# NATIONAL ANTIMALARIAL TREATMENT GUIDELINES

**Preface**
**Foreword**

**OVERVIEW OF THE ANTIMALARIAL GUIDELINES**

- Purpose: To provide guideline for the treatment of malaria in Nigeria
- Target audience: All levels of health care providers

**CLINICAL DISEASE**

**What is malaria?**

Malaria is an infectious disease caused by the parasite of the genus *Plasmodium.* There are four identified species of this parasite causing human malaria, namely, *Plasmodium falciparum, P. vivax, P. ovale and P. malariae*. In Nigeria 98% of all cases of malaria is due to *Plasmodium falciparum* and *t*his is the specie that is responsible for the severe form of the disease that leads to death.

**How do people get malaria?**

This is the principal mode of spread of malaria is from bites from infected female anopheles mosquito. The bites of the mosquito are more frequent at night time. Other uncommon modes of transmission are from blood transfusion and mother to child transmission

**Occurrence and Distribution**

Malaria occurs in the subtropical and tropical areas of the world. People from areas where malaria is endemic develop partial immunity, hence older children and adults in such areas but they may also still have severe malaria

**CLASSIFICATION**

People die from malaria when not appropriately classified. Failure to recognize severe malaria may be fatal. Malaria should be classified as;

**a. Uncomplicated malaria**:

This is systematic malaria that has no life threatening manifestations.

**b. Severe malaria**:

This is when there is *P. falciparum* asexual parasitaemia and no other confirmed cause of their symptoms with the presence of life threatening clinical or laboratory features

## ASSESSMENT AND MANAGEMENT OF UNCOMPLICATED MALARIA

The main manifestation of malaria is FEVER. The clinical features of malaria vary from the asymptomatic to mild to severe disease.

### History

A complete history should include:

- General information such as age, place of residence and recent history of travel within or outside the country.
- Enquiry about the following symptoms:-
  - Fever
  - Chills (feeling cold) and rigors (shaking of the body)
  - Headache
  - Joint weakness or tiredness
- Also ask for the symptoms of other common childhood diseases
  - Cough or respiratory distress
  - Diarrhoea
  - Ear pain and skin rashes in the last three months.

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### Signs

- Increased body temperature > 37.5°C.
- Enlarged spleen or liver, especially in children.
- Pallor (children/pregnant women)
- Exclude signs of severe disease.

### Clinical Diagnosis

**Criteria for diagnosis in stable malaria areas;**

- Fever
- Unexplained pallor (children <5 and pregnant women)

In pregnancy women get acute symptomatic disease that are more severe than when not pregnant. This is particularly true for primigravidas in whom there is high rate of placental infection and chronic anaemia.

**Laboratory Diagnosis**

***A parasitological diagnosis of malaria is always desirable. This may be by standard microscopy or by the rapid diagnostic tests (RDT)***

In children under 5, a clinical diagnosis is adequate for treatment of uncomplicated malaria. This is to avoid any delay in treatment because malaria is very common and may be rapidly fatal in this age group. However, lab diagnosis is needed for confirming the diagnosis and in suspected cases of treatment failure.

**Treatment of Uncomplicated Malaria**

**Treatment Objective:**

The objective of treating uncomplicated malaria is to cure the infection. This will prevent both progression to severe disease and the additional morbidity associated with treatment failure. Cure of the infection means eradication from the body of the infection which caused the illness requiring treatment. Secondary but importance public health objectives are also to prevent the infection from being transmitted and to prevent resistance to the antimalarial drugs.

**Recommended treatment**

The treatment of choice for uncomplicated malaria is Artemisinin Based Combination Therapy (ACT). This consists of the use of an artemisinin derivative and another effective antimalarial medicine.

**Recommended ACT for uncomplicated malaria is Artemether-lumefantrine**

**Dosage chart for Artemether-Lumefantrine**

| weight (Age group) | Number of tablets / dose |
|---|---|
| 5-14kg (6mths-3yrs) | 1 tab twice daily x 3days |
| 15-24kg (4-8yrs) | 2 tabs twice daily x 3days |
| 25-34kg (9-14yrs) | 3 tabs twice daily x 3days |

| | |
|---|---|
| >35kg (>14yrs) | 4 tabs twice daily x3days |

It is important to emphasize that the **6 doses** must be taken by the patient. Absorption of the drugs is enhanced by food**.**

**If the patient shows evidence of inadequate clinical response (refer annex), do the following:**

- Evaluate the patient and review diagnosis
- Exclude sub optimal dosing or inadequate intake
- Seek confirmatory test

**In the rare case of all of the above being normal and malaria is unresponsive use oral Quinine.**

**Dosage of Quinine**

**Other ACTs available**

- Artesunate (4 mg/kg) + amodiaquine (10mg base/kg) daily for 3 days.

- Artesunate 4 mg/kg once daily for 3 days + mefloquine 25 mg base/kg (15 mg/kg on day 2, 10 mg/kg on day 3)

**Monotherapy with dihydroartemisinin, other artemisinin derivatives and other antimalarial medicines are not recommended. Treatment must be used in combination with another effective antimalarial drug.**

**Practical Issues in Management of Uncomplicated Malaria**

- ***Use of antipyretics***
  If temperature is high temperature > 38.5°C advice to wipe the body with wet towel, avoid over clothing and give paracetamol 10 mg/kg in children or 500-1000 mg in adults 4 times daily.
- Vomiting
- Febrile Seizures
- Use of Iron
- Where oral administration of drug is not possible
- Hyperpyrexia

**FOLLOW-UP**

- Tell the patient to return:
  - If Fever persists for two days after commencement of treatment

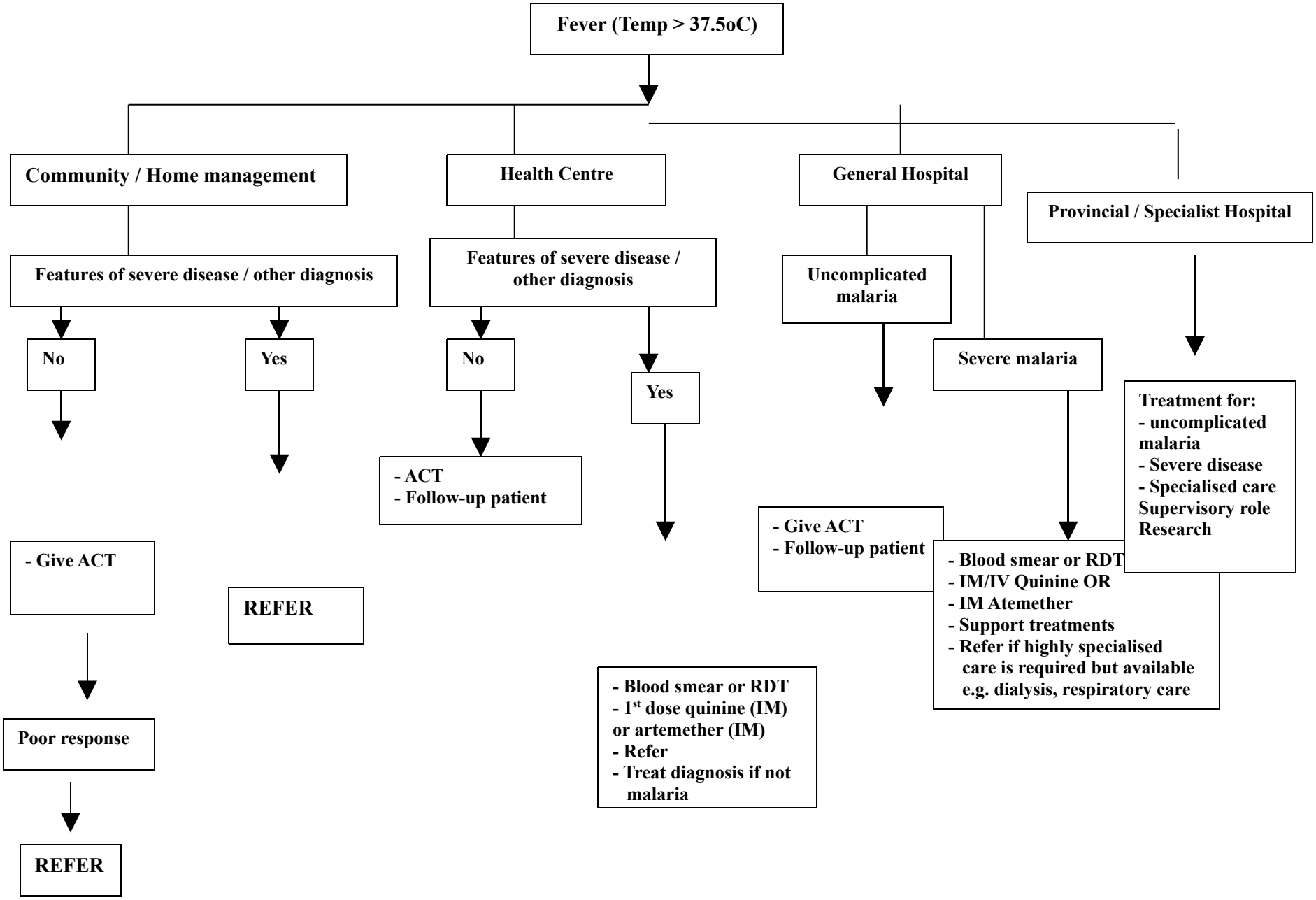
    - Immediately, if condition gets worse or develops signs of severe disease.
- When patient returns:
    - Check that they complied with the treatment as advised
    - Repeat or do blood smear for malaria parasites.
    - Do a complete assessment to exclude any other possible cause of fever.

**KEY MESSAGES FOR ORAL DRUGS AT HOME**

- Determine the appropriate drug and dosage according to weight and age.
- Tell the patient or the child’s caregiver the reason for giving the drug.
- Demonstrate how to take or give the correct dose.
- Watch the patient taking the drug.
- Explain that the tablets must be used to finish the course of treatment even if the patient feels well.
- Advise them on when to return.
- Check that the patient or caregiver has understood the instructions before leaving the clinic.

- Special considerations
    - Uncomplicated malaria in pregnancy
    - HIV Positive patients
- Treatment failure
    - Definition
    - Criteria
    - Recommended actions

## ALGORITHM FOR MANAGEMENT OF UNCOMPLICATED MALARIA AT DIFFERENT LEVELS OF HEALTH CARE IN NIGERIA



## ASSESSMENT AND MANAGEMENT OF SEVERE MALARIA

### Definition

A patient has severe malaria when there is *P. falciparum* asexual parasitaemia and no other confirmed cause of their symptoms, in the presence of the following clinical or laboratory features:

| Clinical manifestations or laboratory findings | Frequency [a] | |
|---|---|---|
| | **Children** | **Adults** |
| ▪ Prostration *(i.e. generalized weakness or inability to sit, stand or walk without support)* | +++ | +++ |
| ▪ Impaired consciousness *(confusion or drowsiness or coma)* | +++ | ++ |
| ▪ Respiratory distress *(difficulty in breathing, fast deep breath)* | +++ | + |
| ▪ Multiple convulsions *(>2 generalized seizures in 24 hrs with regaining of consciousness)* | +++ | + |
| ▪ Severe anaemia *( Hb <5 gm/dl)* | +++ | + |
| ▪ Circulatory collapse *(shock)* | + | + |
| ▪ Pulmonary oedema *(respiratory distress /radiology)* | +/- | + |
| ▪ Abnormal bleeding *(disseminated intravascular coagulopathy)* | +/- | + |
| ▪ Jaundice *(yellow discoloration of the eyes)* | + | +++ |
| ▪ Haemoglobinuria *(Coca-Cola coloured urine)* | +/- | + |
| ▪ Hyperparasitaemia[b] *Density of asexual forms of P. falciparum in the peripheral smear exceeding 5% of erythrocytes (more than 250,000 parasites per µl at normal red cell counts)* | ++ | + |
| ▪ Renal failure *(Urine output of less than 400 ml in 24 hours or <12ml/kg per 24 hours in children and a serum creatinine of more than 265 µ mol/l (> 3.0 mg/dl), failing to improve after rehydration)* | +/- | ++ |

[a] on a scale from + to +++; +/- indicates infrequent occurrence.

### Explanatory notes on the features of severe malaria

**Anaemia:**

This is the commonest complication of malaria. It occurs as a result of destruction of parasitised red blood cell by the spleen, TNF mediated depression of erythropoiesis and immune mediated haemolysis.

**Cerebral Malaria:**

For a diagnosis of cerebral malaria, the following criteria should be met:

i. *Deep, unarousable coma*: Motor response to noxious stimuli is non-localising or absent. However management should be instituted once there is an altered consciouness.
ii. *Exclusion of other encephalopathies*:
iii. *Confirmation of P. falciparum infection*:

**Abnormal neurological manifestations:**

Convulsions may be as a result of very high temperature, hypoglycaemia, hypoxaemia severe anaemia or the effect of herbal concoction.

**Hypoglycaemia:**

This may occur as a result of decrease intake, increased glucose utilization, antimalarial mediated reduction, glycogen depletion or impaired gluconeogenesis.

**Acidosis:**

This is due to elevated levels of lactic acid results from tissue anaerobic glycolysis, particularly in skeletal muscles.

**Breathing Difficulties:**

Patients with severe malaria may present with difficulty in breathing as a result of any of the following:

- Heart failure resulting from severe anaemia.
- Pulmonary oedema (following administration of excessive fluids) usually there is frothing from the mouth and marked respiratory distress.
- Acidosis causes deep and rapid respiration.
- Aspiration

**Renal Failure:**

Renal failure develops due to low blood pressure as a result of dehydration or shock.

**Haemoglobinuria:**
This occurs as a result of excessive breakdown of red blood cells by parasites or drugs like sulphonamides and primaquine.

**Who are the people at risk for severe malaria?**

- **Children < 5 years**
- **Pregnant women**
- People returning or coming to Nigeria after living in a malaria free areas
- Sickle cell anaemia individuals
- People who have had splenectomy

**History**
In addition to the general history as in uncomplicated malaria you should ask about the following

***In all patients*** *ask about*:-

- **Extreme weakness** (Prostration): inability to eat and drink or do anything without support. **Progressive weakness should immediately alert you that the patient may be developing severe malaria**.
- **Abnormal behaviour or altered consciousness**- ask relatives to tell you any observed changes in the patients' behaviour since the illness started or when the unresponsiveness started.
- **Convulsions**;- ask about the number of episodes, part of the body involved, previous history and time onset of last episode. Focal or multiple convulsions over a period of 24 hours is indicative of severe disease.
- **Drowsiness** or deteriorating level of consciousness.
- **Time of last drink or food** since the onset of the illness.
- **Fast breathing** which may occur due to pulmonary oedema or acidosis.
- **Reduced urinary out put** (time patient last passed urine).
- **Colour of urine** whether dark or Coca-Cola coloured (this may suggest excessive breakdown of red blood cells or dehydration).
- **Pregnancy** in adult females.

**Ask history to exclude other severe diseases**

**Drug History:**

- Ask about antimalarial drugs, salicylates and herbal concoctions that may influence treatment or cause some of the symptoms.

**Previous illnesses:**

- Ask about any history of recent febrile illness and treatment which may suggest treatment failure or relapse (consider typhoid, malaria and other infections).

**Physical Examination:**

In the physical examination you should aim at

- Assessing for the presence of signs of severe malaria.
- Identifying other possible causes of disease.

***Central nervous system***

Assess the level of consciousness using an objective scale such as the AVPU scale, Glasgow coma scale or the Blantyre coma scale:

The AVPU scale is as show below

**A** = alertness (is the patient alert)

**V** = response to voice command (does the patient respond to his name)

**P** = response to pain (does the patient feel pain or cry if a child)

**U** = unresponsive. (Patient does not respond at all)

***Respiratory system***

- Check for respiratory distress (fast, deep or laboured breathing)
- Listen to the chest for rales or other added sounds.

***Cardiovascular***

- Examine the rate, rhythm and volume of the pulse.
- Cold extremities or poor capillary refill at the tips of the fingers *(delay for >3 seconds).*
- Check blood pressure

***Abdomen***

- Feel for the spleen and the liver

**Differential Diagnosis:**

- Meningitis- patient may have a stiff neck.
- Encephalopathy- Repeated convulsions or deep coma.
- Diabetes Mellitus- Patient may be dehydrated, acidotic or in coma.
- Septicaemia- Usually very ill and toxic with warm extremities.

- Epilepsy- Usually no temperature and will have history of convulsions before.

**Laboratory Investigations:**

Laboratory investigation in aimed at confirming diagnosis, assess severity of disease and exclude other possible causes of severe disease.

Recommended tests include:

- Blood smear for malarial parasites
- Haematocrit (PCV)/Haemoglobin
- Blood sugar level
- Lumbar puncture in unconscious patients.
- Urinalysis for:-
  Sugar (to exclude diabetes)
  Proteins (exclude pregnancy-induced hypertension)

**Notes about diagnosis of severe malaria**:

- High index of suspicion in patients with fever and any of the features discussed above.
- Absence of fever does not exclude a diagnosis of severe malaria.
- Microscopic diagnosis should not delay antimalarial treatment if there is a clinical suspicion of severe malaria, with-holding treatment may be fatal.
- Patients' progress should be monitored and management changed as deemed necessary.

**TREATMENT**

Severe malaria is a medical emergency requiring in-patient care. Deaths from severe malaria can result either from direct effect of the disease or the complications. First attend to the immediate threats to life.

**URGENT TREATMENT**

**1. Coma or unconscious patient**

- Ensure airway is patent; gentle suction of nostrils and the oro- pharynx.
- Make sure the patient is breathing.
- Nurse the patient lying on the side or with the head side ways.
- Insert a naso-gastric tube (NGT).
- Establish an intravenous line. It will be necessary for giving drugs and fluids.
- Correct hypoglycaemia:

***Children:*** 0.5 ml/kg of 50% dextrose diluted to 10-15%.
***Adults:*** 25 ml of 50%dextrose.
-Where intravenous access is not possible, give dextrose or any sugar solution through the naso-gastric tube.

**xlviiiConvulsions**

- Ensure patent airway and that the patient is breathing.
- Correct hypoglycaemia or control temperature.
- In children give rectal diazepam 0.5 mg/kg or IM paraldehyde 0.1 ml/kg. If convulsions continue, give IM phenobarbitone 10-15 mg/kg.
- In adults give 10 mg diazepam IV.

**xlixSevere dehydration or shock**

- Give 20-30 ml/kg of normal saline and reassess the patient within 30 minutes to decide on the next fluid requirement according to the degree of dehydration.
- After correction of the fluid deficit it is important to reduce the maintenance fluid to two thirds of the required volume when the patient is well hydrated.

**1.Severe Anaemia**

- Give urgent blood transfusion to patients with ***severe pallor/anaemia*** in heart failure. **The blood must be screened to ensure that it is HIV, Hepatitis B and C negative.**
- Use packed cells (10 ml/kg in children) or whole blood (plus frusemide).
- Where blood is not available, give pre-referral treatment and **refer urgently** to a health facility with blood transfusion services.

## SPECIFIC ANTIMALARIAL TREATMENT

### Treatment Objectives

The primary objective of antimalarial treatment in severe malaria is to save life. Prevention of recrudescence and avoidance of minor adverse effects are secondary. Quinine or Artemisinin derivatives given parenterally are choice of treatment for severe malaria.

### QUININE

It can be administered by either IV or IM route, depending on the availability of infusion facilities.

**Recommended dosage:**

Intravenous quinine

***Children***:

Give 20 mg/kg of Quinine dihydrochloride **salt** as loading dose diluted in 10 ml/kg of 4.3% dextrose in 0.18% saline or 5% dextrose over a period of 4 hours. Then 12 hours after the start of the loading dose, give 10 mg **salt** /kg infusion over 4 hours every 8 hours until when patient is able to take orally.

Change to quinine tablets 10 mg/kg 8 hourly to complete a total of 7 days treatment OR give a full dose of artemether-lumefantrine.

***Adults:***

Quinine dihydrochloride 20 mg/kg of **salt** to a maximum of 1.2gm (loading dose) diluted in 10 ml/kg isotonic fluid by intravenous infusion over 4 hours then, 8 hours after the start of the loading dose, give 10 mg/kg **salt** to a maximum of 600 mg over 4 hours every 8hours patient is able to take orally.

Change to quinine tablets 10 mg/kg 8 hourly to complete a total of 7 days treatment OR give a full dose of artemether-lumefantrine

**NOTE:**

- **If intravenous quinine is required for over 48 hours, reduce the dose to 5-7mg/kg to avoid toxicity. A practical way of doing this is to reduce the dosing frequency to every 12 hours**
- **If there is a history of prior administration of quinine in appropriate doses in the last 24 hours do not use loading dose.**

**Intramuscular Quinine:**

Where intravenous access is not possible give quinine dihydrochloride at a dosage of 20 mg/kg **salt** (loading dose), diluted to 60-100mg/ml intramuscularly (divided sites), then 8hours after the loading dose give 10mg/kg 8hourly until patient is able to take orally.

Thereafter Change to quinine tablets 10 mg/kg 8 hourly to complete a total of 7 days treatment OR give a full dose of artemether-lumefantrine

**NOTE: Intramuscular injections should be given with maximum sterile precautions into the anterior thigh, NOT THE BUTTOCK.**

| **Quinine in pregnancy:**<br>**Use the above-recommended dose.** |
|---|

***Quinine is safe in pregnancy and it does not cause abortion or premature delivery, rather it is the severe malaria that causes these complications.***

**ARTEMISININ DERIVATIVES:**

Artemisinin derivatives can be used as alternatives to quinine for severe malaria

**Dosages:**

**Artesunate**:- 2.4 mg/kg IV bolus, repeat 1.2 mg/kg after 12 hours and then 1.2 mg/kg daily for 6 days. Alternatively, once patient can tolerate oral medication give a full dose of artemether-lumefantrine.

**Artemether**:- 3.2 mg/kg loading IM, followed by 1.6 mg/kg daily for six days. Alternatively, once patient can tolerate oral medication give a full dose of artemether-lumefantrine.

**PRE-REFERRAL TREATMENT**

The risk of death for severe malaria is greatest in the first 24 hours. To survive, a patient with severe illness must get access rapidly to a health facility where parenteral treatment and other supportive care can be given safely and as appropriate. The affected patient may die on the way to hospital or be admitted with advanced disease and complications. It is recommended that the patients be treated with one of the recommended parenteral treatment pre-referral, preferably rectal artesunate or artemisinin, should be used.

**Dosage and Administration:**

The appropriate single dose of Artesunate Suppositories should be administered rectally as soon as the presumptive diagnosis of malaria is made. In the event that an Artesunate suppository is expelled from the rectum within 30 minutes of insertion, a second suppository should be inserted and, especially in young children, the buttocks should be held together, or taped together, for 10 minutes to ensure retention of the rectal dose of artesunate

***Adults:*** One or more Artesunate Suppositories inserted in rectum as indicated in Table Adults. Dose should be given once and followed as soon as possible by definitive therapy for malaria.

**Table Adults:**

**Dosage for Initial Treatment of Acute Malaria in Adult Patients (aged 16 years and older)**

| Weight (kg) | Artesunate | Dosage Regimen (Single Dose) |
|---|---|---|
| < 40 | 10 mg/kg | Use appropriate number of 100 mg rectal suppositories see |

| | | |
|---|---|---|
| | | Table below |
| 40 - 59 | 400 mg | One 400 mg Suppository |
| 60 - 80 | 800 mg | Two 400 mg Suppositories |
| > 80 | 1200 mg | Three 400 mg Suppositories |

***Pediatric Patients:*** One or more Artesunate Suppositories inserted per rectum as indicated in Table. Dose should be given once and followed as soon as possible by definitive therapy for malaria

**Table Children:**

**Dosage for Initial Treatment of Acute Malaria in Pediatric Patients (2-15 years old) and weighing at least 9 kg.**

| Weight (kg) | Age | Artesunate | Dosage Regimen (Single Dose) |
|---|---|---|---|
| 5 - 8.9 | 0-12months | 50mg | One 50mg Suppository |
| 9 - 19 | 12-42 months | 100 mg | One 100 mg Suppository |
| 20 - 29 | 43-60months | 200 mg | One 100 mg + one 50mg Suppository |
| 30 - 39 | 6 - 13 years | 300 mg | Three 100 mg Suppositories |
| > 40 | > 14 years | 400 mg | One 400 mg Suppository |

**SUPPORTIVE TREATMENT**

*High temperature*

- Give paracetamol (oral/rectal) if temperature is > 38.5 $^{o}$C, wipe the body with wet towel and fan the patient to lower the temperature.

*Pulmonary oedema*

- Prop up the patient, give oxygen and furosemide 2-4 mg/kg IV and exclude anaemia as the cause of the heart failure.

*Renal failure*

- Give fluids if patient is dehydrated 20 ml/kg of normal saline and challenge with furosemide 1-2 mg/kg.
- Pass a urinary catheter to monitor urinary output.
- If patient does not pass urine within the next 24 hours refer for peritoneal or haemodialysis.

*Profuse bleeding*

- Transfuse with screened fresh whole blood, give pre-referral treatment and refer urgently.

*Other possible treatments:-*

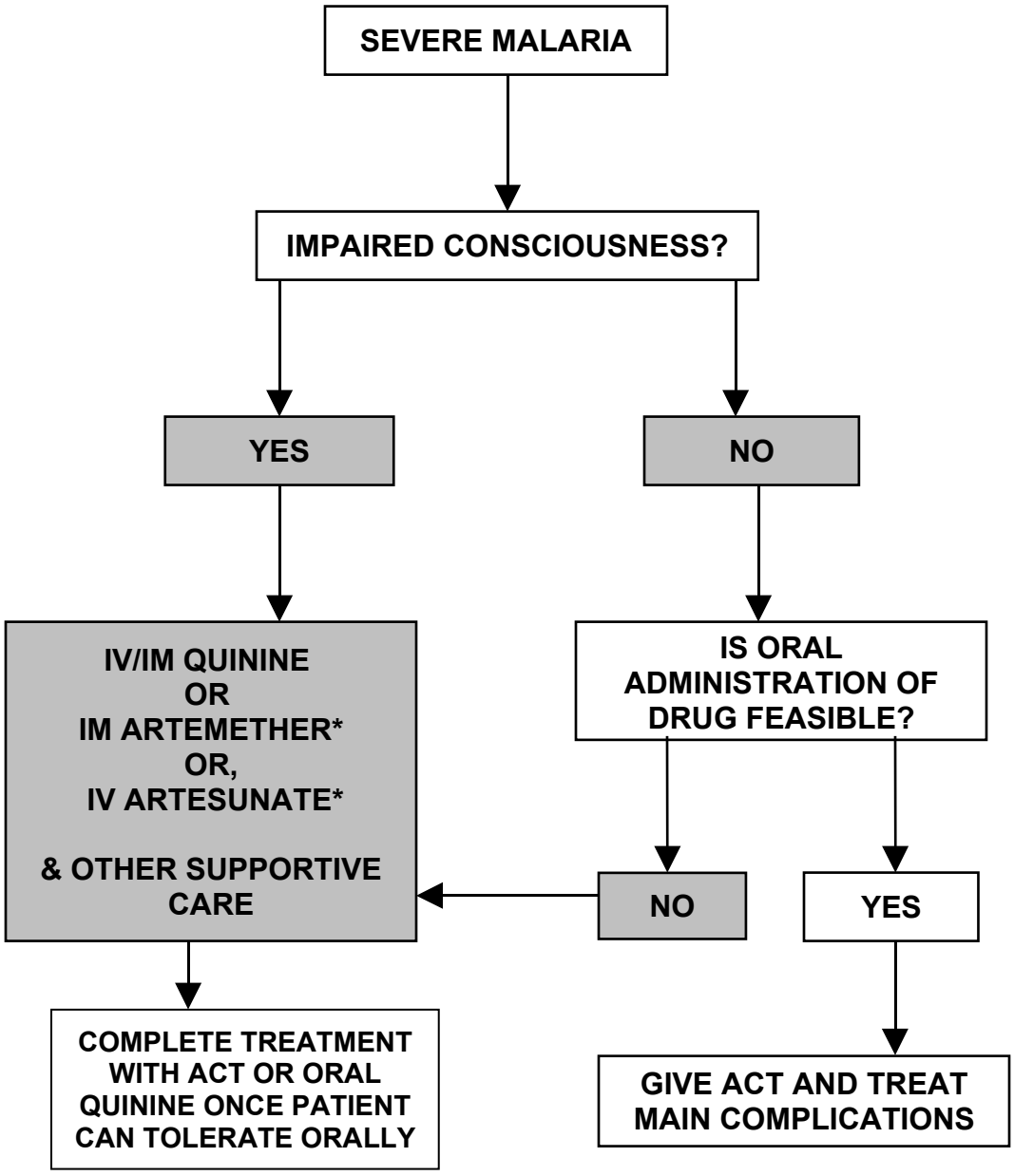
- If meningitis is suspected and you can not exclude it immediately by a lumbar puncture, give appropriate antibiotics.
- Other severe diseases should be treated accordingly.

**Treatments not recommended:**

The following drugs have no role in the treatment of severe malaria.

- Corticosteroids and other anti-inflammatory agents
- Agents used for cerebral oedema e.g Urea
- Adrenaline
- Heparin

# TREATMENT ALGORITHM FOR SEVERE MALARIA




* IF PATIENT IS KNOWN TO BE PREGNANT QUININE IS PREFERRED OVER ARTEMISININ DERIVATIVES IN THE FIRST TRIMESTER

## NURSING AND QUALITY OF CARE

Severe malaria is a serious condition and the clinicians and nurses should closely monitor patients. Therefore nursing care should include all the following:-

### 1.Monitor vital signs

1. Pulse
2. Temperature
3. Respiratory rate
4. Blood pressure

These should be monitored at least every 6 hours but may be more frequent at the initial stages.

### 2.Monitor input and output

A strict 24-hour input /output chart should be kept in all patients with severe malaria. Examine regularly for signs of dehydration or fluid overload.

### 3.Monitoring unconscious patient

Unconscious or comatose patients need close monitoring of all vital signs more regularly to assess their progress. Monitor the level of consciousness at least every 6 hours. Patients should be turned in bed regularly to avoid bedsores.

### 4.Drug chart

A clear drug chart where all drugs given are recorded should be kept and should include dose given, time given and number of times a day.

### 5.Pregnant women

These should be monitored closely ensuring the well being of the fetus and the women don’t become hypoglycaemic . Watch out for severe anaemia and pulmonary oedema.

## LABORATORY MONITORING

### 6.Monitor the parasitaemia

Do blood smears daily. If high after 2-3 days, review adequacy of the drug dose.

### 7.Monitor blood glucose

Do blood glucose or maintain dextrose containing infusion

**8.Monitor Haemoglobin/haematocrit**

**ASSESSMENT OF RECOVERY AND HEALTH EDUCATION**

When the patient recovers assess for possible residual problems of the disease or treatment.

- Assess the ability of the patient to do what he/she was able to do before the illness.
- Assess vision and hearing by asking whether they can see or hear; for children use objects or noisy rattles.
- Organize for follow up of your patient for those on severe malaria.

**Health Education and Prevention**

Health education should focus on:

- The importance of early diagnosis and prompt treatment.
    - Seeking treatment and taking appropriate antimalarials promptly, in adequate doses, when they have fever.
- Counsel patients about their illness and treatment.
- Prevention and personal protection
    - Mosquito screening devices in the design of houses and protective dressing.
    - Use of insecticide treated nets(ITN)/materials should be encouraged.
    - Use of insecticides and mosquito repellants.
    - Environmental management especially reducing mosquito breeding sites.
- **Community mobilization for malaria control**
    - Use community health workers to follow up the patients
    - Work with existing community development committees and other community organizations and leaders.
    - Work with people from other sectors (like partners and stake holders) that are concerned with social and economic development of the community.

# Antimalarial drug resistance

Antimalarial drug resistance has arisen to all classes of antimalarial drugs except the artemisinin derivatives. It has resulted in a global resurgence of malaria and it is a major threat to malaria control. Widespread and indiscriminate use of antimalarial drugs places a strong selective pressure on malaria parasites to evolve mechanisms of resistance. Prevention of antimalarial drug resistance is one of the main goals of these antimalarial treatment recommendations. Resistance can be prevented by combining antimalarial drugs with different mechanisms of action, and ensuring very high cure rates through full adherence to correct dose regimens (further detail is provided in Annex CC).

## *6.1 Determinants of antimalarial drug resistance*

Antimalarial drugs destroy the malaria parasites and reduce their multiplication. This is their main therapeutic effect. Antimalarial drug resistance is a shift to the right of the dose-response curve; in other words doses or concentrations which kill sensitive parasites will not kill the resistant parasites.

Malaria infections with resistant parasites are more likely to fail treatment, i.e. recrudesce, and as resistance gets worse these will respond more slowly to treatment. Both increased rates of recrudescence and slow responses to treatment increase the probability of generating gametocyte densities sufficient for transmission. Thus resistant infections are more likely to transmit to others than sensitive infections. It is this transmission advantage which drives the spread of resistance.

The mechanisms of resistance, and the way in which resistance emerges and spreads are described in the Annexe CC.1.

## *6.2 Impact of resistance*

The impact of antimalarial drug resistance is insidious initially. The initial symptoms of the infection resolve and the patient is better for weeks. When symptoms recur, usually more than two weeks later, anaemia has worsened, and there is a greater probability of carrying gametocytes (which in turn carry the resistance genes) and transmitting malaria. But the patient and the doctor or dispenser may interpret this as a newly acquired infection. At this stage unless drug trials are conducted, resistance may be unrecognised. As resistance worsens the interval between primary infection and recrudescence shortens, until eventually the symptoms fail to resolve. At this stage mortality begins to rise. Antimalarial drug resistance accounts for our failure to control malaria in many areas of the tropical world and the consequent increasing global mortality. But resistance can be prevented, or its onset slowed considerably with judicial use of the limited number of effective drugs currently available to treat malaria.

## *6.3 A summary of the global distributions of drug resistance*

Resistance to antimalarial drugs has been documented for *P. falciparum, P. vivax*, and recently *P.malariae.* With some differences with respect to the geographical distribution and the level and rate of spread, resistance of *P. falciparum* has been observed against almost all currently used antimalarials, except for the artemisinins, while for *P. vivax* only resistance against chloroquine is described. The epidemiology of drug resistant malaria (Fig y) has been the subject of several reviews and a more detailed summary and maps are included in ANNEX CC.2.

## *6.4* Plasmodium falciparum *resistance*

### Chloroquine

Chloroquine resistance has been reported from all falciparum-endemic areas, with the exception of Central America and the Caribbean. Resistance was first documented on the border between Thailand and Cambodia and in Columbia in the

late 1950s. Since then, chloroquine resistance has spread throughout the tropical world. In Africa, chloroquine resistance was first detected in Tanzania in the late 1970s, and has since spread and intensified across the Continent.

## Amodiaquine

Amodiaquine is generally more effective than chloroquine. However, there is cross-resistance between the two drugs, and the efficacy of amodiaquine is declining in many areas. High levels of resistance are present in much of Asia, and there is increasing resistance in East Africa, Papua New Guinea, and in the Amazon region. The drug is still reasonably effective in many countries in Central and West Africa, and in parts of South America.

## Sulfadoxine-pyrimethamine

Very high levels of resistance are found in many parts of South-East Asia, southern China, the Amazon region. In many parts of Eastern and Southern Africa SP treatment failure rates have risen to unacceptable levels. Lower levels of resistance are found on the Pacific coast of South America, southern Asia east of Iran, western Oceania and parts of central and Western Africa.

## Quinine

Despite widespread use of quinine, resistance levels are low, and quinine is still generally effective. It remains the first drug of choice for the treatment of severe falciparum malaria in many countries. Decreasing sensitivity has been observed in some areas of South-East Asia, where it has been used extensively for many years as first-line treatment.

## Mefloquine

Mefloquine resistance is prevalent in Eastern Myanmar, Thailand, Cambodia and Southern Vietnam. In the Amazon region, low level mefloquine resistance has been reported. In Africa, mefloquine resistance is rare, but a few treatment failures have been observed in Tanzania, Malawi and Nigeria.

## Artemisinin and its derivatives

Confirmed resistance to artemisinin and its derivatives (artemether, artesunate, and dihydroartemisinin) has not been reported. But as these drugs are so valuable it is essential that they be protected from resistance development. This is done by prescribing only antimalarial combinations which ensure that no malaria parasites are exposed to an artemisinin compound alone, but only together with longer-acting antimalarials such as mefloquine, lumefantrine, amodiaquine etc.- Even in areas of multidrug resistance, such as in the border area of Thailand and Myanmar, artemisinin combinations (ACTs) have maintained a high level of efficacy for over ten years.