Chapter 23

MALARIA DIAGNOSIS, PREVENTION & TREATMENT

There are five *Plasmodium* species that are known to infect humans. In South Africa malaria is endemic in the north-eastern reaches of the three provinces of KwaZulu-Natal, Limpopo and Mpumalanga. The risk of infection peaks during the summer rainfall season, typically between September and May. The predominant malaria species in South Africa is *Plasmodium falciparum*, transmitted by *Anopheles* mosquitoes. Neighbouring countries such as Zimbabwe and Mozambique also have malaria-endemic areas and are an important source of imported malaria into South Africa.

PLASMODIUM SPECIES	NOTES
Plasmodium falciparum	• Responsible for the majority of cases in southern Africa • Associated with severe and fatal disease • Incubation period is 7–21 days after being bitten by an infected mosquito • Presentation more than four weeks after returning from the endemic area is unusual but may occur in patients who have had either inappropriate chemoprophylaxis or who did not adhere to the prescribed regimen
Plasmodium vivax	• Has dormant liver stages called hypnozoites that can activate and cause infection several months or years later
Plasmodium ovale	
Plasmodium malariae	• Occurs in Africa, Southeast Asia, Oceania and South America with a relatively low prevalence
Plasmodium knowlesi	• Circulates naturally in the long-tailed macaques in South East Asia • Sporadic cases of human infection

MALARIA PREVENTION

PREVENTING MOSQUITO BITES

Since no chemoprophylactic agent is 100% effective, measures to avoid being bitten by mosquitoes are important and include:

- Avoiding mosquitoes by limiting exposure during times of feeding (i.e. dawn, dusk)
- Wearing long-sleeved clothing
- Using insect repellents containing DEET (N, N-diethyl-m-toluamide). Apply 95% DEET, which lasts up to 10–12 hours, or 35% DEET, which lasts four to six hours. In children, use a concentration of DEET less than 35%; apply sparingly only on exposed skin and remove when no longer exposed.
- Using bed nets that are treated with permethrin

CHEMOPROPHYLAXIS

Chemoprophylaxis with antimalarials in patients travelling to endemic areas is recommended, in addition to the above measures. Pregnant women and children under five years of age should avoid travelling to malaria areas if possible.

SUMMARY OF MALARIA CHEMOPROPHYLAXIS

PATIENT	MEFLOQUINE	DOXYCYCLINE	ATOVAQUONE-PROGUANIL
Immunocompetent adults	Can be used	Can be used	Can be used
Pregnant women	Safe in all trimesters of pregnancy	Contraindicated	Contraindicated
Children < 5 years of age	Can be used if > 3 months of age or > 5 kg	Can be used if > 8 years of age	Paediatric tablets can be given if > 11 kg. Breaking adult tablets NOT recommended
HIV-infected		Best option for prophylaxis	
Long term travellers	Can be used up to 3 years (use with caution)	Can be used up to 2 years	Can be used up to 1 year

DRUG OPTIONS FOR MALARIA CHEMOPROPHYLAXIS

MEFLOQUINE (LARIUM®)

Start one week before entering a malaria area, take once weekly while in the malaria area, and for 4 weeks after leaving the malaria area.

Adult dose

250 mg PO once per week

Paediatric dose

5–19 kg	0.25 tablet PO once per week
20–30 kg	0.5 tablet PO once per week
31–45 kg	0.75 tablet PO once per week
> 45 kg	1 tab PO once per week

Adverse effects

Gastrointestinal, headache, dizziness, imbalance, mood changes, insomnia, nightmares and rarely, psychosis. Increased risk of eye disorders. Contraindications: epilepsy, neuropsychiatric disorders; those who require fine motor co-ordination such as divers and pilots – rather use an alternative agent.

Note: Mefloquine can be used in pregnancy, but generally only in the second and third trimester. It may also be used in breastfeeding mothers.

Mefloquine should not be given to children < 5 kg

DOXYCYLINE

Taken daily, starting one day before entering the malaria area, then daily while in the malaria area, and for 4 weeks after leaving the malaria area.

Adult dose

100 mg/day PO daily

Paediatric dose

< 8 years	Do not administer
> 8 years	2 mg/kg/day PO up to 100 mg/day

Adverse effects

Skin photosensitivity, oesophagitis, upper gastrointestinal symptoms, vaginal candidiasis and diarrhoea.

Note: Doxycycline is the preferred option for HIV-infected patients taking antiretrovirals.

ATOVAQUONE-PROGUANIL (MALANIL®)

Taken daily, starting one to two days before entering the malaria area, then daily while in the malaria area, and for seven days after leaving the area. May be a good prophylactic option for patients who are visiting areas with chloroquine-resistant malaria and who cannot tolerate mefloquine.

Adult dose

Each tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride. The dose is 1 tablet daily taken orally.

Paediatric dose

Dosage for children is based on body weight. A lower-dose paediatric tablet (62.5 mg of atovaquone and 25 mg of proguanil hydrochloride) is available.

11–20 kg	1 paediatric tablet PO daily
21–30 kg	2 paediatric tablets PO daily
31–40 kg	3 paediatric tablets PO daily
>40 kg	As for adults

Adverse effects

Adverse reactions are uncommon and include headache, nausea, vomiting, abdominal pain and diarrhoea.

Atovaquone-proguanil is not recommended for children under 11 kg.

CHEMOPROPHYLAXIS IN LONG-TERM TRAVELLERS

- A long-term traveller is defined as a person staying permanently in an area for six months or longer.
- Long-term travellers to high-risk areas should take malaria chemoprophylaxis, even if this is necessary over several years.
- Options include:
  - Mefloquine: The best-documented drug for long-term travellers and can be used for prolonged periods > 12 months. Neuropsychiatric side effects are common and can persist for months or years after discontinuing mefloquine. If the drug is to be administered for a prolonged period, periodic evaluations including liver function tests and evaluations for neuropsychiatric effects should be performed.
  - Doxycycline: Can be used for up to two years but side effects, especially vaginal candidiasis in women, is a problem for long-term users.
  - Atovaquone-proguanil: Has been shown to be safe for continuous use up to 12 months.

MALARIA INFECTION

CLINICAL

- Any patient with unexplained fever must be tested for malaria, even in the absence of a recent travel history.
- **Symptoms:** non-specific and may include a flu-like illness with fever, headache, malaise, fatigue and muscle aches. Some patients present with diarrhoea and other GI symptoms.
- **Signs:** most patients with malaria have no physical findings, but splenomegaly may be present.
- **Laboratory findings:** thrombocytopaenia, relative lymphopaenia, atypical lymphocytes, and an elevated lactate dehydrogenase (LDH) level may be present.

SEVERE MALARIA: COMPLICATIONS

- **Cerebral malaria:** This is almost always caused by *P. falciparum* infection. Coma may occur and can usually be distinguished from a post-ictal state secondary to a generalised seizure if the patient does not regain consciousness after 30 minutes. When evaluating patients with malaria-associated coma, hypoglycaemia and other central nervous system (CNS) infections should be excluded.
- **Severe anaemia:** The anaemia associated with malaria is multifactorial and is usually associated with *P. falciparum* infection. In non-immune patients, anaemia may be secondary to erythrocyte infection and a loss of infected red blood cells (RBCs). In addition, uninfected RBCs are inappropriately cleared, and bone marrow suppression may be involved.

- **Renal failure:** This is a rare complication of malaria infection. Infected erythrocytes adhere to the microvasculature in the renal cortex, often resulting in oliguric renal failure. Renal failure is typically reversible, and supportive dialysis is often needed until kidney function recovers.
- **Respiratory symptoms:** Patients with malaria may develop metabolic acidosis and associated respiratory distress. In addition, pulmonary oedema can occur.
- **Metabolic acidosis**

LABORATORY TESTS FOR MALARIA

- A diagnosis of malaria should preferably be supported by the identification of the parasites on thick and thin blood smears.
- The highest yield of peripheral parasites occurs during or soon after a fever spike; however, smears should not be delayed while awaiting fever spikes.

MICROSCOPIC TESTS	
Thick smears	• 20–40 times more sensitive than thin smears, but speciation may be more difficult • Slower turn-around time: 100–400 fields are examined by an experienced technologist before negative result is reported
Thin smears	• Less sensitive than thick smears • Facilitates speciation • Allows for quantification of the level of parasitaemia which is usually expressed as a percentage of parasitised red blood cells • > 4% parasitaemia is generally associated with severe disease
Quantitative buffy coat (QBC)	• More sensitive than thick smears • Rapid and technically easy to perform • Involves acridine orange staining of a centrifuged and concentrated red blood cells with examination under a UV light • Speciation is not possible

If all the microscopic tests are negative it makes the diagnosis of malaria unlikely. However, microscopic tests should be repeated every six to 12 hours for 48 hours if malaria is still clinically suspected, especially if antimalarials, or antibiotics which have anti-malaria activity such as fluoroquinolones, tetracyclines or cotrimoxazole, have been taken recently.

RAPID ANTIGEN DETECTION TESTS	
Rapid antigen tests	• Usually done when the laboratory does not have sufficient expertise to do blood smears, e.g. small peripheral laboratories • Can detect either *P. falciparum* only or *P. falciparum* and some of the other *Plasmodium* species • Not able to detect mixed infections; must perform microscopic or PCR tests • Generally insensitive for the detection of any non *P. falciparum* species • False-positive and false-negative results may occur; microscopic tests remains mandatory in patients with suspected malaria • Should not be used for follow-up patients as the test remains positive for many weeks following successful treatment

POLYMERASE CHAIN REACTION (PCR)	
	• Two PCR tests are available: one that detects all *Plasmodium* species (screening malaria PCR) and one that can detect and differentiate the *Plasmodium* species (malaria speciation PCR) • PCR testing is more sensitive than thick smears and the QBC microscopic technique and can detect malaria when all the microscopic techniques are negative • PCR testing is recommended when: – Malaria is strongly suspected, and all malaria microscopic tests (including the QBC) tested negative – The malaria rapid antigen detection assay is positive and all microscopic tests were negative – Specific identification is required when malaria parasites have been detected by any of the microscopic tests, but species identification is not possible due to low level parasitaemia or when a mixed infection is suspected

OTHER LABORATORY TESTING

- Blood cultures should be drawn in a febrile patient: typhoid and other bacterial infections often form part of a differential diagnosis in patients returning from tropical areas. In addition, patients from tropical areas may have more than one infection and additional or secondary infections should be considered when patients do not respond to antimalarials.
- Blood glucose: hypoglycaemia may occur in patients with malarial infection and should be ruled out in patients with mental status changes.
- Full blood count: Haemoglobin (decreased in 25%, often profound in young children), platelet counts (thrombocytopaenia in ~ 50–68%).
- Liver function (results abnormal in ~ 50%), including lactate dehydrogenase (LDH) level.
- Monitor renal function and electrolytes.
- Monitor parameters suggestive of haemolysis (haptoglobin, LDH, reticulocyte count).
- If the patient is to be treated with primaquine, a glucose-6-phosphate dehydrogenase (G-6-PD) level should be obtained because primaquine can result in severe haemolysis in patients with a G-6-PD deficiency.

TREATMENT OF MALARIA

GENERAL POINTS

- Choice and route of treatment depends on:
  - The disease severity:
    - Uncomplicated malaria: symptomatic infection without evidence of vital organ dysfunction.
    - Severe malaria: persistent vomiting, clinical jaundice, change in mental status or increase in respiratory rate (see criteria for the diagnosis of severe malaria in this chapter).
  - The *Plasmodium* species responsible for the infection.
  - The presence of mixed infections.

- Drugs that should not be used for treatment include:
  - Halofantrine: due to frequent cardiac side-effects.
  - Chloroquine and sulphadoxine-pyrimethamine (Fansidar®): due to widespread *P. falciparum* resistance and the availability of more effective agents.

UNCOMPLICATED MALARIA

SUMMARY OF UNCOMPLICATED P. FALCIPARUM TREATMENT

PATIENT	1ST CHOICE	ALTERNATIVE
Adults	Artemether-lumefantrine (Coartem®)	Oral quinine, combined with 7 days of doxycycline
Children	Artemether-lumefantrine (Coartem®)	< 8 years: Oral quinine combined with 7 days of clindamycin ≥ 8 years of age: Oral quinine combined with 7 days of doxycycline
Pregnant women 1st trimester	Oral quinine combined with 7 days of clindamycin	None
Pregnant women 2nd and 3rd trimester	Artemether-lumefantrine (Coartem®)	Oral quinine combined with 7 days of clindamycin

UNCOMPLICATED FALCIPARUM MALARIA: ARTEMISININ

- Artemisinin and its derivatives are powerful medicines known for their ability to swiftly reduce the number of *Plasmodium* parasites in the blood of patients with malaria.
- Artemisinin-based combination therapies (ACTs) combine two active ingredients with different mechanisms of action:
  - The role of the artemisinin compound is to reduce the main parasite load during the first three days of treatment.
  - The role of the partner drug is to eliminate the remaining parasites.
- The WHO recommends ACTs for the treatment of uncomplicated *P. falciparum* malaria in children and adults, except for pregnant women in their first trimester.
- In South Africa, artemether-lumefantrine (Coartem®) is the most commonly available ACT:
  - For optimal absorption, Coartem® must be taken with milk or fat-containing food.
  - Coartem® is considered safe and efficacious during the second and third trimesters of pregnancy.
  - Treatment dosage should be weight-based:
    - Coartem® is registered for use only for patients weighing ≤ 65 kg. Treatment should be administered for three days.
    - Minimal pharmacokinetic data exist for larger patients; one study suggests a trend towards increased risk of treatment failure in patients > 80 kg. To optimise treatment success for patients > 80 kg: ensure compliance, fat co-administration and increase duration of treatment to five days.

UNCOMPLICATED FALCIPARUM MALARIA: QUININE

- Oral quinine plus doxycycline or clindamycin remains an alternative to Coartem®.
- For women in their first trimester of pregnancy or children younger than eight years, a supervised seven-day course of oral quinine plus clindamycin should be used (doxycycline is contraindicated).
- Doxycycline or clindamycin add no early treatment benefit, so they are started only once symptoms improve, as gastrointestinal side-effects may exacerbate those of quinine.

UNCOMPLICATED NON-FALCIPARUM AND MIXED INFECTION

- Where doubt exists about the presence of *P. falciparum* in addition to other *Plasmodium* species, the patient should be treated for *P. falciparum* as this is the species most frequently associated with severe infections and complications.
- *P. vivax* and *P. ovale* infections require primaquine in order to eliminate the hypnozoites (liver phase) and prevent relapse.
  - Primaquine is given after the treatment course of Coartem® and after excluding glucose-6-phosphate dehydrogenase (G-6PD) deficiency.
  - Primaquine is not currently registered in South Africa but can be obtained on a named-patient basis with Section 21 MCC approval.

PLASMODIUM SPECIES	NOTES
Mixed *P. vivax* and *P. ovale*	Artemether-lumefantrine (Coartem®) for initial therapy followed by primaquine for uncomplicated infection
Mixed *P. falciparum* and *P. ovale* or *P. vivax*	Artemether-lumefantrine (Coartem®) followed by primaquine for uncomplicated infection
Mixed P. falciparum and P. malariae	Treated as for *P. falciparum*
P. malariae only	Chloroquine monotherapy OR Artemether-lumefantrine (Coartem®)

DOSES OF ORAL ANTI-MALARIAL DRUGS

ARTEMETHER-LUMEFANTRINE (COARTEM®)

Contains a fixed ratio of 20 mg artemether and 120 mg lumefantrine (1:6 parts)

< 35 kg body weight: use paediatric dosing; take 6 doses over a 3 day period as described for adults

≥ 35 kg body weight: one dose is 4 tablets; take 6 doses over a 3 day period

Adult dose

Day 1: Take 1 dose (4 tablets), followed 8 hours later by 1 dose

Day 2: Take 1 dose twice daily

Day 3: Take 1 dose twice daily

Paediatric dose

Number of tablets per dose by body weight

< 5 kg	Do not administer
5 to < 15 kg	1 tablet/dose
15 to < 25 kg	2 tablets/dose
25 to < 35 kg	3 tablets/dose
≥ 35 kg	Administer as for adults (4 tablets per dose)

ORAL QUININE

Adult dose

600 mg (2 tablets) PO 8 hourly for 7–10 days with oral doxycycline

Paediatric dose

10 mg/kg/day PO divided into 3 doses for 7–10 days with oral doxycycline if older than 8 years

DOXYCYCLINE

Adult dose

100 mg PO 12 hourly for 7 days with quinine; usually added 2–3 days after commencement of quinine

Paediatric dose

< 8 years: do not administer

≥ 8 years: 3.5 mg/kg/day PO divided into two doses for 7 days with oral quinine

CLINDAMYCIN

Adult dose

10 mg/kg PO 12 hourly for 7 days; usually added 2–3 days after commencement of quinine

Paediatric dose

10 mg/kg PO 12 hourly for 7 days; usually added 2–3 days after commencement of quinine

CHLOROQUINE

Adult dose

600 mg base PO (1 Nivaquine® tablet contains 150 mg chloroquine base), then

300 mg base PO after 6 hours, then repeat 300 mg base orally at 24 hours and 48 hours

Paediatric dose

10 mg/kg base PO (not to exceed 600 mg base), then

5 mg/kg base at 6 hours, 24 hours, and 48 hours

℞ **PRIMAQUINE**

Adult dose

Dosage: 1 tablet PO once daily for 14 days

Administered for hypnozoite stage of *P. vivax* and *P. ovale* to prevent relapse

Patient with severe glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should not be treated with primaquine due to the risk of severe haemolytic anaemia.

1 tablet contains 26.3 mg primaquine phosphate which is equivalent to 15 mg primaquine base

Paediatric dose

Dosage: 0.3 mg/kg base (0.5 mg/kg of primaquine phosphate) PO once daily for 14 days

Contraindicated in children less than 1 year of age

MANAGEMENT OF SEVERE MALARIA

Severe malaria is a medical emergency requiring prompt parenteral treatment, intensive care nursing, and careful monitoring and management of complications particularly hypoglycaemia, fluid management and the treatment of associated sepsis.

THE FOLLOWING FEATURES ARE ASSOCIATED WITH SEVERE MALARIA

CLINICAL FEATURES	BIOCHEMICAL FEATURES	HAEMATOLOGICAL FEATURES
• Impaired consciousness or convulsions • Respiratory distress: – acidosis – ARDS – pulmonary oedema • Jaundice • Bleeding • Shock	• Renal impairment – serum creatinine > 265 μmol/L or rapidly rising creatinine – urine output < 400 mL/day (adult) • Acidosis: – plasma bicarbonate < 15 mmol/L – serum lactate > 5 mmol/L • Hepatic impairment: transaminases > 3 times normal • Hypoglycaemia: blood glucose < 2.2 mmol/L • Hypoxaemia: PaO2 < 8 kPa on room air	• Parasitaemia > 4% or > 3 + • Haemoglobin < 6 g/l or haematocrit < 20% • > 5% neutrophils contain malaria pigment • Presence of schizonts of P. falciparum in the peripheral the blood smear • Evidence of DIC

TREATMENT OF SEVERE MALARIA

- Artesunate and quinine are intravenous anti-malarial drugs that are available for the treatment of severe complicated malaria.
- If severe mixed infection with *P. falciparum* and *P. ovale* or *P. vivax* is present treatment should consist of IV artesunate or IV quinine followed by oral primaquine.

TREATMENT: SEVERE MALARIA

FIRST-LINE TREATMENT

Adults

Artesunate 2.4 mg/kg IV at 0, 12 and 24 hours then once daily

Switch to a full course of oral artemether-lumefantrine (Coartem®) when the patient can take oral medication

NOTE

- Preferred treatment for severe malaria including pregnant women
- Associated with lower mortality and fewer complications, particularly hypoglycaemia, compared to IV quinine
- Artesunate is currently not registered and only available on a named patient basis with Section 21 MCC approval. An IV artesunate access programme is being run by the UCT Department of Pharmacology can be accessed by contacting the Secretariat at 021 406 6779 or the UCT Medicines Information Centre at 0800 212 506.

ALTERNATIVE TREATMENT

Adults and Children

- Loading dose: Quinine dihydrochloride 20 mg/kg IV diluted in 5–10 mL/kg body weight of dextrose over 4 hours via rate-controlled infusion
- Six to eight hours after the loading dose the maintenance dose is given: Quinine dihydrochloride 10 mg/kg IV 8 hourly infused over 4–6 hours
- Reduce dose by one third (to 5–7 mg/kg) if used parenterally for more than 72 hours
- IV quinine should be given every 8 hours
- Switch to a full course of oral artemether-lumefantrine (Coartem®) when the patient can take oral medication

NOTE

- The loading dose should be given strictly according to the body weight
- Quinine is given by slow, controlled IV infusion, never by means of a bolus injection as it is cardiotoxic
- The most frequent complication is hypoglycaemia, especially in pregnant women and children
- Blood glucose needs to be monitored 4–6 hourly and managed by bolus doses of 50% dextrose water IV

OTHER IMPORTANT MANAGEMENT PRINCIPLES INCLUDE

- A central venous catheter should be inserted to assist with fluid management. Although resuscitative and general supportive measures are critical, one needs to be cautious about excessive fluid administration which can precipitate or worsen ARDS.
- Broad spectrum antibiotics should routinely be given to all patients with severe malaria, as bacteraemia and septicaemia is common, particularly in children. Antibiotics should cover both Gram-positive and Gram-negative organisms.