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CLINICAL REVIEW

Investigation and treatment of imported malaria in non-endemic countries

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Every year, several thousand people with malaria arrive in non-endemic countries, and about 1600 arrive in the United Kingdom alone. Case fatality in the UK, as elsewhere, is around 1% overall but varies by age and previous exposure to malaria.[1-3] This rate is similar to that seen in endemic countries, but the age profile of deaths is very different. In Africa mortality is highest in young children, but in imported cases it is highest in older patients, especially those over 65 years.[4-6] If malaria is treated early, with widely available drugs before it becomes severe, death is avoidable and a full recovery almost guaranteed. Late presentation carries a higher risk of death. The management of severe malaria is a medical emergency. This review describes how to recognise and diagnose malaria, the current treatment of uncomplicated malaria, and the management of patients with severe disease. It concentrates on adults and recent advances relevant to non-endemic high resource countries such as Europe and North America. Different challenges arise in low resource endemic settings and are not covered in this review.

What is malaria?

Malaria is a tropical parasitic disease of red blood cells transmitted by anopheles mosquitoes. Five species affect humans. The most serious, and in Europe the most common, imported form is *Plasmodium falciparum* malaria, which causes most deaths from imported malaria. The other common imported form is *P vivax* malaria. It is generally less severe but can recur several months after treatment owing to relapse from hypnozoites ("sleeping" parasites) in the liver. *P ovale* malaria is similar to *P vivax* malaria, as is *P malariae* malaria although it does not relapse. *P knowlesi* is a monkey malaria parasite that has recently been recognised to infect humans and is rare in imported cases.

Who is at risk of acquiring and dying from malaria?

Several countries that are frequented by tourists and people visiting friends and relatives have regions where the average person gets clinical malaria four or more times a year. One observational study found that around one in five travellers with a history of fever returning from sub-Saharan Africa had malaria.[7] Rates are much lower (maybe 1/100) in unwell travellers returning from malaria endemic Asia and Latin America, although the risk of malaria varies widely in these continents.[6] Failure to take effective prophylaxis is associated with acquiring malaria in several observational studies. Travellers whose families emigrated from malaria endemic countries, and who are visiting friends and relatives, are at particularly high risk of acquiring malaria, especially those of west African heritage.[2] People who travelled to visit friends and relatives account for around 65% of all malaria cases in the UK, and their reported chemoprophylaxis use is lower than for other travellers. Vivax malaria, the form of malaria most commonly imported from Asia and Latin America, had been declining over the past two decades in the UK.[8]

Observational studies of imported febrile illnesses in travellers have shown that malaria remains one of the most common potentially life threatening causes of fever in travellers.[9] Such studies also show that increasing age, delay to diagnosis,[6] and presenting in an area where malaria is seldom seen or treated increase the risk of dying from falciparum malaria once acquired (evidence from the UK only).[6] Although in Africa most deaths are in children, in non-endemic high resource settings observational studies show that older people have the greatest risk of dying from malaria if acquired, with minimal risk in children and young adults and a steadily increasing risk over the age range; case fatality in those over 65 years is 4.6% in the UK.[5 6]

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Summary points

- Malaria is a common cause of fever in people returning from the tropics
- Falciparum malaria is potentially fatal unless treated early, and patients over 65 years are at particular risk
- In most cases, vivax malaria can be treated with chloroquine in the outpatient setting
- Resistance to antimalarial drugs used to treat falciparum malaria is widespread
- Artesunate is the drug of choice for severe malaria, but if this is not available do not delay treatment with quinine

Sources and selection criteria

We searched the Cochrane Library and PubMed for recent relevant trials and observational studies on imported malaria. The search was supplemented where relevant by data from the UK Malaria Reference Laboratory and expert opinion from the PHE Advisory Committee on Malaria Prevention in UK Travellers (ACMP) and World Health Organization expert guidelines. Good epidemiological data are available on imported malaria in Europe and North America and on diagnostic tests. There are high quality trials of malaria treatment in endemic countries but few large well conducted trials of treatment in travellers, so data on treatment have to be extrapolated from endemic settings.

How to recognise malaria in adults

The symptoms and signs of malaria are non-specific and overlap with many other common infections. Influenza is a common misdiagnosis, and case reports show that malaria has also been misdiagnosed as gastroenteritis, hepatitis, and lower respiratory tract infection.[10] The key to diagnosing malaria is to take a travel history for all patients and request a malaria test in anyone who feels unwell and has recently been to an endemic country. A history of fever will be present in most patients with malaria, but around half will have no fever at the time of presentation; absence of fever cannot exclude disease.[7] Headache, malaise, and rigors are common symptoms but not invariable. Certain symptoms and signs of severe or potentially complicated malaria—such as jaundice, seizures, or rapid breathing—can result in the misdiagnosis of malaria—for example, as hepatitis (table 1⇓). It is therefore essential to exclude malaria with a thick and thin blood film rather than rely on clinical diagnosis based on symptoms; attempts to produce algorithms that reliably predict malaria on the basis of symptoms have been unsuccessful.[11] In patients returning from malaria endemic countries, any symptom or sign compatible with an infection should raise the possibility of malaria. Although most cases of falciparum malaria present within three months of return, case reports and Public Health England data show that some cases in travellers present up to a year after return, and many cases of non-falciparum malaria occur over a year later.[12]

How is malaria diagnosed?

The gold standard for malaria diagnosis in clinical practice remains microscopic examination of a blood film. Good rapid diagnostic tests for falciparum malaria with sensitivity and specificity above 97%, and fairly good ones for non-falciparum malaria,[13] are now widely available to hospitals in Europe. Most, however, are not as sensitive as an experienced microscopist and give no information about parasite density, which is important for prognosis and treatment decisions. Therefore these rapid tests should be seen as an adjunct to, rather than an alternative to, conventional microscopic diagnosis, and their sole use is not recommended. Newer polymerase chain reaction based diagnostic methods are currently used only in research settings, although they will probably become clinically useful in non-endemic settings within the next decade, especially to detect mixed infections and potentially drug resistant cases.[14]

What are the indicators of severe or complicated disease in adults?

Once malaria is diagnosed, the priority is to determine the severity of disease because this determines treatment. Table 1 shows modified World Health Organization indicators of severe disease; patients with any one of these will need parenteral treatment with antimalarial drugs. HIV positive patients have an increased risk of severe malaria and of drug interactions.[15] Observational studies have shown that three severe syndromes predominate in adults: cerebral malaria—in practice, malaria with reduced level of consciousness, neurological signs, or seizures; renal failure; and acute lung injury (or acute respiratory distress syndrome).[16] Disseminated intravascular coagulation and shock are less common and seldom occur in isolation. In addition, jaundice (due to recent major haemolysis) or a parasite count in the blood of greater than 2%, even if the patient does not appear clinically unwell, is a sign that severe malaria is more likely to develop.

What are the indicators of severe or complicated disease in children?

Multicentre observational studies, mainly from Africa, have shown that anaemia, raised respiratory rate due to acidosis (rather than lung injury), and cerebral malaria are the most common signs of severity in young children, although this pattern varies by age, with cerebral malaria becoming more common in older children.[17]

What about malaria in pregnancy?

Treat pregnant women as having potentially complicated malaria, although not all will need parenteral treatment. The risks associated with severe disease are greater than in non-pregnant women, and there are serious risks to the pregnancy, including miscarriage, in otherwise non-severe disease.[18] The management of malaria in pregnancy has particular challenges,[19] because of the risks the disease poses to the pregnancy and because the theoretical risks of teratogenicity of antimalarial drugs need to be balanced with the substantial risks of undertreating; specialist advice is strongly recommended. Data from animals suggest that artemisinin drugs are teratogenic in early pregnancy, but human data are reassuring, with no current evidence of increased risk.[20] Hypoglycaemia is a problem in pregnant women with malaria,[21] and any pregnant woman with a reduced level of consciousness should be given glucose while awaiting blood glucose measurements.

How is uncomplicated non-falciparum malaria managed?

Several case reports indicate that vivax malaria, and possibly ovale and malariae malaria, cause severe disease more often than was once thought,[22] and their label as "benign" malaria is misleading. However, patients with non-falciparum malaria need to be admitted only if they have indicators of severe disease (table 1) or cannot take oral drugs. Provided the laboratory making the diagnosis is experienced and unlikely to have mistaken falciparum or rare mixed species infection (<1%), chloroquine remains the drug of choice to treat vivax, ovale, and malariae malaria. There is limited but growing chloroquine resistance in vivax in eastern Asia and the Pacific.[23] Evidence from clinical trials and a systematic review shows that most patients with vivax malaria, even those from South Asia or East Asia, respond to chloroquine within three days (see table 2⇓ for dosing).[24] Good evidence from clinical trials shows that artemisinin combination treatment (ACT) or quinine both work against vivax malaria at the same doses as those used for falciparum malaria (see below) if there is uncertainty about species or in patients with mixed infections.[25]

The biggest difficulty in managing patients with vivax or ovale malaria is that they can relapse several times after an initial episode, often more than a year after initial infection. Chloroquine and ACT treat the initial infection but do not kill the hypnozoites in the liver, which cause recurrent malaria. Primaquine is the only drug currently licensed to kill these hypnozoites and prevent or reduce the risk of relapse.[26] Apart from the need for a two week course, primaquine has two disadvantages. Firstly, resistance is gradually spreading, particularly in Oceania and eastern Asia, so that higher doses are now needed.[27] In the United States and UK, the current recommended dose for vivax malaria in adults is 30 mg a day for 14 days (15 mg a day for ovale). In addition, case reports and observational studies have found that treatment with primaquine in patients with phenotypic glucose-6-phosphate dehydrogenase (G6PD) deficiency can lead to haemolysis, which can be life threatening. G6DP deficiency therefore needs to be excluded before the drug is taken.[28] G6PD deficiency can affect more than 10% of the population in malaria endemic countries, although its prevalence is lower in people with malaria.[29 30] Patients should not take primaquine until their G6PD status is known, but treatment with chloroquine must not be delayed. Unfortunately, the only new anti-hypnozoite drug likely to be licensed in the next few years, tafenoquine, has similar risks with G6PD deficiency.

How should uncomplicated falciparum malaria be managed?

The severity of uncomplicated falciparum malaria is difficult to assess at presentation owing to the complex life cycle of the parasites, so all patients presenting with falciparum malaria in non-endemic countries should be admitted. Patients can seem well initially and then deteriorate despite treatment, and in around 20% of patients the parasite count rises in the first 24 hours despite adequate treatment.[7] Do not assume that patients who once lived in endemic countries but now are settled in non-endemic countries retain immunity. Clinical studies show that although being born in endemic Africa reduces the risk of dying from malaria, admission to intensive care and death can still occur.[6 31]

Provided oral treatments can be tolerated, parenteral treatment is not needed if there are no clinical or laboratory signs of severity (table 1). Because of a lack of evidence, guidelines vary about the threshold parasite count above which to give parenteral treatment in patients without symptoms or signs of severity: UK guidelines (designed for non-endemic countries) suggest parasite counts over 2%, whereas WHO suggests over 5%. Chloroquine resistance is near universal, so this drug should not be used. A variety of drug combinations are effective against uncomplicated falciparum malaria (table 2). Falciparum malaria should always be treated with a combination of at least two drugs. Commonly used options include ACTs, quinine combined with another drug, and atovaquone-proguanil. Most non-endemic countries have evidence based expert recommendations that are periodically updated on the basis of trends in epidemiology of imported malaria, emerging drug resistance, and local availability of drugs.[32 33]

There is good evidence from large trials and systematic reviews that ACT or quinine based combinations will be effective in malaria from Africa, most of Asia, and Latin America; ACT drugs are generally better tolerated and reduce parasite counts more rapidly.[34] Two ACTs, artemether-lumefantrine and dihydroartemisinin-piperaquine, are currently licensed in Europe and may become available in the US.

Is malaria resistance increasing?

P falciparum has developed resistance to several older antimalarials, and resistance continues to evolve. Several clinical studies show clear evidence of early emerging artemisinin resistance in South East Asia (Cambodia, Thailand, and parts of Burma), although ACTs still work clinically.[35] Clinical trials have also noted partial quinine resistance in the same area. Several recent trials have found no evidence that quinine or artesunate resistance is a serious clinical problem outside these areas. Resistance to some older companion drugs (such as sulfadoxine-pyrimethamine) is widespread, but well conducted trials (in endemic countries) and observational data (in imported cases) show that the combinations in table 2 are effective for most (>95%) cases of imported malaria. Atovaquone-proguanil has been associated with occasional treatment failure in some case reports, so many centres do not use it as first line treatment[36]; it should not be used in people who have been taking it prophylactically. Atovaquone-proguanil may be appropriate second line treatment for the rare cases of treatment failure with effective first line combinations, particularly those from South East Asia. Falciparum malaria does not relapse and patients can be reassured that they are unlikely to have recurrent malaria if they complete a full course of treatment. Any further attacks (generally within six weeks) usually represent treatment failure. Warn travellers about the growing problem of poor quality and counterfeit antimalarial drugs in many endemic countries.[37]

How should severe and potentially complicated malaria be managed?

Severe malaria is a medical emergency, and the main priority is for patients to receive adequate doses of effective drugs as soon as possible. Quinine (quinidine in the US, which is broadly equivalent) or artesunate are the two drugs used for parenteral treatment of severe malaria. Clear evidence from large randomised trials now shows that although quinine remains effective, artesunate is associated with a survival advantage (relative risk reduction of 22-34%) in adults and children in Asia and Africa.[38 39] Previously, the poor quality and limited availability of parenteral artesunate has been a problem in many non-endemic countries. However, although not licensed in

Europe or the US, parenteral artesunate of reliable quality can now be sourced (including through the Centers for Disease Control and Prevention in the US). Patients should always be started on parenteral quinine while trying to obtain artesunate if it is not initially available to avoid delay in effective treatment. In adults, artesunate confers the greatest survival benefit in those with very high parasite counts (>10%).[22] Parenteral quinine and quinidine are associated with hypoglycaemia and arrhythmia so should be used with caution in patients with cardiac problems.

Other than antimalarials, good management of patients with severe malaria largely depends on supportive care, including dialysis or haemofiltration in those with renal failure and respiratory support for those with acute lung injury. Various adjunctive treatments have been tried in cerebral malaria—including steroids, mannitol, and anti-tumour necrosis factor—none of which has shown a survival advantage.

For many years, there has been controversy over the use of exchange transfusion or automated red blood cell exchange to reduce parasite counts in patients with hyperparasitaemia (generally >10%).[40] The advent of treatment with artesunate, when available, renders this debate irrelevant. Unlike quinine, artesunate kills parasites of all stages and rapidly reduces parasite counts. Exchange transfusion is now rarely indicated and should be used only after discussion with a specialist centre.

The optimum management of fluids in adults and children has, in the absence of good data, been highly controversial. A recent trial in African children showed convincingly that aggressive fluid management was associated with increased mortality.[41] Good data on the optimal management of fluids in adults or children in high resource settings are limited. In adults, particularly those with renal failure, the risks of undertreating acidosis and any pre-renal component if fluids are withheld must be balanced against provoking pulmonary oedema if excess fluids are used. Most doctors used to treating severe malaria are wary about the overuse of fluids once pre-renal failure has been ruled out by short, small fluid challenges; unlike in bacterial sepsis, shock is rare in adults with malaria.

Clinical observational studies have shown a clear association between severe malaria and Gram negative sepsis in children, and reductions in the incidence of malaria in populations have been associated with reductions in Gram negative bacteria.[42 43] Broad spectrum antibiotics should therefore be considered in all children with severe malaria. Data from adults are limited, but the association seems to be less pronounced, so routine antibiotics are not needed.[44] Case reports suggest that broad spectrum antibiotics should be given to the rare adult patients who have shock with malaria.

Acute respiratory distress syndrome is the most feared late complication of malaria in adults. In severe malaria, this can occur several days after treatment has started, including when parasites have cleared from the blood. As with other causes of the syndrome, it is important to maintain oxygenation with respiratory support in intensive care and treat the underlying infection. No adjunctive treatments have been shown to improve outcomes in patients with this complication. Respiratory distress is also a poor prognostic sign in African children,[11] but less so in Asia (perhaps because of greater availability of blood transfusions)[45]; it is almost always caused by acidosis rather than lung injury.[11]

What is the prognosis after malaria?

The outlook for adults who survive an initial episode of malaria is good, even for those with severe malaria. Serious neurological sequelae occur in less than 5% of adults with severe malaria, although few series have been large enough to provide confident estimates. Many of the estimates in the literature are based on expert opinion rather than data.[46 47] Renal failure and lung injury almost invariably resolve if patients survive. Neurological deficits in children who have had cerebral malaria are now recognised to be more common, up to 30% in some series,[48] but these are often more subtle than for other serious neurological infections, such as meningitis.[49]

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Additional educational resources

Resources for healthcare professionals

WHO World Malaria Report 2012. www.who.int/malaria/publications/world_malaria_report_2012/en/. Describes the current state of malaria in the world

WHO management of severe malaria: a practical handbook. 2013. www.who.int/malaria/publications/atoz/9789241548526/en/index.html. Explains the management of severe malaria

Resources for patients

National Travel Health Network and Centre. www.nathnac.org/travel/factsheets/malaria_chemoprophylaxis.htm. Information leaflet for travellers on chemoprophylaxis

Advisory Committee on Prevention of Malaria in UK. www.hpa.org.uk/infections/topics_az/malaria/guidelines.htm. Travellers' handbook

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Tables

Table 1 | WHO criteria for severe malaria, modified for non-endemic high resource settings (any one indicates potentially severe disease)*

Symptoms, signs, and laboratory indicators of severe disease	Adults	Children
Reduced level of consciousness	+++	+++
Seizures	+	++
Respiratory distress	++	++
Severe anaemia (haemoglobin <70 g/L)*	+	+++
Hypoglycaemia†	+	++
Renal failure	+++	+
Hyperparasitaemia (>10% red cells parasitised)	++	++
Disseminated intravascular coagulation	+	+
Shock	+	+
Warning signs of potentially complicated malaria (requires parenteral treatment):		
Jaundice	+	+
Parasite count >2%	+++	+

*+=rare; ++=uncommon; +++=common (definition depends on age, state of immunity, and other factors).
†Common in pregnant women.

Table 2| Common licensed drugs, drug combinations, and drug doses for malaria

Drug	Dose in adults	Notes
Uncomplicated vivax, ovale, and malariae malaria		
Chloroquine	620 mg base, then 310 mg base at 6, 24, and 48 hours	
Primaquine (after chloroquine)	30 mg per day for 14 days	Test for G6PD deficiency before patients take it
Uncomplicated falciparum malaria		
Artemether-lumefantrine	4 tablets (adult) initially, followed by 5 further doses of 4 tablets at 8, 24, 36, 48, and 60 hours	
Quinine combinations	600 mg every 8 hours for 7 days or until parasites have cleared	Follow with clindamycin for 7 days, doxycycline for 7 days, or sulfadoxine-pyrimethamine once; ringing in ears a common side effect
Atovaquone-proguanil	4 tablets once a day for 3 days	Avoid if patients were on atovaquone-proguanil prophylaxis
Severe or potentially complicated malaria		
Quinine	20 mg/kg quinine intravenously, followed by 10 mg/kg 8-12 hourly until parasites have cleared	By slow infusion over 4 hours; hypoglycaemia and arrhythmias are side effects
Artesunate	2.4 mg/kg intravenously, followed by 2.4 mg/kg at 12 hours, then 2.4 mg/kg daily until parasites have cleared	As a bolus over 5 minutes

G6PD=glucose-6-phosphate dehydrogenase.