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Guidelines for Diagnosis and Treatment of Malaria in India





Guidelines for Diagnosis and Treatment of Malaria in India 2014



NATIONAL INSTITUTE OF MALARIA RESEARCH
NEW DELHI



NATIONAL VECTOR BORNE DISEASE CONTROL PROGRAMME
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Preface

Malaria is a major public health problem in India, accounting for sizeable morbidity, mortality and economic loss. Apart from preventive measures, early diagnosis and complete treatment are the important modalities that have been adopted to contain the disease. In view of the widespread chloroquine resistance in *Plasmodium falciparum* infection, and other recent developments, the national drug policy has been revised to meet these challenges.

The guidelines for 'Diagnosis and Treatment of Malaria' in India (2009) were developed during the brainstorming meeting organized by the National Institute of Malaria Research (NIMR) and sponsored by the WHO Country Office in India and were revised in the light of changed national drug policy in 2010. **Recently, due to treatment failures to artesunate + sulfadoxine-pyrimethamine in *P. falciparum* malaria, the national drug policy for malaria was changed in North-Eastern states. This led to the change in *P. falciparum* malaria therapy in these states to artemether lumefantrine.**

These guidelines are the collaborative effort of the National Vector Borne Disease Control Programme (NVBDCP), the National Institute of Malaria Research (NIMR) and experts from different parts of the country. The aim of this endeavour is to guide the medical professionals on the current methods of diagnosis and treatment based on the national drug policy. This manual deals with the treatment of uncomplicated malaria and specific antimalarials for severe disease. The general management should be carried out according to the clinical condition of the patient and judgement of the treating physician. The warning signs of severe malaria have been listed so as to recognize the condition and give the initial treatment correctly before referring to a higher facility. It is hoped that these guidelines will be useful for health care personnel involved in the diagnosis and treatment of malaria at different levels.

Director, NIMR
Director, NVBDCP

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1. INTRODUCTION

Malaria is one of the major public health problems of the country. India reports around one million malaria cases annually. In India, *P. falciparum* and *P. vivax* are the most common species causing malaria, their proportion being around 50% each. *Plasmodium vivax* is more prevalent in the plain areas, while *P. falciparum* predominates in forested and hilly areas.

Malaria is curable if effective treatment is commenced early. Delay in treatment may lead to serious consequences including death. Prompt and effective treatment is also important for controlling the transmission of malaria.

In the past, chloroquine was effective for treating nearly all cases of malaria. In recent studies, chloroquine-resistant *P. falciparum* malaria has been observed with increasing frequency across the country.

A revised National Drug Policy on Malaria has been adopted by the Ministry of Health and Family Welfare, Govt. of India in 2013 and these guidelines have been prepared for healthcare personnel including clinicians involved in the diagnosis and treatment of malaria.

2. CLINICAL FEATURES

Fever is the cardinal symptom of malaria. It can be intermittent with or without periodicity or continuous. Many cases have chills and rigors. The fever is often accompanied by headache, myalgia, arthralgia, anorexia, nausea and vomiting. The symptoms of malaria can be non-specific and mimic other diseases like viral infections, enteric fever etc.

Malaria should be suspected in patients residing in endemic areas or who have recently visited endemic area and presenting with above symptoms. Malaria is known to mimic the signs and symptoms of many common infectious diseases, the other causes of fever should also be suspected and investigated in the presence of manifestations like running nose, cough and other signs of

respiratory infection, diarrhoea/dysentery, burning micturition and/or lower abdominal pain, skin rash/infections, abscess, painful swelling of joints, ear discharge, lymphadenopathy, etc.

All clinically suspected malaria cases should be investigated immediately by microscopy and/or Rapid Diagnostic Test (RDT).

3. DIAGNOSIS

3.1 Microscopy

Microscopy of stained thick and thin blood smears remains the gold standard for confirmation of diagnosis of malaria. The advantages of microscopy are:

- The sensitivity is high. It is possible to detect malaria parasites at low densities. It also helps to quantify the parasite load.
- It is possible to distinguish different species of malaria parasites and their different stages.

3.2 Rapid Diagnostic Test

Rapid Diagnostic Tests are based on the detection of circulating parasite antigens. Several types of RDTs are available (<http://www.wpro.who.int/sites/rdt>). Some of them can only detect *P. falciparum*, while others can detect other parasite species also. The NVBDCP has recently rolled out bivalent RDTs (for detecting *P. falciparum* and *P. vivax*) for use in the public health sector.

RDTs are produced by different manufacturers, so there may be differences in the contents and in the manner in which the test is done. The user manual should always be read properly and instructions followed meticulously. The results should be read at the specified time. It is the responsibility of the health care personnel doing a rapid test for malaria to ensure that the kit is within its expiry date and has been transported and stored under recommended conditions. Failure to observe these criteria can lead to incorrect results. **It should be noted that *Pf* HRP-2 based kits may show positive result up to three weeks after successful treatment and parasite clearance. In these cases, results should be correlated with microscopic diagnosis.**

Early diagnosis and complete treatment of malaria aims at:

- Complete cure
- Prevention of progression of uncomplicated malaria to severe disease
- Prevention of deaths
- Interruption of transmission
- Minimizing risk of selection and spread of drug resistant parasites

4. TREATMENT OF UNCOMPLICATED MALARIA

All fever cases diagnosed as malaria by RDT or microscopy should promptly be given effective treatment.

4.1 Treatment of *P. vivax* malaria

Confirmed *P. vivax* cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg as per the age-wise dosage schedule given in Table 1. In some patients (ranging 8 to 30%) *P. vivax* may cause relapse (A form of *P. vivax* or *P. ovale* parasites known as hypnozoites which remain dormant in the liver cells can later cause a relapse). For its prevention, primaquine should be given at a dose of 0.25 mg/kg body weight daily for 14 days under supervision. The age-wise dosage schedule of primaquine is given in Table 2. **Primaquine is contraindicated in pregnant women, infants and known G6PD deficient patients.** Primaquine can lead to hemolysis in G6PD deficiency. Caution should be exercised before administering primaquine in areas known to have high prevalence of G6PD deficiency. Patient should be advised to stop primaquine immediately if he/she develops any of the following symptoms and should report to the doctor immediately:

- (i) dark coloured urine
- (ii) yellow conjunctiva
- (iii) bluish discolouration of lips
- (iv) abdominal pain
- (v) nausea
- (vi) vomiting
- (vii) breathlessness, etc.

Table 1. Chloroquine for *P. vivax*

Age (years)	Number of tablets		
	Day 1 (10 mg/kg)	Day 2 (10 mg/kg)	Day 3 (5 mg/kg)
<1	½	½	¼
1 – 4	1	1	½
5 – 8	2	2	1
9 – 14	3	3	1½
>15	4	4	2

Table 2. Primaquine for *P. vivax* (Daily dosage for 14 days)

Age (years)	Daily dosage (in mg base)
< 1	Nil
1 – 4	2.5
5 – 8	5.0
9 – 14	10.0
>15	15.0

The strength of the tablet available is 2.5, 7.5 and 15 mg. Number of tablets should be given accordingly.

Note: Primaquine should be given for 14 days under the supervision with education of the patient regarding warning signals. Do not give Primaquine to pregnant women, infants and known G6PD deficient individuals.

Considering the varying relapse rates, G6PD deficiency and facilities for G6PD testing, individual clinicians should weigh risks versus benefits while prescribing primaquine.

4.2 Treatment of *P. falciparum* malaria

Artemisinin Combination Therapy (ACT) should be given to all the confirmed *P. falciparum* cases found positive by microscopy or RDT. This is to be accompanied by single dose of primaquine (0.75 mg/kg body weight) on Day 2.

ACT consists of an artemisinin derivative combined with a long-acting antimalarial (amodiaquine, lumefantrine, mefloquine, piperazine or sulfadoxine-pyrimethamine). The ACT recommended in the National Programme all over India **except northeastern states** is artesunate (4 mg/kg body weight) daily for

Table 3. Dosage schedule of AS+SP and PQ for *P. falciparum* malaria

Age group (years)	1 st day		2 nd day		3 rd day
	AS	SP	AS	PQ	AS
0–1	1 (25 mg)	1 (250+12.5 mg)	1 (25 mg)	Nil	1 (25 mg)
1–4	1 (50 mg)	1 (500+25 mg)	1 (50 mg)	1 (7.5 mg base)	1 (50 mg)
5–8	1 (100 mg)	1 (750+37.5 mg)	1 (100 mg)	2 (7.5 mg base each)	1 (100 mg)
9–14	1 (150 mg)	2 (500+25 mg each)	1 (150 mg)	4 (7.5 mg base each)	1 (150 mg)
15 & above	1 (200 mg)	2 (750+37.5 mg each)	1 (200 mg)	6 (7.5 mg base each)	1 (200 mg)

Figures in parentheses indicate doses and outside the parentheses number of tablets.

3 days and sulfadoxine (25 mg/kg body weight) -pyrimethamine (1.25 mg/kg body weight) [AS+SP] on Day 0. The dosage schedule of AS+SP for different age groups is given in Table 3.

In the **northeastern states (Arunachal Pradesh, Asom, Manipur, Meghalaya, Mizoram, Nagaland, and Tripura)**, due to the recent reports of late treatment failures to the current combination of AS+SP in *P. falciparum* malaria, the presently

MONOTHERAPY OF ORAL ARTEMISININ DERIVATIVES IS BANNED IN INDIA

Artemisinin derivatives are the only rapidly acting antimalarials as of date and if used alone, can lead to the development of artemisinin resistance. Hence, they should not be administered as monotherapy for uncomplicated malaria except for specific studies on artemisinin resistance after consultation with NVBDCP and NIMR or as injectables for severe malaria. **Injectable artemisinin derivatives should be used only in severe malaria.**

Table 4. Dosage schedule of AL

Co-formulated tablet AL	Total dose of AL (twice daily for 3 days)	No. of tablets in the packing	Administration (twice daily for 3 days) tablets
5–14 kg (>5 months to <3 years)	20 mg/120 mg	6	1
15–24 kg (≥3 to <9 years)	40 mg/240 mg	12	2
25–34 kg (≥9 to <14 years)	60 mg/360 mg	18	3
>34 kg (≤14 years)	80 mg/480 mg	24	4

Not recommended during the first trimester of pregnancy and for children weighing <5 kg.

recommended ACT in national drug policy is fixed dose combination (FDC) of **Artemether-lumefantrine (AL)**. The dosage schedule of AL for different age groups is given in Table 4.

Although the ACT used in the national programme in NE states is AL and rest of India is AS+SP, the other fixed dose combinations registered for marketing in India are artesunate-amodiaquine, artesunate-mefloquine and arterolane-piperazine (for adults only) and can be used for treatment of uncomplicated *P. falciparum* or mixed infections.

4.3 Treatment of malaria in pregnancy

The ACT should be given for treatment of *P. falciparum* malaria in second and third trimesters of pregnancy, while quinine is recommended in the first trimester. *Plasmodium vivax* malaria can be treated with chloroquine.

4.4 Treatment of mixed infections

Mixed infections with *P. falciparum* should be treated as falciparum malaria. Since AS+SP is not effective in vivax malaria, other ACT should be used. However, anti-relapse treatment with primaquine can be given for 14 days, if indicated.

4.5 Treatment based on clinical criteria without laboratory confirmation

All the efforts should be made to diagnose malaria either by microscopy or RDT. However, special circumstances should be addressed as mentioned below:

- If RDT for only *P. falciparum* is used, negative cases showing signs and symptoms of malaria without any other obvious cause for fever should be considered as 'clinical malaria' and treated with chloroquine in full therapeutic dose of 25 mg/kg body weight over three days. If a slide result is obtained later, the treatment should be completed according to species.
- Suspected malaria cases not confirmed by RDT or microscopy should be treated with chloroquine in full therapeutic dose.

4.6 General recommendations for the management of uncomplicated malaria

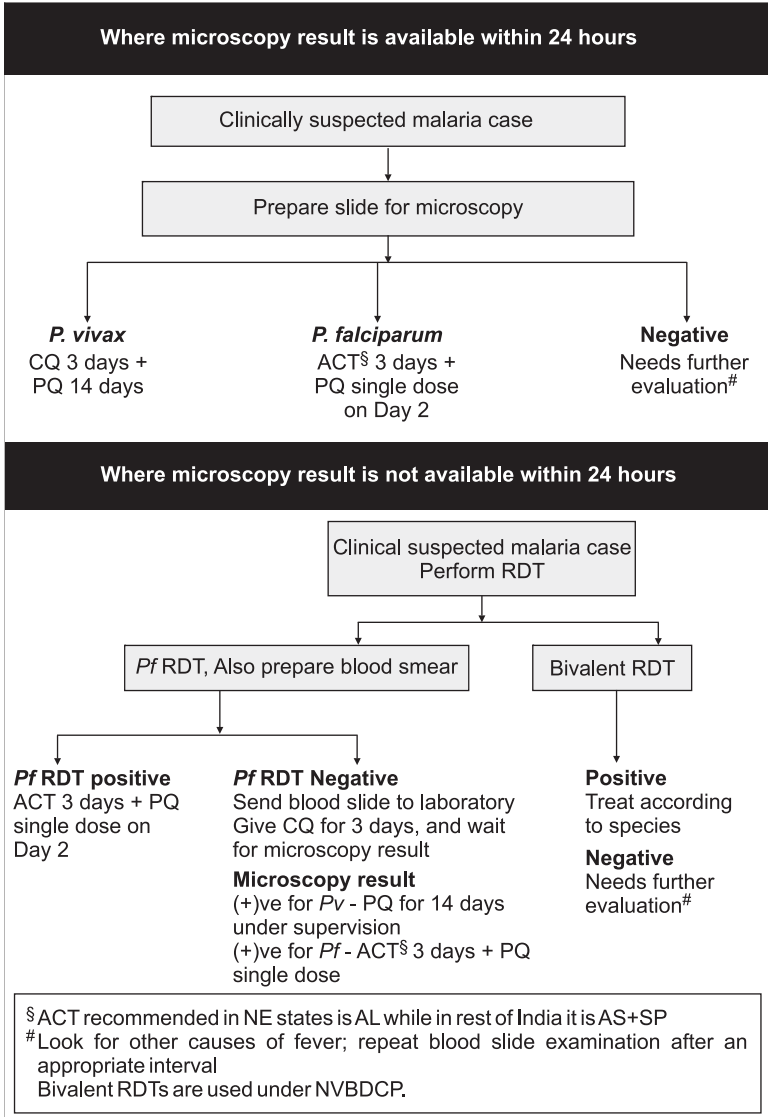
- Avoid starting treatment on an empty stomach. The first dose should be given under observation.
- Dose should be repeated if vomiting occurs within half an hour of antimalarial intake.
- The patient should be asked to report back, if there is no improvement after 48 hours or if the situation deteriorates.
- The patient should also be examined and investigated for concomitant illnesses.
- The algorithm for diagnosis and treatment is shown in Chart 1.

5. TREATMENT FAILURE/DRUG RESISTANCE

After treatment patient is considered cured if he/she does not have fever or parasitaemia till Day 28. Some patients may not respond to treatment which may be due to drug resistance or treatment failure, especially in falciparum malaria. If patient does not respond and presents with following, he/she should be given alternative treatment.

Early treatment failure (ETF): Development of danger signs or severe malaria on Day 1, 2 or 3, in the presence of parasitaemia; parasitaemia on Day 2 higher than on Day 0, irrespective of axillary

Chart 1: Algorithm for diagnosis and treatment of malaria



temperature; parasitaemia on Day 3 with axillary temperature $>37.5^{\circ}\text{C}$; and parasitaemia on Day 3, $>25\%$ of count on Day 0.

Late clinical failure (LCF): Development of danger signs or severe malaria in the presence of parasitaemia on any day between Day 4 and Day 28 (Day 42) in patients who did not previously meet any of the criteria of early treatment failure; and the presence of parasitaemia on any day between Day 4 and Day 28 (Day 42) with axillary temperature $>37^{\circ}\text{C}$ in patients who did not previously meet any of the criteria of early treatment failure.

Late parasitological failure (LPF): Presence of parasitaemia on any day between Day 7 and Day 28 with axillary temperature $<37.5^{\circ}\text{C}$ in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Such cases of falciparum malaria should be given alternative ACT or quinine with Doxycycline. Doxycycline is contraindicated in pregnancy, lactation and in children up to 8 years. Treatment failure with chloroquine in *P. vivax* malaria is rare in India.

6. TREATMENT OF SEVERE MALARIA

6.1 Clinical features

Severe manifestations can develop in *P. falciparum* infection over a span of time as short as 12–24 hours and may lead to death, if not treated promptly and adequately. Severe malaria is characterized by one or more of the following features:

- Impaired consciousness/coma
- Repeated generalized convulsions
- Renal failure (Serum Creatinine >3 mg/dl)
- Jaundice (Serum Bilirubin >3 mg/dl)
- Severe anaemia (Hb <5 g/dl)
- Pulmonary oedema/acute respiratory distress syndrome
- Hypoglycaemia (Plasma Glucose <40 mg/dl)
- Metabolic acidosis
- Circulatory collapse/shock (Systolic BP <80 mm Hg, <50 mm Hg in children)
- Abnormal bleeding and Disseminated intravascular coagulation (DIC)

- Haemoglobinuria
- Hyperpyrexia (Temperature >106°F or >42°C)
- Hyperparasitaemia (>5% parasitized RBCs)

Foetal and maternal complications are more common in pregnancy with severe malaria; therefore, those need prompt attention.

6.2 Diagnosis of severe malaria cases negative on microscopy

Microscopic evidence may be negative for asexual parasites in patients with severe infections due to sequestration and partial treatment. Efforts should be made to confirm these cases by RDT or repeat microscopy. However, if clinical presentation indicates severe malaria and there is no alternative explanation these patients should be treated accordingly.

6.3 Requirement for management of complications

For management of severe malaria, health facilities should be equipped with the followings:

- Parenteral antimalarials, antipyretics, antibiotics, anticonvulsants
- Intravenous infusion facilities
- Special nursing for patients in coma
- Blood transfusion
- Laboratory with clinical chemistry and haematology facilities
- Facility for Oxygen administration

It is desirable to have dialysis facility, ventilator, etc.

6.4 Specific antimalarial treatment of severe malaria

Severe malaria is an emergency and treatment should be given promptly. Parenteral artemisinin derivatives or quinine should be used as specific antimalarial therapy. Intravenous route should be preferred over intramuscular.

- **Artesunate:** 2.4 mg/kg body weight i.v. or i.m. given on admission (time=0), then at 12 and 24 hours, then once a day (Care should be taken to dilute artesunate powder in 5% Sodium bi-carbonate provided in the pack).

- **Quinine:** 20 mg quinine salt/kg body weight on admission (i.v. infusion in 5% dextrose/dextrose saline over a period of 4 hours) followed by maintenance dose of 10 mg/kg body weight 8 hourly; infusion rate should not exceed 5 mg/kg body weight per hour. Loading dose of 20 mg/kg body weight should not be given, if the patient has already received quinine. NEVER GIVE BOLUS INJECTION OF QUININE. If parenteral quinine therapy needs to be continued beyond 48 hours, dose should be reduced to 7 mg/kg body weight 8 hourly.
- **Artemether:** 3.2 mg/kg body weight i.m. given on admission then 1.6 mg/kg body weight per day.
- **α - β Arteether:** 150 mg daily i.m. for 3 days in adults only (not recommended for children).
- Intravenous preparations should be preferred over intramuscular preparations. Parenteral treatment should be given for minimum of 24 hours once started.

Note: – Once the patient can tolerate oral therapy or after at least 24 hours of parenteral therapy, further follow-up treatment should be as below:

- Patients receiving artemisinin derivatives should get full course of oral ACT. However, ACT containing mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications.
- Patients receiving parenteral quinine should also be treated with full course of oral ACT.
- **In first trimester of pregnancy, parenteral quinine is the drug of choice.** However, if quinine is not available, artemisinin derivatives may be given to save the life of mother. In second and third trimester, parenteral artemisinin derivatives are preferred.

6.5 Severe malaria due to *P. vivax*

In recent years, increased attention has been drawn to severe malaria caused by *P. vivax*. Some cases have been reported in India, and there is reason to fear that this problem may become more common in the coming years. Severe malaria caused by *P. vivax*

should be treated like severe *P. falciparum* malaria, however, primaquine should be given for 14 days for preventing relapse as per guidelines after the patient recovers from acute illness and can tolerate primaquine.

7. CHEMOPROPHYLAXIS

Chemoprophylaxis is recommended for travellers, migrant labourers and military personnel exposed to malaria in highly endemic areas. Use of personal protection measures like insecticide-treated bed nets should be encouraged for pregnant women and other vulnerable populations.

7.1 Short-term chemoprophylaxis (less than 6 weeks)

Doxycycline: 100 mg daily in adults and 1.5 mg/kg body weight for children more than 8 years old. The drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area.

Note: Doxycycline is contraindicated in pregnant and lactating women and children less than 8 years.

7.2 Long-term chemoprophylaxis (more than 6 weeks)

Mefloquine: 5 mg/kg body weight (up to 250 mg) weekly and should be administered two weeks before, during and four weeks after leaving the area.

Note: Mefloquine is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.

8. RECOMMENDED READINGS

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