



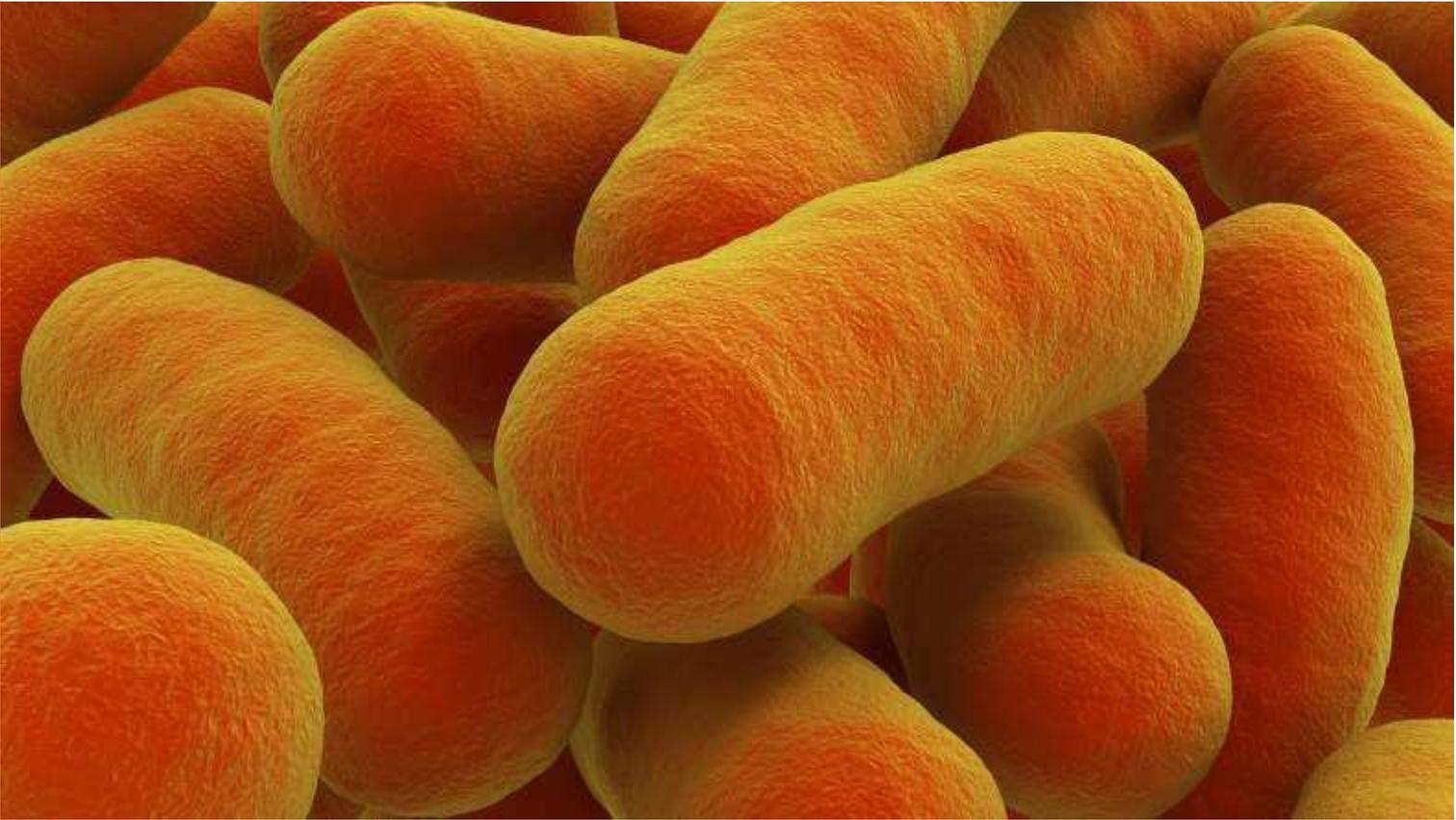
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Directorate of
Malaria Control



Ministry of National Health Services, Regulations & Coordination

National Malaria Case Management Guidelines

Directorate of Malaria Control
Pakistan



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FOREWORD



About this Guideline

Malaria case management, consisting of early diagnosis and prompt effective treatment, remains a vital component of malaria control and elimination strategies. This Guideline for the treatment of malaria contains national case management recommendations based on changing malaria trends and WHO's regional and global pragmatic recommendations.

Malaria remains an important cause of illness and death in Pakistan. In order to control malaria, it requires an integrated approach, including prevention and prompt and effective treatment with suitable antimalarial agents.

This document is designed for health professionals who are involved in malaria case management at primary, secondary and tertiary health care facilities of Pakistan. This document will focus on the current nationally recommended malaria case management policies. This document is designed to provide basic and necessary information on all the aspects of malaria case management. The treatment recommendations in this document are brief; for those who wish to study in more detail, they can refer to participant manual which is provided along with.

Objectives of the guidelines

The objective of appropriate malaria diagnosis and treatment is to reduce morbidity, mortality and socio-economic losses. The use of National Malaria Case Management Guidelines is key to achieving this objective. In addition, the aim is to attain uniform malaria case management in the country. The guiding principle of antimalarial drug policy is to promote safe, effective, good quality, affordable, accessible and acceptable malaria treatment. At the same time, it will ensure to encourage rational drug use in order to minimize the development of drug resistance.

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List of Abbreviations

ACT	Artemisinin Based Combination Therapy
BHU	Basic Health Unit
CQ	Chloroquine
DHA	Dihydro Artemisinin
DHAP	Dihydro Artemisinin Piperaquine
G6PD	Glucose 6 Phosphate Dehydrogenase
Hb	Hemoglobin
HCT	Hematocrit
IM	Intramuscular
IV	Intravenous
PQP	Piperaquine
RDT	Rapid Diagnostic Test
RHC	Rural Health Center
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection

SUMMARY

Early diagnosis and administration of effective treatment is paramount not only in the reduction of Malaria related morbidity and mortality but also for the effective control of Malaria in Pakistan. The National Malaria Case Management Guidelines ensure the provision of evidence based effective treatment for the malaria patients.

Case Definition

Uncomplicated Malaria

Patient with fever of $>37.5^{\circ}\text{C}$ or history of fever in the last 72 hours associated with one or more of the following signs and symptoms; headache, body aches, nausea, vomiting, chills, rigors etc. with no other obvious cause of fever and absence of symptoms and signs of severity and vital organ dysfunction should be considered a suspected case of uncomplicated malaria.

Severe/Complicated Malaria

Patient with fever of $>37.5^{\circ}\text{C}$ or history of fever in the last 72 hours associated with presence of at least one of the following signs/symptoms of vital organ involvement; Impaired consciousness, Prostration, Multiple Convulsions, Acidosis, Hypoglycemia, Severe malarial anemia, Renal Impairment, Jaundice, Pulmonary Edema, Significant Bleeding, Shock, Hyperparasitaemia occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

Diagnosis of Malaria

Every suspected case of malaria must be parasitologically confirmed either by Malaria Rapid Diagnostic Test (RDT) or Microscopy.

Malaria Case Management

Clinical Case

In the absence of parasitological confirmation of suspected malaria case, the patient may be treated as having vivax malaria. Chloroquine 25mg/kg base over 3 days (10 mg base/kg on Day 1, 10mg base/kg on Day 2 and 5mg base/kg on Day 3) should be prescribed. Patient must be called for follow-up after 48 hours.

Confirmed Vivax Malaria

Patient with confirmed vivax malaria should be administered Chloroquine 25mg base/kg over 3 days (10 mg base/kg on Day 1, 10mg base/kg on Day 2 and 5mg base/kg on Day 3) plus primaquine 0.25mg/kg daily for 14 days with following exceptions

- Pregnant women
- Children <5 years,
- Lactating mothers
- Patients with severe G6PD deficiency

If the G6PD diagnosis is available and the patient is negative for G6PD deficiency, primaquine can be give above the ages of 6 months. Similarly, if the patient is a lactating woman, G6PD test can be performed on the infant > 6months and if test is negative for deficiency, 14 days course of primaquine can be safely prescribed to the lactating mother.

If on G6PD testing if patient is diagnosed with mild to moderate G6PD deficiency, primaquine can be given at dose of 0.75mg/kg once a week for 8 weeks above the ages of 5 years.

Confirmed Falciparum Malaria (Un-Complicated)

First Line Treatment

Patient with confirmed falciparum malaria should be administered Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses) plus single dose of 0.25 mg /kg primaquine on the first day of treatment. Primaquine is contraindicated in pregnancy

Second Line Treatment

In case of treatment failure within 28 days, patient should be given Dihydroartemisinin Piperazine (DHAP) (4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperazine) once a day for 3 days. All cases of suspected treatment failure must be parasitological confirmed by microscopy before administering 2nd line treatment.

Mixed Infection

Patient with confirmed simultaneous falciparum and vivax malaria should be administered Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses) plus primaquine 0.25mg/kg daily for 14 days with following exceptions

- Pregnant women and Lactating mothers
- Children <5 years,
- Patients with severe G6PD deficiency

If the G6PD diagnosis is available and the patient is negative for G6PD deficiency, primaquine can be give above the ages of 6 months. Similarly, if the patient is a lactating woman, G6PD test can be performed on the infant > 6months and if test is negative for deficiency, 14 days course of primaquine can be safely prescribed to the lactating mother.

On G6PD testing if patient is diagnosed with mild to moderate G6PD deficiency, primaquine can be given at dose of 0.75mg/kg once a week for 8 weeks above the ages of 5 years.

Malaria in Pregnancy

Confirmed Vivax Malaria

Pregnant ladies in all trimesters with vivax malaria should be prescribed Chloroquine 25mg/kg base over 3 days (10 mg base/kg on Day 1, 10mg base/kg on Day 2 and 5mg base/kg on Day 3). Primaquine is contraindicated in pregnancy

Confirmed Falciparum Malaria (Un-Complicated)

First Line Treatment in First Trimester



Pregnant ladies in first trimester with falciparum malaria should be administered Quinine 10 mg salt/kg body weight (maximum 600mg) three times a day plus Clindamycin 10 mg/kg body weight (maximum 600mg) twice per day for 7 days. Primaquine is contraindicated in pregnancy.

Second Line Treatment in First Trimester

In case of treatment failure within 28 days, Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses) should be given. All cases of suspected treatment failure must be parasitological confirmed by microscopy before administering 2nd line treatment.

First Line Treatment in Second & Third Trimesters

Pregnant women in second and third trimesters with falciparum malaria should be given Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses). Primaquine is contraindicated in pregnancy.

Second Line Treatment in Second & Third Trimesters

In case of treatment failure within 28 days, Dihydroartemisinin Piperaquine (DHAP) (4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine) once a day for 3 days should be given. All cases of suspected treatment failure must be parasitological confirmed by microscopy before administering 2nd line treatment.

Confirmed Mixed Infection

First Trimester

Pregnant women in first trimester with parasitological confirmation of presence of both P. falciparum and P. vivax infections should be administered Quinine 10 mg salt/kg body weight (maximum 600mg) three times a day plus Clindamycin 10 mg/kg body weight (maximum 600mg) twice per day for 7 days. **Primaquine is contraindicated in pregnancy.**

Second Line Treatment in First Trimester

If on microscopy, asexual parasites of either P.falciparum or P.vivax or both are present, consider this patient as having treatment failure and must be given Artemether + Lumefantrine

(1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine; 1 tablet of A+L 80/480) twice daily for 3 days (total six doses).

Second & Third Trimesters

Pregnant women in second and third trimesters with mixed infection malaria should be given Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses). Primaquine is contraindicated in pregnancy.

Second Line Treatment in Second & Third Trimesters

In case of treatment failure within 28 days, Dihydroartemisinin Piperaquine (DHAP) (4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine) once a day for 3 days should be given. All cases of suspected treatment failure must be parasitological confirmed by microscopy before administering 2nd line treatment.

Severe/Complicated Malaria

Treatment at Primary Health Care Facilities

All the severe/complicated malaria patients must be quickly stabilized and given the initial single dose of intra muscular Artesunate 2.4mg/kg (maximum 240 mg) as pre-referral treatment and then the patient must be referred to an appropriate health care facility for further care. Referral notes must accompany the patient with mention of time of administration of parenteral Artesunate (first dose, 0 hours)

Treatment at Secondary and Tertiary Health Care Facilities

Rapidly assess and stabilize the patient. Review the referral notes if available for initial dose (dose 0) and start parenteral Artesunate 2.4mg/kg (maximum 240 mg) at admission (0 hour), second dose will be giving after 12 hours of first dose and third dose will be giving after 24 hours after first dose, it will continue one dose a day for 7 days. Parenteral Artesunate should be administered to all adults, children, infants, pregnant women in all trimesters and lactating women.

If parenteral artesunate is not available, intramuscular Artemether can be administered in doses of 3.2 mg/kg (maximum 160mg) by intramuscular injection on day1, then 1.6 mg/kg (maximum 80mg) daily to complete 7 days course.



If injection artesunate and artemether are not available, give Quinine (first, loading dose of 20mg salt/kg bw, which is twice the maintenance dose), then give the maintenance dose of quinine (10 mg salt/kg bw) at 8 h intervals, starting 8 h after the first (loading dose). If there is no improvement in the patient's condition within 48 h, the dose should be reduced by one third, i.e. to 10 mg salt/kg bw every 12 h. Anytime during these days parenteral treatment the patient can swallow then stop the injection and give full treatment course of 3 days oral Artemether + Lumefantrine as per guideline (full treatment course of 7 days oral Quinine plus Clindamycin in case of pregnant women in first trimester). Primaquine is contraindicated in pregnancy

Malaria Case Diagnosis & Management

Case Definition

Patient with fever of $>37.5^{\circ}\text{C}$ or history of fever in the last 72 hours associated with one or more of the following sign and symptoms; headache, body aches, nausea, vomiting, chills, rigors etc. with no other obvious cause of fever should be considered a suspected case of malaria.

Malaria case diagnosis is based upon a complete case history, a physical examination, and laboratory investigations

When a patient presents with fever or history of fever, proceed as:

Ask

1. About the history of fever
 - a. Low or high grade
 - b. Continuous or intermittent
2. Chills
3. Headache, body aches
4. Nausea/Vomiting
5. Sweating
6. Anorexia
7. Inability to drink or breast feed
8. Symptoms of other febrile illnesses like URTI, LRTI, UTI
9. Travel history to Malaria endemic area
10. Medication currently taking

Examine

1. Temperature
2. Pulse
3. Spleen
4. Anemia
5. Danger Signs for Complicated Malaria
 - a. Altered consciousness

- 
- b. Repeated convulsions (fits) – 2 or more within 24 hours.
 - c. Neck stiffness
 - d. Inability to sit and stand unaided
 - e. Respiratory rate
 - f. Sub costal recession
 - g. Generalized body swelling
 - h. Delayed capillary refill time
 - i. Fundoscopy (if available)
 - j. Hypothermia (axillary temperature of 35.7°C or below).
 - k. Persistent hyperpyrexia in children (axillary temperature >38.5°C)
 - l. Circulatory collapse or shock, (feeble, weak, rapid pulse and cold extremities).
 - m. Acute renal failure (little or no urine)
 - n. Obvious jaundice (yellowish coloration of the sclera of the eyes).

Based on history and examination, if the patient fulfils the criteria mentioned in case definition, the patients can be classified as suspected malaria case. If patient has sign and symptoms of severe disease and vital organ dysfunction, the patient is labeled as suspected uncomplicated malaria and if sign and symptoms are suggestive of severe disease and vital organ dysfunction, the patient is classified as suspected severe/complicated malaria

Confirmation of Malaria

Where facilities of parasitological confirmation are available, every suspected case must be parasitological confirmed before starting the treatment.

At RHC level and above, send the patient to laboratory for parasitological confirmation through microscopy. At BHU level or below, send the patient to Malaria supervisor for RDT

Treating Clinical Case of Malaria

All suspected malaria cases first should be tested by microscopy or RDT for parasitological confirmation and then treated accordingly. Where confirmation by microscopy or RDT is not available, the suspected uncomplicated malaria should be treated as possible vivax malaria with Chloroquine 25mg/kg base over 3 days

Dosage Guidelines

Chloroquine is given at an initial dose of 10 mg base/kg (maximum 600 base) on Day 1, followed by 10 mg base/kg on Day 2 (maximum 600 base) and 5 mg base/kg on the Day 3 (maximum 300 base).

The dose of Chloroquine per kg of body weight is calculated up to 50 kg. Patients with more than 50 kg body weight, full adult dose of 600mg base is given on Day 1 and 2 and 300mg base on Day 3

First dose must be given under supervision and observe for half an hour. The dose must be repeated if patient vomits within 30 minutes. Second and third dose of CQ is given along for continued treatment at home. Patient must be asked to return after 2 days for assessment. If the sign and symptoms are not resolved, diagnosis must be revisited and if sign and symptoms are still suggestive of suspected Malaria, patient must be sent for parasitological confirmation to the nearest diagnostic center

In young children, high fevers are often associated with vomiting, regurgitation of medication and seizures. They should be concomitantly treated with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if the core temperature is $> 38.5^{\circ}\text{C}$.

To prevent dehydration; explain to caregivers that it is important for infants to breastfeed frequently, and older children and adults to drink plenty of fluids.

Treating Confirmed Malaria Case

If the microscopy smear or RDT is positive for malaria parasite (either *P.falciparum*, *P.vivax* or both), immediately start species specific treatment

Treatment of Confirmed *P. falciparum* Malaria

Assess the patient for complicated malaria based on the sign and symptoms discussed above. If warning signs are observed, the patient must be given IM Artesunate 2.4mg/kg body weight (maximum of 240 mg) immediately and referred to Secondary or Tertiary health care facility with referral notes and Artesunate dose administration time.



If parenteral artesunate is not available, use intramuscular artemether 3.2 mg day 1 and refer. If referral is not possible then 1.6 mg/kg IM once a day from day 2 onwards to complete a total of 7 days treatment. However, anytime during the treatment if the patient can swallow then stop the injection and give full treatment course of 3 days oral Artemether + Lumefantrine plus single dose of primaquine as per guideline. However, the goal is to immediately refer patient with severe falciparum malaria to the secondary or tertiary health care center.

If the patient has no warning sign and symptoms for complicated Malaria, treat this patient as uncomplicated *P. falciparum* malaria case

Treatment of Uncomplicated *P.falciparum* Malaria

Patient having uncomplicated *P.falciparum* Malaria should be prescribed first line treatment of Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses) plus single dose of 0.25 mg/kg primaquine (maximum 15mg), on the first day of treatment following exceptions

- Pregnant women
- Children <5 years,
- Lactating mothers

If the G6PD diagnosis is available and the patient is negative for G6PD deficiency, primaquine can be give above the ages of 6 months.

Weight base calculation for primaquine is considered up to 50 kg. In patients having body weight above 50 kg, give full dose of 15mg primaquine. The dose of Artemether + Lumefantrine per kg of body weight is calculated up to 34 kg. In patients with 35 kg and above body weight, full adult dose is given. Lumefantrine absorption is enhanced by co-administration with fatty food or milk. It is essential that patients are informed that this ACT should be taken immediately after a meal or a glass of milk

Dosage Guidelines

Artemether + Lumefantrine							
Body Weight Kg	Age	DAY 1		DAY 2		DAY 3	
5 - 14	6 months- 3 years	1 (20/120)	1 (20/120)	1 (20/120)	1 (20/120)	1 (20/120)	1 (20/120)
15-24	3-8 years	2 (20/120)	2 (20/120)	2 (20/120)	2 (20/120)	2 (20/120)	2 (20/120)
25-34	8-12 years	3 (20/120)	3 (20/120)	3 (20/120)	3 (20/120)	3 (20/120)	3 (20/120)
≥ 35	> 12 years	1 (80/480)	1 (80/480)	1 (80/480)	1 (80/480)	1 (80/480)	1 (80/480)

Tablets may be crushed and mixed with one to two teaspoons of water immediately prior to administration to children who cannot swallow tablets.

If vomiting occurs within 30 minutes of taking Artemether + Lumefantrine, the dosage of the ACT should be repeated. If vomiting stops, the patient must take subsequent doses as per instructions. If vomiting persists ask the patient to come back to health facility. Persistent vomiting may suggest severe/complicated malaria and should be assessed for warning signs and referred to appropriate health facility.

Explain to caregivers that it is important for infants to breastfeed frequently, and older children and adults to drink plenty of fluids, to prevent dehydration. Explain to caregivers that if someone is abnormally sleepy or difficult to wake, or has convulsions, or has difficulty in breathing, seek treatment immediately. Ask the patient to return after 2 days if there is no improvement.

Treatment of fever with paracetamol is a recommended part of supportive care for malaria, especially in children. Paracetamol in tablet, syrup or suppository forms may be given every 4-6 hours until the temperature is normal

Dosage Guidelines for Paracetamol

Paracetamol Tablets (500 mg)		
Age (years)	Dose	Number of tablets
< 1	125 mg	¼ tab
1-5	250 mg	½ tab
6-9	500 mg	1 tab
10-14	750 mg	1½ tabs
>14	1000 mg	2 tabs

Paracetamol Syrup (120mg per 5ml syrup)		
Age	Dose	Volume of Syrup
0-6 months	60 mg	2.5 ml
7-24 months	120 mg	5 ml
2-4 years	180 mg	7.5 ml

Treatment Failure *P.falciparum* Malaria

Treatment failures should be suspected when a patient with confirmed uncomplicated *P.falciparum* malaria deteriorates clinically at any time during treatment or symptoms persists or reappear within 28 days after initiation of drug therapy in accordance with the recommended treatment regimen.

Development of symptoms 28 days after initiation of therapy where there has been prior clearance of symptoms should be considered as a new infection and be treated with the first line drug.

Patients who have been diagnosed with malaria and treated with first line may fail to improve for various reasons including:

- The presenting symptoms, such as fever, were due to a cause other than malaria.

- The treatment was inadequate (the patient was not prescribed the full recommended dose; or did not take the medication as directed).
- The patient may have vomited the medication.
- The drug administered may have been of poor quality.
- The malaria parasite may be resistant to the medication administered.

If patient return within 28 days, he/she should be tested for malaria parasite and that too only by microscopy. If there is asexual parasitaemia on a blood smear, consider treatment failure and prescribe second line anti-malarial Dihydroartemisinin Piperazine (DHAP)

Dosage Guidelines Second Line Antimalarial

Dihydroartemisinin Piperazine is given at a dose of 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperazine once a day for 3 days (therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/day piperazine. DHAP per kg is calculated up to 75 kg, above 75 kg full dose is given.

Two different strength of tablets are available: 20 mg of DHA and 160 mg of PQP; 40 mg of DHA and 320 mg of PQP.

Dosage recommendations for dihydroartemisinin piperazine (DHA-PQ)

Body weight (kg)	Tablet strength and number of tablets per dose
5 to 8	1 tablet of 20/160 mg
9 to 16	2 tablets of 20/160 mg
17 to 24	3 tablets of 20/160 mg
25 to 35	2 tablets of 40/320 mg
36 to 74	3 tablets of 40/320 mg
75 to 100	4 tablets of 40/320 mg

Note: Children <25kg should receive a minimum of 2.5mg/kg/day of dihydroartemisinin and 20 mg/kg/day of piperazine

Tablets must be taken between meals with a little water. Tablets may be crushed and diluted in a little water for children who are unable to swallow them.



If a patient vomits within 30 minutes of taking, the whole dose should be re-administered; if a patient vomits between 30-60 minutes, half the dose should be re-administered. Re-dosing with should not be attempted more than once. If the second dose is vomited, ask the patient to come back to health facility. Persistent vomiting may suggest severe/complicated malaria and should be assessed for warning signs and referred to appropriate health facility.

Explain to caregivers that it is important for infants to breastfeed frequently, and older children and adults to drink plenty of fluids, to prevent dehydration. Explain to caregivers that if someone is abnormally sleepy or difficult to wake, or has convulsions, or has difficulty in breathing, seek treatment immediately. Ask the patient to return after 2 days if there is no improvement.

Treatment of fever with paracetamol is recommended as part of supportive care for malaria, especially in children. Paracetamol in tablet, syrup or suppository forms may be given every 4-6 hours until the temperature is normal.

Note:

- *In patients with treatment failure and treated with second line drug DHAP, single dose of 0.25mg/kg of primaquine is not required as Piperaquine has gametocidal activity against P. falciparum*
- *Patients initially treated for falciparum malaria that return with confirmed vivax infections on microscopy should be treated with CQ.*
- *Similarly, patients initially treated for vivax malaria that return with confirmed falciparum infections on microscopy should be treated with Artemether+Lumefentrine as first line treatment. These are not treatment failures and the 2nd line treatment should not be given to these groups of patients.*

Treatment of Uncomplicated Vivax Malaria

Patient having uncomplicated P.vivax malaria, oral Chloroquine at a total dose of 25 mg base/kg body weight given over three days is effective and well tolerated. This should be combined with primaquine, anti-relapse medicine, at a dose of 0.25mg base/kg body weight (maximum 15 mg), taken with food once daily for 14 days with following exceptions

- Pregnant women

- Children <5 years,
- Lactating mothers
- Patients with severe G6PD deficiency

If the G6PD diagnosis is available and the patient is negative for G6PD deficiency, primaquine can be given above the ages of 6 months. Similarly, if the patient is a lactating woman, G6PD test can be performed on the infant > 6 months and if test is negative for deficiency, 14 days course of primaquine can be safely prescribed to the lactating mother.

On G6PD testing if patient is diagnosed with mild to moderate G6PD deficiency, primaquine can be given at dose of 0.75mg/kg once a week for 8 weeks above the ages of 5 years.

Dosage Guideline

Chloroquine is given at an initial dose of 10 mg base/kg (maximum 600 base) on Day 1, followed by 10 mg base/kg on Day 2 (maximum 600 base) and 5 mg base/kg on the Day 3 (maximum 300 base).

The dose of Chloroquine per kg of body weight is calculated up to 50 kg. Patients with more than 50 kg body weight, full adult dose of 600mg base is given on Day 1 and 2 and 300mg base on Day 3. Chloroquine is generally well tolerated at the doses used for treatment of *P. vivax*, and is considered safe in pregnancy.

In young children, high fevers are often associated with vomiting, regurgitation of medication and seizures. They should be concomitantly treated with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if the core temperature is > 38.5 °C. If patient vomits within 30 min, dose must be repeated. If vomiting stops, the patient must take subsequent doses as per instructions. If vomiting persists ask the patient to come back to health facility. Persistent vomiting may indicate severe malaria and require admission

Explain to patient/caregivers that it is important for infants to breastfeed frequently, and older children to drink plenty of fluids, to prevent dehydration. Explain to patient/caregivers that if someone is abnormally sleepy or difficult to wake, or has convulsions, or has difficulty in breathing these are danger signs of severe illness. Seek treatment immediately. Ask the patient to return after 2 days if there is no improvement.

Anti-Relapse Treatment for Confirmed Vivax Malaria:

Some of the vivax parasites remain dormant in liver in the form of hypnozoites which causes relapse. To prevent these relapses, primaquine should be given at a dose of 0.25mg/kg daily (maximum 15 mg) for 14 days to all patients except in pregnant ladies, lactating mothers, children <5 years of age and patients with known status of sever G6PD deficiency. G6PD is an enzyme, which deficiency can lead to hemolytic anemia when certain drugs are prescribed including primaquine.

If the facility is available, patients with confirmed vivax malaria should be tested for G6PD status. If there is no G6PD deficiency, primaquine can be safely administered in all patients above the ages of **6 months** except in pregnant ladies. For lactating mothers, in addition to G6PD status of mother, G6PD status of infant should also be assessed. If the infant is above 6 months and has no G6PD deficiency, the lactating mother can safely be administered 14 days regimen of primaquine

However, if G6PD quantitative test suggests that the patient has mild to moderate G6PD deficiency, 0.75mg base/kg (maximum 45 mg) once a week for 8 weeks can be given above the age of 5 years. At this dose and schedule, severe hemolysis in-patient with mild to moderate G6PD deficiency is rare.

If the G6PD testing facilities are not available and G6PD status is unknown, Primaquine should be given at a dose of 0.25mg base/kg (maximum 15 mg) once a day for 14 days under close medical supervision to detect and manage possible cases of hemolysis.

Before administering primaquine, patients should be informed about the following:

- Explain the benefit of primaquine administration.
- Enquire the patient for a medical history of hemolysis.
- Inform the patient about the risk for acute hemolytic anemia when taking primaquine.
- Instruct the patient to monitor for following danger signs
 - o Back pain

- 
- o Dark (red or black) urine
 - o Jaundice
 - o Fever
 - o Dizziness
 - o Breathlessness
- Instruct the patient to stop taking primaquine if he/she observes passing dark color urine, jaundice or is breathless.
 - Ensure the patient that this hemolysis is self-limiting once primaquine is stopped
 - Inform the patient where to seek medical advice if the sign and symptoms of hemolysis appear (the nearest hospital with blood transfusion services).

Management of Side Effects of Primaquine

Patients presenting with history of primaquine intake as part of malaria treatment and having one or more of the following sign and symptoms should be suspected as having adverse drug reaction to primaquine

- Back pain
- Dark (red or black) urine
- Jaundice
- Fever
- Dizziness
- Breathlessness

Such patients should be tested for hemolysis by

1. Complete Blood Count
2. Serum Bilirubin
3. Urine Routine Examination



If patient has raised reticulocyte count or has Indirect hyperbilirubinemia and hemoglobinuria on Urine R/E, this indicates an acute hemolytic episode. In such patients, following steps should be taken to manage side effects of primaquine.

- Stop administering primaquine
- Ensure patient that as primaquine is eliminated rapidly, hemolysis is self-limiting once administration is stopped
- Give oral hydration.
- Refer to an inpatient facility.
- Make a clinical assessment.
- Check hemoglobin or hematocrit.
- Check plasma or serum creatinine or urea (blood urea nitrogen) if possible.
- Give a blood transfusion, if necessary, under following conditions
 - Hemoglobin < 7 g/dL: **transfuse**
 - Hemoglobin < 9 g/dL with concurrent hemolysis: **transfuse**
- Hemoglobin 7–9 g/dL or > 9 g/dL and no evidence of concurrent hemolysis: careful fluid management with monitoring of urine color/hemoglobinuria

Treatment Failure *P.vivax* Malaria

Treatment failures should be suspected when a patient with confirmed uncomplicated *P.vivax* malaria deteriorates clinically at any time during treatment or symptoms persists or re appear within 28 days after initiation of drug therapy in accordance with the recommended treatment regimen.

Development of symptoms 28 days after initiation of therapy where there has been prior clearance of symptoms should be considered as a new infection and should be treated with the first line drug.

Management of Treatment Failure

If patient return within 28 days with either persistence or deterioration of initial sign and symptoms, he/she should be tested for malaria parasite by microscopy. If there is asexual parasitaemia on a blood smear, consider treatment failure and prescribe second line anti-malarial



treatment of Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses).

Note:

- If the patient is already taking daily or weekly dose of primaquine, advise the patient to complete the advised course of primaquine treatment.

Mixed Infection

In mixed infection, RDT is positive for both species and malaria microscopy reveals asexual parasitemia of *P.vivax* and *P.falciparum*. Mixed species infections can not only complicate diagnosis, but also alter the severity and morbidity of the disease. Mixed infection requires ACTs which are effective against both *P.vivax* and *P.falciparum*.

Patients presenting with signs and symptoms suggestive of suspected Malaria and parasitological confirmation reveals both species should receive Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine) twice daily for 3 days (total six doses)

As the patient has both plasmodium species, the Primaquine should be prescribed in doses of 0.25 mg/kg (maximum 15 mg) once daily for 14 days under close medical observation with following exceptions

- Pregnant women
- Children <5 years,
- Lactating mothers
- Severe G6PD deficiency

If the G6PD diagnosis is available and the patient is negative for G6PD deficiency, primaquine can be given above the ages of 6 months. Similarly, if the patient is a lactating woman, G6PD test can be performed on the infant > 6 months and if test is negative for deficiency, 14 days course of primaquine can be safely prescribed to the lactating mother.

On G6PD testing if patient is diagnosed with mild to moderate G6PD deficiency, primaquine can be given at a dose of 0.75mg/kg once a week for 8 weeks above the ages of 5 years.



At this dose primaquine will not only act as gametocidal for *P. falciparum* but will also prevent relapse by hypnozoites in *P. vivax* Malaria.

Artemether and Lumefantrine is equally effective against both *P. vivax* and *P. falciparum*

Note: *Prerequisites for primaquine administration, discussed earlier, should be strictly followed*

Treatment Failure in Mixed Infection

As with treatment failure in *P. falciparum* Malaria, if the diagnosed case of mix infection presents within 28 days after starting treatment with either deterioration or persistence of symptoms, the patient must be parasitologically confirmed by microscopy.

If there is asexual parasitaemia on a blood smear, consider treatment failure and prescribe second line anti-malarial Dihydroartemisinin Piperazine (DHAP) 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperazine once a day for 3 days (therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/day piperazine)

Note:

- On microscopy if parasitemia is present for both species or either one of the species, only DHAP in the recommended dose should be given.
- If the patient is already taking daily or weekly dose of primaquine, advise the patient to complete the prescribed course of primaquine treatment

Malaria in Pregnancy

Pregnancy increases the risk of malaria infection in all women. Malaria during pregnancy causes febrile illness, anemia and increases the risk of maternal illness and death, miscarriage, stillbirth, low birthweight and neonatal death. Although women in their first and second pregnancies are at greatest risk of the effects of malaria, all pregnant women living in malaria risk areas should be advised on malaria prevention measures and cases of malaria must be treated promptly with effective antimalarials.

In high transmission areas, Malaria sometimes can have an unusual presentation. Patient might present with severe anemia in absence of fever. Therefore, in malaria endemic areas, pregnant ladies with severe anemia must be tested for Malaria parasite.

Confirmed Uncomplicated Vivax Malaria

Pregnant ladies having parasitologically confirmed P.vivax malaria, oral Chloroquine at a total dose of 25 mg base/kg body weight is recommended over three days. Chloroquine is given at an initial dose of 10 mg base/kg (maximum 600 base) on Day 1, followed by 10 mg base/kg on Day 2 (maximum 600 base) and 5 mg base/kg on the Day 3 (maximum 300 base).

Primaquine is contraindicated in pregnancy. Primaquine is given at usual dose when pregnancy is over and mother fulfils the criteria for primaquine administration as discussed previously

The dose of Chloroquine per kg of body weight is calculated up to 50 kg. Patients with more than 50 kg body weight, full adult dose of 600 mg base is given on Day 1 and 2 and 300mg base on Day 3. Chloroquine is generally well tolerated at the doses used for treatment of P.vivax, and is considered safe in pregnancy.

Confirmed Falciparum Malaria (Un-Complicated)

First Line Treatment in First Trimester

In first trimester, pregnant women with parasitological confirmation of P.falciparum malaria with no sign and symptoms of severity and vital organ involvement, Quinine in oral dosage of

10mg/kg (maximum of 600mg) three times a day plus oral Clindamycin 10mg/kg (maximum of 600mg) twice a day for 7 days should be given. **Primaquine is contraindicated in pregnancy.**

In first trimester, pregnancy is commonly associated with nausea and vomiting. If vomiting occurs within 30 minutes, the dosage should be repeated. If vomiting stops, the patient must take subsequent doses as per instructions. If vomiting persists ask the patient to come back to health facility. Persistent vomiting may suggest severe/complicated malaria and should be assessed for warning signs and referred to appropriate health facility.

Treatment of fever with paracetamol is recommended as part of supportive care for malaria. Paracetamol may be given every 4-6 hours until the temperature is normal.

Second Line Treatment in First Trimester

If patient returns within 28 days with either deterioration or persistence of symptoms, malaria microscopy should be used to assess suspected treatment failure. If asexual parasitaemia is found on a blood smear, consider treatment failure and prescribe second line anti-malarial, which in case of pregnant women is, Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine; 1 tablet of A+L 80/480) twice daily for 3 days (total six doses). **Primaquine is contraindicated in pregnancy.**

First Line Treatment in Second & Third Trimester

Pregnant women in second and third trimester of pregnancy with confirmed *P.falciparum* malaria should be given Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine; 1 tablet of A+L 80/480) twice daily for 3 days (total six doses) should be given. **Primaquine is contraindicated in pregnancy.**

Second Line Treatment in Second & Third Trimester

If patient returns within 28 days during second and third trimesters with either deterioration or persistence of symptoms, malaria microscopy should be used to assess suspected treatment failure.. If there is asexual parasitaemia on a blood smear, consider treatment failure and second line anti-malarial Dihydroartemisinin Piperavaquine (DHAP) should be prescribed as 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperavaquine once a day for 3 days (therapeutic dose range



between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/day piperaquine. DHAP per kg is calculated up to 75 kg, above 75 kg full dose is given.

Dihydroartemisinin–piperaquine has been shown to be safe and effective for the treatment of malaria in pregnancy.

Confirmed Mixed Infection

Treatment in First Trimester

Pregnant women in first trimester with parasitological confirmation of presence of both *P. falciparum* and *P. vivax* infections, either by microscopy or rapid diagnostic test, and no symptoms or signs of severity or vital organ dysfunction should be treated by prescribing Quinine in oral dosage of 10mg/kg (maximum of 600mg) three times a day plus oral Clindamycin 10mg/kg (maximum of 600mg) twice a day for 7 days.

Patient should be asked to come for follow up after completion of 7 days treatment. Patient's blood should be sent for smear for assessment of the treatment response and presence of asexual parasites of *P.vivax* and *P. falciparum*.

Second Line Treatment in First Trimester

If on microscopy, asexual parasites of either *P.falciparum* or *P.vivax* or both are present, consider this patient as having treatment failure and must be given Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine; 1 tablet of A+L 80/480) twice daily for 3 days (total six doses). **Primaquine is contraindicated in pregnancy.**

First Line Treatment in Second & Third Trimester

Pregnant women in second and third trimesters of pregnancy with mixed malaria infections should be given Artemether + Lumefantrine (1.7mg/kg body weight Artemether, 12 mg/kg Lumefantrine; 1 tablet of A+L 80/480) twice daily for 3 days (total six doses). Primaquine is contraindicated in pregnancy.



Second Line Treatment in Second & Third Trimester

If mixed infection patient returns within 28 days during second and third trimesters with either deterioration or persistence of symptoms, operationally treatment failure is suspected. The patient blood should be sent for microscopy. If there is asexual parasitaemia of either or both species (*P.falciparum* or *P.vivax*) on a blood smear, consider treatment failure and second line anti-malarial Dihydroartemisinin Piperaquine (DHAP) should be prescribed as 4 mg/kg/day dihydroartemisinin and 18 mg/kg/day piperaquine once a day for 3 days (therapeutic dose range between 2–10 mg/kg/day dihydroartemisinin and 16–26 mg/kg/day piperaquine. DHAP per kg is calculated up to 75 kg, above 75 kg full dose is given.

Sever/Complicated Malaria

Severe/Complicated malaria is a medical emergency. Delay in diagnosis and inappropriate treatment of uncomplicated malaria especially in infants and children can lead to the rapid development of severe/complicated malaria. It mostly occurs in children under five (5) years of age, pregnant women and nonimmune individuals. The principles of diagnosis and treatment for adults are the same as in children.

The keys to effective management are early recognition, assessment, and appropriate antimalarial and supportive therapy. The commonest cause of severe malaria is *P. falciparum*. Very rarely though, *P. vivax* may also manifest as severe disease.

As with uncomplicated malaria, the diagnosis of severe/complicated malaria is based on a comprehensive history taking, examination and confirmation with laboratory testing. The patient is likely to have experienced some of the typical symptoms of malaria. These may have included: chills, rigors, headache, body aches, sweating, nausea/vomiting, loss of appetite, and/or abdominal pain. In all patients, clinical diagnosis of severe/complicated malaria should be made in a patient fulfilling following case definition:

Severe/Complicated Malaria

Patient with fever of $>37.5^{\circ}\text{C}$ or history of fever in the last 72 hours associated with presence of at least one of the following sign symptoms of vital organ involvement; Impaired consciousness, Prostration, Multiple Convulsions, Acidosis, Hypoglycemia, Severe malarial anemia, Renal Impairment, Jaundice, Pulmonary Edema, Significant Bleeding, Shock, Hyperparasitaemia occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

- Prostration i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance
- Altered level of consciousness (including unarousable coma)
- Multiple convulsions more than two episodes within 24h
- Respiratory distress

- Circulatory collapse or shock, systolic blood pressure < 80mm Hg in adults and < 50mm Hg in children;
- Pulmonary edema
- Jaundice
- Hemoglobinuria
- Abnormal bleeding

Management of Severe/Complicated Malaria at Primary Health Care Facilities

When severe/complicated malaria is identified in the outpatient setting, parenteral IM artesunate should begin promptly. Blood samples should be taken for microscopy or RDTs but if patient's condition does not allow it, treatment and referral should not be delayed in the quest of waiting for test results.

The Artesunate is given IM at doses of 2.4mg/kg body weight (maximum of 240 mg) immediately and referred to Secondary or Tertiary health care facility with referral notes and Artesunate dose administration time. Children weighing less than 20 kg should receive a higher parenteral dose of artesunate (3mg/kg/dose) to ensure equivalent drug exposure.

If it is not possible to immediately refer the severe malaria patient to the appropriate facility for further care, then 2nd and 3rd dose can be given 12 hours apart in the facility with general management of the complication such as treating hypoglycemia, convulsions and hyperpyrexia.

If parenteral artesunate is not available, use intramuscular artemether 3.2 mg (maximum 160mg) on day 1 and refer. If referral is not possible then give 1.6 mg/kg IM (maximum 80 mg) once a day for maximum of 7 days treatment. However, any time after 24 hours of parenteral treatment, if the patient can swallow then stop the injection and give full treatment course of 3 days oral Artemether + Lumefantrine plus single dose of primaquine as per guideline. However, the goal is to immediately refer patient with severe falciparum malaria to the tertiary health care center.

Management of Severe/Complicated Malaria at Secondary & Tertiary Health Care Facilities.

Patients either referred or presenting to the tertiary health care center with sign and symptoms suggestive of severe/complicated malaria must have immediate initial assessment along with general management of complications. Assessment should include:

History

The parents or other relatives should be questioned about:

- residence and history of travel
- duration of illness
- alteration in behavior
- previous treatment with antimalarial or other drugs; (referral notes, time of IM artesunate)
- recent fluid intake and urine output (color of urine)
- recent or history of convulsions.

Physical Examination

The initial physical assessment must include

- level of consciousness
- evidence of seizures or subtle seizure
- posturing (decorticate, decerebrate or opisthotonic), which is distinct from seizures
- rate and depth of respiration
- presence of anemia
- pulse rate and blood pressure
- state of hydration
- neck stiffness
- capillary refill time
- temperature
- funduscopy for retinal hemorrhages and papilledema.

- Weigh the patient, or estimate the body weight (for calculation of medication and fluid regimens).

Laboratory Investigation

Do the following laboratory tests during initial assessment

- Microscopy for malaria parasites-thick and thin blood films. (If microscopy is not available, an RDT should be used.)
- Blood Glucose
- Hemoglobin (Hb) and/or Hematocrit (Hct). If Hb<5gm/dl and Hct <15-20%, do grouping and cross-matching for possible transfusion.
- Lumbar Puncture (LP) for cerebrospinal fluid analysis (in cerebral malaria)
- Urea, Creatinine, and Serum Electrolytes.
- Liver Function Tests
- Clotting studies, Blood Culture, Plasma Bicarbonate, Plasma Lactate (if required)

Note: Only the results of a lumbar puncture can rule out bacterial meningitis with suspected cerebral malaria. If lumbar puncture is delayed, antibiotics must be given to cover the possibility of bacterial meningitis.

General Management and Resuscitation

Start resuscitation and general management of complication while awaiting results. Ensure following

- Airway – ensure airway is open with no foreign objects. Consider intubation if required
- Put the patient semi prone position. An unconscious child with possible raised intracranial pressure should be nursed in a supine position with the head raised to 30°
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure Pulse rate and Blood pressure
- Insert intravenous cannula
 - In case patient is unconscious, immediately administer intravenous 75-80 ml 20% glucose or 150-160 ml of 10% glucose (the volume will be determined by the clinical scenario).

- In case of convulsion, treat convulsions with intravenous diazepam, 0.3mg/kg IV or 0.5mg/kg intrarectally in children and 0.15 mg/kg (maximum 10 mg) in adults as a slow bolus ('push') over 2 mins. Diazepam may be repeated if seizure activity does not stop after 10min. Patients with seizures, not terminated by two doses of diazepam, should be considered to have status epilepticus and given phenytoin (18mg/kg loading dose, then a maintenance dose of 5mg/kg per day for 48h). If this is not available or fail to control seizures, give phenobarbitone (15mg/kg intramuscularly or slow intravenous loading dose, then a maintenance dose of 5mg/kg per day for 48h). When phenobarbitone is used, monitor the patient's breathing carefully, as it may cause respiratory depression requiring ventilatory support. High-dose (20mg/kg) phenobarbitone may lead to respiratory depression and increased the risk for death. One must be prepared to use 'bag and-mask' manual ventilation if the patient breathes inadequately or to use mechanical ventilation if available.
- Insert Nasogastric tube (if indicated)
 - For feeding and medication
- Insert urethral catheter (if indicated) for
 - Urine for dipstick
 - Urinary output measurement
- Nursing care and monitoring
 - Fluid input and output chart
 - Level of consciousness
 - Temperature, PR, RR and BP
 - Repeat investigations: Hb, Glucose, Creatinine, electrolytes if indicated
- Administer Antimalarial treatment for severe malaria

Antimalarial Treatment for Severe Malaria

Following rapid clinical assessment of patient fulfilling criteria for severe/complicated Malaria, full parenteral doses of Artesunate should be started without delay, even if parasitological confirmation is pending.

Artesunate 2.4mg/kg (maximum 240 mg), if not given as pre referral treatment, should be administered at the admission (0 hour), second dose should be given after 12 hours of the first dose and third dose should be administered after 24 hours of the first dose, then continue with OD dose for up to 7 days. However, any time after 24 hours (3 doses) of parenteral treatment, if the patient can swallow then stop the injectable artesunate and give full treatment course of 3 days oral Artemether + Lumefantrine along with single dose primaquine as per guidelines

Children weighing less than 20 kg should receive a higher parenteral dose of artesunate (3mg/kg/dose) to ensure equivalent drug exposure

Reconstituting Parenteral Artesunate

Artesunate is dispensed as a powder of artesunic acid in vials of 30mg, 60mg or 120mg and usually in packs containing sodium bicarbonate solution and normal saline.

Before reconstitution, check the brand available at your facility and follow the general instructions provided with the product. For the purpose of this guideline, steps for the constitution of 60mg vial of artesunate is considered here

Step 1

Weigh the patient

Step 2

Determine the number of vials needed

Weight	< 25 kg	26-50 kg	51-75 kg	76-100 kg
60mg Vials	1	2	3	4

Step 3

Reconstitute the 60mg vial (immediately before use)

- Inject full contents of bicarbonate ampoule (1 ml) into artesunate vial.
 - Shake until dissolved

- Solution will be cloudy
- The reconstituted solution will clear in about 2 mins.
- Discard if not clear

Step 4

Dilution

- Reconstituted artesunate + saline solution (or dextrose 5%)
- Volume for dilution

Solution	IV	IM
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	6 ml	3 ml

- Withdraw all the air from the vial.
- Inject required volume of saline into the reconstituted solution
- Artesunate solution is now ready for use.

Step 5

Calculate the Dose

- Calculate and withdraw the required dose in ml according to route of administration:

Dose calculation for less than 20 kg

For intravenous route (IV)
Concentration: 10 mg/ml

$3.0 \text{ mg} \times \text{body weight (kg)}$
 IV artesunate solution
 concentration **10 mg/ml**
 Round up to the next whole number

Example:
 Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{10} = 2.4 \text{ ml}$$
 2.4 ml rounded up to **3 ml**

Weight kg	Dose	
	mg	ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

For intramuscular route (IM)
Concentration: 20 mg/ml

$3.0 \text{ mg} \times \text{body weight (kg)}$
 IM artesunate solution
 concentration **20 mg/ml**
 Round up to the next whole number

Example:
 Dose needed (ml) for 8 kg child:

$$\frac{3.0 \times 8}{20} = 1.2 \text{ ml}$$
 1.2 ml rounded up to **2 ml**

Weight kg	Dose	
	mg	ml
6 - 7	20	1
8 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

Dose calculation for more than 20 kg

Concentration: 10 mg/ml

$\frac{2.4 \text{ mg} \times \text{body weight (kg)}}{\text{IV artesunate solution concentration 10 mg/ml}}$
Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{10} = 6.24 \text{ ml}$$

6.24 ml rounded up to 7 ml

Concentration: 20 mg/ml

$\frac{2.4 \text{ mg} \times \text{body weight (kg)}}{\text{IM artesunate solution concentration 20 mg/ml}}$
Round up to the next whole number

Example:

Dose needed (ml) for 26 kg child:

$$\frac{2.4 \times 26}{20} = 3.12 \text{ ml}$$

3.12 ml rounded up to 4 ml

Weight kg	Dose	
	mg	ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

Weight kg	Dose	
	mg	ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Step 6

Administration of parenteral Artesunate

- IV: slow bolus 3-4 ml per minute.
- IM: Inject slowly. Spread the doses of more than 2 ml over different sites for babies and 5 ml for adults.

Step 7

Dosing Schedule

- Give 3 parenteral doses over 24 hours
- Give parenteral doses for a minimum of 24 hours once started irrespective of the patient's ability to tolerate oral treatment earlier.
 - **Dose 1:** on admission (0 Hours) **Dose 2:** 12 hours later **Dose 3:** 24 hours after first dose
- When the patient can take oral medication, prescribe a full 3-day course of recommended first line oral Artemether + Lumefantrine.
- The first dose of Artemether + Lumefantrine should be taken between 8 and 12 hours after the last injection of artesunate.
- Until the patient is able to take oral medication, continue parenteral treatment (one dose a day) for a maximum of 7 days.
- A course of injectable artesunate should always be followed by a 3-day course of Artemether + Lumefantrine and a single dose of 0.25mg/kg primaquine as per guideline
- Evaluate the patient's progress regularly by smear for parasite count and biochemical tests.

Monitoring of Patients With Severe Malaria

All patients with severe malaria should be closely monitored as described in table below.

Regularly Observe	Possible Observation	Appropriate Action
Breathing	Increased respiratory rate: <ul style="list-style-type: none">• < 2 months: 60 or more per minute• 2 up to 12 months: 50 or more per min• 1 year up to 5 years: 40 or more per min• 5 years and above: 20 or more per min Or difficulty in breathing	<ul style="list-style-type: none">• Check position of the patient• Put the patient in semi-prone (Fowler's) position• Give oxygen if there is respiratory distress• Review urine output• Examine lung, heart and size of the liver• Chest X ray if available• If pulmonary oedema is demonstrated, or seems likely treat appropriately
Axillary Temperature	>38.5°C If temperature remains high or rises despite 24 hours of artesunate therapy	<ul style="list-style-type: none">• Give paracetamol if not given within the past 4 hours• Fanning/Tapid Sponging• Reassess and investigate for other possible

		<p>causes and co infections while continuing treatment</p> <ul style="list-style-type: none"> • Check for parasite count and compare with previous report for response to Artesunate
Blood Pressure	<p>BP Falls:</p> <ul style="list-style-type: none"> • <80 mmHg systolic in an adult • < 50 mmHg in infants and children (using pediatric cuff) 	<ul style="list-style-type: none"> • Review fluid balance, urine output, and hematocrit. • If hypovolemic, give saline infusion where indicated. • Look for hemorrhage • Take blood for bacteriological culture and sensitivity if facilities are available • Give broad spectrum antibiotic (for possible bacteremia)
Urine Output	<p>Oliguria:</p> <ul style="list-style-type: none"> • <17 ml/hr in an adult or • <0.3 ml/kg/hr in infants and children 	<ul style="list-style-type: none"> • Review fluid input and status of hydration • Correct fluid deficit if necessary • Prevent or manage acute renal failure if suspected • Catheterize if acute renal failure
Coma Score	<p>Deterioration Use Glasgow and Blantyre coma scale</p>	<ul style="list-style-type: none"> • Reassess and investigate for other possible causes while continuing treatment • Immediately check blood glucose (correct hypoglycemia if suspected) • Lumbar puncture
Convulsions	<p>These can recur, or develop for the first time during treatment and may be due to hyperpyrexia, abnormal blood glucose or electrolyte imbalance or other causes</p>	<ul style="list-style-type: none"> • Check axillary temperature if >38.5^oC, treat as above • Check blood glucose (correct hypoglycemia if suspected) • Check fluid balance • Check electrolytes if possible (to detect hyponatremia) • Give anticonvulsant drugs
Bleeding from venipuncture sites or Spontaneous Hemorrhage	<p>Prolonged bleeding time suggesting Disseminated intravascular coagulopathy (DIC) -</p>	<ul style="list-style-type: none"> • Check bleeding time • Grouping and cross matching of blood • Give whole fresh blood as needed to correct blood loss and bleeding tendency (20 ml/kg for children, 2 units in adults)
Pulmonary Edema	<ul style="list-style-type: none"> • Restlessness • Frothy sputum • Basal crepitations • Low oxygen saturation (< 95%) 	<p>Give</p> <ul style="list-style-type: none"> • Oxygen • IV frusemide • Mechanical ventilation may be needed.
Anemia	<ul style="list-style-type: none"> • Hb <5g/dl • Packed cell volume <15%; 	<ul style="list-style-type: none"> • Transfuse with 10ml per kg body weight packed cells or 20ml per kg of whole blood as appropriate. (Frusemide is given first in

	<ul style="list-style-type: none"> • In anemic patient with <ul style="list-style-type: none"> ○ shock ○ signs of heart failure (dyspnea, enlarged liver, gallop rhythm). ○ respiratory distress (acidosis) ○ hyperparasitaemia (> 20%). 	cases of heart failure).
Glucose	<ul style="list-style-type: none"> • Altered consciousness • Sweating • Coma 	<ul style="list-style-type: none"> • Check blood glucose every 4 hours • Correct hypoglycemia with hypertonics in case of coma • Maintain blood glucose level by either oral glucose or infusion of Dextrose Saline
Parasitemia	<ul style="list-style-type: none"> • Remains high for 2–3 days, or remains positive for > 5 days. • Commonly remains at the initial level for 12–24h, even when medicines are fully effective, then falls. 	<ul style="list-style-type: none"> • Review adequacy of antimalarial medicine and dosage. • Consider alternative or give an additional medicine. • Artemisinin derivatives are so effective that exchange transfusion is usually unnecessary

Non-response to Artesunate Therapy

Non-response to parenteral Artesunate therapy should be suspected if there is:

- Persistence of clinical features of severe malaria
- Failure of clearance of parasites after 5 days of treatment
- Other possible causes of illness which have not been investigated

Patients with malaria who have not responded to Artesunate and repeated smears suggest no reduction in parasitemia, such patients should be given parenteral Quinine. At an initial dosed of 20 mg/kg (loading dose) I.V. followed by 10 mg/kg IV 8 hourly for up to 7 days or until the patient can take medication orally. The dose of quinine must be decrease to 10mg salt/kg every 12 hours if patient still requires intravenous quinine after 48 hours. However, anytime during these 7 days parenteral treatment, if the patient can swallow then stop the injection and give full treatment course of 3 days oral Artemether + Lumefantrine and a single dose of 0.25mg/kg primaquine as per guideline

Alternates of Artesunate

Artemether or quinine is an acceptable alternative if parenteral artesunate is not available:

Artemether:

Artemether is administered at 3.2mg/kg body weight intramuscularly given at admission, then 1.6 mg/kg IM once daily for a total of 7 days,

Quinine

Quinine should be given as a loading dose of 20mg/kg (maximum 1200mg) diluted in 15ml/kg (maximum 500ml) of isotonic solution (5% dextrose or normal saline) is given intravenously to run over 4 hours. 8 hours from commencement of the initial dose of quinine, give maintenance dose of 10mg/kg (maximum 600mg) diluted in 10ml/kg (maximum 500ml) of isotonic solution (5% dextrose or normal saline) to run over 2 hours. The rate of IV quinine transfusion should not exceed 5mg/kg/hr.

Repeat 10mg/kg quinine infusion every 8 hours for up to 7 days or until the patient can take medication orally. The dose of quinine must be decrease to 10mg salt/kg every 12hrs if the patient still requires intravenous quinine after 48 hours. However, anytime during these 7 days parenteral treatment, if the patient can swallow then stop the injection and give full treatment course of 3 days oral Artemether + Lumefantrine and single dose of 0.25mg/kg primaquine as per guideline.

Assessment of Recovery

Your records and observations will provide some indications of patient recovery e.g. lowering temperature, decreasing parasite count, and an improving coma score. In addition, the patient's ability to drink, eat, talk, sit, stand or walk should be recorded. When a patient has clinically recovered, an assessment should be made of possible sequelae of the disease or the treatment. In particular the physician should:

Perform a neurological examination

In particular, assess the patient's functional capacity to hold and use objects, ability to feed, the gait and posture. Try to determinate whether the patient can do the things that he or she was able to do before the illness began. For a young child this requires asking parents or guardians about the child's previous activities. Neurological examination must also include looking for possible neurological sequelae



Assess vision and hearing

Use the best available methods. Simple bedside measures can be used, especially for infants and children (e.g. does the child turn his/her head towards a noise? does the child watch the mother when she moves?). Use audiometry and vision charts if these are available.

Repeat packed cell volume (PCV) or hemoglobin and blood films

Optimally these should be repeated on day 7 and day 14 after recovery and again one month later. It is important to check on day 7 whether the hemoglobin is continuing to fall. If it is, there may be another cause of anemia that needs to be investigated. By day 14 full recovery should have taken place.

Severe/Complicated Malaria in Pregnancy

Like all the cases severe/complicated malaria is a medical emergency in the pregnant women and must be quickly identified. The pregnant women with suggestive sign symptoms of severe/complicated malaria must be quickly assessed, stabilized and should be started with antimalarial appropriate treatment.

The pregnant women must be managed same as other cases of complicated malaria with following additions

- Pregnant women with severe malaria should be transferred to intensive care if possible.
- Blood glucose should be monitored frequently.
- Obstetric help should be sought, as severe malaria usually precipitates premature labour.
- Once labour has started, fetal or maternal distress may indicate an intervention, and the second stage might have to be shortened by the use of forceps, vacuum extraction or caesarean section.

Sever/Complicated Malaria in All Trimesters

Pregnant ladies with severe/complicated malaria in all trimester should receive IV/IM artesunate as other cases of sever/complicated malaria for at least 24 hours and until they can tolerate oral medication.

Dosage Guidelines

Artesunate should be administered at dosage of 2.4mg/kg body weight: on admission (**Dose 1; 0 Hours**) **Dose 2:** 12 hours after first dose **Dose 3:** 24 hours after first dose. Until the patient is able to take oral medication, parenteral treatment should be continued (one dose a day) for a maximum of 7 days.

However, anytime during these 7 days parenteral treatment, if the patient can swallow then stop the parenteral treatment and give full treatment course of oral antimalarials which in case of first trimester is tablet Quinine in dosage of 10mg/kg (maximum of 600mg) three times a day plus Clindamycin 10mg/kg (maximum of 600mg) twice a day for 7 days.



In second and third trimesters, give oral Artemether + Lumefantrine for 3 days in recommended dosage mentioned in previous sections. The first dose of Artemether + Lumefantrine should be taken between 8 and 12 hours after the last injection of artesunate. **Primaquine is contraindicated in pregnancy.** Like all cases of severe/complicated malaria, the pregnant women must be closely monitored for the complication and managed accordingly as discussed above.

If injection artesunate is not available or the patient is not responding to parenteral Artesunate and repeated smears suggest no reduction in parasitemia, the suitable alternate in pregnancy is parenteral Quinine which should be given at an initial loading dose of 20 mg/kg (loading dose) I.V. followed by 10 mg/kg IV 8 hourly for up to 7 days or until the patient can take medication orally. The dose of quinine must be decrease to 10mg salt/kg every 12 hours if patient still requires intravenous quinine after 48 hours. However, anytime during these 7 days parenteral treatment, if the patient can swallow then stop the injection and give full treatment course of oral antimalarials depending upon the trimester

Malaria Treatment During Outbreaks

In outbreak situation, parasitological diagnosis either by the rapid diagnostic tests or microscopy is crucial and should continue to confirm the cases of malaria, monitor the epidemic curve and confirm the end of an epidemic, and follow progress of patients with severe malaria and probable treatment failures. However, once a malaria outbreak is confirmed, all fever cases should be screened, irrespective of fulfilling case definition criteria, and must receive species specific treatment. The principles of treatment of uncomplicated and severe/complicated Malaria remains same.

Patients Co-Infected with Tuberculosis or HIV

Rifampicin used in treatment of Tuberculosis decreases the bioavailability of Artemether and Lumefantrine. Thus, exposing such patients to a higher risk of recrudescence infections and should be closely monitored and followed up for complete parasitological clearance.



HIV related immune suppression may lead to severe manifestations of malaria. Such patients should be closely monitored and followed up for complete parasitological clearance