

Malaria is a notifiable disease

6. TREATMENT^{11,12,13}

It is recommended that patients receive prompt treatment with the most effective treatment regimen available. Ideally, treatment should be initiated in hospital.

The choice of chemotherapy for malaria is dependent on the severity of disease, the known or suspected resistance pattern of the parasite in the area where the malaria infection was acquired, the species of parasite, patient characteristics (age, pregnancy, co-morbidity, allergies, other medications) and the presence or absence of vomiting. In South Africa, malaria treatment varies in the different provinces due to differences in the resistance patterns. These treatment guidelines may not be appropriate for infections contracted in other countries (eg Thailand, Myanmar, Cambodia) with high levels of multi-drug resistance.

Drug choices may change over time depending on future development of parasite resistance and availability of other antimalarial treatment.

6.1. UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

6.1.1 CHEMOTHERAPY

It is important to attempt to differentiate between uncomplicated and severe malaria. Patients with uncomplicated malaria include: those who have mild symptoms, are ambulant and have no evidence of organ dysfunction either clinically or on laboratory tests and in whom the parasite count is less than 5% (see severe malaria section for details). However, uncomplicated malaria may progress to severe malaria rapidly if the patient is not treated appropriately.

For patients with uncomplicated malaria, the recommended chemotherapy is artemether plus lumefantrine (Coartem®) or alternatively quinine plus either doxycycline or dindamycin (See 6.1.3.2). However, artemether lumefantrine is only currently registered for the treatment of drug resistant malaria in endemic areas in patients weighing less than 65kg.

In Mpumalanga and Limpopo (Northern) provinces, sulfadoxine-pyrimethamine (SP) is currently used as first line therapy. Combination therapy using an artemisinin derivative will be introduced in the near future. A combination of SP and artesunate will replace all SP monotherapy. This combination is not effective for malaria acquired in KwaZulu-Natal as significant SP resistance is present in this area (See 6.1.3.2).

6.1.2 GENERAL MANAGEMENT

Adequate fluids should be given as well as antipyretics (if required). The clinical and parasitological response of patients to treatment should be monitored regularly and carefully, in particular, the mental state, respiratory rate and urine output. It is easy to underestimate the severity of disease. Complications may arise despite apparent appropriate chemotherapy.

Patients should experience a clinical response to therapy within 24 - 48 hours, although fever may persist for up to 5 days after treatment has commenced. A repeat peripheral blood smear should be performed where possible after 72 hours of treatment by which time a decrease of at least 75% of the initial parasite count is expected with effective treatment. Drug resistance (or non-compliance) should be considered if clinical or parasitological responses are poor, and alternative therapy may be necessary. For patients who fail initial SP therapy, quinine or

artemether lumefantrine should be used. Either artemether lumefantrine (or mefloquine) should be used for the rare cases of quinine resistance.

6.1.3 DRUGS USED IN THE TREATMENT OF *PLASMODIUM FALCIPARUM* MALARIA

6.1.3.1 Quinine ^{12,13}

Quinine is a rapidly acting, effective antimalarial drug for both uncomplicated and severe malaria acquired in sub-Saharan Africa. Quinine resistance is rare in this area. Oral quinine therapy is recommended in uncomplicated malaria, but the initial doses of quinine should be administered intravenously if the patient is vomiting. Quinine therapy should be continued for 7 - 10 days. The addition of a second, effective, anti-malarial drug, i.e. doxycycline or clindamycin, is indicated to ensure complete parasite clearance and improve cure rates. One of these agents should be added 2 - 3 days after commencement of the quinine, to ensure that possible adverse effects from the quinine are not confused with those of the second agent. In patients less than 8 years of age or during pregnancy, clindamycin may be used but doxycycline or other tetracyclines are contra-indicated. Shortened courses of quinine (3 days) cannot be recommended for treatment of non-immune patients.

Minor adverse effects, causing a syndrome known as cinchonism, are frequent during the treatment of malaria with quinine. Mild hearing impairment (notably high tone deafness), tinnitus, headache, nausea and slight visual disturbances are common, occurring in up to 70% of patients during quinine therapy and are not an indication to discontinue therapy. Major side effects include arrhythmias, hypersensitivity and hypoglycaemia. Hypoglycaemia is the most frequent serious adverse reaction.

Quinine toxicity presents with central nervous system (CNS) disturbances (visual and auditory being the most common manifestations) and cardiovascular abnormalities (hypotension, heart block, ventricular arrhythmias), and can be confused with severe malaria. Cardiotoxicity is particularly related to rapid infusion of quinine.

6.1.3.2 Artemisinin derivatives including artemether lumefantrine (Coartem®), artesunate and arteether ^{14,15,16,17}

A number of derivatives of this group of compounds, notably artemether and artesunate have been used successfully in the treatment of drug-resistant *P. falciparum* malaria including multidrug-resistant malaria. A number of different artemisinins are available globally. They differ in their efficacy, absorption, bioavailability, and toxicity. These drugs clear parasites most rapidly from the peripheral blood, have a favourable safety profile and may reduce malaria transmission by decreasing gametocyte development. These drugs are effective for both uncomplicated *P. falciparum* malaria infections as well as the blood stages of *P. vivax* infections. In patients with severe malaria, only parenteral artemisinins are effective. When used as single-drug therapy for short periods, recrudescence is common, and therefore these drugs should always be used in combination with a longer-acting antimalarial. Combination therapy would also have an important role to play in delaying drug resistance. The choice of the second drug will depend on resistance, cost, side effect profile and efficacy. Drugs evaluated in combination include lumefantrine with artemether and SP with artesunate. However, AS/SP is not currently registered for use in South Africa. **Artesunate combination with SP is only to be considered in areas where resistance to SP monotherapy is established to be low.** The rationale for adding artesunate to SP in areas where SP resistance is low is to potentially retard further development of resistance to SP monotherapy.

Artemether is available as a fixed dose combination with lumefantrine as artemether lumefantrine (coartem® - artemether 20mg plus lumefantrine 120mg). Artemether lumefantrine was introduced into KZN in 2001 as first-line therapy for uncomplicated *P. falciparum* malaria, due to high level chloroquine and SP resistance. This drug has been best studied in patients weighing less than 65kg and thus is not yet registered for use in patients weighing greater than 65 kg, although initial results in this group are encouraging. It is contra

indicated in pregnancy and in those patients who have history of allergy to artemether lumefantrine. Data in children less than 1 year of age is limited. **Adequate absorption of the lumefantrine component is critically dependent on co-administration with food containing fat or milk. Absorption of artemether lumefantrine may be decreased in patients with severe malaria, and is therefore not recommended.**

As this is a relatively new drug, no drug interactions or contra-indications other than pregnancy and allergy have been identified. Adverse effects identified include: sleep disturbances, headaches, dizziness, palpitations, abdominal pain, anorexia, cough, arthralgia, myalgia, asthma and fatigue. Rarely, hypersensitivity reactions have been reported. Adverse events or potential drug interactions should be reported to the National Adverse Drug Event Monitoring Centre [021- 4486181 (fax) or 021- 4066234 (tel)].

Parenteral artemisinin derivatives notably artemether and artesunate have been successfully used for treating severe malaria. The only parenteral artemisinin currently available in South Africa is arteether. Arteether is an oil based preparation given intramuscularly. Absorption (and therefore its efficacy) in severely ill patients may be compromised.¹⁷ Animal (but not human) studies have shown evidence of brain stem damage. Parenteral quinine remains the preferred treatment for severe malaria in Africa.

6.1.3.3 Sulfadoxine-Pyrimethamine (SP)

The fixed dose combination of sulfadoxine and pyrimethamine (SP, Fansidar®) is used as first line treatment for uncomplicated malaria in some malaria areas with chloroquine resistance. The use of this combination is, however, limited due to the emergence of SP resistant parasites.

In KZN, high level (>60%) SP resistance emerged in 1999/2000 leading to a significant number of treatment failures, necessitating replacement of SP as first-line therapy.

SP is currently recommended for the treatment of uncomplicated infections in the malaria control programmes in Mpumalanga and Limpopo provinces. A combination of SP with an artemisinin derivative (artesunate) will be introduced in the near future for these areas where SP resistance has not reached significant levels, to delay the emergence of this resistance.

Sulfadoxine is a sulphonamide and is contra-indicated in patients with sulphonamide hypersensitivity and those with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

SP is a slow acting schizonticide and should not be used alone when there is a high risk of severe malaria. Severe cutaneous adverse effects have been reported.

6.1.3.4 Mefloquine

Mefloquine is not registered in South Africa for treatment of malaria, but is one recommended option for chemoprophylaxis. It may be considered for treating uncomplicated malaria when multi-drug resistance, including quinine resistance, is suspected. Neuropsychiatric adverse effects, including psychotic episodes, depression and anxiety are significantly more frequent with treatment doses than with prophylactic doses of mefloquine.

6.1.3.5 Halofantrine¹⁸

Halofantrine has been used for treatment of *P. falciparum* malaria. Reports of cardiotoxicity, and variable bio-availability preclude it being recommended for use for routine management of malaria. Halofantrine should never be used following mefloquine prophylaxis because of potential cardiotoxicity.

6.1.3.6 Tetracyclines

The tetracyclines are slow acting anti-malarial drugs. They should never be used alone for the treatment of malaria but are indicated in addition to quinine to improve cure rates. A seven day course of a long-acting tetracycline such as doxycycline should be commenced approximately 3 days after initiation of quinine treatment. Doxycycline is considered an effective chemoprophylactic agent for malaria.

6.1.3.7 Clindamycin ^{19,20}

Clindamycin should never be used alone for the treatment of malaria, but is indicated in addition to quinine to improve cure rates. Clindamycin can be used in pregnant women and children less than 8 years, in combination with quinine.

6.1.3.8 Chloroquine

Although chloroquine was previously the treatment of choice for malaria, the use of chloroquine is now limited because of widespread resistance globally.

Rates of resistance to chloroquine are too high to recommend its use as treatment for *P. falciparum* infections in South Africa (and in almost all other malaria endemic areas).

6.2 TREATMENT OF NON *PLASMODIUM FALCIPARUM* INFECTIONS

In sub-Saharan Africa, between 5 - 10% of the malaria infections are due to one of the other *Plasmodium* species, namely *P. vivax*, *P. ovale* or *P. malariae*. Infections contracted in the Caribbean and some countries in Central America and the Middle East are mostly due to *P. vivax*. Generally, disease due to infection with the non-falciparum malaria is uncomplicated, although *P. vivax* has rarely caused acute respiratory distress syndrome, and *P. malariae* may be associated with the nephrotic syndrome in children. The parasite species should be reliably confirmed microscopically. If unsure of the species, standard treatment for *P. falciparum* should be administered. *P. ovale* and *P. malariae* are currently chloroquine-sensitive, but rare cases of chloroquine-resistant *P. vivax* have been documented in Oceania and Brazil.

Pure infections of *P. malariae* can be treated with chloroquine monotherapy, while infections with *P. vivax* or *P. ovale* should be treated with chloroquine and a follow-up course of primaquine to eradicate the residual intrahepatic phase to prevent relapse.

Primaquine is **contra-indicated** in children less than 1 year of age and during pregnancy. In pregnant women eradication of the intrahepatic stage must be delayed until after delivery. Patients with severe **glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (<10% residual enzyme activity)** should not receive primaquine due to the risk of severe haemolytic anaemia. There is no proven alternative for these patients, although continuing weekly prophylactic chloroquine, (usually for 3 years) may be effective. Primaquine can be taken by patients with mild deficiency of G-6-PD (10 - 60% residual enzyme activity) at a reduced dose of 0.5 - 0.7mg/kg body weight, once every 7 days for 8 weeks. Such patients should be evaluated for anaemia and haemoglobinuria at 3, 7, and 10 days after the start of primaquine²¹.

6.3 TREATMENT OF MIXED *PLASMODIUM* INFECTIONS

In patients with confirmed or suspected mixed infections i.e. *P. falciparum* with either *P. vivax* or *P. ovale*, the standard therapy for uncomplicated or severe *P. falciparum* malaria plus a follow-up course of primaquine is recommended. A mixed infection of *P. falciparum* and *P. malariae* should be managed as for *P. falciparum* malaria. The severity of the *P. falciparum* infection should dictate choice of initial therapy. Doubt frequently exists about the presence of *P. falciparum* in addition to other *Plasmodium* species. The patient should then be treated for *P. falciparum*, as this is the species most frequently associated with severe infections and complications.

6.4 TREATMENT OF PREGNANT WOMEN^{22,23}

Pregnant women with malaria should receive prompt treatment with the most effective antimalarial available, since both the pregnant woman and her baby are at high risk of a fatal outcome. Malaria is frequently misdiagnosed as a pregnancy related infection.

In pregnancy the disease is frequently more severe, with higher parasitaemias and may lead to abortion, intra-uterine death, premature labour, low birth weight or rarely congenital malaria. Eclampsia and post-partum haemorrhage may affect the mother. **Severe anaemia, cerebral malaria, hypoglycaemia** (often refractory to treatment) and **acute respiratory distress syndrome** are serious malaria complications in the mother. The mortality rate from malaria is 2 - 10 times greater in pregnancy. The pregnancy-related morbidity and mortality from malaria extends into the early post-partum period.

The treatment of choice for malaria in pregnancy is quinine. Quinine has proved to be safe when used in normal therapeutic doses, and since the risks of malaria are great, there is no debate about using a less effective therapy. Quinine's main adverse effect in pregnancy is hypoglycaemia and patients should be closely monitored for this. Quinine may be oxytocic, but this effect may also be due to the malaria itself. The incidence of teratogenesis is unknown, although congenital abnormalities, notably CNS anomalies and limb defects have been rarely reported with quinine use in the first trimester.

With the doses used to treat malaria, the benefits of quinine therapy outweigh the risks. Currently the artemisinin group of drugs are not recommended routinely in pregnancy because of a lack of safety data.

6.5 TREATMENT OF INFANTS AND YOUNG CHILDREN^{23,24,25,26,27}

Infants and young children (especially those < 5 years) are particularly at risk for severe malaria and complications can develop very rapidly without warning. The symptoms of malaria in children may differ from those in adults, and therefore malaria should be suspected if a child exposed to malaria develops a febrile illness. Poor feeding, lethargy, irritability, coughing and convulsions (frequently subtle), are important presenting features. **Hypoglycaemia, cerebral malaria, anaemia, and metabolic acidosis** are important complications.

Agitation and respiratory distress (as a result of metabolic acidosis) are ominous signs. Secondary bacterial infections, including septicaemia, are common and broad-spectrum antibiotics should be given to children with severe malaria. Renal failure and acute respiratory distress syndrome are rare in young children. Meningitis is important in the differential diagnosis of malaria.

For children with uncomplicated malaria the treatment of choice **ideally should be quinine**. This is because of the potential for complications to develop rapidly. Artemetherlumefantrine may be considered an alternative agent in children greater than 1 year of age. In Mpumalanga and Limpopo (Northern) province SP is currently used.

Intravenous quinine is indicated for severe malaria and in children in whom vomiting is a problem. Particular care must be taken to ensure that the correct dosage is administered. Where intravenous quinine is not promptly available, or cannot be given safely, initial administration of quinine by deep intramuscular injection using scrupulous aseptic technique, should be considered prior to referral. When given intramuscularly, quinine dihydrochloride should be diluted to reduce pain and prevent sterile abscess formation. Dilutions to **between 60 and 100 mg/ml** should be made.

As there is no quinine syrup available, quinine can be difficult to administer to children. Crushed tablets mixed in mashed bananas, chocolate syrup or jam can be used to make the quinine more palatable.