Government of Malawi

MINISTRY OF HEALTH

GUIDELINES FOR THE TREATMENT OF MALARIA IN MALAWI

5th Edition, November 2019

National Malaria Control Programme
Community Health Sciences Unit
Private Bag 65
Lilongwe
MALAWI

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ACRONYMS & ABBREVIATIONS

ACTs – Artemisinin-based Combination Therapies

AIDS – Acquired Immunodeficiency Syndrome

ANC – Antenatal Clinic

ART – Antiretroviral Therapy

ASAQ – Artesunate Amodiaquine

CCP – Critical Care Pathway

CHAI – Clinton Health Access Initiative

DOT – Directly Observed Therapy

Hb – Haemoglobin

HIV – Human Immunodeficiency Virus

HRP 2 – Histidine Rich Protein 2

IM – Intramuscular

IPTp – Intermittent Preventive Treatment in pregnancy

IV – Intravenous

LA –Lumefantrine-Artemether

LA (D) – Lumefantrine-Artemether Dispersible

LA (ND) – Lumefantrine-Artemether Non-dispersible

MCH – Maternal and Child Health

MoH – Ministry of Health

MP – Member of Parliament

mRDTs – malaria Rapid Diagnostic Tests

NMCP – National Malaria Control Program

PCV – Packed Cell Volume

PHC – Primary Health Care

PMI – Presidents Malaria Initiative

Pf – *Plasmodium falciparum*

RA – Rectal Artesunate

RBCs – Red Blood Cells

SD – Standard Diagnostics

SP – Sulfadoxine Pyrimethamine

TBA – Traditional Birth Attendant

WHO – World Health Organization

Foreword

Malaria continues to be the leading cause of morbidity and mortality, particularly in children under five years of age. It is the commonest cause of outpatient visits, hospitalization and death. Malaria is also a development problem as it has a serious socioeconomic impact on families and the nation, through loss of work, school absenteeism and high levels of expenditure on malaria treatment, especially those with low social economic status.

Organized malaria control efforts started in 1984 with the establishment of the National Malaria Control Programme (NMCP) to spearhead and coordinate responses to malaria control by both Malawi Government and the development partners.

In 2007, the Ministry of Health (MoH) through the NMCP changed its national malaria treatment policy from Sulfadoxine-Pyrimethamine (SP) to a more expensive artemisinin-based combination therapy (ACT) with Lumefantrine-Artemether (LA), following significant scientific evidence of malaria parasite resistance to SP.

In 2011, dispersible LA was introduced after noting that regular tablets of LA are difficult to dissolve in water since the tablets are fixed, very bitter and difficult to be crushed for administration to young children.

After twelve years of implementing regular tablets of LA (20/120mg), there have challenges with compliance due to pill burden. In order to address this, MoH has adopted use of double strength LA to replace the regular tablets.

There is substantial evidence globally showing significant malaria mortality reduction if parenteral artesunate is used in the management of severe malaria compared to quinine. Artesunate has also been shown to significantly reduce the incidences of convulsions, coma and hypoglycaemia developing in hospitalized severe malaria patients. In line with the current WHO recommendation, the MoH has adjusted the dose of injectable artesunate in children < 20 kgs. In view of these changes, it is necessary to revise these guidelines to reflect current trends.

This 5th Edition of the Guidelines for the Treatment of Malaria in Malawi, therefore, marks an important milestone in malaria control and prevention, particularly in younger children who are most at risk for malaria in Malawi.

My Ministry is optimistic that these revised treatment guidelines will help us all to ensure that malaria cases are promptly and adequately treated in order to reduce the burden of malaria in Malawi.

Hon. Jappie Mhango, MP
Minister of Health

Acknowledgements

The Ministry of Health (MoH) is indebted to the National Malaria Advisory Committee (comprising Prof. J. Wirima (Chairperson), Dr. G. Malenga, Dr. P.N. Kazembe, Dr. N. Kumwenda, Prof. Y. Nyasulu, Dr. B. Makanani, and Mr. E.H. Kapeya) and the committee's co-opted members consisting of Prof. Malcolm Molyneux, Prof. Kamija Phiri, Dr. Benson Chilima and Dr. Don Mathanga for spearheading the review process and providing technical and policy directions in the revision of this 4th Edition of the Guidelines for the Treatment of Malaria in Malawi.

We acknowledge contributions from various partners, such as the Clinton Health Access Initiative (CHAI), the President's Malaria Initiative (PMI), SSDI-Services, UNICEF, the World Health Organization (WHO) and the MoH officials under the leadership of the National Malaria Control Program who reviewed and revised these Guidelines.

The Ministry is grateful to Dr Storn Kabuluzi, Director of Preventive Health Services for providing technical direction in the review process.

We finally acknowledge with thanks the contributions and critical reviews of this guide made by various partners during the consultative meeting in Blantyre. These include Mr Wilfred Dodoli, Dr. A. Likaka, Dr. Peter Troell and the team from PMI, Mr. I. Zungu, Mrs Khonje (Reproductive Health Unit), Mr. Cary Reid, Mr. John Munthali, and the NMCP team comprising Mrs. Doreen Ali, Mr. John Sande, Mr. Misheck Luhanga, Mr Austin Gumbo, Mr Evance Kaunda, Mrs Flora Kalimba and Mr. Dubulao Moyo. Their comments were valuable in the revision of these guidelines.

Dr Dan Namarika
Secretary for Health

Introduction

This document has been developed to outline the policies and guidance for the treatment of uncomplicated and severe malaria. It also serves as a concise reference for health workers managing malaria in the country.

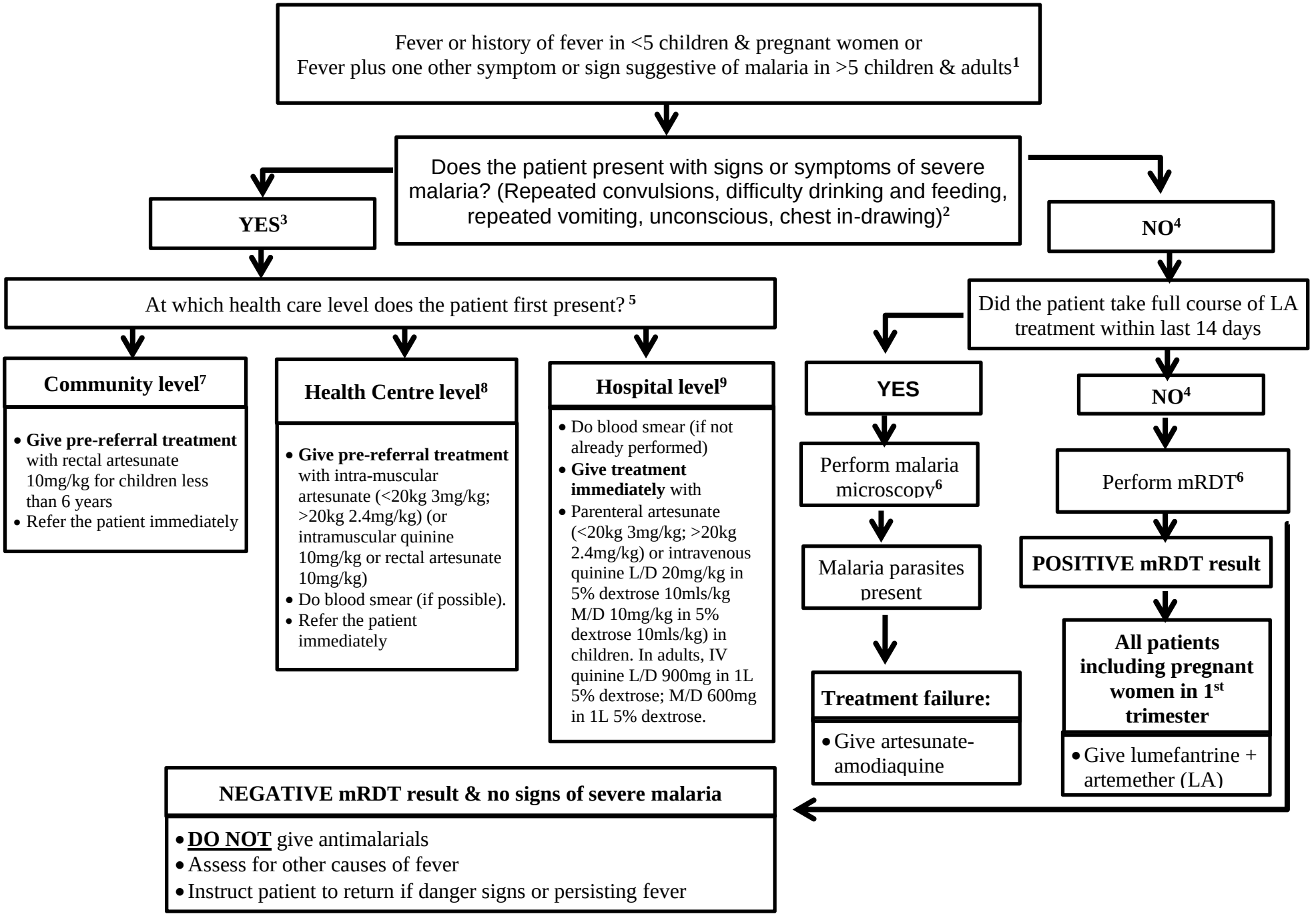
In 2007, the Ministry introduced Lumefantrine-Artemether (LA) as the first-line treatment and Artesunate-Amodiaquine (ASAQ) as the second-line treatment for uncomplicated malaria. The introduction of these drugs is in line with the WHO recommendation to use artemisinin-based combination therapies (ACT) to improve malaria treatment and prolong the therapeutic life of available antimalarial drugs. Through regular studies conducted at sentinel sites throughout the country, the efficacious rate for LA is 98% while that of ASAQ is 99.1%.

Since 2010, the MoH has banned the manufacturing, importation and use of oral artemisinin-based monotherapies in Malawi. However the use of parenteral and rectal artesunate monotherapies is recommended in the initial phase of severe malaria treatment. Only parenteral artesunate is recommended as a definitive treatment of severe malaria.

This 5th Edition of the Guidelines for the Treatment of Malaria in Malawi includes a recommendation for the treatment of uncomplicated malaria in pregnant women in the first trimester and children weighing less than 5 kg using oral using ACTs.

The MoH is now recommending parenteral artesunate as definitive treatment for severe malaria at district and central hospitals. At the health centre level, intramuscular (IM) artesunate is the recommended pre-referral treatment. However, IM quinine may be used when IM artesunate is not available or is contraindicated. *IM quinine should be administered in the thigh, not in the buttocks*. If neither IM therapy is available, rectal artesunate should be used. Rectal artesunate is recommended for children < 6 years as pre-referral treatment of severe malaria at the community level.

Flow Chart for the Diagnosis and Treatment of Malaria



SECTION 1: UNCOMPLICATED MALARIA

1.1 Case Definitions

1.1.1 Suspected Malaria

Malaria should be suspected in any under five children or pregnant women who present with fever (or history of fever) and in over five children and adults with fever or history of fever plus one other symptom or sign suggestive of malaria. The health care personnel in this case must try to clinically exclude other common causes of fever, such as tonsillitis, chest infections, abscess, urinary tract infection, and otitis media.

1.1.2 Confirmed Malaria

A malaria case is confirmed by demonstration of asexual forms (trophozoite stage) of the parasite in the thick or thin peripheral blood film or by a positive malaria rapid diagnostic test (mRDT) result in the presence of fever or history of fever.

1.2 Diagnosis of malaria

Malaria is clinically classified as uncomplicated and severe. Proper history and physical examination are important in the management of malaria. All suspected uncomplicated malaria cases should be confirmed using either microscopy or mRDT. Based on the type of mRDT used in Malawi (HRP2), which remain in blood circulation for not less than two weeks, it is recommended that all suspected severe malaria cases and treatment failures should only be confirmed using microscopy.. Clinical diagnosis in uncomplicated malaria is not recommended.

1.1.3 Uncomplicated malaria

A patient who presents with symptoms of malaria and positive parasitological tests [microscopy or mRDT] but with no features of severe malaria is defined as having uncomplicated malaria [refer section 2 page 7 for severe malaria]
For uncomplicated malaria, treatment should only be given to those patients who test positive.

1.2.1 Malaria Rapid Diagnostic Tests (mRDTs)

All suspected uncomplicated malaria cases at all levels of the health care delivery system should be tested using an approved mRDT prior to initiating treatment. (Refer to national malaria diagnostic guidelines).

Advantages of mRDTs:

(1) They provide a quick result;
(2) They are less expensive than microscopy;
(3) Their use is readily taught.

Disadvantages of mRDTs:

(1) They continue to be positive in patients who have recently (within two weeks) been treated with effective anti-malarial medicines;
(2) They cannot indicate parasite density.

MoH recommends WHO pre-qualified brands of mRDTs to be used in Malawi. New mRDTs brands are selected for national use every 4-5 years after field-testing to determine user friendliness, field performance of individual test (sensitivity and specificity) and heat stability under Malawi's conditions. (Refer to the national diagnostic guidelines for further information).

1.2.2 Microscopy

Microscopy remains the gold standard for the diagnosis of malaria in Malawi. However, as the capacity for microscopy is limited, microscopy will be used for the following purposes:

1. To confirm malaria diagnosis in all in-patients with suspected severe malaria (No MRDT SHOULD BE USED);
2. To monitor treatment progress in all severe malaria cases receiving either parenteral artesunate or parenteral quinine;
3. To confirm first-line treatment failures before second-line treatment is used;
4. To identify malaria parasite species; and
5. To assess malaria parasite densities.
6. To confirm uncomplicated malaria cases where there is capacity.

For microscopic diagnosis of malaria, thick and thin blood films are required and Giemsa stain is to be used. Thick films are recommended for parasite detection and quantification and are used to monitor response to treatment. Thin films are recommended for species identification. In Malawi, approximately 95% of malaria infections are due to *P. falciparum* (MIS 2017).

The following microscopy results will be reported on the laboratory result form:

- Presence or absence of infection (or no malaria parasite seen-NMPS);
- Species of malaria parasite seen
- Stage of the parasite;
- Parasite density i.e., $\frac{\text{Number of parasite counted x 8000}}{\text{Number of WBCs counted}}$**(µl)**

- *(see Table 1.1 below for correct interpretation).

Table 1.1: Correlation between parasite density per micro-litre (µl) of blood and percentage of red blood cells parasitized

Parasites per micro-litre (µl) of blood	% of red blood cells parasitized
40 – 400 parasites ring stage per µl	0.001 – 0.01%
400 – 4000 parasites ring stage per µl	0.01 – 0.1%
4000 – 40000 parasites ring stage per µl	0.1 – 1%
40000 – 400000 parasites ring stage per µl	1 – 10%

1.3 Treatment of Uncomplicated Malaria

The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and prevent progression to severe disease. 'Cure' is defined as elimination of all parasites from the body. The public health objectives are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs

1.3.1 First–line Treatment [Artemisisnin Combination Therapy]

Artemisinin Combination Therapy [ACT] is a combination of rapidly acting artemisinin derivative with a longer acting [more slowly eliminated partner drug] the artemisinin component rapidly clears parasites from the blood [reducing parasite numbers by a factor of 48-hr asexual cycle] And is also active against the sexual stages of parasite that mediate onward transmission to mosquitoes. The longer acting partner drug clears the remaining parasite and provides protection against resistance to artemisinin derivative. Partner drugs with longer elimination half life also provides a period of post treatment prophylaxis.

Note. Artemisinin Combination treatments should be used to treat malaria in pregnant women in the first trimester of pregnancy except where the other partner drug is contraindicated as in Artesunate + Sulphadoxine Pyremethamine (SA+SP)

Table

1.3.1.1 Lumefantrine-Artemether [LA]

The first-line treatment of uncomplicated malaria in Malawi is LA. Lumefantrine-artemether is a highly effective ACT and comes in "fixed-dose combinations". Each tablet of either dispersible or regular LA contains artemether, a synthetic derivative of artemisinin, (20 mg) and lumefantrine (120 mg). Lumefantrine-artemether has a high clinical and parasitological cure rate and produces rapid gametocyte clearance.

Lumefantrine-artemether comes in two oral formulations. These are 1) dispersible LA [LA (D)], 2) non-dispersible LA [LA (ND)]. There are two forms of LA (ND); these are regular tablets and double strength LA [LA (DS)] tablets. LA (ND) should be used in older children weighing 25 kg or more and adults. LA (D) should be used in children weighing less than 25 kg. Table 1.2 below presents the dosing schedule for non-dispersible and dispersible LA.

Table 1.2: Dosage schedule for dispersible Lumefantrine-Artemether (LA)

Body Weight in kg (age in years)	**No. of tablets at approximate timing of dosing**					
	Day 1		**Day 2**		**Day 3**	
	Start dose	**8 hrs.**	**AM**	**PM**	**AM**	**PM**
LA (D) <15 kg (<3)	1	1	1	1	1	1
LA (D) 15 – <25 kg (3 – <9)	2	2	2	2	2	2

Table 1.3: Dosage schedule for Double strength Lumefantrine-Artemether (LA)

Body Weight in kg (age in years)	Strength	No. of tablets at approximate timing of dosing					
		Day 1		Day 2		Day 3	
		Start dose	8 hrs.	AM	PM	AM	PM
LA (DS) 15 - < 25 (3 – <9)	40/240 mg	1	1	1	1	1	1
LA (DS) 25 – <35 kg (9 – <14)	60/360 mg	1	1	1	1	1	1
LA (DS) ≥ 35 (> 14)	80/480 mg	1	1	1	1	1	1

Note. LA (DS)

Most of the reported events associated with LA have been mild, and most studies have shown no indications of cardiotoxicity. However, the manufacturer of LA recommends avoiding medications that prolong the QT interval, including antimalarials such as quinine, should be used cautiously following administration of LA. There is decreased blood concentration of LA in patients who are receiving rifampicin therefore their response to treatment should be monitored more closely and their full adherence ensured. There should be an interval of 8 hours between the last dose of artesunate and the first dose of LA. Similarly, the interval between the last dose of quinine and the first dose of LA should be 12 hours. The following are some of the commonly reported side effects for lumefantrine-artemether: dizziness, abdominal pain, palpitations, myalgia, arthralgia, headache, and skin rash.

1.3.1.2 Dispersible Lumefantrine-Artemether

Dispersible lumefantrine-artemether is a tablet formulation recommended for babies and children weighing less than 25 kg or less than 9 years of age. The dispersible tablets of LA are specially formulated to disintegrate rapidly when put in water. They come in 6x1 and 6x2 blister packs and are available in all Government and CHAM health facilities, as well as all community village clinics. Pharmacologically, LA (D) is similar to LA (ND). LA (D) is cherry flavoured and sweetened to mask the bitter taste of lumefantrine. This makes it more acceptable to children. The other advantage of LA (D) is that it is easy to prepare, as it does not require crushing.

The treatment regimen for LA (D) is six doses (twice per day for three days) according to the body weight or age. The second dose is given 8 hours after the first dose, thereafter doses are given after every 12 hours. Table 1.2 above presents the dosing schedule for dispersible LA.

It is recommended that each dose of LA should be taken with food to optimize absorption. Milk has been shown to improve the absorption of the lumefantrine component of the combination. The dose should be repeated if the medicine is vomited within 30 minutes of ingestion.

Figure 1.1: Preparation and administration of dispersible LA

Use Drinking Water (1 table spoonful or equivalent)

5 kg to < 15 kg (or **< 3 years of age)**

LA (D) 1 TABLET TWICE A DAY FOR 3 DAYS

15 kg to < 25 kg (or **3 years to <9 years of age)**

LA (D) 2 TABLETS TWICE A DAY FOR 3 DAYS

5 kg to < 15 kg (or **< 3 years of age)**

LA (D) 1 TABLET TWICE A DAY FOR 3 DAYS

15 kg to < 25 kg (or **3 years to <9 years of age)**

LA (D) 2 TABLETS TWICE A DAY FOR 3 DAYS

5 kg to < 15 kg (or **< 3 years of age)**

LA (D) 1 TABLET TWICE A DAY FOR 3 DAYS

15 kg to < 25 kg (or **3 years to <9 years of age)**

LA (D) 2 TABLETS TWICE A DAY FOR 3 DAYS

5 kg to < 15 kg (or **< 3 years of age)**

LA (D) 1 TABLET TWICE A DAY FOR 3 DAYS

15 kg to < 25 kg (or **3 years to <9 years of age)**

LA (D) 2 TABLETS TWICE A DAY FOR 3 DAYS

1.3.1.3 Double strength Lumefantrine-Artemether

1.4 Treatment failure

Treatment failure is the persistence of signs and symptoms of malaria in a patient with a positive blood film for malaria parasites after three days of completing a recommended first-line treatment taken in adequate dosage. Treatment failure is not always due to drug resistance.

Causes of real or apparent treatment failure may include:

- Unreported poor adherence to treatment
- Drug resistance
- Inadequate drug exposure due to:
    - Unrecognized incorrect dosage
    - Vomiting within one hour of administration
    - Unusual pharmacokinetic properties in that individual
- Misdiagnosis
- Counterfeit or defective drug
- Drug-drug interaction

Treatment failure should be suspected if symptoms persist or the patient clinically deteriorates three to 14 days after initiation of drug therapy.

Note: If the patient develops symptoms and has a positive blood smear after14 days [need to check the data substantiating the 14 days] of initiation of therapy where there has been prior clearance of symptoms and /or parasites, this should be considered as a new infection and be treated with the first-line drug.

- If, after 14 days, diagnosis or adherence or dosage is found to have been incorrect, then 'treatment failure' is excluded and the primary treatment should be repeated correctly.

- If, however, treatment failure is confirmed, the patient should be treated with the second-line treatment (artesunate-amodiaquine), according to the recommended dosing schedule.

1.4.1 Second-line Treatment

Second-line treatment should be used in the following conditions:

1. Treatment failures within 14 days of initial treatment with LA;
2. All patients with contraindications or intolerance to LA;

1.4.1.1 Artesunate-Amodiaquine

The recommended second-line treatment for uncomplicated malaria in Malawi is ASAQ. It is available in fixed-dose combinations with tablets containing 25 mg /67.5 mg, 50 mg /135 mg and 100 mg /270 mg of artesunate and amodiaquine, respectively. The recommended total treatment dose per day is 4 mg/kg/day of artesunate and 10 mg/kg/day of amodiaquine given once a day for 3 days. Do not give Artesunate amodiaquine in HIV positive patients who are taking zidovudine, cotrimoxazole and efavirenz. Instead give quinine and clindamycin. The dosing schedule is indicated in Table 1.4 below.

Table 1.4: Dosage schedule for fixed combination dose of artesunate-amodiaquine

Body Weight (kg)	Age	Daily dose for 3 days artesunate-amodiaquine	Preparation strength per tablet
5.0 – 8.9	2 – 11 months	1 tablet	25 mg/67.5 mg
9.0 – 17.9	1 – 5 years	1 tablet	50 mg/135 mg
18.0 – 35.9	6 – 13 years	1 tablet	100 mg/270 mg
≥ 36	14 years old and above	2 tablets	100 mg/270 mg

Note: Confirmed treatment failures with ASAQ should be treated with quinine and doxycycline for seven days if not contraindicated. For children under 8 years, give oral quinine and clindamycin.

For children weighing less than 5kg with treatment failure to LA, they should be given quinine and clindamycin.

SECTION 2: SEVERE MALARIA

2.1 Case Definition and Diagnosis

Severe malaria is defined as malaria due to *P. falciparum* infection that is sufficiently serious to be an immediate threat to life. It is a medical emergency, which requires hospitalization. Most severe malaria occurs in children under 5 years of age. However, some adults are also at risk of severe disease, including:

- Malawians returning from long stay (at least one year) in a non-malarious country;
- Expatriates from non-malarious countries;
- Pregnant women;
- Splenectomised individuals; and
- Patients with HIV/AIDS

Although most children with malaria have fever or history of fever, the fever may be variable in patients who have progressed to severe malaria. Children with suspected severe malaria should be examined for other conditions (e.g. pneumonia, meningitis) as a possible cause of their symptoms. If these diseases are found, they should be managed accordingly. If severe malaria is diagnosed in the out-patient setting, treatment should be commenced and the patient referred immediately to a hospital for further evaluation and management.

The health worker should regard a patient as having severe malaria if he or she has one or more (mostly seen in combination) of the following conditions:

Table 2.1: Clinical manifestations and some laboratory findings

Clinical manifestations	Some laboratory findings
• Respiratory distress (acidotic breathing) • Impaired level of consciousness (cerebral malaria) • Repetitive convulsions • Shock (weak pulse, cold extremities) • Hypovolaemia • Spontaneous bleeding (mouth, nose, skin, eyes) • Pulmonary oedema • Prostration • Excessive or persistent vomiting • Extreme pallor • Jaundice (yellowish coloration of eyes) • Little or no urine output (think about acute kidney injury) • Very dark coloured urine	• Severe anaemia: (Hb<5 g/dl) (i.e. Hb <5 g/dl or Hct < 15 %) • Hypoglycaemia: (<2.2 mmol/l or <40 mg/dl) • Hyperlactataemia (lactic acidosis) (blood lactate >4 mmol/l) • Electrolyte imbalance (hyponatraemia <135 mmol/l) • Acute kidney injury (serum creatinine >265 µmol/l or more than 1.4mg/dl) • Haemoglobinuria

❖ **NOTE:** A patient with any of the above features must be treated urgently as a case of severe malaria. Patients with hyperparasitaemia: (40,000 – 400,000/µl or ring stage $\geq$ 5% of RBCs) who do not have any of these indicators of severe disease should be admitted for observation. Treat with first-line antimalarial (LA).

The most common and important complications of *P. falciparum* infection in children are cerebral malaria, severe anaemia, respiratory distress (acidosis) and hypoglycaemia. The differences between severe malaria in adults and in children are shown in Table 2.2 below.

Table 2.2: Different presentations of Severe Malaria between Adults and Children

Sign or symptom	Adults	Children
Duration of illness	5-7 days	1-2 days
Resolution of coma	2-4 days	1-2 days
Neurological sequelae	Uncommon	Common
Jaundice	Common	Uncommon
Pre-treatment hypoglycaemia	Less common	Common
Pulmonary oedema	Uncommon	Rare
Acute respiratory distress syndrome	Common	Rare
Acute kidney injury	Common	Rare
CSF opening pressure	Usually normal	Usually raised
Respiratory distress (acidosis)	Common	Common
Bleeding/clotting disorders	Uncommon	Rare
Invasive bacterial infection (co-infection)	Uncommon	Common

2.2 Treatment of Severe Malaria

Severe malaria is a medical emergency and as such treatment should begin immediately, whether the patient presents at the community level, health centre, or at a hospital. The commencement of life-saving therapy must not be delayed.

2.2.1 Pre-referral Treatment of Severe Malaria

When severe malaria is suspected at the community level, pre-referral treatment should be initiated immediately with rectal artesunate and the patient should be referred to the nearest health facility for further evaluation and management. Refer to **Table 2.3**

At the health centre level, intramuscular (IM) artesunate is the recommended pre-referral treatment. However, intramuscular quinine – administered in the thigh, not the buttock – may be used when IM artesunate is not available or is contraindicated. If neither IM therapy is available, rectal artesunate should be used only to children below the age of 6 years. Personnel at health centres should refer any patient with suspected severe malaria to a hospital for further evaluation and management.

2.2.1.1 Pre-referral Treatment at the Community Level

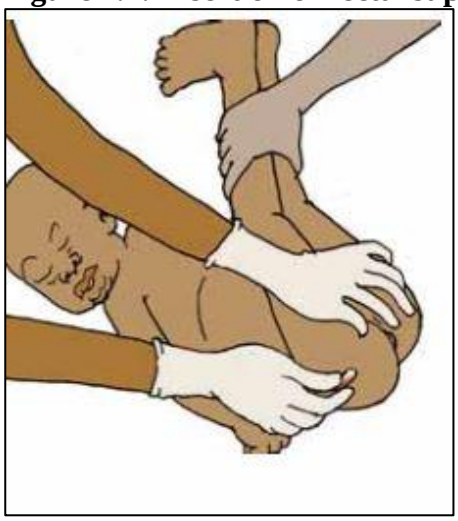
2.2.1.1. Rectal Artesunate

For children: One or more artesunate suppositories inserted in the rectum should be given immediately and followed as soon as possible by definitive therapy for severe malaria at a hospital. The buttocks should be held together for 10 minutes to ensure retention of the rectal dose, especially in young children. Table 2.3 shows the recommended pre-referral doses of artesunate suppositories for children aged < 6 years. If referral is not possible within 12 hours, a second dose of rectal artesunate should be administered at 12 hours after the initial dose. Thereafter rectal artesunate may be given every 24 hours. However this treatment is suboptimal and every effort should be made to refer the patient as soon as possible.

Table 2.3: Initial (pre-referral) Dosage of Artesunate Suppositories for Children Aged <6 Years

Age (Months)	Weight (Kg)	Artesunate dose (mg)	Regimen (single dose)
6 months to < 3 years	5 to < 10	100	One 100 mg suppository
> 3 years to 6 years	11 to 20	200	Two 100 mg suppositories

Figure 2.1: Insertion of rectal suppository



Here are 4 easy steps to insert a suppository:

- Put on a new pair of gloves (i.e., not used before)
- Ask the caregiver to hold the child for you in the position shown
- Insert the suppository, roundthe larger rounded side first, pushing it with one of your fingers. Hold child's buttocks together for 10 minutes or so to make sure that the suppository is not expelled
- Dispose of the gloves so that they cannot be reused

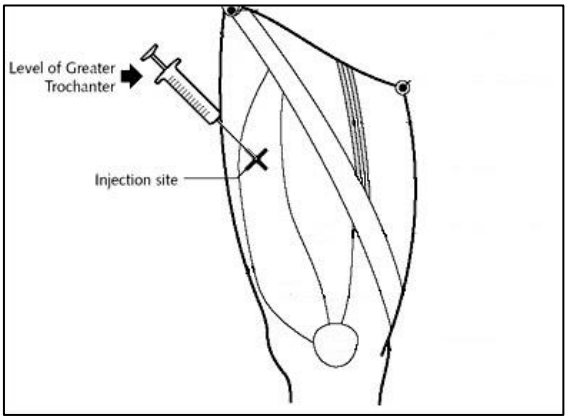
2.2.1.2 Pre-referral Treatment at the Health Centre Level

The medicine of choice for pre-referral treatment of severe malaria at the health centre level is IM artesunate. If IM artesunate is unavailable or contraindicated, treat with IM quinine, administered in the thigh not the buttock. If neither is available, rectal artesunate should be used.

2.2.1.2. Intramuscular Artesunate

The recommended dose of IM artesunate for infants and children whose body weight is <20kg should be 3mg/kg (0.15ml/kg). For children weighing 20 kg and above, and adults the dosage should be 2.4 mg/kg (0.12 ml/kg) body weight. Artesunate should be given by intramuscular injection into the upper-outer quarter of anterior thigh and should not be injected into the buttocks.

Figure 2.2: Administration of Intramuscular Injections



To prepare IM artesunate, weigh the patient and determine the number of vials needed for treatment, according to Table 2.4 below.

Table 2.4: Number of Required Vials for Parenteral Artesunate by Body Weight

Weight	60 mg vials required
<20 kg	1
20 kg – 50 kg	2
51 kg – 75 kg	3
>75 kg	4

Each 60 mg vial of injectable artesunate must be reconstituted with 1 ml of sodium bicarbonate. Dilute the artesunate-bicarbonate mixture with **2 ml** of 5% dextrose solution or normal saline (0.9% Sodium Chloride) to produce a 20 mg/ml solution. Withdraw the appropriate volume in a syringe ((children <20kgs, give 3 mg x body weight in kg, and children > 20kg and adults, give 2.4 mg x body weight in kg)/10 mg/ml)) for intramuscular injection, rounding to the next whole number in milliliters.

Administration of pre-referral IM artesunate should be followed as soon as possible by definitive therapy for malaria at a hospital. If referral is not possible within 12 hours, a second dose of IM artesunate should be administered at 12 hours after the initial dose. If referral is still not possible after 24 hours, a third dose of IM artesunate should be given.

2.2.1.2.2 Intramuscular Quinine

Intramuscular quinine should be used for pre-referral treatment of severe malaria in instances where IM artesunate is either unavailable or contraindicated. The recommended dose of IM quinine is 10 mg (0.2 ml) per kg body weight.

To administer intramuscular quinine, use a 10 ml sterile syringe to draw 5 ml of sterile water for injection, then into the same syringe draw up 300 mg (1 ml) from an ampoule of quinine. The syringe now contains 50 mg of quinine per ml. Withdraw the appropriate volume and administer into the upper outer thigh. If the volume to be injected exceeds 3 ml, give half into each thigh. An example of body weights and dosing (ml) for IM quinine is given in Table 2.5 below.

Table 2.5: Sample Dosages of IM Quinine by Body Weight

Body weight	Quinine (ml)
Under 5 kg	1.0 ml
5.1 – 7.5 kg	1.5 ml

7.6 – 10.0 kg	2.0 ml
10.1 – 12.5 kg	2.5 ml
12.6 – 15.0 kg	3.0 ml
15.1 – 17.5 kg	3.5 ml
17.6 – 20.0 kg	4.0 ml
20.1 – 22.5 kg	4.5 ml
22.6 – 25.0 kg	5.0 ml
25.1 – 27.5 kg	5.5 ml
27.6 – 30.0 kg	6.0 ml

Administration of pre-referral IM quinine should be followed as soon as possible by definitive therapy for malaria at a hospital. If referral is not possible within 12 hours, a second dose of IM quinine should be administered 12 hours after the initial dose. If referral is still not possible after 24 hours, a third dose of IM quinine should be given.

2.2.2 Management of Severe Malaria in the in-Patient Setting

The 8-8-8 schedule

The health worker should consider following the 8-8-8 schedule (described in Boxes 1-3 below) in the management of patients with severe malaria.

Box 1: Take 8 Immediate Measures:

1. Start resuscitation, particularly maintenance of a patent airway.
2. Establish IV line.
3. Make a thick blood smear for immediate malaria parasite count, (if microscopy is not available, an mRDT may be useful to indicate whether malaria infection is present or not)
4. Assess for severe dehydration (lethargy, sunken eyes, dry mouth and reduced skin turgor). Assess patient's fluid requirements and correct accordingly.
5. Control fever if the axillary temperature is 38 ºC or above: Tepid sponge, fanning and oral paracetamol (10mg/kg every 6-8 hours) or rectal paracetamol (15 mg/kg every 4 to 6 hours).
6. Manage convulsions: maintain airway, treat with rectal diazepam (0.5 mg/kg) or slow IV diazepam (0.3 mg/kg, maximum 10 mg in an adult), or paraldehyde 0.1 ml/kg IM. Remember to correct any hypoglycaemia or hyperpyrexia in a convulsing patient.
7. Detect and treat hypoglycaemia: hypoglycaemia can be induced by high parasitaemia, fasting and quinine therapy. Hypoglycaemia can recur, especially in pregnant women and children. If blood glucose ≤3 mmol/l or ≤54 mg/dl; give 1 ml/kg of 50% dextrose IV, diluted with an equal volume of 0.9% saline or 5% dextrose, give slowly over 3-5 minutes, and check blood glucose after 30 minutes and as required after treatment. Follow with 10% dextrose infusion at 5 ml/kg/hr. If there is no test for blood glucose, treat as if the patient is hypoglycaemic.

8. **Start intravenous or intra-muscular artesunate. Dosage schedule is provided from section 2.2.2.2 below. If intravenous or intra-muscular artesunate is unavailable, use intravenous or intra-muscular quinine.**

Box 2: Look for and Deal with the Following 8 Complications:

1. **Shock**: If cold peripheries, delayed capillary refill, or Systolic BP <50 mmHg in children 1 – 5years or <80 mmHg in >5 years, suspect Gram-negative septicaemia. In such cases take blood samples for culture. Give parenteral broad-spectrum antimicrobials. Correct fluid disturbance, and then continue with maintenance fluid as follows:

    - **for children weighing <10 kg**, give 4 ml/kg/hr.;
    - **for children weighing 10 – 20 kg**, give 40 ml/hr. *plus* additional 2 ml per kg for each kg of weight in excess of 10 kg;
    - **for children weighing >20 kg**, give 60 ml/hr., *plus* additional 1 ml per kg for each kg of weight in excess of 20 kg. Give oxygen if possible.

2. **Altered consciousness and/or convulsions:** Check for hypoglycaemia, hyperpyrexia and 'subtle' seizures. *In a comatose patient, convulsions (seizures) may be 'subtle' – i.e. minor movements [flicker of eyelid, mouth or finger] or unusual repetitive movements [a rhythmical cry, unusual breathing, or 'pedalling' of legs].* If seizure suspected, treat as in item 6 in Box1.

3. **Severe anaemia:** Consider the need for blood transfusion: Assess the degree of pallor (no pallor, some pallor or severe pallor – look especially at palms of hands, also mucous membranes). Assess signs that increase the danger of severe anaemia - respiratory distress, altered consciousness, shock and hyperparasitaemia.

    Note: *The decision to transfuse with blood should not only be based on low laboratory values, but on a full assessment of the patient**. As a guide, **all** patients with PCV<12% or Hb<4 g/dl should be transfused, whatever the clinical state; those with any of the above danger signs may be transfused even if PCV is 13-18% or Hb 4-6g/dl.*

4. **Transfuse packed red cells in most cases; in shock or severe acidosis, use whole blood. The volume transfused should be 20 ml/kg.**

5. **Metabolic acidosis** (deep, fast breathing): **exclude or treat** hypoglycaemia, hypovolaemia and gram negative septicaemia. Give isotonic saline 20 ml/kg of body weight rapidly or screened whole blood 10 ml/kg if PCV <18% or Hb<6 g/dl. Rule out lactic acidosis.

6. **Spontaneous bleeding or coagulopathy:** If patients have underlying malnutrition, concomitant hepatic obstruction and bile salt excretion defects or prolonged fasting for more than 3 days, transfuse screened fresh whole blood, give Vitamin K 10 mg IV slowly once a day for 3 days. For Children give 2 – 3 mg/day slow IV. Vitamin K injections should not be given to "all" severe malaria patients with spontaneous bleeding, the risks and benefit of Vitamin K administration should be considered. Serious adverse events of Vitamin K injection include hypotension, difficulties in breathing, bradycardia or anaphylaxis.

- **Acute pulmonary oedema**: prevent by avoiding excessive rehydration. Treatment: prop patient up; give oxygen. Stop IV fluids if pulmonary oedema is due to over-hydration, give a diuretic (furosemide IV 40 mg for adult and 0.5 – 1 mg/kg/dose for children).

- **Acute respiratory distress syndrome**: supportive treatment +/- ventilation

7. **Acute kidney injury**: detect this by monitoring fluid balance. Identify and correct any dehydration or hypovolaemia. Maintain strict fluid balance. Consider peritoneal dialysis if oliguria persists beyond a few days.

8. **Common infections** and other conditions that present like severe malaria: Perform urinalysis, lumbar puncture (unless contraindicated), blood culture if possible, and chest x-ray.

********Many children recover from severe anaemia with the help of antimalarial drugs alone. Because of the risk of blood transfusion (HIV, hepatitis), give blood only if it is essential for the child's recovery.*

Box 3: Monitor the Following 8 Observations:

Where possible use Critical Care Pathways (CCPs).

1. Level of consciousness (using coma score, see annex)

2. Vital signs every 4 hours (temperature, pulse, respiration, blood pressure)

3. Fluid balance (urine volumes, intake volumes – IV and oral – puffy eyes, chest crepitation, elevated jugular venous pressure)

4. Increasing anaemia (pallor, heart failure with increasing liver size)

5. Occurrence of convulsions – see item 2 in previous Box

6. Blood glucose every 4 hours while unconscious and also if convulsions occur

7. [Hb]/Packed Cell Volume – at least daily, or more often if anaemia is suspected

8. Ability to suck, drink, eat, sit and walk – measures of overall strength.

Educate the patient and relatives about home prevention of malaria. Wait for the patient to recover before counselling.

2.2.2.2 Treatment Options for Severe Malaria in the In-Patient Setting

The following are the recommended definitive antimalarial treatments for severe malaria:
1. Parenteral artesunate, or if not available or contraindicated
2. Parenteral quinine

2.2.2.2.1 Severe Malaria Treatment with Parenteral Artesunate

Intravenous (IV) artesunate is the treatment of choice for the management of severe malaria. Artesunate may also be administered intramuscularly, if intravenous bolus is not feasible.

For children < 20 kgs, give artesunate **3 mg/kg body weight** while children > 20kgs and adults, give artesunate **2.4 mg/kg body weight** IV or IM on admission (at 0 hour), repeat at 12 hours and 24 hours, after initiating the first dose then once daily for not more than six days. However, once the patient can take oral treatment and at least 24 hours of parenteral artesunate has been administered, discontinue parenteral therapy and commence full course of LA. **There should be an interval of at least 8 hours between the last dose of artesunate and the first dose of LA.**. Refer to Table 1.3 above for dosing schedule of oral quinine plus clindamycin.

Artesunate is dispensed as a powder of artesunic acid. This must be dissolved in 5% sodium bicarbonate to form sodium artesunate. The solution is then diluted in approximately 5% dextrose. When given intramuscularly, it should be injected into the upper-outer quarter of anterior thigh**. Artesunate or quinine should never be injected into the buttocks.** The solution should be freshly prepared prior to administration and should **never** be stored.

Preparation and Administration of Parenteral Artesunate

To prepare IV artesunate, weigh the patient and determine the number of vials needed for treatment, according to Table 2.6 below.

Table 2.6: Number of Required Vials of Parenteral Artesunate by Body Weight

Weight	60 mg vials required
<20kg	1
21 kg – 50 kg	2
51 kg – 75 kg	3
76 kg – 100 kg	4

Each vial of 60 mg injectable artesunate must be reconstituted with 1 ml of sodium bicarbonate. For IV bolus injection, dilute the artesunate-bicarbonate mixture with 5 ml of 5% dextrose solution or normal saline (0.9% Sodium Chloride) to produce a 10 mg/ml solution. Withdraw the appropriate volume in a syringe ((children <20kgs, give 3 mg x body in kg and children > 20kg and adults, give 2.4 mg x body weight in kg)/10 mg/ml) for IV bolus injection, rounding to the next whole number in milliliters.

To prepare IM artesunate, dilute the artesunate-bicarbonate mixture with 2 ml of 5% dextrose solution or normal saline (0.9% Sodium Chloride) to produce a 20 mg/ml solution. Withdraw the appropriate volume in a syringe ((2.4 mg x body weight in kg)/20 mg/ml) for IM injection, rounding to the next whole number in milliliters.

2.2.2.2.2 Severe Malaria Treatment with Parenteral Quinine

Parenteral quinine should be used for the treatment for severe malaria only in situations in which parenteral artesunate is not available or is contraindicated.

For children, intravenous quinine is administered as follows:

- Initial (‘loading’) dose 20 mg (quinine salt)/kg body weight: inject this dose into 10 ml/kg of 5% dextrose or half strength Darrow’s and infuse over 3-4 hours.
- If patient has already received quinine for this illness, the first dose IV infusion should be 10 mg/kg diluted as above and given over 3-4 hours with no loading dose.

- Subsequent doses of 10 mg/kg should be given every 12 hours. The infusion should run for 3 – 4 hours. Continue the 5% dextrose or half strength Darrow's IV fluid (10 ml/kg given over 3 – 4 hours) between doses of quinine.

Stop intravenous quinine as soon as the patient can take food and fluids orally and at least 24 hours of parenteral quinine has been administered. Give age or weight appropriate doses of LA beginning 12 hours after the last dose of quinine. For children <5 kg, give oral quinine plus clindamycin for a total of 7 days. Refer to Table 1.3 above for dosing schedule of oral quinine plus clindamycin.

Note: Quinine dosage should be timed from the start of the IV infusion. The preferred route for parenteral quinine is intramuscular, see section 2.2.1.2.2 for dosing and administration.

For adults, if the patient can be weighed, intravenous quinine is administered in the same manner as for children. If the patient cannot be weighed, IV quinine should be given as follows:

- First dose 900 mg in one litre of 5% dextrose or ½-strength Darrow's fluids given over 3 – 4 hours
- Subsequent doses 600 mg in one litre 5% dextrose or ½-strength Darrow's fluids every 12 hours given over 3 – 4 hours
- Continue the same IV fluids or Ringer's lactate (10 ml/kg given over 3 – 4 hours) between doses of quinine (Give a maximum of about 3 litres per 24 hours to avoid fluid overload)

Stop intravenous quinine as soon as the patient can take food and fluids orally and at least 24 hours of parenteral quinine has been administered. Give the appropriate dose of LA beginning 12 hours of the last dose of quinine. For pregnant women in the first trimester give oral quinine plus clindamycin for a total of 7 days. Refer to Table 1.3 above for dosing schedule of oral quinine plus clindamycin.

NB: LA should only be taken 12 hours after last dose of quinine to avoid cardiotoxicity

SECTION 3: MALARIA IN PREGNANCY

Pregnancy increases the risk of malaria infection in all women. Malaria during pregnancy causes febrile illness, anaemia and increases the risk of maternal illness and death, miscarriage, stillbirth, low birth weight and neonatal death. Women in their first and second pregnancies and all HIV infected women are at increased risk of the effects of malaria. All pregnant women living in malaria risk areas should be advised on malaria prevention measures and clinical cases of malaria treated promptly with effective anti-malarials.

3.1 Intermittent Preventive Treatment of Malaria in pregnancy

Intermittent Preventive Treatment (IPTp) of malaria in pregnancy is one of the major malaria preventive strategies in Malawi. **The policy for IPTp is for women to receive at least three doses of sulfadoxine-pyrimethamine (SP) after the first trimester.** Administer three tablets of SP with each scheduled antenatal care visit from 13 weeks gestation. **The doses should be administered at least four weeks apart and given as directly observed therapy (DOT).** The last dose of SP can be delivered safely up until the time of delivery. Sulfadoxine-pyrimethamine can be given either on an empty stomach or with food. **HIV positive women receiving cotrimoxazole prophylaxis should not receive SP.**

There are advantages of three or more doses of SP as follows:

- Increased the mean birth weight by about 56 g
- Reduced the number of low-birth-weight infants by about 20%
- Reduced placental parasitaemia by about 50%
- Reduced maternal parasitaemia by about 33%

Although IPTp reduces the risk of malaria in pregnancy, breakthrough clinical malaria episodes can occur in patients who have received IPTp.

3.2 Management of Malaria in Pregnancy

3.2.1 Clinical Features of Malaria in Pregnancy

As in non-pregnant adults, malaria in pregnancy may manifest as uncomplicated febrile illness or as complicated (severe) disease. The clinical manifestations of malaria in pregnancy are similar to those in non-pregnant women. However, pregnant women are at particular risk of hypoglycaemia (especially as a consequence of treatment with quinine), anaemia, and pulmonary oedema.

3.2.2 Management of Uncomplicated Malaria in Pregnancy

Management of malaria in pregnancy includes: treatment of malaria, management of complications and management of labour.

Treatment should be initiated as early as possible. LA is safe in all trimesters of pregnancy. As such, all pregnant women should be treated with LA. Refer to Table 1.3 above.

Note: If there is a confirmed LA treatment failure for pregnant women in the 1st trimester, give oral quinine in combination with clindamycin. However, for pregnant women in second and third trimesters, give ASAQ as in Table 1.4 above. Remember that pregnant women are susceptible to hypoglycaemia when taking quinine.

Table 3.1: Dosing schedule for Quinine and Clindamycin

First trimester	Quinine tablets 600 mg every 8 hrs. for 7 days, plus Clindamycin tablets 30 0mg every 8 hrs. for 7 days

3.2.3 Management of severe malaria in pregnancy

In the management of severe malaria in pregnancy, special attention must be paid to anaemia, hypoglycaemia and pulmonary oedema. See Box 4 below for further information on the management of complications.

Box 4: Management of complications: (see The 8-8-8 schedule above)

These are the same as for any adult. Of special importance in pregnancy are:

- Pulmonary oedema: careful fluid management, diuretics if necessary, oxygen if possible, nurse patient in semi-upright position.
- Hypoglycaemia: consider this complication if there is altered consciousness or seizure.
  - Treat as in Item 2 in Box 2.
- Anaemia: be prepared for blood transfusion, especially if the patient is close to parturition. Otherwise, indications for blood transfusion are the same as in others – (see Box 2).
- Acute kidney injury: a particular danger if there has been eclampsia or shock. Identification and management as above.
- Shock: consider concealed haemorrhage, continuing blood loss, and septicaemia. Pay special attention to fluid needs. Culture blood if possible. Administer broad spectrum antibiotics in addition to quinine.

3.2.4 Treatment of Severe Malaria in Pregnancy

Parenteral artesunate is the recommended treatment for severe malaria in all pregnant women. Give artesunate **2.4 mg/kg body weight** IV bolus or IM on admission (at 0 hour), repeat at 12 hours and at 24 hours, then once daily, for no more than 6 days. However, once patient can take oral treatment and at least 24 hours of parenteral therapy has been administered, discontinue parenteral therapy and commence a full 3-day course of LA..

Pregnant women in all trimesters can be treated with parenteral quinine if parenteral artesunate is not available or contraindicated. The dose is 20 mg salt/kg body weight as loading dose, followed by 10 mg salt/kg 12-hourly until patient is able to take oral medication and at least 24 hours of parenteral therapy has been administered.

- If the patient cannot be weighed, start with infusion of 900 mg of quinine in 1 litre of 5% dextrose.
- If quinine cannot be given by infusion, give 10 mg/kg by IM injection. Make sure you give 10% glucose or of 5% glucose before administration of quinine; be careful not to induce pulmonary oedema. Random blood glucose should be measured before and after quinine administration.

Switch to LA as soon as the patient is able to take oral medication and at least 24 hours of parenteral therapy has been administered.

3.3 Specific Messages for Pregnant Women

1. An important part of health messages concerning pregnant women should be the encouragement of all pregnant women to attend antenatal clinics early in pregnancy, especially as soon as they suspect that they are pregnant.
2. Pregnant women presenting with fever should be tested for malaria and treated accordingly.
3. Using drugs for malaria prevention should be done in conjunction with other personal protection measures that are available and acceptable.
4. Malaria treatment and prevention services in the ANC should be viewed as an integral part of the MCH services in the improvement of the mother's and child health.

SECTION 4: GUIDE TO COMA SCALES

4.1 Assessing Level of Consciousness using Coma Scales

All patients fulfilling the clinical diagnosis of cerebral malaria, (i.e. a patient with malaria and a reduced level of consciousness) should be assessed using a coma scale to follow the patient's response to treatment.

The Blantyre Coma Scale (Table 4.1) is used for assessing the level of consciousness in children less than 12 years old, while the Glasgow Coma Scale (Table 4.2) is used for assessing the level of consciousness in children 12 years of age and older and in adults.

4.1.1 Blantyre Coma Scale

For the Blantyre Coma Scale, the scoring can be done quickly and easily by any health worker. The maximum score is five. Table 4.1, below, summarizes the assessment of patients using this scale. A score is assigned for each of the three responses (i.e. motor, verbal and eye movement or ability to follow the mother's face or a coloured object). The three scores are then added. This total is the coma score. The maximum score for a fully conscious child is 5/5. The scores can be done daily or more frequently to follow the patient's response to treatment.

Table 4.1 Blantyre Coma Scale (for children <12 years)

Eye Movement	-Follows (watches)	1
	-Does not follow	0
Verbal	-Appropriate cry	2
	-Moan or Inappropriate cry	1
	-None	0
Best motor response	-Localises painful stimulus (a or c)	2
	-Withdraws limb from pain (b)	1
	-Non-specific or absent response	0
Total		0-5

(a) Press knuckles firmly on the patients sternum
(b) Press firmly on the thumbnail bed with side of a horizontal pencil
(c) Press knuckle firmly on the supra-orbital ridge (eyebrow)
Add the scores for each column, to get a total out of 5

The scale can be applied repeatedly to assess improvement or deterioration. Total score for a fully conscious child is 5/5, and for a totally unresponsive child is 0/5.

4.1.2 Glasgow Coma Scale

The Glasgow Coma Scale provides a score in the range of three to 15. Patients with scores of three to eight are usually said to be in a coma. To determine the Glasgow coma score, calculate the score for each section add the three figures. The scores for adults are outlined in Table 4.2 below.
(Note that the minimum possible Glasgow Coma Scale score is 3, while the minimum Blantyre Coma Scale score is zero).

Table 4.2: The Glasgow Coma Scale (for adults and children 12 years and older)

Eyes open	- Spontaneously	4
	- To speech	3
	- To pain	2
	- Never	1
Best verbal response	- Oriented	5
	- Confused	4
	- Inappropriate words	3
	- Incomprehensible sounds	2
	- None	1
Best motor response	- Obeys commands	6
	- Localizes pain	5
	- Withdraws from pain	4
	- Flexion to pain	3
	- Extension to pain	2
	- None	1
Total		3-15

SECTION 5: SELECTIVE ANTIMALARIAL CHEMOPROPHYLAXIS

5.1 Risk Groups

The following high-risk groups should be given antimalarial chemoprophylaxis:

- Patients who have had a splenectomy;
- Those taking cytotoxic or immunosuppressive drugs for malignant disease;
- Hyper-reactive malarial splenomegaly (previously known as tropical splenomegaly syndrome);
- Children who have had recurrent severe malaria;
- Individuals with sickle cell disease;
- Visitors from countries where there is no malaria transmission.

5.2 Giving Advice about Malaria Prophylaxis

Emphasize that no prophylaxis is 100% effective. (e.g. "Don't assume the fever could not be malaria, just because you have been taking these tablets.") Advise other measures also (especially to sleep under an insecticide-treated bed net every night and to promptly seek care in the event of a fever)

5.3 Antimalarial Prophylaxis Regimens

1. **Doxycycline** 100 mg daily. It can cause photosensitivity skin reactions. Doxycycline is strongly contraindicated during pregnancy and in children aged <8 years of age.

2. **Mefloquine** (Lariam) 250 mg weekly. Some people react badly – headache, insomnia, and feeling of unreality. In very few people there may be serious effects - psychosis, ataxia, convulsions. Therefore contraindicated in pilots etc. Avoid mefloquine in people with a history of cardiac disease, neurological disease or depression, and in those taking beta-blocking drugs. Quite expensive, and not widely available within Malawi.

3. **Atovaquone-Proguanil (Malarone)** one tablet daily. Extremely expensive, so suitable only for short-term use. It has the advantage (for travellers) that it needs to be taken only once a day and for only one week after exposure ends.

4. **Chloroquine** 300 mg (base) (2 tablets) weekly. If the above options are not possible, chloroquine may now be efficacious in Malawi, but should be combined with daily proguanil (see below). [*P falciparum* resistance to chloroquine was extensive in Malawi in the 1990s, but is now diminished (2007-2012)]. Chloroquine causes itching in 40% of black people. Avoid in persons with psoriasis or epilepsy.

   Note: *There is risk of retinal damage if chloroquine is taken every week for more than 5 years. For clients expected to use chloroquine for longer than 5 years, a baseline retinal exam should be conducted at the onset of prophylaxis, and annual exams should be conducted beginning after 5 years of use.*

5. **Proguanil** (Paludrine) 200 mg daily. Very few problems. Mouth ulcers sometimes troublesome. Moderately effective. Should combine with an additional drug such as weekly chloroquine.

Chloroquine and proguanil are safe in pregnancy. There is no evidence that mefloquine is harmful in pregnancy. However, many prefer not to use it during pregnancy.

5.4 Health Education Messages for Persons Receiving Chemoprophylaxis

Health education should be provided to the individuals at risk and to the general population through the health care workers, PHC system and existing village structures. The chemoprophylactic drug regimen should be explained carefully to all patients or guardians to ensure compliance at home.