

# MALARIA: DIAGNOSIS, TREATMENT, AND PREVENTION IN PRIMARY CARE

*Malaria is arguably the most important travel-related disease, and one that presents numerous pitfalls for the unwary practitioner. Despite this, the essentials of malaria management in primary care practice are quite straightforward.*



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Four species of *Plasmodium* cause malaria in man: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. All of these probably trace their evolutionary origins to non-human primates, and even today there is evidence that monkey plasmodia cross the species barrier and infect man.

Of the four major human species, *falciparum* is the most pernicious. As a consequence this article focuses mainly on *falciparum* malaria. *P. falciparum* causes progressive disease in non-immune individuals, with an annual death toll that approaches 3 million. Most of these deaths occur in sub-Saharan Africa.<sup>1</sup>

Plasmodia have a complex life cycle, with the definitive host being female *Anopheles* mosquitoes. Different *Anopheles* species transmit the disease in different ecological niches, making for a broad distribution of malaria in tropical and subtropical regions worldwide.

## DIAGNOSIS OF MALARIA

The diagnosis of malaria can only be made when parasites are demonstrated in the blood-stream, but the diagnosis can never be excluded if the parasites are not seen. Additionally, the initial symptoms of malaria are often beguilingly mild. These two pitfalls have misled many practitioners, with unnecessary loss of life and reputation the consequence.

The cardinal symptom of malaria is fever; rigors may or may not be present. There may be no particular pattern to the fever, despite the descriptions of tertian and quartan patterns in older texts, and these terms are no longer in common clinical use — in very young infants fever may not be observed at all. Other presenting symptoms are likely to be equally nonspecific and suggest influenza or gastro-enteritis. Malaria may occasionally even present with an urticarial-like rash.<sup>2</sup> There are no pathognomonic clinical signs.

The nonspecific nature of malaria presentation dictates that all patients with a history of potential exposure to malaria who present with fever should be regarded as having malaria until proven otherwise. All such patients should be treated as emergencies, and have blood smears taken for urgent examination. Important for the primary care practitioner to ensure is that smears are handled and examined urgently by the laboratory — experience has shown that some laboratories, particularly in smaller centres, do not always understand this urgency.

Malaria may also be diagnosed using rapid antigen tests. These have sensitivities and specificities of at least 90% for *falciparum* malaria,<sup>3</sup> making them suitable for use in the consulting room. The advantage of using such a test is that the diagnosis may be instantly confirmed, and treatment started immediately. A dis-

advantage is that the result is revealed simply as a 'positive' or 'negative', with no indication of parasite density (or percentage parasitaemia) given.

Rapid antigen tests may remain positive for 3 weeks or more after cure, and are therefore not useful for monitoring therapy or diagnosing recrudescence. Although some of the newer tests are able to diagnose the non-falciparum malaras as well as *P. falciparum*, they detect these other malaras less reliably.

Negative blood smears and rapid antigen tests do not rule out the diagnosis of malaria. Testing should be repeated at 8-hourly intervals until the diagnosis is confirmed, or a firm alternative diagnosis reveals itself. In the event of the latter, the cautious practitioner

**Table I. Signs of complicated malaria\***

The presence of any of the following indicates complicated malaria:

- A decreased Glasgow coma score — any decrease in level of consciousness, confusion, or drowsiness
- Generalised convulsions
- Significant anaemia (Hb < 10g/dl)
- Hypoglycaemia
- Metabolic acidosis with respiratory distress
- Fluid and electrolyte disturbances
- Acute renal failure or poor urine output
- Pulmonary oedema
- Adult respiratory distress syndrome
- Circulatory collapse/shock
- Evidence of septicaemia
- Abnormal bleeding\*
- Jaundice
- Haemoglobinuria
- Fever > 39°C
- Parasitaemia ≥ 5%

\* Thrombocytopenia is usual with malaria. As an isolated finding it does not indicate complicated malaria.

**Table II. Treatment of falciparum malaria**

	<b>Complicated</b>	<b>Uncomplicated</b>
Quinine	Loading dose: 20 mg/kg IV over 4 h Follow with 10 mg/kg infused over 2 - 8 h every 8 h  Switch to oral therapy with 10 mg/kg tds when tolerated  IV fluids  Paracetamol  Start treatment and refer urgently  Quinine may be used regardless of preceding prophylaxis, but omit loading dose if mefloquine was used for prophylaxis	10 mg/kg tds for 5 days, plus doxycycline 3 mg/kg daily for 7 days  May be used regardless of preceding prophylaxis  Paracetamol
Atovaquone-proguanil (Malarone)	Not recommended	2 tablets twice daily with food (preferably fatty) for 3 days
Artemether-lumefantrine (Coartem)	Not recommended	4 tablets per dose at 0, 8, 24, 36, 48, 60 h Take with fatty food Caution — may cause degree of permanent hearing loss
Sulphadoxine-pyrimethamine (Fansidar)	Not recommended — high levels of resistance	
Halofantrine (Halfan)	Not recommended — may cause fatal arrhythmias	

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might still entertain the prospect of dual pathology.

### TREATMENT OF MALARIA

For practical purposes, it can be assumed that all patients seen by South African primary care practitioners are 'non-immune' i.e. they have not grown up and remained resident in a malarious area. This means the doctor will be dealing with an aggressive and potentially fatal disease, liable to catastrophic deterioration at any time; this danger mandates close clinical monitoring and supervision.

The principal question a practitioner should ask him/herself when faced with a case of falciparum malaria is 'Am I dealing with complicated or uncomplicated malaria?' The differentiation of complicated from uncomplicated malaria is straightforward: the presence of any one of the criteria listed in Table I indicates complicated malaria.<sup>4</sup> Complicated cases should be started on therapy with quinine (see Table II) and admitted without delay to the highest level of care available.

Primary care practitioners may feel more comfortable treating uncomplicated malaria. While it has been customary to treat all patients with malaria in hospital, there has been a move in recent times to manage the disease on an outpatient basis.<sup>5,6</sup> Social and economic circumstances may at times dictate this. Despite such exigencies, falciparum malaria remains a disease for which practitioners will never be faulted for having been too cautious, and admission should always be considered an option.

Regardless of the treatment setting, patients with uncomplicated malaria should have daily full blood counts and smears taken. The emergence of any of the criteria listed in Table I, or failure of the parasite density to decrease on monitoring, is indication for urgent referral.

### TREATMENT OF THE RELAPSING MALARIAS

Clinical malaria is caused by the presence of parasites in the blood-stream, and is cured by the administration of drugs active against the blood phase of the parasite's life cycle (Table II). However, the prevention of relapse by vivax and ovale parasites dormant in the liver requires additional treatment. Currently the only drug available for this 'radical cure' is primaquine, which is available on a named-patient basis only. Primaquine causes haemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals, and patients requiring radical cure of either vivax or ovale malaria are probably best referred. Given the usually less severe nature of these malarias and the symptom-free period between clinical episodes, such referral does not need to be urgent.

### PREVENTION OF MALARIA

It is the deadly nature of falciparum malaria that underpins the logic of prevention, which itself relies on two complementary strategies: the adoption of personal protection measures, and the use of chemoprophylaxis. Of the two modalities, chemoprophylaxis

is the more important, but neither modality should be adopted at the expense of the other. It is important to note that no preventive strategy or chemoprophylactic regimen is 100% effective, and malaria may still be contracted despite the best preventive efforts.

### Personal protection measures

Personal protection measures are intended to prevent mosquitoes from biting the traveller. To this end effective measures include:

- application to exposed skin of DEET-containing mosquito repellents
- permethrin impregnation of clothing
- wearing of long sleeves and trousers
- tucking of trousers into sock or boot tops
- sleeping under mosquito nets, preferably permethrin impregnated
- screening of sleeping quarter doors and windows
- air conditioning of sleeping quarters
- use of insecticidal coils, vaporisers or sprays at night in sleeping quarters.

### Chemoprophylaxis

Chemoprophylaxis is intended to kill malaria parasites in the human host before they reproduce in sufficient number to cause clinical disease and kill their host. Chemoprophylaxis is undoubtedly lifesaving, and it is negligent to recommend against it for travel to most sub-Saharan destinations. Currently three principal options offer reliable prophylactic efficacy: doxycycline, mefloquine, and atovaquone-proguanil. All have advantages and disadvantages, and prescribing essentials are summarised in Table III. The worldwide dominance of chloroquine-resistant *P. falciparum* has rendered chloroquine virtually useless as a chemoprophylactic agent, especially in Africa; the combination of proguanil with chloroquine in chemoprophylactic regimens is of dubious benefit, may increase the incidence of adverse effects, and is best avoided.<sup>7</sup>

Table III. **Commonly prescribed efficacious antimalarial chemoprophylactic agents**

	<b>Mefloquine</b>	<b>Doxycycline</b>	<b>Atovaquone-proguanil</b>
Experience	In use many years Well understood	In use many years Well understood	Constituent drugs well understood Less experience with combination
Contraindications	Avoid with neuropsychiatric or convulsive disorders	Avoid in porphyria	Not specifically contraindicated with neuropsychiatric disorders
Children	Has been used safely in children $\geq 5$ kg	Avoid in children of 8 years or younger	Has been used in children $\geq 11$ kg
Pregnancy	Use in pregnancy with caution	Avoid in pregnancy	Inadequate data on use in pregnancy
Adverse effects	Vivid dreams, nightmares and insomnia	Gastro-oesophageal irritation possible Enteric-coated tablets preferred	Diarrhoea
	Mood alterations in susceptible individuals Dizziness and nausea	Photosensitivity occasionally (uncommon) Vaginal thrush	Drug rash (uncommon) Nausea and vomiting
Dosing frequency	Once-weekly dosage	Once-daily dosage	Once-daily dosage
First dose	Start at least 1 week before departure	Start 2 days before departure	Start 2 days before departure
Duration of treatment	Should be taken for 4 weeks after return	Should be taken for 28 days after return	Should be taken for 7 days after return
Relative cost	Inexpensive	Least expensive	Most expensive

Chemoprophylaxis needs to be prescribed on an individualised basis, with attention paid to medical history, concurrent medication, and contraindications. Provided this is done and patients are instructed in their proper use, all three of the commonly prescribed chemoprophylactic agents should be well tolerated.

**Mefloquine**

This drug achieves a prophylactic efficacy exceeding 93% and is deserving of wider use.<sup>7,8</sup> The drug's poor reputation in the lay media is ill deserved, and reflects poor prescribing habits more than any lack of safety. Travellers with any history of a neuropsychiatric or convulsive disorder should not receive this drug; likewise travellers with cardiac conduction abnormalities or travellers taking drugs that interfere with intracardiac conduction. Anecdotal evidence supports the view that the drug is best

avoided in heavy imbibers of alcohol. Prudence dictates its avoidance in pilots, divers, and individuals for whom spatial orientation and fine motor co-ordination are critical, e.g. surgeons.

A popular misconception is that should mefloquine prophylaxis fail, then treatment with quinine is contraindicated, on the basis of additive potential to cause cardiac dysrhythmia. Clinical study has debunked this, and quinine treatment may follow mefloquine prophylaxis.<sup>9</sup>

**Doxycycline**

Doxycycline's efficacy is similar to that of mefloquine and it too is a valuable member of the antimalarial armamentarium.<sup>10,11</sup> The drug has a reputation for causing photosensitivity; it is always good practice to recommend the use of sunscreen by travellers to the tropics, and this message assumes increased

importance for doxycycline users. Oesophagitis is a well-known doxycycline side-effect, and is brought about by the highly acidic doxycycline molecule coming into contact with the oesophageal mucosa. This adverse effect can be largely prevented by:

- prescribing an enteric-coated formulation
- washing down the medication with generous quantities of liquid
- taking the medication during a meal
- avoidance of recumbency after taking the medication.

**Atovaquone-proguanil**

This recent addition to the South African market is a combination of two well-known drugs that exhibit synergistic action. It is at least as efficacious as mefloquine, and in a pivotal multicentre study was better tolerated than placebo.<sup>12</sup> Principal adverse events reported are gastrointestinal.

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The author's South African experience of adverse events in over 3 000 prescribed courses includes one case of challenge-proven rash, and two of moderate diarrhoea. The principal drawback with this drug remains cost, although the requirement for just 7 rather than 28 days of continued use after leaving malarious areas may mitigate this in some cases, e.g. short duration travel. Atovaquone-proguanil may well become the drug of choice for the short-term traveller. A paediatric formulation is likely to become available in South Africa in the future.

Atovaquone-proguanil is registered in many countries, although not in South Africa, for treatment as well as prophylaxis. Its use for treatment in South Africa thus remains a reasonable option, although clearly not in cases where atovaquone-proguanil prophylaxis has been used.

### **Azithromycin and other chemoprophylactics**

For the rare individual unable to tolerate one of the above chemoprophylactic drugs, more exotic choices can be arranged. This is usually best done in consultation with a travel medicine

expert. An alternative to be discouraged, but which seems nevertheless to enjoy an undeserved popularity, is azithromycin: clinical studies have shown it to offer an unacceptably low level of protection.<sup>11</sup>

### **WHAT'S NEW IN MALARIA?**

There is a paucity of effective anti-malarials available, and a number of newer agents are under development. One such is tafenoquine, chemically related to primaquine. This agent has an exceptionally long half life, and may come into use soon, both for chemoprophylaxis and treatment.<sup>13</sup> Like primaquine, it causes haemolysis in G6PD-deficient subjects.

Artemisinin combination therapy is gaining popularity for treatment, with the combination of artesunate and clindamycin looking promising.<sup>14</sup> Synthetic derivatives of the artemisinins are being pursued as treatment options, although some questions around the neurotoxicity of artemisinin combinations require resolution.<sup>15</sup>

The holy grail of malaria research remains the discovery of an effective vaccine. A number of vaccines are currently in trial, including the RTS,S/AS02 vaccine, which demonstrated a degree of efficacy in semi-immune Gambian adults.<sup>16</sup> It is unlikely that a truly effective vaccine for travellers will emerge in the near future, however.

### **CONCLUSION**

Falciparum malaria is an always progressive disease in the non-immune traveller, and any potential case should be regarded as a medical emergency. Reference to World Health Organization criteria will determine whether the patient has complicated malaria, and will dictate treatment options.

Travellers to malarious areas should all be advised on the use of personal protection measures, and individualised chemoprophylaxis should be prescribed.

The day when a simple jab replaces weeks of chemoprophylaxis for the traveller unfortunately remains as distant as ever.

*References available on request.*

### **IN A NUTSHELL**

Any patient presenting with fever and a history of travel to a malaria area within the preceding 6 months should be regarded as having falciparum malaria until proven otherwise.

Falciparum malaria is a medical emergency.

Malaria cannot be diagnosed on clinical grounds, and its suspicion demands urgent investigation.

A negative blood smear or rapid antigen test does not rule out the diagnosis of malaria.

It is negligent to advise against chemoprophylaxis for most malarious destinations, especially in sub-Saharan Africa.

Currently available efficacious chemoprophylactic agents are mefloquine, doxycycline, and atovaquone-proguanil.

Chloroquine and azithromycin are best avoided as antimalarials.

Personal protection measures against mosquito bites should be recommended in addition to, but not instead of, chemoprophylaxis.