Management of uncomplicated malaria

Early diagnosis and treatment is the key to effectively managing malaria.

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The key issues in the successful management of malaria are early and accurate diagnosis and urgent treatment with effective drugs. Disease presentation is, however, not specific – progression to complicated disease may be rapid in non-immune persons, particularly in young children and pregnant women, and parasite drug resistance significantly influences treatment outcome.[1]

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There are four species of human malaria parasite, but this brief review focuses on the most prevalent and pathogenic species, *Plasmodium falciparum*. The outcome of a falciparum malaria attack depends on the interaction of host, parasite and environmental factors, and ranges from asymptomatic or mildly symptomatic disease, through severe, complicated malaria, to death. Severe or fatal malaria is almost invariably caused by *P. falciparum*. This reflects the ability that the falciparum parasite has evolved for attachment (cytoadherence) of the schizont-infected erythrocyte to the capillary walls of the brain and other organs. Through various mechanisms, the end results are organ dysfunction, damage or failure, which are reflected in the severe and complicated forms of malaria.[1]

Presentation and diagnosis

The prompt and accurate diagnosis of malaria is critically important because of the potential for rapid clinical progression to complicated and possibly fatal disease. Three components contribute to an optimal diagnostic outcome:

- a high index of suspicion in travellers to or residents in malaria transmission areas and their health care providers, who should take an adequate travel history in any person with fever or flu-like illness
- clinical astuteness and experience, and
- diagnostic tests.

The presentation of malaria is highly variable and mimics many other diseases, most commonly influenza, but also bacterial septicaemia, East African trypanosomiasis, meningitis, typhoid fever, tick bite fever, viral haemorrhagic fever and viral hepatitis. Paroxysms of fever and rigors are typical in adults. Some of the following symptoms may occur: headache, tiredness, myalgia, abdominal pain, diarrhoea, loss of appetite, nausea and vomiting, and cough. In young children malaria may present with fever, lethargy, poor feeding, vomiting, diarrhoea and cough. Malaria is frequently missed or misdiagnosed in pregnancy and needs to be differentiated from complications of pregnancy including intrauterine sepsis and pyelonephritis, as signs and symptoms may be similar, notably abdominal pain and fever.[2,3]

Examination of patients with suspected malaria may reveal minimal physical signs. The presence of fever or a history of fever in the previous 3 days is usual, but does not invariably occur. An enlarged spleen is uncommon in areas of low-intensity malaria transmission; therefore the absence of splenomegaly does not exclude malaria.

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The patient should be carefully examined for complications of malaria, such as shock, altered level of consciousness, jaundice, anaemia, and respiratory distress, including acidotic-type respiration and bleeding. The presence, on examination, of another disease does not necessarily exclude malaria, and both diseases would need to be investigated and managed. The health practitioner should be warned against attributing fever to the presence of minor respiratory infections, e.g. pharyngitis, in patients who have been exposed to malaria. Likewise, malaria is often missed in patients with co-morbid disease because signs and symptoms are attributed to the underlying disease, even when there is a history of malaria exposure.[2,3]

Malaria transmission very rarely occurs outside malaria transmission areas – in the form of Odyssean or airport malaria, or needle and transfusion malaria. Therefore it is prudent that, when there is no other obvious cause of fever, malaria should still be excluded,[4] even if a recent history of visiting or living in a malaria area is not forthcoming.

Laboratory testing for parasites should be done and results obtained urgently in all patients with a clinical suspicion of malaria, irrespective of the season or whether the patient has/has not taken chemoprophylaxis.

Microscopy of thick blood smears stained with Giemsa remains the mainstay of diagnosis. This requires skill and experience that is not always available. Examination of a thin blood smear will give an indication of the parasite species and density of parasitaemia, both of which will influence treatment.[5]

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Rapid diagnostic tests (see article by Dini and Bell), based on lateral-flow immunochromatographic (dipstick) detection of malaria antigens, are suitable for use by persons without specific laboratory training. Most commercially available tests detect the *P. falciparum* histidine-rich protein 2 (PfHRP-2) antigen. As HRP-2 persists after successful treatment rapid tests are used only for initial diagnosis of malaria and cannot be used to monitor treatment response. Parasite density cannot be quantified with rapid diagnostic tests.[6,7]

Alternative techniques, such as acridine orange (AO) staining and the quantitative buffy coat (QBC) method, have high sensitivity but may be associated with problems of interpretation and species identification.

A negative test does not exclude the diagnosis and repeat testing within 8 - 24 hours, without attempting to coincide with fever peak timing, is mandatory until a positive result is reported or an alternative definitive diagnosis is made. Prophylaxis and antibiotic use may prolong incubation periods and suppress malaria parasite densities below detectable levels.[5]

In the absence of, or if there is a delay in obtaining, a definitive parasitological diagnosis patients with severe malaria, or at high risk thereof, should be presumptively treated for malaria on clinical grounds.

Thrombocytopenia is a common finding in patients with malaria. A blood smear should be checked for malaria parasites whenever this laboratory finding is made unexpectedly.

Assessment of disease severity[3,8]

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction. In acute falciparum malaria there is a continuum from mild to severe malaria. Young children, pregnant women and non-immune adults with malaria may deteriorate particularly rapidly. The common tendency is to underestimate the severity of disease. The risks of under-treating severe malaria considerably exceed those of giving parenteral treatment to a patient who does not need it. The presence of one or more of the clinical or laboratory features listed in Table I classifies the patient as suffering from severe malaria. The presence of acidosis is a particularly accurate predictor of poor outcome.

Treatment

The choice of treatment depends on disease severity, malaria species, patient characteristics (pregnancy, extremes of age, co-morbidity, allergies, concurrent medication) and presence of vomiting.

Treating uncomplicated falciparum malaria[3,8]

The objective of treating uncomplicated malaria is to eradicate the *Plasmodium* parasite, prevent progression to severe malaria, and prevent additional morbidity associated with treatment failure. From a community perspective the goals are to reduce malaria transmission and to prevent the emergence and spread of antimalarial resistance. To achieve these objectives the WHO now recommends treatment with artemisinin-based combinations (ACTs).[9] Evidence of their superiority compared with monotherapies has been clearly documented.[8] Artemether-lumefantrine(AL, Coartem) is the first ACT to be registered in South Africa and has been the standard drug for the treatment of uncomplicated malaria in KwaZulu-Natal since 2001, Limpopo

Table I. Clinical and laboratory criteria for severe malaria

Clinical
Impaired consciousness, multiple convulsions
Respiratory distress, acidotic breathing, pulmonary oedema
Circulatory collapse
Jaundice
Bleeding
Prostration

Laboratory
Hypoglycaemia (blood glucose <2.2 mmol/l)
Acidosis (plasma bicarbonate <15 mmol/l or serum lactate >5 mmol/l)
Hepatic transaminases >3 times normal
Renal impairment (serum creatinine >265 µmol/l or rapidly rising creatinine or urine output <400 ml/day in an adult)
Haemoglobin <5 g/l
Parasitaemia ≥5%
≥ 5% neutrophils contain malaria pigment
Presence of schizonts of *P. falciparum* in peripheral blood smear

Table II. Dosing schedule for artemether-lumefantrine

Body weight	Age	Number of tablets and approximate time of dosing					
		0 hrs	8 - 12 hrs	24 hrs	36 hrs	48 hrs	60 hrs
5 - 14 kg	(<3 yrs)	1	1	1	1	1	1
15 - 24 kg	(3 - 8 yrs)	2	2	2	2	2	2
25 - 34 kg	(9 - 14 yrs)	3	3	3	3	3	3
35+ kg	(>14 yrs)	4	4	4	4	4	4

since 2004, and Mpumalanga since 2005. AL had a cure rate of 99%,[10] and is now recommended nationally for the treatment of uncomplicated malaria.[3]

AL is available as co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The total recommended AL treatment is a 6-dose regimen given twice daily over 3 days (Table II). Treatment should preferably be dosed according to body weight rather than age. An advantage of this particular combination is that lumefantrine is not available as a monotherapy and has never been used by itself for the treatment of malaria. Lumefantrine absorption is enhanced by co-administration of fat. Low drug levels, and the resultant treatment failure, could result from inadequate fat intake. It is therefore essential that patients or caregivers are informed of the need to take AL with milk or fat-containing food (1.2 g of fat, equivalent to 100 ml milk) – particularly on the second and third days of treatment.[11]

Oral quinine for 7 days, combined with either doxycycline or clindamycin, remains an alternative to AL, but compliance with this poorly tolerated regimen is seldom achieved in an outpatient setting.

Ideally, treatment should be initiated in hospital, as disease severity is frequently underestimated and progression to severe malaria in non-immune individuals can occur despite treatment. The clinical and parasitological response of patients to treatment, particularly their mental state, respiratory rate and urine output, should be monitored regularly and carefully. If hospital admission is not feasible, patients should at least be observed for 1 hour after treatment to ensure that the medication is absorbed and not vomited. Patients who cannot tolerate oral treatment because of repeated vomiting will require parenteral quinine (10 mg/kg). Adequate (but not excessive) fluids should be given, along with paracetamol (15 mg/kg) and tepid sponging, if required.

Patients should respond clinically and parasitologically to AL within 24 - 48 hours. Patient adherence is a major determinant of the response to antimalarial therapy; therefore patients and caregivers need to be given a clear explanation of the times of dosing and be adequately motivated to complete the treatment regimen even if symptoms resolve earlier. Poor compliance and possible drug resistance should be considered if patients have not improved significantly within 72 hours, when rescue treatment with quinine may be necessary. In the rare event of patients who fail AL treatment despite full compliance, a full treatment course of oral quinine (plus doxycycline or clindamycin) should be given under observation in hospital. Limited data support the use of the same regimen in patients weighing more than 65 kg, although this group has been less well studied.

The safety of AL is supported by a reasonable evidence base, but mainly from clinical trials conducted primarily in South-East Asia.[12] Rare but serious side-effects are often not detected in clinical trials. It is essential that health care workers report any suspected, serious adverse drug reactions, particularly to new medicines, to the National Adverse Drug Event Monitoring Centre (tel (021) 406-6234 for an ADR report form).

Treatments not recommended for falciparum malaria

Monotherapies (antimalarial agents used on their own) are no longer recommended for the treatment of falciparum malaria. Chloroquine and sulfadoxine-pyrimethamine (Fansidar, Roche) are not used after the emergence of high-level resistance in much of Africa, including South Africa. Artemisinin derivatives (artemether, artesunate) should not be used as monotherapy as these could select for drug resistance and compromise the value of the ACTs on which we rely heavily for effective treatment.[8] Compliance with the 7-day monotherapy regimen required to effect a cure is hard to achieve when symptoms are generally relieved within 48 hours. Although no artemisinin monotherapies are registered in South Africa, there is concern with regard to the availability of these in neighbouring countries and over-the-counter herbal and homeopathic preparations. In South Africa mefloquine is registered only for prophylaxis and not for treatment, given the higher incidence of severe neuropsychiatric adverse effects associated with treatment doses.[12] Halofantrine treatment is not advisable given the associated cardiotoxicity, variable bioavailability and drug interactions in patients who have taken mefloquine prophylaxis. Clindamycin and doxycycline are too slow acting to be used as monotherapies, but are used in combination with quinine.

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In a nutshell

- Malaria requires urgent diagnosis and urgent treatment.
- It is easy to underestimate disease severity.
- Uncomplicated malaria may progress to severe disease despite recommended treatment.
- Careful monitoring and management of complications are critically important.