GUIDELINES FOR THE TREATMENT OF MALARIA IN SOUTH AFRICA

2009

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PREFACE

Considerable success has been achieved in the control and management of malaria in South Africa in recent years. This is despite the ongoing development of parasite and vector resistance to drugs and insecticides, respectively.

It gives me great pleasure to introduce these guidelines on the treatment of malaria in South Africa.

The **objectives** of these publications are to provide all those involved in the management of malaria with clear and practical guidelines for the diagnosis and appropriate treatment of malaria.

The intended treatment **outcomes** are the prevention of malaria morbidity and mortality. In addition the recommendations are intended to contribute to a reduced malaria transmission and to limit resistance to anti-malarial drugs.

These guidelines are based on the World Health Organization's guidelines for the treatment of malaria. Additional literature surveys have been undertaken. Factors that were considered in the choice of therapeutic options included: effectiveness, safety, and impact on malaria transmission and on the emergence and spread of anti-malarial resistance.

The previous guidelines were compiled in August 2002. Advances in the availability of anti-malarial drugs and changes in respect of transmission, intensity, drug resistance and health care delivery in South Africa have prompted revision of these guidelines.

It is hoped these guidelines will facilitate effective, appropriate and timeous treatment of malaria, thereby reducing the burden of this disease in our communities and in South Africa.

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Minister of Health
Date:

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ABBREVIATIONS

ACT	Artemisinin-based combination therapy
ARDS	Acute respiratory distress syndrome
CDC	Communicable Disease Control
CNS	Central nervous system
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
KZN	KwaZulu-Natal
NSAIDS	Non-steroidal anti-inflammatory drugs
RDT	Rapid diagnostic tests
SP	Sulphadoxine-pyrimethamine

SUMMARY

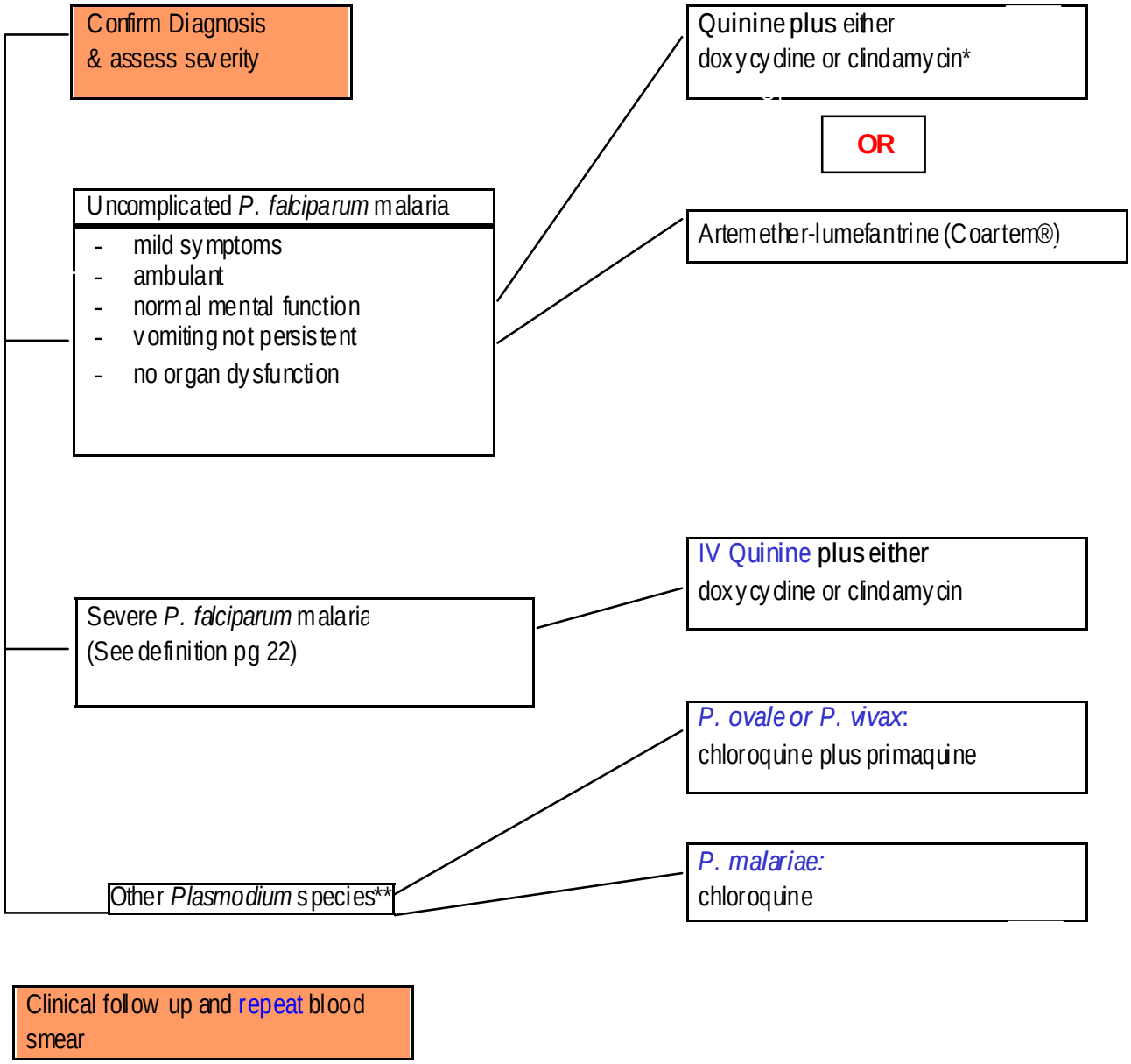
Plasmodium falciparum accounts for the majority of malaria cases in Southern Africa and may be associated with **severe and fatal disease.** Almost all South Africans are non-immune, including residents of seasonal malaria transmission areas, and are therefore at risk for developing severe malaria.

The diagnosis and management of malaria is urgent. Delayed diagnosis and inappropriate treatment are associated with significantly increased morbidity and mortality. Classically, malaria presents with fever, rigors, headache and body pains, but the clinical features are non-specific and may be confused with many other diseases, especially influenza. A definitive diagnosis should be made promptly by demonstrating the parasite on microscopy of a blood smear or by using a rapid malaria antigen test.

The choice of anti-malarial agents is dependent on the severity of illness and the pattern of drug resistance of the parasite in the geographical area where malaria was acquired. In keeping with the WHO recommendations, using anti-malarial drugs in combination is essential, and artemisinin-based combinations are preferred. For uncomplicated malaria acquired in South Africa, artemether-lumefantrine (Coartem®) or alternatively quinine plus either doxycycline or clindamycin is recommended. High-level resistance precludes the use of chloroquine for falciparum malaria. Sulfadoxine-pyrimethamine (SP) is no longer recommended.

For severe malaria, quinine (with the addition of doxycycline or clindamycin) is currently recommended. Patients with severe malaria will require hospital admission. All patients with malaria require careful clinical and parasitological follow-up. The major complications of malaria include: cerebral malaria, hypoglycaemia, anaemia, renal failure, acute respiratory distress syndrome (ARDS) and metabolic acidosis, and these carry high mortality rates especially in children, pregnant woman and in those living with HIV and AIDS. These complications require specific management.

Treatment of Malaria in South Africa- Summary Flowchart 2006



* Add clindamycin or doxycycline as soon as can be tolerated **after** quinine is started. Clindamycin is preferred in children <8 years and pregnant women.

** If unsure of species, treat as for *P. falciparum.* If mixed infection of *P. falciparum* plus *P. vivax / ovale*, treat as for *P. falciparum* plus follow with primaquine

1. INTRODUCTION

The relentless development of drug resistance in malaria parasites (notably *P. falciparum*), has necessitated ongoing updates of chemoprophylaxis and treatment policies globally.

In South Africa, chloroquine resistance was first demonstrated in KwaZulu-Natal (KZN), and later in Mpumalanga. This prompted a policy change from chloroquine to sulphadoxine-pyrimethamine (SP) as first line treatment for uncomplicated malaria in KZN in 1988 and in Mpumalanga and Limpopo provinces in 1997.

The development of significant SP resistance in KZN led to a further policy change in 2001, with artemether-lumefantrine replacing SP as first line treatment for uncomplicated *P. falciparum* infections. Subsequently, in December 2004, Limpopo Province also replaced SP with artemether-lumefantrine. Mpumalanga Province used SP-artesunate in the public sector from 2001 to end of 2005, but moved to an artemether-lumefantrine policy in January 2006.

In order to combat the pattern of continued drug resistance of sequential single drug therapy, combination chemotherapy, preferably using an artemisinin derivative, is the decided policy. Additional benefits include improved treatment outcomes and a decrease in malaria transmission, resulting in greater cost-effectiveness.

These guidelines have been compiled using both international and local information. In South Africa there is ongoing monitoring of malaria prevalence and distribution, and the therapeutic efficacy of anti-malarial drugs. New information arising from such monitoring activities will inform future guidelines.

2. OBJECTIVES

The objectives of malaria treatment are:

- To prevent mortality
- To prevent disease progression and development of severe malaria
- To reduce morbidity
- To eliminate parasitaemia to minimise transmission, and
- To limit the emergence and spread of drug resistance

3. PARASITE SPECIES

More than 90% of human malaria infections in sub-Saharan Africa are due to ***Plasmodium falciparum*** while the rest are due to *Plasmodium ovale, Plasmodium vivax,* or *Plasmodium malariae.* Occasionally mixed infections occur. Infections due to *P. falciparum* may be severe and complicated. These complications occur almost invariably as a result of delay in diagnosis and/or treatment of an uncomplicated infection, the use of ineffective therapy or under dosing with effective drugs.

4. RISK GROUPS

South Africans are non-immune, including residents in areas where malaria transmission occurs. Partial immunity may be acquired after long-term, repeated exposure to *P. falciparum* infection, a situation that occurs in residents of high transmission areas, such as parts of Mozambique, Malawi, Tanzania and some other southern African countries.

Particular high-risk groups for the development of severe *P. falciparum* malaria in South Africa include: non-immune travellers to malaria areas and residents (of all age groups) in malaria areas. Pregnant women, young children, the elderly, splenectomised and immuno-compromised individuals are particularly vulnerable.

There is increasing data on the interaction between HIV and malaria, showing increased clinical attacks of malaria and higher parasite densities in semi-immune adults who are HIV infected. There is also evidence that non-immune patients co-infected with HIV have a higher risk of severe malaria and malaria-related mortality.

5. CLINICAL PRESENTATION AND DIAGNOSIS

A high index of suspicion is the most important element in the diagnosis of malaria. Malaria areas in South Africa include north-eastern KwaZulu-Natal, and low altitude areas of Mpumalanga and Limpopo provinces, particularly those bordering Zimbabwe, Mozambique and Swaziland (see map). Very rarely, malaria is contracted in the North-West and Northern Cape provinces adjacent to the Molopo and Orange rivers respectively.

Malaria transmission occurs in almost all countries in sub-Saharan Africa with the exception of Lesotho. Within each country, geographical distribution of malaria will vary, and year-round transmission with seasonal disease peaks is usual. In southern Africa these peaks are typically from September to May.

5.1 SYMPTOMS AND SIGNS

Symptoms and signs of malaria may present as early as 7 days after exposure, with an average of 10 - 21 days elapsing after being bitten by an infected mosquito. Longer incubation periods may occur in patients who have been on chemoprophylaxis or selected antibiotics e.g. cotrimoxazole, tetracycline, macrolides, chloramphenicol and quinolones. Very rarely, incubation periods for *P. falciparum* of 6 - 18 months have been recorded. Malaria due to infections with *P. vivax, P. ovale* or *P. malariae* can take up to 12 months to first manifest clinically.

As signs and symptoms of malaria are very non-specific, a high index of suspicion is critical.

Signs and symptoms could include the following:

Symptoms in Adults
Fever Headache Rigors (cold shivers and hot sweats) Myalgia Weakness Dizziness Loss of appetite Diarrhoea Nausea and vomiting Sore throat

Symptoms in children
Fever Vomiting Weakness Lethargy Diarrhoea Cough Poor feeding

Clinical signs in adults and children	
Uncomplicated Malaria	Severe Malaria
Fever Splenomegaly and/or hepatomegaly	Fever Severe prostration Splenomegaly and/or hepatomegaly Pallor Jaundice Increased respiratory rate Change in the level of consciousness Reduced urine output Bleeding Shock

Presentation of *P. falciparum* malaria is very variable and may mimic many other diseases (and vice versa) including **influenza,** viral hepatitis, meningitis, septicaemia, typhoid, tick bite fever, gastroenteritis, viral haemorrhagic fever, trypanosomiasis, HIV seroconversion illness, urinary tract infection and relapsing fever.

Non-immune patients with uncomplicated malaria are at increased risk of disease progression to severe *P. falciparum* malaria. Life-threatening complications can develop rapidly in these patients. Malaria should be suspected in any person presenting with any of the above symptoms who has a history of travel to, or residence in, a malaria transmission area (See malaria risk map).

In a febrile patient in South Africa where there is no other obvious cause of fever and a recent history of visiting or living in a malaria area is not forthcoming, malaria should still be considered as infected mosquitoes have been occasionally documented to travel long distances by road, rail and air transport.

5.2 LABORATORY DIAGNOSIS

A diagnosis of malaria cannot be confirmed or excluded clinically. Since the clinical presentation is non-specific and may mimic many other diseases, patient's blood should be examined immediately to confirm or exclude the diagnosis. A blood test for parasites should be done irrespective of the time of the year or whether the patient has or has not taken chemoprophylaxis.

In the majority of malaria cases, examination of correctly stained blood smears will reveal malaria parasites. However, a **negative smear does not exclude the diagnosis**; repeat specimens should be examined regularly and urgently without waiting for fever peaks, until the diagnosis is confirmed, the patient has recovered or another definitive diagnosis is made. Examination of the peripheral blood smear will give an indication of the species of parasite as well as the parasite density. High levels of parasitaemia (>4% or ≥3+)[*] should be treated as severe malaria in non-immune patients. Importantly, the converse may not be true, with severe disease also occurring with low parasitaemias in the peripheral blood. The interpretation of a low parasite count must always be considered in conjunction with the patient's clinical condition and other laboratory results (See 7.1: Severe malaria).

A number of commercial rapid diagnostic tests (RDTs) are available for early diagnosis in health facilities where microscopy is not immediately available. These kits detect parasite antigen namely histidine-rich protein 2 (or lactate

[*]The parasite density refers to the parasite load in the peripheral blood expressed semi-quantitatively (1 to 5+) or as a percentage of infected red blood cells. Quantification is often inaccurate and does not necessarily reflect the total parasite load in the patient.

dehydrogenase or aldolase). The majority of the tests will only detect *P. falciparum*; while a few will detect the other malaria species but are less sensitive for these. The rapid tests for P*. falciparum* are generally highly sensitive. Performance is, however, dependent on the correct storage, usage and interpretation of results and the quality of the particular test used. These tests should be used only for diagnosis of acute malaria infections, and **not for follow-up**, as they may remain positive for several weeks even after successful treatment. The test may be negative early in the disease, and false positives may be encountered rarely.

If the diagnosis of malaria cannot be confirmed (unavailability of laboratory tests, or negative tests), the decision to commence malaria therapy should be made on clinical grounds, based on whether exposure to malaria parasites was possible and the severity of the clinical features. In cases of severe malaria a blood smear or rapid malaria test is likely to be positive. However, some patients with severe malaria may rarely have a negative smear due to sequestration of parasitized red blood cells. In patients who are treated empirically for malaria, it is imperative to continue to look for alternative diagnoses and to follow-up patients very carefully.

Thrombocytopenia is a common finding in patients with malaria. A blood smear should be checked for malaria parasites or an RDT performed whenever this laboratory finding is made unexpectedly. A malaria smear is indicated in patients with recurrent symptoms and a negative RDT, to exclude non-falciparum malaria.

5.3 REFERRAL CRITERIA

NOTE: Clinical judgement must be applied

Ideally all patients with malaria should be treated in hospital. Definite indications for hospital admission:

- All children ≤ 1 year (and consider admitting children up to 5 years where possible)
- All pregnant patients
- All patients ≥ 65 years
- Immuno-compromised patients where possible

- All patients with features of severe malaria or danger signs:
- Confusion
- Decreased level of consciousness
- Convulsions
- Extreme weakness (prostration)
- Jaundice
- Decreased urine output
- Haemoglobinuria
- Severe anaemia (Hb ≤ 6 g/dl)/ HCT ≤ 20%)
- Persistent vomiting (unable to tolerate oral medication)
- Respiratory distress
- Shock
- Suspected treatment failure (including reappearance of parasites within 6 weeks of treatment).

Malaria is a notifiable disease

The notification of all malaria cases is mandatory. The procedure to follow for notifiable medical conditions:

1. **Healthcare worker** (not necessarily a medical doctor): Diagnose (preferably a definitive diagnosis) and notify the malaria case using GW17/5 or applicable notification form, **immediately**, as some of the important information required on the notification form may not be available after the patient has left the healthcare facility. If possible, the malaria species should be specified in the notification form.
2. **Local authority**/hospital/district (whoever is responsible for disease containment) submits the GW17/3 summary of cases and GW17/4 summary of deaths forms weekly.
3. **Regional/district office health information unit** will collate and use this information to plan and monitor the impact of malaria control and case management interventions.

NOTE: As thousands of malaria cases present in non-malaria areas in South Africa each year, it is critical that these cases also get notified to the local

authority to facilitate adequate provision of malaria diagnosis and management resources to healthcare facilities in these areas.

6. TREATMENT

Patients should receive prompt treatment with the most effective regimen available. Where patients present in non-malaria areas, treatment should ideally be initiated in hospital. In malaria areas the majority of patients with uncomplicated malaria can be treated at primary health care level.

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, concomitant medications) and the presence or absence of vomiting.

Drug choices may change over time with the development of parasite resistance or the availability of new anti-malarial treatments.

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 section 7: Severe malaria, for details). However, uncomplicated malaria may rapidly progress to severe malaria if the patient is not treated appropriately.

For patients with uncomplicated malaria, the recommended chemotherapy is the fixed dose artemisinin-based combination, artemether-lumefantrine (Coartem®) in all patients over 1 year of age and non-pregnant patients. In children ≤ 1 year and all pregnant patients, the recommended chemotherapy is **quinine plus clindamycin.**

When artemether-lumefantrine (Coartem®) is not available, uncomplicated malaria can also be treated with quinine plus either doxycycline or clindamycin. It is advisable that quinine only be used as observed treatment of inpatients, due to the possibility of adverse drug reactions and the poor tolerability of this 7-day regimen.

All first doses of drugs must be given under supervision and patients must be observed for at least an hour as vomiting is common in patients with malaria and treatment must be repeated if the patient vomits within the first hour. Vomiting oral treatment is one of the commonest reasons for treatment failure.

6.1.2 General management

It is easy to underestimate the severity of disease and complications may arise despite apparent appropriate chemotherapy. Patients with malaria should be carefully assessed and closely monitored. The clinical and parasitological response of patients to treatment should be monitored regularly; in particular, the mental state, respiratory rate and urine output. Adequate fluids should be given, and antipyretics (paracetamol) administered when needed. Ibuprofen has been used but there is less experience with this compound. Other non-steroidal anti-inflammatory drugs (NSAIDS) should be avoided as they may increase the risk of renal failure in patients with malaria.

If patients with uncomplicated malaria cannot be admitted to hospital for treatment, they (or their caregivers) should be warned of the symptoms and signs of severe malaria and advised of the urgency of then returning for hospitalisation and appropriate treatment.

Patients should experience a clinical response to therapy within 24 - 48 hours. A repeat peripheral blood smear should be performed where possible after 72 hours of treatment: a decrease of at least 75% of the initial parasite count is expected with effective treatment.

Treatment failure in malaria may manifest as:

Early treatment failure:

- Failure to respond clinically and/or achieve ≥75% decrease in parasite count by 72 hours
- No decrease or an increase in asexual/erythrocytic forms of the parasites in peripheral blood 48 hours after starting treatment

Late treatment failure

- Recurrence of parasitaemia within 6 weeks of treatment (which could be either from recrudescence of the original infection or, if in a malaria transmission area, a new infection)
- Presence of parasites 7 days after treatment (excluding presence of gametocytes)

Treatment failure may be due to:

- Parasite resistance to the anti-malarial drug used
- Vomiting of oral medication
- Non-compliance with medication
- Failure to take fat/food with artemether-lumefantrine leading to poor absorption of lumefantrine component
- Re-infection (apparent treatment failure)
- Relapse due to *P. ovale* or *P. vivax* due to failure to treat hypnozoites

NOTE: On a malaria peripheral blood smear, the presence of gametocytes, the stage of malaria parasite's lifecycle responsible for malaria transmission, does not indicate treatment failure, as these may be present for several weeks after successful treatment.

Treatment failures after completing a full course current first-line therapy of either 7-days of quinine (plus doxycycline or clindamycin) or a 3-day artemether-lumefantrine regimen are rare, as both these treatments have very high cure rates. Patients who have failed first-line treatment with artemether-lumefantrine should then be given a course of quinine with either doxycycline or clindamycin. Treatment failures following quinine treatment of uncomplicated malaria could be

treated with artemether-lumefantrine, provided malaria complications are carefully excluded.

6.1.3 Drugs used in the treatment of P*lasmodium falciparum* malaria

6.1.3.1 Artemisinin-based combination therapy

Artemisinin-based combination therapies (ACTs) are now generally considered as the best current treatment for uncomplicated falciparum malaria (WHO 2006). ACTs have the advantages of rapid clinical and parasitological response, improved cure rate, decreased malaria transmission and the potential to delay anti-malarial resistance. A number of artemisinin derivatives have been used successfully in the treatment of *P. falciparum* malaria including multi-drug resistant malaria and for the blood stages of *P. vivax* infections. The most evidence of efficacy and safety is currently available for the derivatives artemether and artesunate. This class of anti-malarial has a favourable safety profile. When used as single-drug therapy (monotherapy) for less than 7 days recrudescence is common. **Therefore the artemisinin derivatives should always be used in combination with an effective, longer-acting anti-malarial.** Combination therapy is essential for delaying development of resistance to this crucial class of drugs. The choice of the second drug will depend on resistance, cost, side effect profile and efficacy. The only artemisinin derivative currently registered in South Africa is the combination of artemether with lumefantrine (Coartem). In patients with severe malaria, parenteral artemisinins are effective and intravenous artesunate reduced malaria related deaths by 32%.

Artemether-lumefantrine (Coartem®)

This fixed dose combination containing 20mg artemether plus lumefantrine 120mg is the recommended first line treatment for uncomplicated malaria in all malaria transmission areas in South Africa. It has the advantages of a shorter treatment course (6 doses over 3 days) and far better tolerability than the only effective alternative, quinine. However, its indication is limited to the treatment of uncomplicated malaria as there is no evidence of its efficacy in more severe disease. Artemether-lumefantrine is contra-indicated in pregnancy and in those patients who have a history of allergy to artemether or 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 or drink containing 1.3 g of fat (e.g. 100 ml milk).** This drug has been best studied in patients weighing less than 65 kg and thus is not yet registered for use in patients weighing greater than 65 kg, although initial results in this group are encouraging. 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)].

Intravenous artesunate

Parenteral artemisinin derivatives, notably artemether and artesunate, have been successfully used for treating severe malaria. In a randomized controlled trial of severe malaria in adults living in areas of low malaria transmission in Asia, the death rate was one-third lower among the adults who received intravenous artesunate compared to those who received quinine. **Patients treated with IV artesunate have a 1/20 to 1/11 better survival rate than those getting IV quinine.** This is the first published study on severe malaria, which showed a clear difference in mortality between the two treatments. **Artesunate is also easier to use and is not associated with hypoglycemia, which can be caused or exacerbated by quinine.** Similar studies are now being conducted in children in Africa. Until these results are available, and an intravenous parenteral artesunate is registered in South Africa, quinine remains the recommended treatment for severe malaria in South Africa.

6.1.3.2 Quinine

Quinine is a rapidly acting, effective anti-malarial drug used for both uncomplicated and severe malaria acquired in sub-Saharan Africa. Quinine resistance is rare in this area, although increasing slowly in Southeast Asia. Oral quinine therapy is an alternative option recommended in uncomplicated malaria but the initial doses of quinine should be administered intravenously if the patient

is vomiting repeatedly. 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 as soon as can be tolerated (usually 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 old or during pregnancy, clindamycin should be used rather than doxycycline or other tetracyclines. Shortened courses of quinine (3 days) cannot be recommended for treatment. Patients initially treated for severe malaria with quinine should complete the course of treatment with the same drug, as completion of therapy initiated with quinine with a course of artemether-lumefantrine has not been adequately evaluated.

It is most important that patients (or caregivers) understand that it is essential to complete the course of 7-10 days of quinine (with doxycycline or clindamycin) as adherence with this poorly tolerated treatment is generally low. 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 occur 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 (primarily visual and auditory) and cardiovascular abnormalities (hypo tension, heart block, ventricular arrhythmias), and can be confused with severe malaria. Cardio toxicity is particularly related to rapid infusion of quinine.

6.1.4 Treatments not recommended for falciparum malaria

Monotherapies (anti-malarial agents used on their own) are no longer recommended for the treatment of falciparum malaria. **Artemisinin derivatives** should never be used as monotherapy as this could select for resistance and compromise the value of artemisinin-based combination treatments (ACTs); taking artemisinin monotherapies for less than 7 days is strongly associated with treatment failure (recrudescence of infection). **Chloroquine** is not recommended

following the emergence of high-level resistance in most parts of the world including South Africa. **Sulphadoxine-pyrimethamine** is no longer recommended in South Africa, due to the availability of more effective combination therapy, coupled with high-level resistance in some parts of the country.

Mefloquine is registered only for prophylaxis but not treatment, given the higher incidence of severe psychiatric adverse effects associated with treatment doses. **Halofantrine** treatment is not advisable given the associated cardio toxicity, variable bioavailability and drug interactions in patients who have taken mefloquine prophylaxis. **Clindamycin** and **doxycycline** are slow acting anti-malarials and should never be used as monotherapy, but are added to quinine treatment regimens to improve cure rates.

6.2 TREATMENT OF NON-*PLASMODIUM FALCIPARUM* INFECTIONS

In sub-Saharan Africa, a minority 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 malarias is uncomplicated, although *P. vivax* has rarely caused severe malaria 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, Brazil, and Indonesia.

In South Africa *P. ovale* is the most common of the non-falciparum malarias. Anaemia may complicate chronic *P. ovale* infection. Pure infections of *P. malariae* can be treated with chloroquine monotherapy, while the extra-hepatic phases of infections with *P. vivax* or *P. ovale* can be treated with chloroquine (or quinine or artemether-lumefantrine). **For *P. vivax* or *P. ovale* a follow-up course of primaquine is essential to eradicate the residual hepatic phase to prevent relapse.**

Primaquine must be given for 14 days at the recommended dosages. Primaquine is **contra-indicated** in children less than 1 year of age and during pregnancy. In pregnant women eradication of the hepatic 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 may be taken by patients with mild deficiency of G-6-PD (10 - 60% residual enzyme activity) at a reduced dose of 0.5 - 0.7 mg/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 primaquine.

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 (either quinine or artemether-lumefantrine) 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 DURING PREGNANCY

Pregnant women, particularly in the second and third trimesters of pregnancy, are more likely to develop severe malaria than other adults and have a higher malaria-related mortality rate. Malaria in pregnancy is particularly associated with complications such as cerebral malaria, hypoglycaemia, and pulmonary oedema/ARDS. In addition, maternal malaria increases the risk of spontaneous abortion, stillbirth, premature delivery, low birth weight (a leading cause of child mortality) and rarely, congenital malaria. Foetal distress may occur peripartum. The risk of severe malaria extends into the early postpartum period. It is important to carefully follow up pregnant women treated for malaria, and their

infants, to promptly diagnose and adequately manage the known complications of malaria in pregnancy.

6.4.1 Diagnosis of malaria in pregnancy

A high index of suspicion is the most important element in the diagnosis of malaria. Malaria is frequently missed or misdiagnosed in pregnancy and needs to be differentiated from complications of pregnancy e.g. intrauterine sepsis, eclampsia, or pyelonephritis, as signs and symptoms may be similar.

Suspect malaria if the patient is resident in or has travelled to a malaria transmission area. A history of visiting a malaria transmission area should be explored in all pregnant women with fever. A malaria smear (repeated if initially negative) or malaria antigen test is mandatory for any pregnant patient with fever and a history of malaria exposure.

Fever is common, but may be absent in some cases.

It is important to attempt to differentiate between uncomplicated and severe malaria. However, uncomplicated malaria may progress rapidly to severe malaria in pregnancy if the patient is not treated urgently and appropriately.

All pregnant women with malaria must be admitted to hospital and those with severe malaria should be transferred to the highest level of care available (either a level 2 or level 3 hospital)

6.4.2 Management of uncomplicated malaria in pregnancy

The treatment of choice for uncomplicated malaria is **quinine followed by a course of clindamycin.** Doxycycline is contraindicated. 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 occasionally 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 artemisinins are only recommended when no effective alternative anti-malarial is available. There is increasing experience with artemesinin derivatives in the 2nd and 3rd trimesters of pregnancy, and no adverse effects on the mother or human foetus have been documented to date. However, some animal studies have shown teratogenicity, particularly with high doses. Sub-optimal absorption of lumefantrine (as in artemether-lumefantrine) in pregnancy has been suggested in one study. In lactating women, uncomplicated malaria should be treated with artemether-lumefantrine, and quinine and clindamycin used for severe malaria.

6.4.3 Management of severe malaria in pregnancy

- In severe malaria parenteral quinine in full dosages should be given
- Obstetric advice should be sought early
- The role of early Caesarean section for the viable live fetus is unproven
- Termination of pregnancy is not generally indicated
- **Hypoglycemia** should be expected and is often recurrent if the patient is receiving quinine, and may be refractory to glucose administration. Hypoglycemia must be considered urgently in any pregnant woman with malaria who presents with convulsions, confusion or a depressed level of consciousness
- It may be difficult to differentiate cerebral malaria from eclampsia. If a pregnant woman living in a malaria area has fever, headaches or convulsions and malaria cannot be excluded, it is essential to treat the woman for both malaria and eclampsia
- Respiratory failure due to ARDS is a particular problem of malaria in pregnancy and is difficult to manage and carries a high mortality rate
- It is critical therefore to **monitor fluid balance very carefully. Fluid overload may potentiate the development of ARDS.** Hypovolaemia however, may potentiate renal failure, metabolic acidosis and circulatory collapse. Accurate recording of fluid input and output is essential (CVP $\leq$ 5 cm H2O). ARDS commonly occurs several days after treatment is initiated

- The risk of severe malaria extends into the early post partum period. Postpartum bacterial infection is a common complication in these patients

6.5 TREATMENT OF INFANTS AND YOUNG CHILDREN

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 who has been in a malaria transmission area 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.

6.5.1 Managing uncomplicated (non-severe) malaria in young children

In children over 1 year of age with **uncomplicated malaria,** recommended treatment is artemether-lumefantrine or quinine plus clindamycin. However, children have a higher risk of developing complicated malaria so should ideally be admitted for treatment under close supervision.

For children ≤ 1 year of age with uncomplicated malaria the treatment of choice is **quinine plus clindamycin.** This is because of the risk of rapid development of complications. As there is no quinine syrup available, it 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. Pharmacists may be able to specially prepare quinine syrup.

Children who are vomiting but who have no other indications of severe malaria should be given parenteral quinine in the recommended doses (see Section 9,

Dosage Guidelines) until the child can take medication orally. Particular care must be taken to ensure that the correct dosage is administered. Once oral intake is confirmed then switch to any of the 2 regimens above (depending on the child's age).

Suspect severe malaria in any child at risk of malaria with any of the following signs:

- Unable to drink or breastfeed
- Vomits everything
- Has had convulsions
- Lethargic or unconscious
- Stiff neck or bulging fontanelle

Children with severe malaria need to be managed differently to children with uncomplicated/non-severe malaria. Section 6.5.2 explains the management of severe malaria in children.

6.5.2 Managing severe malaria in young children

Intravenous (parenteral) quinine is indicated for severe malaria in children and the usual loading dose of 20mg/kg is used. 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 intra-muscular 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.

Management of severe malaria in young children
• Check airway, breathing, circulation (ABC) • Agitation and respiratory distress (as a result of metabolic acidosis) are ominous signs • Children who present with shock and acidosis should be given a bolus (20 mg/kg) of fluid, either colloid (plasma) OR crystalloid (Ringers lactate, or normal saline if this is unavailable) • Secondary bacterial infections, including septicaemia, are common and broad-spectrum antibiotics e.g. third generation cephalosporins 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 with a change depressed level in the level of consciousness or convulsions • Convulsions in children with malaria may be due to hypoglycaemia, cerebral malaria or pyrexia

Artemisinin derivatives have been shown to be safe and highly effective in children, including cases of severe malaria and multi-drug resistant malaria. Rectal artesunate is being developed to provide anti-malarial cover while a patient is being transferred to a hospital from a primary healthcare facility where parenteral treatment is not safely available. Intra-muscular artemether and intravenous artesunate have been shown to be safe and effective in the treatment of severe malaria in children. None of rectal artesunate, intra-muscular artemether or intravenous artesunate is registered for use in South Africa, although when these products become available they are expected to provide a safer and possibly more effective alternative to quinine.

6.6 MALARIA AND HIV

A large number of HIV-infected patients either live in areas where malaria transmission occurs, or travel to these areas. Overlap of symptoms of the two diseases, especially fever, may result in HIV-positive patients with malaria presenting late to health facilities and the diagnosis of malaria being missed. Although acute malaria causes a temporary increase in replication of HIV and hence in plasma viral load, there is no evidence that malaria has a substantial effect on the clinical progression of HIV infection, HIV transmission or response to antiretroviral treatment. HIV-infected individuals who live in areas of stable malaria transmission and are thus expected to be malaria semi-immune, are at

increased risk of symptomatic parasitaemia and/or may exhibit higher levels of peripheral parasitaemia than semi-immune adults who are HIV-negative. HIV-infected patients who are malaria non-immune are at higher risk of severe malaria and of dying from malaria. As HIV progresses and immuno-suppression worsens, the risks of severe malaria increase. Renal failure has been identified as a particular complication in this group of patients. Secondary bacterial infection is common and empiric antibiotic treatment should be given, e.g. a third generation cephalosporin. Electrolyte disturbances are common and close monitoring is essential. Thus, patients co-infected with HIV/AIDS and malaria should be admitted for treatment and close monitoring at the highest level of care available, preferably a level 2 or level 3 hospitals.

It is unclear how HIV infection modifies the therapeutic response to anti-malarials. Increased parasite burdens and reduced host immunity, both of which occur with HIV infection, may be associated with delayed parasite clearance and increased failure rates. Patients with HIV infection who develop malaria should receive the recommended anti-malarial regimens, although more closely monitored, to ensure an adequate response. There are limited data regarding interaction of anti-malarials with antiretroviral drugs. Pharmacological interactions between certain anti-retrovirals (ARVs) and anti-malarial drugs are theoretically possible and might lead to toxicity or sub-therapeutic drug levels. However there are no documented interactions. WHO suggests that patients receiving protease inhibitors and the NNRTI delavirdine should avoid halofantrine (Note: this drug is not recommended for malaria treatment in South Africa). Since lumefantrine is related to halofantrine, the combination artemether-lumefantrine may therefore have the potential to interact with ARVs.

7. SEVERE MALARIA

Unless *P. falciparum* malaria is promptly diagnosed and treated, the clinical picture may deteriorate rapidly. Severe malaria carries a significant morbidity and mortality.

Young children, pregnant women, immuno-suppressed patients and any non-immune persons are at risk for the development of complications. One can assume that all South Africans living in the malaria areas in this country and all South African travellers are non-immune.

7.1 FEATURES INDICATING SEVERE MALARIA

Clinical Features

- **Prostration**
- **Impaired consciousness (Glasgow & Blantyre coma scales)**
- **Multiple convulsions**
- **Respiratory distress (acidotic breathing)**
- **Circulatory collapse**
- **Pulmonary oedema (radiological)**
- **Acute respiratory distress syndrome (ARDS)**
- **Abnormal bleeding**
- **Jaundice**
- **Haemoglobinuria**

Biochemical Features

- **Renal impairment – serum creatinine >265 μmol/litre or rapidly rising creatinine (>2.5 μmol/kg/day) or urine output <400 ml/day (adult)**
- **Acidosis (plasma bicarbonate <15 mmol/litre) (serum lactate > 5 mmol/liter)**
- **Hepatic impairment (transaminases > 3 times normal)**
- **Hypoglycaemia (blood glucose <2.2 mmol/liter)**
- **Hypoxia (PO_2 - < 8 Kpa in room air)**

Haematological Features

- **Parasitaemia ≥ 5% or ≥ 3+**
- **Anaemia: haemoglobin < 6 g/dL or haematocrit <20%**
- **≥5% neutrophils contain malaria pigment**
- **Presence of schizonts of *P. falciparum* in peripheral blood smear**
- **Evidence of DIC**

The Glasgow Coma Scale

Best motor response	**Score**
Carrying out request (obeying command)	6
Localising response to pain	5
Withdraws to pain	4
Flexor response to pain	3
Extensor posturing to pain	2
No response to pain	1
Best verbal response	
Orientated	5
Confused conversation	4
Inappropriate speech	3
Incomprehensible speech	2
None	1
Eye opening	
Spontaneous eye opening	4
Eye opening in response to speech	3
Eye opening to response to pain	2
No eye opening	1

An overall scale is made by adding the score in the three areas assessed, e.g.:
No response to pain + no verbalisation + no eye opening = 3
Severe injury, GCS < 8
Moderate injury GCS 9-12
Minor injury GCS 13-15

Blantyre paediatric coma scale

Motor Response	
Localises to pain	**2**
Withdraws from pain stimuli	**1**
No response	**0**
Verbal Response	
Appropriate cry	**2**
Inappropriate cry/moan	**1**
No cry	**0**
Eye Response	
Directed	**1**
Not Directed	**0**

4-5 normal
2-3 mild impairment
0- severe impairment

7.2 TREATMENT

The patient should be treated in the highest level of care available. Management of severe malaria comprises 4 main areas: clinical assessment of the patient, specific anti-malarial treatment, adjunctive therapy and supportive care.

SEVERE MALARIA IS A MEDICAL EMERGENCY

Initial Assessment:

- The airway should be secured in unconscious patients and breathing and circulation assessed
- The patient should be weighed or body weight estimated so that drugs, including anti-malarials, and fluids can be given on a body weight basis
- An intravenous cannula should be inserted and an immediate measurement of blood glucose (rapid test) done
- A detailed clinical examination should be conducted, with particular note of the level of consciousness and record of the coma score
- A lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis should be considered in unconscious patients
- The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate level should therefore be measured if possible. If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock
- Submit blood urgently for full blood count, platelet count, and measurement of urea, creatinine and electrolytes and obtain results urgently
- The assessment of fluid balance is critical in severe malaria. Respiratory distress, with acidotic breathing, in severely anaemic children, often indicates hypovolaemia and requires prompt rehydration and, where indicated, blood transfusion.

7.3 CHEMOTHERAPY

Quinine is the drug of choice for the treatment of severe malaria in South Africa. Intravenous quinine is the preferred route of administration, especially where the patient is comatose, vomiting or severely ill. Quinine administration is always by **slow,** rate-controlled intravenous administration, **never by bolus injection.**

Where intravenous quinine administration is not feasible, not available or considered unsafe, the intra-muscular route may be used initially.

7.4 LOADING DOSES

In severe malaria **an initial loading dose must be given, by slow intravenous infusion over 4 hours.** The rationale for the loading dose is to rapidly reach a therapeutic level.

The loading dose is quinine dihydrochloride salt, **20 mg/kg** body weight diluted in 5-10 ml/kg body weight of 5% dextrose water over 4 hours. **The loading dose is given strictly according to body weight.** The disposition of quinine in very obese patients is not known. It has been suggested that there is a ceiling dose above which quinine should not be given, but there is no evidence to support this.

The loading dose should be omitted if the patient has received quinine, or mefloquine prophylaxis, in the preceding 24 hours. In these cases, ECG monitoring is necessary.

7.5 MAINTENANCE DOSES

Six to eight hours after starting the loading dose, a maintenance dose of quinine dihydrochloride salt, 10 mg/kg **diluted** in 5-10 ml/kg body weight of a dextrose-containing solution should be commenced and infused over 4-6 hours. Intravenous quinine should be administered every 8 hours until the patient can take oral medication (usually by 48 hours). For obese patients, the maintenance dose should be calculated according to ideal body weight. Ideal body weight can be calculated for adults by a formula as follows:

Males: IBW (Kg) = 0.9 x height in cm - 88

Females: IBW (Kg) = 0.9 x height in cm - 92

The total duration of therapy is 7-10 days.

The use of additional doxycycline or clindamycin does not add initial therapeutic benefit for severe malaria and may contribute to drug side effects. They should be added once the patient is improving.

Once the patient is improving, oral treatment should be continued as per the recommendations for uncomplicated malaria. The dose of quinine should be reduced in renal failure (See 7.8.4).

Quinine has a narrow therapeutic window, although serious side effects (cardiovascular or nervous system) during anti-malarial treatment are unusual. The most frequent side effect during intravenous therapy is hypoglycaemia, especially in pregnant women and children. Hypotension, heart block, ventricular arrhythmias, tinnitus and neurological problems, including convulsions and visual disturbances, occur rarely.

7.6 OTHER CHEMOTHERAPEUTIC OPTIONS

In cases of suspected quinine resistance, where there has been a poor parasitological response to quinine, an artemisinin derivative (not yet registered in SA) may be considered, when available. Parenteral artemisinin derivatives, notably artemether and artesunate, have been successfully used for treating severe malaria. See Section 6.1.3.1.

7.7 GENERAL MANAGEMENT OF SEVERE MALARIA

The following measures should be applied in the management of all patients with clinically diagnosed or suspected severe malaria:

- Patient should be admitted to the **highest level of care,** ideally an intensive care unit. Good nursing care is vital

- **Appropriate anti-malarial chemotherapy** must be commenced **urgently.** Ideally the drug should initially be given **intravenously**

- If parasitological confirmation of malaria is not readily available, a blood film should be made and treatment started on the basis of the

clinical presentation, in very ill patients with febrile disease with no other obvious cause

- Doses must be calculated on a mg/kg of body weight basis. **A loading dose of drug should be administered immediately on diagnosis.** It is therefore important, whenever possible, to weigh the patient (see 7.5 on ideal IBW). This is particularly important for children. Do not confuse the doses of salt and base. Quinine doses are usually prescribed as salt (10 mg of salt = 8.3 mg of base)

- Other treatable causes of coma (e.g. meningitis, hypoglycaemia and severe anaemia) should be excluded

- A rapid initial check of the blood glucose level and frequent monitoring for **hypoglycaemia** are important. Where this is not possible and the patient has a depressed level of consciousness and/or convulsions, glucose should be given as 50% dextrose solution intravenously. See section 7.8.2

- Regular monitoring of the core temperature, respiratory rate, blood pressure, level of consciousness and other vital signs is mandatory

- Laboratory measurements should include: regular checks of haemoglobin, glucose, urea and creatinine, electrolytes and liver functions, acid-base status where possible and parasite density

- Monitor **fluid balance** carefully. Avoid over- and under-hydration. Fluid overload is extremely dangerous as it may precipitate potentially fatal respiratory failure. Hypovolaemia however, may potentiate renal failure, metabolic acidosis and circulatory collapse. Accurate recording of fluid input and output is essential as fluid balance should be according to urine output and normal and excess fluid loss. Frequent central venous pressure (CVP) monitoring is recommended; maintain

the CVP at between 0-5 cm of water. Consider risk of bleeding due to thrombocytopenia when inserting CVP line

- Monitor urine output constantly and carefully observe for the appearance of haemoglobinuria

- Reduce high body temperatures (> 39^{o}C) by vigorous tepid sponging and fanning. Antipyretics may also be given. Avoid aspirin-containing compounds and non-steroidal anti-inflammatory drugs

- Look for and manage any complicating or associated infections. A broad-spectrum antibiotic is recommended e.g. a 3rd generation cephalosporin

7.8 COMPLICATIONS

7.8.1 Anaemia

Definition

A haemoglobin level ≤ 6 g/dL or a haematocrit ≤ 20%.

Anaemia is a common complication of malaria, especially in young children and pregnant women. It occurs as a result of haemolysis and/or bone marrow dysfunction. Severe anaemia may manifest as cardiac failure, shock, hypoxia or confusion. There may be other causes contributing to anaemia in some patients.

Management

Blood transfusion should be considered in patients in whom the Hb is 6 g/dL or less, or the haematocrit is less than 20%, especially those with cardiovascular decompensation and shock. Caution should be exercised and fluid overload should be avoided. If no fresh blood is available packed red cell concentrate may be used.

7.8.2 Hypoglycaemia

Definition

A blood glucose level <2.2 mmol/l.

Hypoglycaemia is common in severe malaria, particularly in pregnancy, in children, and in patients on intravenous quinine. Blood glucose should be monitored 4-6 hourly. Hypoglycaemia may not always present with classical symptoms of sweating, anxiety, dilatation of pupils or tachycardia. **It must always be excluded in patients with malaria who present with depressed levels of consciousness, including coma and convulsions.**

Management

Adults: 50 ml of 50% dextrose water given intravenously as a bolus.

Children: 1 ml of 50% dextrose water/kg body weight. This should be followed by continuous intravenous infusion of 5 or 10% dextrose solution. Avoid fluid overload.

7.8.3 Cerebral malaria

Definition

Any patient with a depressed level of consciousness, ranging from agitation or confusion, to coma.

Cerebral malaria can resemble bacterial or viral infections of the central nervous system, or any cause of raised intra-cranial pressure. The clinical features are not specific; the patient may be flaccid, spastic, exhibit meningism, photophobia or symmetrical upper motor neurone signs. Papilloedema or cerebral oedema is not usually found. It is very important to exclude **hypoglycaemia.** If meningitis is suspected, a lumbar puncture should be performed. Cerebral malaria may occur as an isolated complication, or as part of multi-organ failure.

Convulsions may occur as a result of cerebral malaria, accompanying fever or in association with hypoglycaemia.

Management

Prophylactic anticonvulsants are currently not recommended. Treatment of convulsions is with standard anticonvulsant drugs and supportive measures.

Supportive treatment should include: treatment of convulsions, monitoring of level of consciousness and effective protection of the airway when the GCS <9. Dexamethasone and mannitol are not recommended.

7.8.4 Renal failure

Definition

A serum creatinine greater than 265 μmol/l, or a rapidly rising creatinine of more than 2.5 μmol/kg/day, and/or a urine output of less than 0.5 ml/kg/hr or less than 400 ml/day in an adult should be regarded as renal failure. When patients present in a polyuric phase it is critical to replace fluid losses adequately.

Renal failure is generally an early complication of malaria in adults, and occurs rarely in children. Hypovolaemia, sequestration of parasitized red cells in the renal vasculature, intravascular haemolysis and haemoglobinuria are incriminated in the development of renal dysfunction in malaria. This may lead to acute tubular necrosis and renal failure. Acute renal failure is usually reversible with appropriate management.

Management

Dehydration, if present, must be corrected carefully. Excessive administration of fluids should be avoided to minimise the risk of pulmonary oedema. A central venous catheter should be inserted where possible and maintained between 0-5 cm of water. Meticulous attention to fluid intake and output is essential to avoid fluid overload.

Early dialysis is recommended, where available, as renal failure in malaria occurs against a background of a hypercatabolic state. Early referral for dialysis is recommended if the serum creatinine is rising by more than 2.5 μmol/kg/day. Veno-venous hemofiltration is the most effective mode of dialysis in malaria.

Patients with impaired renal function require a reduction in maintenance quinine dihydrochloride salt to 5-7 mg/kg every 8 hours, after 48 hours of treatment with the full dose. Quinine is not removed by dialysis.

7.8.5 Circulatory collapse

Definition

Systolic blood pressure less than 80 mmHg in adults and children >13 years. In younger children (<13 years) clinical assessment can be a more reliable indication of circulatory collapse than blood pressure measurement because, firstly, the correct cuff size is often unavailable and secondly, children are able to maintain normal blood pressure in the face of severe circulatory collapse more efficiently than adults. Use the following signs to indicate circulatory collapse in children:

- Tachycardia
- Cool/cold and clammy extremities e.g. limbs
- Mottled/pale skin indicating poor perfusion

An exact cut-off point for systolic blood pressure in children is difficult as blood systolic blood pressure increases with age from approximately 75 mmHg (at birth) to 124 mmHg at 13 years. However a systolic blood pressure <50 mmHg at any age indicates severe circulatory collapse.

Circulatory collapse may be seen in patients with metabolic acidosis, severe anaemia, dehydration, ARDS, a ruptured spleen or septicaemia.

Management

Ideally, a central venous catheter should be inserted and hypovolaemia corrected with an appropriate volume expander (blood or plasma) or isotonic saline. Start inotropes if the CVP is >5 cm of water and the patient is still shocked, and start broad-spectrum antibiotics e.g.3rd generation cephalosporin.

7.8.6 Metabolic acidosis

Measurement of acid-base status is a very useful tool in assessing a patient with malaria. Metabolic acidosis, especially lactic acidosis, is an important indicator of severe malaria, even if no other complications are present, and is a poor prognostic sign. **Metabolic acidosis may present as shock and/or respiratory distress;** in children severe anaemia may present with metabolic acidosis.

Management

- **Correct any reversible cause of acidosis, in particular dehydration, convulsions and severe anaemia. Take care not to give excessive fluid. The routine use of bicarbonate is not recommended. Anaemia contributes to metabolic acidosis in children and should be managed as follows:**

  - Hb ≤ 6/dl
    - Packed cells 10-20 ml/kg over 4-6 hours ivi.
    - If deep breathing, reduced skin turgor, cool peripheries or disturbed consciousness
      - 10 ml/kg ivi over 1 hour,
        Then
      - 10 ml/kg ivi over 1-4 hours
  - Hb > 6g/dl
    - Crystalloid (0,9% saline) or Ringers lactate 10-20 ml/kg ivi over 4 hours. (rate of infusion based on clinical judgment)

Exclude metabolic acidosis with a blood gas. Other causes for increased respiratory rate may be excluded with a chest X-ray.

7.8.7 Respiratory complications

Acute respiratory distress syndrome (ARDS) is an uncommon, but often-fatal complication of severe malaria, and is a particularly severe problem in pregnancy. ARDS may appear several days after chemotherapy has been started, and the general condition of the patient appears to have improved.

An increase in the respiratory rate, bilateral crepitations, clinical and laboratory evidence of cyanosis, confusion, agitation, or an arterial oxygen saturation of less than 90%, should alert the clinician to the possibility of ARDS. Pulmonary oedema as a result of iatrogenic fluid overload, or pneumonia, should also be considered.

Management

Treatment depends on the severity of the respiratory complications. Fluids must be restricted. Diuretics should be given where indicated. Oxygen should be administered, and in some patients ventilatory support may be required.

7.8.8 Hepatic dysfunction

Although a raised indirect bilirubin due to haemolysis is a frequent finding in malaria, the clinical presence of jaundice or the finding of raised hepatic transaminases (≥ 3 x normal) should alert the clinician of the probability of severe malaria. **The presence of jaundice combined with renal failure and acidosis is cause for great concern.**

7.8.9 Disseminated intravascular coagulation (DIC)

DIC is rare in patients with severe malaria. Moderate degrees of thrombocytopenia are noted in the majority of cases of uncomplicated malaria, but bleeding is not common. However severe degrees of thrombocytopenia may be an indication of severe malaria and may be associated with bleeding. With effective malaria treatment, platelet counts return to normal within a few days. DIC is mostly associated with multi-organ failure, or hyperparasitaemia, and may in some cases be due to secondary bacterial infection or septicaemia.

Management

Fresh whole blood if indicated, and available; and platelet transfusions if the platelet count is very low or there is evidence of bleeding; alternatively red cell concentrate plus fresh dried plasma and vitamin K.

7.8.10 Secondary infections

Secondary bacterial infections may complicate malaria: aspiration pneumonia, urinary tract infections in catheterised patients, and nosocomial infections in hospitalised patients. Secondary bacterial infections are a particular problem in HIV co-infected patients. In a significant number of patients with severe malaria, especially in children, bacteraemia and septicaemia have been noted, and Gram-

negative and Gram-positive bacteria have been cultured. This syndrome is associated with high mortality, and is a particular problem in children.

Management

Antibiotics (3rd generation cephalosporin) should be administered to all children with severe malaria, HIV-positive patients and to any patient in whom septicaemia is suspected. Although this is a bigger problem in children, most guidelines recommend antibiotics for adults too as the features of bacterial and malarial sepsis overlap. A broad-spectrum antibiotic should be administered to cover both Gram-positive and Gram-negative bacteria e.g. a 3rd generation cephalosporin.

7.8.11 Hyperparasitaemia

In general, peripheral parasite counts above 5% should be regarded as severe malaria as this is associated with increased morbidity. Low parasite counts do not exclude severe malaria or complications, and a parasite count must always be interpreted together with the clinical picture and other laboratory findings. Parasite counts are not always accurate, and counts can vary cyclically, depending on when the smear is taken.

The peripheral parasite count does not accurately reflect the parasite load. In highly endemic malarious areas, semi-immune persons may tolerate high parasite densities, without clinical symptoms and complications. The presence of schizonts of *P. falciparum* in a peripheral blood smear is an important indicator of severe malaria.

Management

The patient should be managed with a rapidly acting effective anti-malarial drug. The use of artemether-lumefantrine in hyperparasitaemia has not yet been studied and it is possible that the course of artemisinsin-derivative would be too short to see the same benefits of 7 days of artesunate. As hyperparasitaemia increases the risk of malaria complications (which are often underdiagnosed) and of malaria mortality, initial intravenous quinine therapy should be considered. The patient should be especially closely monitored for complications, even if

these are not present initially. Exchange transfusion possibly has a role to play in patients with hyperparasitaemia whose parasite counts increase or fail to decrease significantly despite appropriate therapy.

7.8.12 Malarial haemoglobinuria

The pathogenesis is unknown. The condition is seen in patients with G-6-PD deficiencies, which are treated with anti-malarial drugs, notably oxidant drugs like primaquine. The condition occasionally occurs in patients with severe malaria and in those with malaria treated with quinine. Intravascular haemolysis leads to anaemia, passage of haemoglobin in the urine, and varying degrees of renal failure.

Management

Continue appropriate malaria chemotherapy: quinine may be continued (primaquine must be avoided in patients with G-6-PD deficiency). Supportive therapy should include blood transfusions for severe anaemia, adequate fluids and renal dialysis where indicated.

7.8.13 Exchange transfusion

The role of exchange transfusion in severe malaria is controversial and there are no controlled studies to support its use.

Exchange transfusion may be considered for use in selected patients e.g. patients with hyperparasitaemia in whom the parasite count increases despite appropriate chemotherapy, and patients who develop multi-organ dysfunction despite appropriate chemotherapy.

The requirements for exchange transfusion include a safe blood supply, a skilled operator and a haemodynamically stable patient. The exchange volume should be 4-10 litres of blood for an adult.

7.8.14 Splenic rupture

Splenic rupture is a rare complication of malaria, and is more common in *P. vivax* infections.

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Table 7. Immediate clinical management of severe manifestations and complications of falciparum malaria

Manifestation/complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment such as corticosteroids, heparin and adrenaline; intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, cooling blanket and antipyretic drugs.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde.
Hypoglycaemia (blood glucose concentration of <2.2 mmol/l; <40 mg/100ml)	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion.
Severe anaemia (haemoglobin <5 g/100ml or packed cell volume <15%)	Transfuse with screened fresh whole blood
Acute pulmonary oedema[b]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia.
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral antimicrobials, correct haemodynamic disturbances.
Hyperparasitaemia	See section 8.14.

[a] It is assumed that appropriate antimalarial treatment will have been started in all cases.

[b] Prevent by avoiding excess hydration.

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DOSAGE GUIDELINES FOR THE TREATMENT OF MALARIA (JUNE 2009)

DRUG	ADULT DOSAGE	PAEDIATRIC DOSAGE
QUININE (**parenteral**) 1 ampoule (1 ml) usually contains 300 mg quinine dihydrochloride	**Loading dose**: Quinine dihydrochloride salt 20 mg/kg by IV infusion over 4 hours in 5% dextrose saline: [**Important Note**: No loading dose to be given if the patient has definitely received treatment doses of mefloquine, quinine (more than 40 mg/kg in the previous 2 days), or quinidine or halofantrine (in the last 24 hours). If in doubt the loading dose should be given.] **Maintenance dose**: Eight hours after the start of the loading dose, give 10 mg/kg quinine dihydrochloride salt infused over 4-6 hours, repeated every 8 hours until the patient can take oral quinine. **Important Note:** If a treatment dose of mefloquine has been taken in the 12 hours before severe malaria treatment starts, ECG monitoring would be advisable.] The required dose, diluted preferably in 5% dextrose to counteract hypoglycaemia, is given in a total volume of 5-10 ml/kg (depending on patient's fluid balance) by infusion into a large vein. • Where facilities for IV infusion do not exist, quinine can be given IM in the same dosage. The required dose, diluted to between 60 mg and 100 mg/ml, should be given as half the dose in each anterior thigh. • Total quinine (parenteral and/or oral) duration at least 7-10 days, or until smears are negative. • Paediatric dose: Same as adult dose. • All patients should ideally have cardiac monitoring. • The dose of IV quinine should be reduced by 1/3-1/2 (to 5-7 mg/kg) on the third day of treatment if parenteral therapy is required for more than 48 hours because there has been no significant improvement in the clinical condition of the patient, or acute renal failure has developed.	
QUININE (oral) 1 tablet usually contains 300 mg quinine sulphate	600 mg (i.e. usually 2 tablets) every 8 hours for 7 days or 10 mg salt/kg (maximum usually 600 mg) 8 hourly for 7 days	10 mg salt/kg body weight every 8 hours for 7 days. The tablets may be crushed with banana, jam or chocolate syrup.
DOXYCYCLINE (Use in combination with quinine)	Commence as soon as can be tolerated after starting quinine. 200 mg stat; followed by 100-200 mg daily for 7 days. Avoid in pregnancy.	Do not use in children under 8 years old. 4 mg/kg stat, then 2 mg/kg daily for at least 7 days or until negative smears.
CLINDAMYCIN (Use in combination with quinine in pregnancy and children <8 years)	Commence as soon as can be tolerated after starting quinine 10 mg/kg bd for 7 days or 5 mg/kg tds for 7 days.	10 mg/kg bd for 7 days or 5 mg/kg tds for 7 days.

DOSAGE GUIDELINES FOR THE TREATMENT OF MALARIA (continued)

DRUG	ADULT DOSAGE	PAEDIATRIC DOSAGE
ARTEMETHER LUMEFANTRINE 1 tablet contains artemether 20 mg plus lumefantrine 120 mg.	10 - <15 kg: One tablet stat, followed by one after 8 hours and then one twice daily on each of the following two days (total course = 6 tablets) 15-<25 kg: Two tablets stat, followed by two after 8 hours and then two twice daily on each of the following two days (total course = 12 tablets) 25-<35 kg: Three tablets stat, followed by three after 8 hours and then three twice daily on each of the following two days (total course = 18 tablets) 35-<65 kg: Four tablets stat, followed by four after 8 hours and then four twice daily on each of the following two days (total course = 24 tablets). >65 kg: Dose as for > 35 kg above, although inadequate experience in this weight group justifies closer monitoring of treatment response. *Administer with food/milk containing at least 1.3g fat to ensure adequate absorption.*	
CHLOROQUINE (non-falciparum malaria only) 1 tablet contains 150 mg chloroquine base	Orally: 1.5g over 3 days, as follows: initially 600 mg, followed by 300 mg 6-8 hours later, and 300 mg once daily on second and third days.	Initial dose: 10 mg base/kg then 5 mg base/kg at the same dosage intervals as the adult regimen.
PRIMAQUINE 1 tablet usually contains 26.3 mg primaquine phosphate = 15 mg primaquine base.	Orally: 15 mg base daily for 14 days following standard treatment or 0.25 mg base/kg daily for 14 days. In mild G-6-PD Deficiency (10-60% residual G-6-PD activity): 45 mg base weekly/0.5-0.8 mg base/kg body weight once a week for six to eight weeks.	Contra-indicated in children under 1 year old. 0.25–0.3 mg base/kg daily for 14 days following standard treatment. In mild G-6-PD Deficiency: 0.5-0.8 mg base/kg weekly for 8 weeks.
MEFLOQUINE (not registered for treatment of malaria in South Africa) 1 tablet contains 250 mg base	Oral, 25 mg/kg base (maximum total dose 1.5 g) in 2–3 divided doses 6–8 hours apart as follows: loading dose, 750 mg; then 500 mg after 6–8 hours and 250 mg after a further 6-8 hours.	Oral, 25 mg/kg base as a single dose or 2 divided doses.

Adapted with permission from the Malaria Update, edited by A. Swart of the Medicines Information Centre, UCT.

Important Notes:

- Patients, who vomit less than 30 minutes after receiving the drug orally, should be given a second full dose. If they vomit 30-60 minutes after the dose, an additional half-dose should be given.
- When treating severe malaria, oral treatment should be substituted as soon as the patient can take tablets by mouth and at least 3 doses of parenteral quinine have been given.
- For *P. vivax* malaria acquired in Oceania and southeast Asia the dose of primaquine should be increased to 0.33-0.5 mg base/kg daily for 14 days.

Summary of Malaria Treatment Guidelines

Early diagnosis and prompt correct treatment are crucial

Malaria is a progressive and unpredictable disease.

Complications may develop despite treatment.

Severity of disease is frequently underestimated, so careful monitoring of all patients is mandatory.

Uncomplicated malaria

Only patients with malaria who are ambulant, with normal mental state, adequate urine output, able to take oral medication, and not vomiting excessively can be considered as uncomplicated. *Note: All pregnant women and children < 1 year should be regarded as high-risk patients and treated with quinine at the highest level of care available.*

Indicators of severe malaria

- Decreased level of consciousness (prostration, extreme weakness, restlessness, confusion, convulsions, coma)
- Severe vomiting, diarrhoea or dehydration, decreased urine output (<0.5 ml/kg/hr), or impaired renal function
- Unable to take oral medication
- Respiratory distress (respiratory rate > 30 per minute)
- Circulatory compromise (low BP, cold peripheries)
- Spontaneous bleeding (disseminated intravascular coagulation)
- Jaundice
- Parasitaemias of 5% or greater

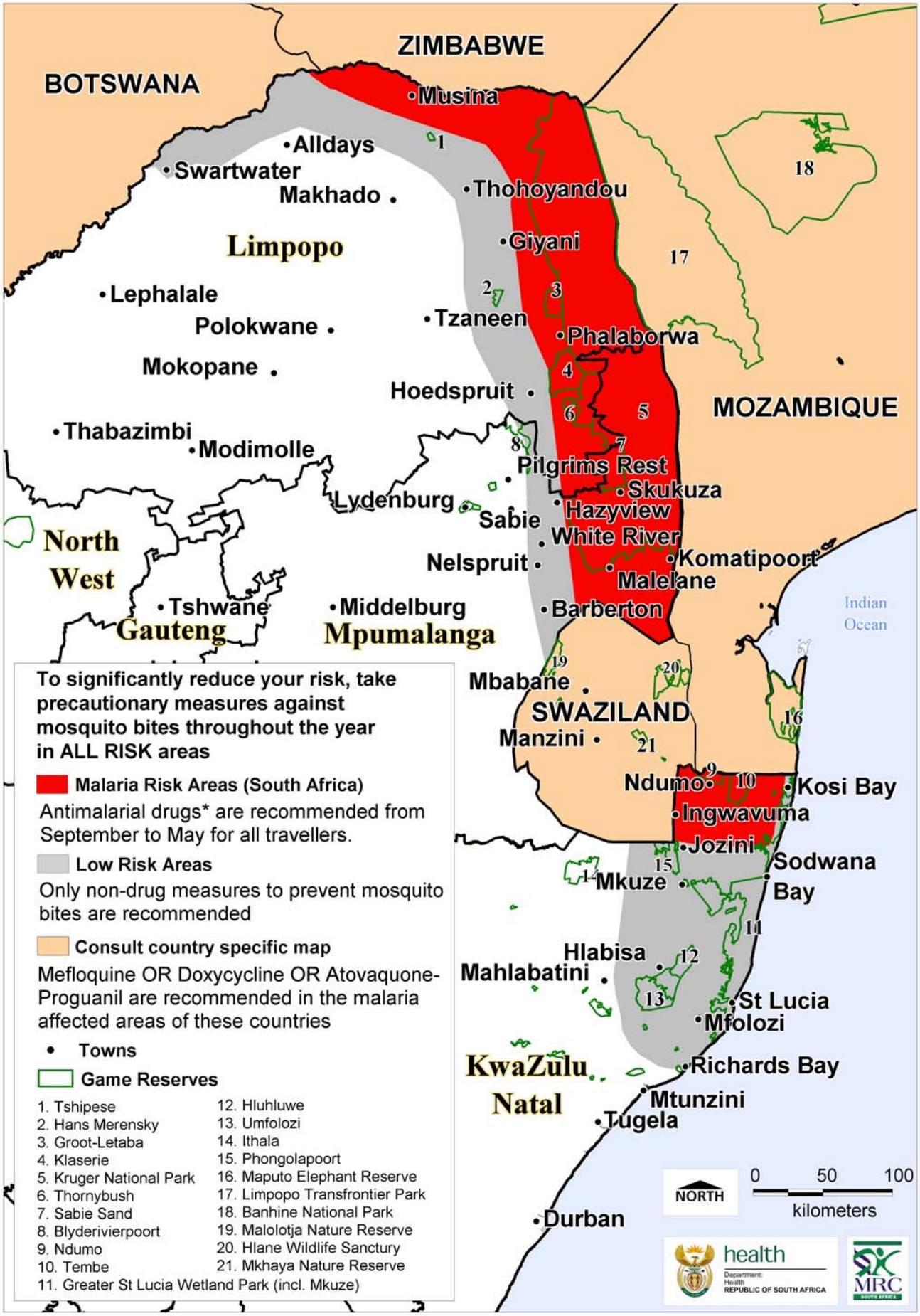
General Management of Severe Malaria

Manage patients in highest level of care available

1. Monitor fluid balance carefully. Avoid over- OR under-hydration. Fluid overload is extremely dangerous as it may precipitate potentially fatal respiratory failure. Hypovolaemia is also dangerous and may potentiate renal failure, metabolic acidosis and circulatory collapse. Accurate recording of fluid input and output is essential. Frequent central venous pressure monitoring is recommended; maintain between 0 and 5 cm H_2O.

2. A rapid initial measurement of blood glucose level and 4-6 hourly monitoring for hypoglycaemia are essential.
3. Regular monitoring of temperature, respiratory rate, blood pressure, and level of consciousness is mandatory.
4. Look for and manage any associated infections. Where indicated, bacterial meningitis should be excluded by lumbar puncture, or covered by appropriate empiric antibiotic treatment.
5. Reduce fever > 39 ºC by tepid sponging, and paracetamol.
6. Transfuse if haemoglobin ≤ 6 g/dl (haematocrit < 20%) or anaemia associated with haemodynamic compromise.
7. Laboratory tests: Regular monitoring of haemoglobin, urea and electrolytes, acid-base status, and an initial assessment of liver function.
8. Level of parasitaemia should be assessed daily; at 72 hours, level of parasitaemia should be less than 25% of baseline.
9. Early dialysis (haemo- or peritoneal dialysis) is recommended and may be life-saving. Indications for dialysis include metabolic acidosis, hyperkalaemia, fluid overload, rapidly rising creatinine or patients who remain anuric after adequate re-hydration.
10. Treat seizures promptly with intravenous benzodiazepines (check for hypoxia and hypoglycaemia).
11. Respiratory failure (ARDS/pulmonary oedema): Administer oxygen, furosemide, assisted ventilation (PEEP) if required.

As malaria complications develop rapidly, regular monitoring and urgent interventions may be lifesaving.


ZIMBABWE
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North West
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Mpumalanga
KwaZulu Natal
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Musina
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Makhado
Thohoyandou
Giyani
Lephalale
Polokwane
Tzaneen
Phalaborwa
Mokopane
Hoedspruit
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Lydenburg
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Komatipoort
Malelane
Tshwane
Middelburg
Barberton
Mbabane
Manzini
Ndumo
Kosi Bay
Ingwavuma
Jozini
Sodwana Bay
Mkuze
Hlabisa
Mahlabatini
St Lucia
Mfolozi
Richards Bay
Mtunzini
Tugela
Durban
To significantly reduce your risk, take precautionary measures against mosquito bites throughout the year in ALL RISK areas
Malaria Risk Areas (South Africa)
Antimalarial drugs* are recommended from September to May for all travellers.
Low Risk Areas
Only non-drug measures to prevent mosquito bites are recommended
Consult country specific map
Mefloquine OR Doxycycline OR Atovaquone-Proguanil are recommended in the malaria affected areas of these countries
Towns
Game Reserves
1. Tshipese
2. Hans Merensky
3. Groot-Letaba
4. Klaserie
5. Kruger National Park
6. Thornybush
7. Sabie Sand
8. Blyderivierpoort
9. Ndumo
10. Tembe
11. Greater St Lucia Wetland Park (incl. Mkuze)
12. Hluhluwe
13. Umfolozi
14. Ithala
15. Phongolapoort
16. Maputo Elephant Reserve
17. Limpopo Transfrontier Park
18. Banhine National Park
19. Malolotja Nature Reserve
20. Hlane Wildlife Sanctury
21. Mkhaya Nature Reserve
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GUIDELINES FOR THE TREATMENT OF MALARIA

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