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Malaria: an update on treatment of adults in non-endemic countries

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Every year people die from malaria in Britain and other industrialised countries. Most of these deaths are avoidable: they occur because a patient or doctor has underestimated the severity of the disease or has not considered the diagnosis early enough. This article provides the essential facts on treating malaria in adults in a non-endemic setting and is based on the best available evidence

Treating uncomplicated falciparum malaria

The key is to give an effective antimalarial at an appropriate dose and ensure that patients complete the course. Several oral drugs have good activity against falciparum malaria, but drug resistance means that drug combinations are always preferable. Most trials of antimalarials have been conducted in endemic countries where there is at least some immunity to malaria, and this means they may overestimate the efficacy of these drugs in non-immune patients (because patients with immunity tend to clear parasites more readily). There are a few systematic reviews of antimalarials, but most are for drugs that are not appropriate for use in Western countries in non-immune people (such as amodiaquine). Systematic reviews, and in particular meta-analyses, are of limited use for assessing the efficacy of drugs such as antimalarials, for which resistance patterns vary widely both in place and time.

The Health Protection Agency Advisory Committee on Malaria Prevention for UK Travellers has reviewed the recent data and considers that the best options for treating uncomplicated malaria are:

- Quinine, either for five days or until the parasites have been cleared from the blood, followed by
- Doxycycline for seven days or
- Clindamycin for seven days or
- Sulfadoxine-pyrimethamine (Fansidar)
- Artemether-lumefantrine for three days (six dose regimen)
- Atovaquone-proguanil for three days.
- Clinical failures can occur with any of these combinations, but failure rates are low if the course is completed. The agency's advice is frequently updated and can be accessed at www.hpa.org.uk/infections/topics_az/malaria/guidelines.htm

Special cases

In patients from South East Asia there is evidence of partial quinine resistance, and the non-quinine combinations may be preferable.

Summary points

Malaria is common: you should assume that patients who are unwell on returning from tropical areas, especially Africa, have malaria until proved otherwise. They do not have to have a fever, although most will have history of fever

The severity of falciparum malaria is easily underestimated: patients can deteriorate rapidly despite treatment. You should admit patients to hospital for initial treatment. Patients with non-falciparum malaria seldom need admission

For patients with a mild or moderate attack of falciparum malaria, consider oral quinine (followed by a second drug), atovaquone-proguanil, or artemether-lumefantrine. The choice of drug may depend on where they have visited; rates of drug resistance vary from country to country

For a patient with severe or potentially complicated disease, you should use parenteral quinine or artesunate. You should give a loading dose for quinine

In pregnant women quinine is advised because its side effect profile in pregnancy is known: it is generally safe, although it increases the risk of hypoglycaemia and may induce labour. Doxycycline is contraindicated in pregnancy. There are insufficient data on atovaquone-proguanil to advise its use in pregnancy. There are concerns about using artemether in early pregnancy, and it should be avoided in the first trimester unless there is a clear reason (such as drug resistance) to recommend it until more data are available.

This article is based on a more detailed module that is available on BMJ Learning (www.bmjlearning.com)

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Quinine followed by a second drug

This is the standard treatment against which other combinations are assessed in the UK. Resistance to sulfadoxine-pyrimethamine monotherapy is now high outside west Africa.

Side effects

Quinine—Nausea, mild deafness, and mild tinnitus (cinchonism) occur almost invariably in patients taking quinine. These are reversible when the patient stops taking the drug. Quinine can induce arrhythmias in people with a pre-existing cardiac condition, although this does not often happen at the doses used in oral treatment.

Sulfadoxine-pyrimethamine—In common with other sulphur containing drugs, this can cause skin rashes, and rare cases of Stevens-Johnson syndrome have been reported.

Doxycycline—This can cause gastritis, photosensitivity, and all the problems associated with broad spectrum antibiotics.

Clindamycin—Possible increased risk of colitis from *Clostridium difficile*.

Evidence

Quinine became established as the standard treatment for falciparum malaria before the development of modern trial methods. No placebo controlled studies were performed, and none would now be ethical. Many studies have compared new treatments against quinine, and its continuing effectiveness in Africa has been repeatedly shown. There is reasonable evidence quinine has become less effective in South East Asia.

Dose

Quinine—600 mg (in adults) three times a day for five days, or until parasites have cleared from the peripheral blood, followed by

Sulfadoxine-pyrimethamine three tablets once only *or*

Doxycycline 100 mg daily for seven days *or*

Clindamycin 450 mg every eight hours for seven days.

Atovaquone-proguanil (Malarone)

This probably has a slightly higher failure rate than quinine combinations, but it is reported to be slightly better tolerated. Evidence for both these statements is weak, with few properly powered comparisons with other effective drug regimens in non-immune adults. Currently, no part of the world has specific problems with atovaquone-proguanil resistance. However, if patients have been taking it as prophylaxis, atovaquone-proguanil is not the best choice for treatment because of the risk that the malaria parasite will be resistant.

Side effects—Gastritis and nausea are relatively common.

Evidence—One systematic review of eight trials found it had equivalent efficacy to that of other regimens for treating uncomplicated falciparum malaria.[1]

Dose—Four tablets once daily for three days in adults.

Artemether-lumefantrine (Coartemether, Coartem, Riamet)

A four dose regimen for this drug has not been proved to be effective, but a six dose regimen seems to be effective against parasites from all parts of the world. It should be taken with fatty foods to achieve maximum drug concentrations.

Side effects—It is generally well tolerated.

Evidence—Systematic reviews suggest that, although the original four dose regimen of artemether-lumefantrine was not effective, the six dose regimen is effective, and the latter regimen should always be used, though evidence for its efficiacy in non-immune adults is limited.[2] No significant difference was seen between six dose artemether-lumefantrine and artesunate-mefloquine in a recent study from Laos.[3]

Dose—For adults, four tablets (each comprising 20 mg artemether and 120 mg lumefantrine) followed by a further four tablets at eight hours and then twice daily for two days.

Treating non-falciparum malaria

When a diagnosis of malaria caused by *Plasmodium vivax*, *P ovale*, or *P malariae* is made, the key to successful management is to be sure that the patient does not have malaria caused by *P falciparum* or a mixed infection. This mistake is easily made, especially in laboratories that rarely see malaria. The following conditions should raise questions about the diagnosis:

A very sick patient

A very high parasite count

A patient arriving from Africa (where over 90% of malaria will be falciparum).

Non-falciparum malaria seldom leads to death, and patients can almost always be treated as outpatients.

Almost all parasites are chloroquine sensitive, and chloroquine remains the drug of choice to treat acute infection. True vivax resistance to chloroquine has been reported, especially in Indonesia, but it remains extremely rare in travellers.

Vivax and ovale malaria lay down hypnozoites in the liver, which can cause relapse after months or even years. Hypnozoites are not reliably killed by chloroquine, or indeed any of the drugs used to treat acute infection. Only one drug, primaquine, that has been shown to work against hypnozoites ("radical cure") is licensed in Europe.

Chloroquine

This works rapidly and reliably where there is no resistance, is safe in usual doses, and is well tolerated. It is considered safe in pregnancy.

Side effects—It can cause gastritis and mild abdominal pain. It can cause itching in some people of African ethnicity (mechanism unknown).

Evidence—Chloroquine became established as the standard treatment for non-falciparum malaria before the development of modern trial methods. Case series suggest it remains effective in almost all geographical areas (>98% cure rates) and should remain the first line treatment, although occasional failures do occur with vivax malaria, especially in cases from eastern Asia.

Dose—600 mg orally and then 300 mg at six hours, 24 hours, and 48 hours.

Primaquine

Used for radical cure of hypnozoites, primaquine needs prolonged courses of treatment (14 days). It is contraindicated in people with glucose-6-phosphate

dehydrogenase deficiency, in whom it can cause severe haemolysis, and it should not be prescribed until a test for deficiency has been performed. Specialist advice should be sought in those with glucose-6-phosphate dehydrogenase deficiency. Primaquine is also contraindicated for pregnant women.

Evidence—There have been no systematic reviews, and many of the case series predate 1977. Studies have shown increased relapse rates with decreased doses or with increasing primaquine resistance.[4] There is increasing evidence that treatment for fewer than 14 days is suboptimal and that 30 mg a day should now be used.

Dose—15 mg twice daily (total of 30 mg a day) for 14 days.

Treating severe falciparum malaria

Early identification of severe or potentially complicated malaria is important. Symptoms and signs that should alert you to this are shown in the box.

In Western countries once patients present to acute medical facilities, deaths occur because of cerebral malaria, usually in the first 48 hours of hospitalisation, or acute respiratory distress syndrome (which can occur later, even after parasites have been cleared). Renal failure can be managed by haemofiltration or dialysis in hospital. Always check for hypoglycaemia if patients are drowsy, unconscious, or fitting.

The key intervention, and the only one for which there is strong evidence, is to give an effective antimalarial at an adequate dose parenterally. All other decisions are secondary.

Antimalarial treatments

The current options are:

- Quinine (intravenous)
- Artesunate (intravenous)
- Artemether (intramuscular)—Probably less effective than artesunate, although no studies have compared them directly.

Compared with quinine, the artemisinins reduce parasite counts faster, and there is now evidence from Asia that they reduce mortality in adults with severe malaria. There are no good studies comparing intravenous quinine with artesunate in Africa, where there are different patterns of drug resistance. Quinine remains a good drug to treat severe malaria. At present, good quality intravenous artesunate is in short supply in Europe and is available only in specialist centres. Preferences for a particular drug should never delay treatment with one of them in adequate doses.

There are a few situations where artesunate should be considered:

- Patients from South East Asia might have relatively quinine resistant malaria, so an artemisinin is preferable. Trial evidence supports such patients being given artesunate
- Quinine is pro-arrhythmogenic, so artemisinins should be considered in patients with a cardiac condition
- Artemisinins reduce parasites faster, so may be preferable in patients with a parasite count >10%, but it is not clear what effect exchange transfusion has on artemisinin blood concentrations, so use only one or the other. There is more evidence to support the use of artesunate than exchange transfusion.

Artemisinins should be used with caution in early pregnancy unless there is a clear indication for them (such as suspected quinine resistant disease from South East Asia). There is insufficient evidence from human studies, and animal studies suggest teratogenicity is a possibility in the first trimester.

Indicators of severe or potentially complicated malaria in adults

Severe malaria

- Any neurological signs, drowsiness, or fitting. Cerebral malaria is strictly defined as unrousable coma in the presence of malaria, but any patient who is drowsy or has neurological symptoms should be treated the same way
- Oliguria, renal failure
- Respiratory distress due to pulmonary oedema or acute respiratory distress syndrome
- Disseminated intravascular coagulation
- Severe anaemia.
- Shock
- High plasma lactate, hypoglycaemia

Potentially complicated malaria

- Parasite count >2%
- Jaundice
- Pregnancy

Side effects

The side effects of intravenous quinine are as for oral quinine, with the addition of arrhythmias and hypoglycaemia. Artemisinins are generally well tolerated.

Evidence

Quinine became established as the standard treatment for severe malaria before the development of modern trial methods. Randomised placebo controlled trials have not been done and would now be unethical. A systematic review of four randomised controlled trials found that loading doses of quinine reduced parasite and fever clearance times compared with standard doses; there was a trend to reduce mortality which failed to reach statistical significance.[5] There was no apparent effect on coma recovery time, neurological sequelae, or seizures.[5]

Two systematic reviews have compared intramuscular artemether with quinine.[6 7] One showed that artemether produced faster parasite clearance but made no difference in mortality, fever clearance, coma recovery time, or neurological sequelae. The combined outcome of death and neurological sequelae was significantly lower for artemether, however. The other review found a small decrease in mortality with artemether (which lost significance when the poorer quality randomised controlled trials were excluded) but no difference in neurological sequelae.

Faster parasite clearance has been seen with artesunate compared with quinine; there were no differences in fever clearance time, coma recovery, neurological sequelae, or mortality in one study,[8] but a

Clinical tips

- Debates about adjunctive treatment, such as exchange transfusion, should never delay giving an effective antimalarial in sufficient doses to patients with malaria. Effective antimalarial drugs are the only interventions that definitely improve outcome
- People repeatedly exposed to malaria can become semi-immune (so getting less severe attacks of malaria), but it is not possible to make accurate judgments of individuals' immune status from their ethnicity or country of residence. It is dangerous to base decisions on such judgments. You should assume that all patients presenting in non-endemic countries (such as the UK) have no immunity
- You should seek up to date advice on the treatment of
  - Patients with severe falciparum malaria travelling from South East Asia (where there is multidrug resistant malaria)
  - Pregnant women.
- Assume that all falciparum malaria is resistant to chloroquine
- Vivax malaria that is resistant to chloroquine is still rare. Chloroquine remains the drug of choice for non-falciparum malaria. Primaquine is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency
- Patients treated with quinine are likely to get transient nausea, deafness, and tinnitus, and they should be warned about this
- Beware of hypoglycaemia in drowsy or comatose patients, especially if they are pregnant
- The Advisory Committee on Malaria Prevention in UK Travellers (ACMP) provides up to date guidance on treatment and prevention of malaria. Advice on managing complex cases can be obtained from the Hospital for Tropical Diseases or the Liverpool School of Tropical Medicine.

more recent, large, multicentre study from South East Asia demonstrated a survival benefit for artesunate in adults.[9]

Dose

Quinine 10 mg/kg (maximum 700 mg) given intravenously twice daily (loading dose 20 mg/kg (maximum 1400 mg))

Artesunate 2.4 mg/kg given intravenously at 0, 12, and 24 hours, and then daily

Artemether 3.2 mg/kg given intramuscularly as loading dose, then 1.6 mg/kg given intramuscularly daily (to total of 640 mg).

Artesunate and artemether should be followed by doxycycline (100 mg daily for seven days) or artemether-lumefantrine, and quinine should be followed by sulfadoxine-pyrimethamine, doxycycline, or clindamycin (as for uncomplicated malaria).

Adjunctive treatments

Various adjunctive treatments have been tried. Few, if any, work, and some are harmful. Among the commonly considered treatments, corticosteroids and mannitol have been shown not to work in cerebral malaria.

Exchange transfusion remains controversial: evidence from trials is contradictory, and it is unlikely that further trials will settle this question. Nobody would advise exchange transfusion for a parasitaemia $<10\%$. At higher parasite counts the evidence is mixed; most centres with expertise in malaria consider exchange transfusion if parasite counts are $>20\%$, but some centres never use it. In practice, there is general agreement that the effect is probably marginal.

Prophylactic anticonvulsants used to be given to patients with cerebral malaria, but, although it reduced the risk of fits, a trial of phenobarbital (in children) suggested an excess mortality. Anticonvulsants should now be reserved for patients who are actively fitting.

Haemofiltration will need to be considered in cases of acute renal failure. Renal failure secondary to malaria almost invariably resolves completely, although this can take days and occasionally weeks.

Antibiotics—Patients whose blood pressure drops may have coexisting sepsis caused by Gram negative bacteria and should be considered for broad spectrum antibiotics. Malaria seldom causes major haemodynamic collapse directly.

Diuretics—Pulmonary oedema can be treated with diuretics, but these may be ineffective in patients with coexisting malaria induced renal failure. In these cases haemofiltration will be needed.

Acute respiratory distress syndrome is the most concerning complication of malaria in adults that develops after the first 24 hours of acute illness. The treatment is as for all other causes of acute respiratory distress syndrome. There is weak evidence that heavy hydration increases the risk of the syndrome developing; patients need to be adequately hydrated, but "running patients wet" is not advised by most centres with expertise in malaria.

Evidence

Corticosteroids—One systematic review examined two randomised controlled trials comparing dexamethasone with placebo in severe cerebral malaria.[10] There were no differences in mortality but increased gastrointestinal bleeding and seizures in the dexamethasone groups.

Sample questions

1. A pregnant woman presents with otherwise uncomplicated malaria in her first trimester after a trip to Kenya. Which is the best drug or combination to use for treatment
   a. Atovaquone-proguanil
   b. Artemether-lumefantrine
   c. Quinine
2. A patient you have started to treat for severe malaria gradually becomes unconscious. Which of the following would be appropriate management in addition to antimalarials?
   a. Checking for hypoglycaemia
   b. Corticosteroids
   c. Mannitol to reduce intracerebral pressure.
3. In a patient with vivax malaria
   a. Chloroquine resistance is now common
   b. Glucose-6-phosphate dehydrogenase deficiency needs to be looked for before primaquine treatment only if the patient is anaemic
   c. In patients from Africa consider double checking the diagnosis

Mannitol—One systematic review failed to identify any randomised or quasi-randomised controlled trials.[11] Mannitol has been shown to control intracranial pressure in children with cerebral malaria, but effects on morbidity or mortality are unclear.[12]

Exchange transfusions—There are no suitable randomised controlled trials for analysis, but a systematic review of case-control studies found variable efficacy and no influence on mortality overall.[13]

Prophylactic anticonvulsants—One systematic review of three randomised controlled trials comparing phenobarbital with placebo (no treatment) found fewer convulsions but increased mortality in the phenobarbital group.[14]

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A bipolar story

Being a medical student has its ups and downs. As I sat in the busy psychiatric outpatient clinic, I was having a particularly "up" day, giggling while the senior house officer vainly tried to hang up the telephone. On the other end was a bipolar patient, currently manic. "Yes, I understand, but I really have to go … Yes, goodbye … No, I am in a clinic…."

"Pressure of speech," I ruminated, proud at how good my psychiatric terminology was coming along on only the second day of my attachment. When my colleague finally managed to disentangle himself from the conversation, he looked at me with a strangely vindictive grin and told me that the patient was being admitted and that she would be a "wonderful candidate" for a detailed case study. My shoulders sagged, my grin turned upside down—I'd been looking forward to lunch and a free afternoon. Little did I know what I was in for.

"Can I see your badge, young lady? It's just I have to make sure you're not an actor pretending to be a medical student. There are a lot of actors here, you know—the patients, the doctors…."

"No further explanations needed," I thought, and duly produced my identity badge. Immediately convinced of the veracity of my identity, my patient sat down in the family room of the inpatient ward, and I proceeded to obtain a full, detailed psychiatric history—or rather, I tried to. The truth is, she just talked—about everything from art, to politics, to literature. Because of my complete inability to direct the interview, I let her carry on. "Been here almost three hours already … Damn, shouldn't have giggled at the SHO. Never mind, I'll just have to come back again tomorrow." Resigned to the fact that I'd have to meet this patient many times before I could get all the relevant facts, I relaxed and was surprised to find myself enjoying all the irrelevant bits of the conversation.

We both laughed and chuckled like a couple of schoolgirls, me and this 65 year old woman, as I got caught up in her contagious joy and boundless energy. Amid deliberations on Monet and reflections on the situation in the Middle East, she told me about her experience of terrible confusion that somehow, like in a dream, makes perfect sense. I heard about her tragic losses and deep despair, about the havoc this disease can wreck on a family and about how her faith had sustained her throughout. "Mania … psychosis … depression." She didn't just give me a history of bipolar illness, she told me a story and took me on a journey to discover a person struggling with a disease but who, in spite of or perhaps because of it, was a whole and wonderful human being.

Now, when I meet a "bipolar," "depressed," or "schizophrenic" patient, I try to look past the diagnosis and often find someone who has had to endure more than most of us and thus has a wealth of experiences and stories to share. While we may not always have the luxury of time to listen, these are people who deserve all our compassion and respect.

"You're my angel," my patient gushed as she gave me a hug. She was wrong, of course, just "over-familiarity." The truth is, she was mine.

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