older patients or those with cardiac disease, because of the potential for quinine to lead to arrhythmias. These patients should have ECG monitoring during intravenous quinine treatment.

When the patient is well enough to take oral medication, treatment should be completed with a full course of an oral

Box 6. Drug treatment of severe or complicated malaria.

- Artesunate regimen: 2.4 mg/kg given as an intravenous injection at 0, 12 and 24 h then daily thereafter. After completion of a minimum of 24 h therapy (maximum five days), a full course of an oral ACT should be taken when the patient can tolerate oral medication.
- Quinine: loading dose of 20 mg/kg quinine dihydrochloride in 5% dextrose or dextrose saline over 4 h. Followed by 10 mg/kg every 8 h for first 48 h (or until patient can swallow). Frequency of dosing should be reduced to 12 hourly if intravenous quinine continues for more than 48 h.
- Parenteral quinine therapy should be continued until the patient can take oral therapy when quinine sulphate 600 mg should be given three times a day to complete five to seven days of quinine in total.
- Quinine treatment should always be accompanied by a second drug: doxycycline 200 mg (or clindamycin 450 mg three times a day for children or pregnant women), given orally for total of seven days from when the patient can swallow.

Box 7. Intensive care management of severe or complicated malaria.

- Careful management of fluid balance to optimise oxygen delivery and prevent pulmonary oedema.
- Regular monitoring for hypoglycemia.
- Consider broad spectrum antibiotics if evidence of shock or secondary bacterial infection.
- Haemofiltration for renal failure or control of acidosis or fluid/electrolyte imbalance.
- Consider medication to control seizures.

agent (Box 4). If quinine is used, a total combined IV and oral course of seven days is appropriate. If intravenous quinine needs to be continued for longer than 48 h, or the patient is in renal failure or has severe hepatic dysfunction, quinine doses should be reduced by a third.^{5,65}

Neither quinine nor artesunate levels are affected by haemofiltration; dose modification is not necessary.

Supportive management^{5,66}

All patients with severe or complicated malaria should be managed in a high dependency unit. Patients may deteriorate rapidly and close observation is vital. Transfer to an intensive care unit should be considered for those with severe acidosis, high lactate levels, pulmonary oedema/acute respiratory distress syndrome, complicated fluid balance problems or renal impairment and those deteriorating despite appropriate treatment (Box 7). Careful fluid balance is important to avoid over-filling, which may exacerbate the increased pulmonary capillary permeability that occurs in severe malaria (Grade 2C). There is evidence that measurement of the central venous pressure is not useful in predicting true volume status in severe malaria and much of the lactic acidosis seen in severe malaria may be due to microvascular obstruction rather than hypovolaemia.⁶⁷ Hypoglycemia may occur in severe malaria, complicated by quinine-induced hyperinsulinemia which may develop late in the clinical course, even after the patient appears to be recovering.^{68,69} Blood glucose levels (using a "stix" method) should be checked routinely every 4 h (Grade 2C), two-hourly during quinine infusion (Grade 2C) and at any time that reduced consciousness occurs (Grade 1A). Infusion of 10% dextrose may be necessary to correct hypoglycemia.

Haemoglobin, clotting, electrolytes (including calcium and sometimes magnesium) and renal function should be closely monitored. Frequent parasite counts are not helpful in the early management of severe malaria; the peripheral parasite count will fluctuate according to the stage of parasite development and it is not uncommon for the parasite count to increase in the first 24–36 h of treatment: this does NOT indicate failure of therapy.³¹ Daily parasite counts are sufficient and are recommended to ensure clearance.

Some patients develop shock which may be secondary to complicating bacteraemia/septicaemia ("algid malaria"). Patients with signs of shock should be treated with a broad spectrum antibiotic (Grade 1C). Platelet transfusion is not indicated even with low counts unless there is active bleeding. Appropriate ventilatory support or renal replacement therapy should be initiated if clinically indicated: haemofiltration appears to be superior to peritoneal dialysis.⁷⁰ Patients with impaired consciousness or coma should be managed appropriately. Corticosteroids, mannitol, N-

acetylcysteine and levamisole have all been shown to be ineffective as adjunctive therapies for the treatment of severe malaria.^{71–75}

Exchange transfusion

The role of exchange transfusion in the management of severe malaria has always been controversial, with no clear evidence of benefit and potential risks, especially in individuals who may have haemodynamic instability.^{76,77} Artesunate has its greatest mortality advantage in those with high parasite counts. The rapid action of artesunate in reducing parasite burden means that any benefit of exchange transfusion is likely to be substantially reduced.⁷⁸ Current opinion is that exchange transfusion is now no longer indicated in severe malaria (Grade 2C). Routine blood transfusion may be indicated in those with symptomatic anaemia.

Malaria in the elderly

There is clear evidence that risks of both falciparum and vivax malaria leading to mortality increase steadily with age over 65.²⁹ All elderly patients should be admitted, and monitored closely.

Pregnant women

Malaria in pregnancy carries a higher risk of severe disease and is also associated with miscarriages or stillbirths. Pregnant women with malaria require prompt treatment and should be managed in collaboration with the obstetric team. Close observation in hospital, including uterine and foetal heart monitoring for development of complications, is necessary and early delivery of a near-term infant at risk may need to be considered. The RCOG has produced specific guidelines for the treatment of malaria in pregnancy.⁷⁹

Uncomplicated falciparum malaria. Neither artemether–lumefantrine (Riamet[®]), atovaquone–proguanil (Malarone[®]) or DHA-PPQ are licenced in pregnancy. There is no evidence of adverse effects of artemether–lumefantrine in the second and third trimester from a limited number of studies.⁸⁰ Data on safety in the first trimester are even more limited but no evidence of harm has been detected. Small studies on atovaquone–proguanil have shown no evidence of adverse effects. Artemether–lumefantrine is considered the treatment of choice in the second and third trimester (Grade 2B) (information on DHA-PPQ is currently more limited). Quinine (seven days) in combination with clindamycin (see dose above) can be used in all

three trimesters. Quinine can increase the risk of uterine contraction and hypoglycemia.

Severe malaria. Severe malaria in pregnancy is associated with high case fatality rates, pregnancy loss and hypoglycemia and pulmonary oedema are particularly common.⁶ There is little published evidence of the use or safety of intravenous artesunate in pregnant women, particularly in the first trimester. On balance of risk, artesunate is preferred to quinine on the basis of its likely higher effectiveness in reducing mortality (Grade 1C). Intravenous quinine (with clindamycin) is an alternative.

Management of malaria in children

Uncomplicated falciparum malaria in children

Oral quinine, atovaquone–proguanil (Malarone[®]), artemether–lumefantrine and DHA-PPQ can all be used for the

treatment of uncomplicated malaria in children (Box 8). There is limited experience in the use of artemisinin combination therapies in a non-endemic paediatric population, although ACTs are recommended as first-line treatment of uncomplicated malaria in children in malaria endemic regions. Despite this, on the basis of evidence from endemic areas, the committee believes that an ACT should be first line therapy for children in the UK (Grade 1A). The combination of oral quinine with seven days of clindamycin or doxycycline (for children greater than 12 years age) remains highly effective in the UK, with very low relapse rates in children. In contrast to the views of some authors,^{6,81} we believe that oral quinine is usually well-tolerated by children and should be used for the treatment of uncomplicated falciparum malaria in the UK if an ACT is not available.^{81,82} Tetracyclines should not be given to children under 12 years of age because of risk of dental hypoplasia and permanent discolouration of teeth.

Box 8. Paediatric doses of antimalarial drugs.

Drug	Dose	
Atovaquone–proguanil	Over 40 kg	4 'standard' tablets daily for 3 days
	31–40 kg	3 'standard' tablets daily for 3 days
	21–30 kg	2 'standard' tablets daily for 3 days
	11–20 kg	1 'standard' tablet daily for 3 days
	9–10 kg	3 'paediatric' tablets daily for 3 days
	5–8 kg	2 'paediatric' tablets daily for 3 days
Artemether-lumefantrine	>35 kg	4 tablets then 4 tablets at 8, 24, 36, 48 and 60 h
	25–35 kg	3 tablets then 3 tablets at 8, 24, 36, 48 and 60 h
	15–24 kg	2 tablets then 2 tablets at 8, 24, 36, 48 and 60 h
	5–14 kg	1 tablet then 1 tablet at 8, 24, 36, 48 and 60 h
Dihydroartemisinin-piperaquine (DHA-PPQ) (WHO recommended regimen; different from SPC)	>35–60 kg,	3 'standard' tablets then 3 'standard' tablets at 24 and 48 h
	25–35 kg	2 'standard' tablets then 2 'standard' tablets at 24 and 48 h
	17–24 kg	1.5 'standard' tablets then 1.5 'standard' tablets at 24 and 48 h
	11–16 kg	1 'standard' tablets then 1 'standard' tablets at 24 and 48 h
	8–10 kg	0.75 'standard' tablets then 0.75 'standard' tablets at 24 and 48 h
5–<7 kg	0.5 'standard' tablets then 0.5 'standard' tablets at 24 and 48 h	
Oral quinine <i>and</i> clindamycin <i>or</i> doxycycline (if >12 years old)	10 mg/kg (of quinine salt)	8 hourly for 7 days
	7–13 mg/kg/dose	8 hourly for 7 days
	200 mg	once daily for 7 days
Intravenous quinine	See dosing in Box 6 (maximum quinine concentration in infusion fluid should be 2 mg/ml)	
Intravenous artesunate	See dosing in Box 6 (2.4 mg/kg IV at 0, 12 and 24 h followed by daily until able to swallow oral medications). Children under 20 kg should receive higher doses (3 mg/kg)	

Box 9. Severe or complicated malaria in children.

- Impaired consciousness or seizures.
- Respiratory distress or acidosis (pH < 7.3).
- Hypoglycemia (2.2 mmol/l).
- Severe anaemia (<8 g/dl).
- Prostration.
- Parasitaemia >2% red blood cells parasitized.

Severe and complicated falciparum malaria in children (Box 9)

The main clinical presentations of severe malaria in children are cerebral malaria, severe anaemia and respiratory distress/acidosis. Features of cerebral malaria include depressed conscious level, seizures, altered respiration and posturing (decorticate or decerebrate). Hypoglycemia, metabolic acidosis, circulatory shock and electrolyte disturbance may also be present. Prostration (the inability to stand or sit) is also an indicator of severe disease in children.

Management of severe or complicated malaria in children involves emergency assessment and provision of supportive care including respiratory and cardiovascular support as outlined by Maitland et al.⁸¹ Children with severe or complicated malaria should be managed in a paediatric intensive care unit or high dependency unit together with support/advice from a paediatric infectious diseases/tropical medicine specialist who has experience in managing malaria. Judicious and slow volume resuscitation is important in those children presenting with shock; the FEAST trial showed a detrimental effect of routine fluid bolus administration.⁸³ Hypoglycemia is a common complication of severe malaria; serial blood glucose estimations must be performed, and hypoglycemia corrected using 5–10% glucose in maintenance fluid.⁶⁸ As it is often difficult to exclude or differentiate concurrent bacterial septic shock or meningitis from severe malaria, empirical broad spectrum antibiotics should be given to children with severe malaria until bacterial infection can be excluded⁸⁴ (Grade 1B). Management of seizures should follow the evidence-based guidelines advocated by the Advanced Paediatric Life Support Group.⁸⁵ Blood transfusions may be required for severe anaemia, although a Cochrane review found that routine transfusion did not reduce mortality, but caused more adverse events.⁸⁶

Clear evidence from a large randomised trial now shows that although quinine remains effective, artesunate is associated with a survival advantage (relative risk reduction of 22.5%) and a significant reduction in clinical complications (development of coma, convulsions and deterioration of coma score).⁵² In line with the WHO guidelines, we recommend that IV artesunate should be used preferentially over quinine as the drug of choice for treatment of severe falciparum malaria in children (grade 1A). Recent WHO guidelines suggest that a higher dose is required for children under 20 kg.⁵ Intravenous quinine is still indicated if artesunate is not immediately available

and treatment should not be delayed whilst awaiting artesunate therapy.

Treatment of non-falciparum malaria

Treating the acute infection

The treatment of non-falciparum malaria consists of treating the erythrocytic asexual forms that cause symptoms and, for infections with *P. vivax* and *P. ovale*, also ensuring eradication of liver hypnozoites to prevent relapse of infection (Box 10). If a mixed infection of either vivax or ovale with falciparum has been treated, there is no need for an additional drug to treat the blood forms of non-falciparum infection, but relapse due to the liver forms will still need to be prevented. Either an oral ACT or chloroquine (25 mg/kg in total over 3 days) can be used to treat the blood forms of all non-falciparum species (Grade 1B). Fever and parasite clearance times are faster with most ACT regimens than chloroquine in non-falciparum malaria; most of the evidence comes from studies in vivax.^{87,88} Chloroquine is highly effective against *P. malariae*, *P. ovale* and *P. knowlesi* and is effective in most cases of vivax malaria.

Chloroquine resistance leading to poor clinical outcomes of chloroquine treatment has been recognised in vivax malaria since 1992. This is an uncommon but increasing problem, particularly in the regions of Papua New Guinea and Indonesia.^{52,89,90} Chloroquine can still be used for vivax infections from such regions with appropriate follow-up but an ACT may be preferred (Grade 1B). ACT regimens should be first line therapy if falciparum malaria cannot be reliably excluded or for treatment of mixed infections that include *P. falciparum*. They also provide an alternative for individuals with non-falciparum malaria who cannot tolerate chloroquine.

Cases of severe or complicated non-falciparum malaria should be treated with parenteral artesunate or quinine as for severe falciparum malaria. Artesunate appears to be highly effective for severe *P. knowlesi* infections.²²

Non-falciparum malaria in pregnancy

Chloroquine is a safe option for treatment of non-falciparum malaria throughout pregnancy. ACTs can be used in the second and third trimesters. Quinine may be used in the first trimester if there is concern about resistant vivax.

Box 10. Treatment of non-falciparum malaria (*expressed as mg base).**Acute treatment**

Chloroquine	Adult	Initial dose 620 mg (*) 310 mg 6–8 h later 310 mg on days 2 and 3	Treatment of acute vivax, ovale, malariae and knowlesi malaria
	Child	Initial dose 10mg/base then 5 mg/kg base 6–8 h later and on days 2 and 3	
Artemether–lumefantrine OR DHA-PPQ		As for uncomplicated falciparum	Treatment of acute vivax, ovale, malariae and knowlesi malaria; dual infection with falciparum or uncertain species Treatment of resistant vivax malaria
Parenteral artesunate (or quinine)		As for complicated falciparum	Complicated single or dual infection

Preventing relapse

Primaquine	Adult	15 mg (0.25 mg/kg) as a single daily dose for 14 days	Prevention of relapse in ovale malaria
	Child	0.25 mg/kg as a single daily dose for 14 days	
Primaquine	Adult	30 mg (0.5 mg/kg) as a single daily dose for 14 day	Prevention of relapse in vivax malaria
	Child	0.5 mg/kg as a single daily dose for 14 days	
Primaquine	Adult	0.75 mg/kg as a single weekly dose for 8 weeks	Prevention of relapse in vivax or ovale malaria in patients with mild- moderate G6PD deficiency
	Child	0.75 mg/kg (max 45 mg) as a single weekly dose for eight weeks	

Prevention of relapse in ovale or vivax malaria

Late presentation or relapse due to hypnozoites in the liver occurs in more than 25% of patients with vivax malaria treated with chloroquine alone.⁹¹ Blood schizonticides such as chloroquine, and all other drugs currently used for treating acute malaria, do not eliminate these liver stages, so a second drug is required to achieve “radical” cure. Primaquine is the drug of choice for elimination of hypnozoites in ovale or vivax malaria (Grade 1A). **Patients should be screened for G6PD deficiency before primaquine treatment, as primaquine may cause haemolysis in G6PD deficient individuals.** The efficacy of primaquine in preventing relapse is highly dependent upon co-administration with chloroquine or an alternative drug to clear the red cell forms.^{91,92} Primaquine also has intrinsic activity against asexual blood forms of *P. vivax* and *P. ovale*, and concomitant administration with chloroquine boosts blood primaquine levels.^{91,93} Administration of the two drugs should therefore overlap (Grade 1C). In centres that commonly see patients with vivax malaria, systems for rapid assessment of G6PD status should be set up.

The standard therapeutic dose of 15 mg primaquine base/day for 14 days is appropriate for the radical treatment of *P. ovale*. However, certain geographical strains of *P. vivax* have long been recognised to be less sensitive to

primaquine and to require higher doses of primaquine to prevent relapse.⁹⁴ There has also been increasing evidence of failure of standard dose primaquine from other geographical areas: clinical relapse occurs in the UK in more than 10% of patients with imported vivax treated with chloroquine followed by unsupervised primaquine 15 mg daily for 14 days.⁹⁵ Higher dose primaquine 30 mg daily (0.5 mg/kg) is more effective than 15 mg daily in South Asia, the source of most UK infections.^{91,96} Administration of primaquine therapy for less than 14 days is associated with higher relapse rates than 14 day regimens.⁹⁷ We therefore recommend that in vivax malaria, primaquine should be given at a dose of 30 mg daily for 14 days to prevent relapse along with treatment with chloroquine. (Grade 1C).

In pregnant or breastfeeding women, weekly suppressive chloroquine prophylaxis (500 mg each week) should be given until primaquine can be given following delivery or completion of breastfeeding.

Expert opinion should be sought when treating patients with G6PD deficiency. In those with mild to moderate G6PD deficiency, alternative regimens of 45 mg (0.75 mg/kg) primaquine weekly for eight weeks may be effective and safely tolerated^{98–101} (Grade 2C). In some cases, particularly those who have previously suffered severe adverse effects of primaquine, it may be prudent to withhold primaquine treatment, but to treat relapses promptly.

Box 11. What to tell the patient.

- Reassure patients they are not infectious to others.
- Discussion about informing fellow travellers of potential risk of having caught malaria and need to present early if symptoms develop.
- Inform patient that he/she will be notified to public health authorities as part of routine national policy.
- Warn patients about possible recrudescence or relapse of malaria following treatment and to report recurrence of fever to their general practitioner.
- Warn patients treated with artesunate about possible haemolysis and the importance of attending for follow-up blood tests.
- At follow up, review results of any tests needed or performed for other travel related infections including HIV infection.
- Discuss period of exclusion from blood donation after malaria – blood donors need to inform and discuss own situation with National Blood Service.
- Reinforce need for up to date advice on malaria prevention during all future travels, for patient and family, and provide information on sources of advice.

Public health implications

There is a statutory obligation to notify all cases of malaria promptly to the appropriate Public Health authorities. The diagnosis should also be verified by the Malaria Reference Laboratory or, in Scotland, by the Scottish Parasite and Diagnostic Reference Laboratory. (Contact details below).

Information for patients and post-treatment follow-up

Patients and their relatives should be provided with a full explanation of the condition and specific issues related to their therapy, including warnings about possible immediate and late complications of their treatment (Box 11). Although there are no systematic studies on the value of early follow-up of patients following treatment for imported malaria, the Committee believes that it is good practice to repeat a blood film and full blood count approximately fourteen days after treatment, particularly if patients have had severe malaria or received artemisinin therapy. It also provides a further opportunity to reinforce the need for appropriate antimalarial precautions to be taken by the patient and his or her relatives next time they travel (<https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk>).

Useful contacts

Malaria Reference Laboratory <https://www.gov.uk/government/publications/malaria-reference-laboratory-mrl-user-handbook>.

Scottish Parasite and Diagnostic Reference Laboratory <http://www.nhs.gov.uk/about-us/professional-support-sites/scottish-microbiology-reference-laboratories/scottish-parasite-diagnostic-reference-laboratory/>
Hospital for Tropical Diseases, UCH, London. 020 3456 7890.

Tropical and Infectious Disease Unit, Royal Liverpool University Hospital. 0151 706 2000.

Conflict of interest

None declared.

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