

## Management of uncomplicated malaria

*Rajesh Mahajan, Bharti Mahajan, Sandeep Puri*

A quarter of a billion people have malaria with almost 900,000 deaths annually according to WHO, 2009. There are mainly four species of Plasmodium, a single-celled protozoan parasite causing human malaria: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. A fifth species, *P. knowlesi*, a zoonotic malarial parasite is an important cause of malaria in parts of Southeast Asia including Malaysia, Indonesia, Thailand, Singapore and Philippines.<sup>1</sup> It should be therefore considered as a potential threat to the travellers returning from these regions. Female anopheles mosquito is the vector for transmission of this parasite. Rarely, the infection can also be acquired congenitally or via transfusions or contaminated needles.<sup>2,3</sup>

### Epidemiology:

*P. falciparum* and *P. vivax* cause a significant majority of malaria infections out of the five Plasmodia species that infect human beings. *P. falciparum* is responsible for the most severe form of malaria and is generally found in tropical regions, such as sub-Saharan Africa and Southeast Asia. *P. vivax* is common in most parts of Asia (especially Southeast Asia), the Eastern Mediterranean and in most endemic countries of the America.

*P. malariae* is wide spread throughout sub-Saharan Africa, much of Southeast Asia, into Indonesia, and on many of the islands of the western Pacific. It is also reported in areas of the Amazon Basin of South America.<sup>4</sup> *P. ovale* is found in Africa and sporadically in Southeast Asia and the Western Pacific. *P. malariae* and *P. ovale* contribute to only a small number of malaria infections, but the incidence of *P. malariae* is probably underestimated. *P. knowlesi* is a primate malaria species that is being increasingly reported from remote areas of Southeast Asia from countries such as Malaysia, Thailand, Viet Nam, Myanmar and Philippines.<sup>5</sup>

### Diagnosis:

Prompt and accurate diagnosis is critical in the effective management of malaria. Delays in diagnosis and treatment are the leading cause of death in many countries.<sup>6</sup> It can be diagnosed based on clinical acumen and laboratory investigations.

### Clinical Findings:

An acute attack of malaria typically begins with a prodrome of headache and fatigue, followed by fever. A classic malarial paroxysm includes chills, high fever and then sweats.<sup>7</sup> Each plasmodium species has a typical incubation period leading to periodicity of fever, although not a reliable clue to the diagnosis of malaria.<sup>8</sup>

**P. Falciparum:**

It causes the most severe disease. It can be classified as uncomplicated and complicated falciparum malaria. Complicated malaria may lead to organ failure and death. When treated early, symptoms of malarial infection usually improve within 24-48 hours. The periodicity of fever is 48 Hours.<sup>8</sup>

**Plasmodium knowlesi:**

Travellers to forested areas of Southeast Asia and South America can become infected by *Plasmodium knowlesi*, This species can cause severe illness and death in humans.<sup>9</sup>

**Non-Falciparum:**

*P.vivax*, *P.ovale*, *P. malariae* are less likely to cause severe manifestations, however, recently more and more complicated *P vivax* cases are being reported. In addition, *P.vivax* and *P.ovale* infections also require treatment for the hypnozoites forms that remain dormant in liver, responsible for relapsing infection.<sup>8</sup> The periodicity of fever associated with each species is 48 h for *P vivax* and *P ovale* (tertian fever) ; 72 h for *P malariae* (quartan fever). Tertian and quartan fevers are due to cyclic lysis of red blood cells as trophozoites complete their cycle in erythrocytes every 2<sup>nd</sup> or 3<sup>rd</sup> day, respectively.<sup>9</sup>

**Laboratory diagnosis:**

Giemsa-stained blood smears remain the mainstay of diagnosis. Thick smears provide efficient evaluations of larger volumes of blood and are more sensitive in detecting malaria but are more difficult to read. Thin smears are simpler and help in parasite identification and quantification.<sup>8</sup> The quantity of infecting parasites has a loose association with the severity of malaria but high parasitemias (> 200,000-500,000 parasites/mcL) or the presence of malarial pigment (a breakdown product of haemoglobin) in >5% of neutrophils are associated with a poor prognosis.<sup>7</sup> However, repeat blood smears should be performed at least every 12-24 h for 2 days if the first smears are negative and malaria is strongly suspected.<sup>10</sup>

There are also other laboratory diagnostic tests which are available. These include rapid diagnostic tests (RDTs) to identify circulating plasmodial antigens with a simple “dipstick” format. RDTs are rapid in detecting the infected patients, but they cannot confirm the species.

Polymerase chain reaction (PCR), a more sensitive and specific test than microscopy can be performed in reference laboratories. It is a useful tool for confirmation of species and to detect drug resistant mutations.<sup>8</sup>

**Management:**

The treatment for malaria should only be initiated when the diagnosis has been established by laboratory investigations. “Presumptive treatment” should be reserved for extreme

circumstances under strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory diagnosis. Appropriate antimalarial treatment must be initiated immediately. Treatment should be guided by the following parameters:<sup>8</sup>

- Plasmodium species and its density: It determines the treatment according to the species
- The clinical status of the patient: “Uncomplicated” or “severe.”
  - Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. The signs and symptoms of uncomplicated malaria are nonspecific. Malaria is, therefore, suspected clinically mostly on the basis of fever or a history of fever.<sup>11</sup>
  - Severe malaria: Symptoms may include confusion, coma, focal neurologic signs, severe anemia, and respiratory difficulties. A patient with symptoms of severe malaria should be assessed quickly and treated immediately. Severe malaria is most often caused by the most dangerous parasite, *P. falciparum*.
- Oral medication: The clinical condition of the patient guides the physician to choose the route of administration.
- Drug susceptibility of infecting parasites:
  - The probability of drug resistance in the infecting parasite can be confirmed through the knowledge of the geographic area from where the infection was acquired. Drug resistance enables the clinician to choose an appropriate drug or drug combinations and the treatment course.<sup>11</sup>

### **Antimalarial drug resistance:**

Antimalarial drug resistance arises through selection of mutants, arising naturally with reduced drug susceptibility.<sup>12</sup>

Chloroquine-resistant forms of *Plasmodium falciparum* malaria first appeared in Thailand in 1957. Mass drug-administration (MDA) programs elsewhere in the world during the 1950s and 1960s contributed to the rise of chloroquine resistance which then spread through South and Southeast Asia and by the 1970s were being seen in sub-Saharan Africa and South America. The rise in chloroquine resistance contributed to a worldwide increase in malaria-related mortality, particularly in sub-Saharan Africa.

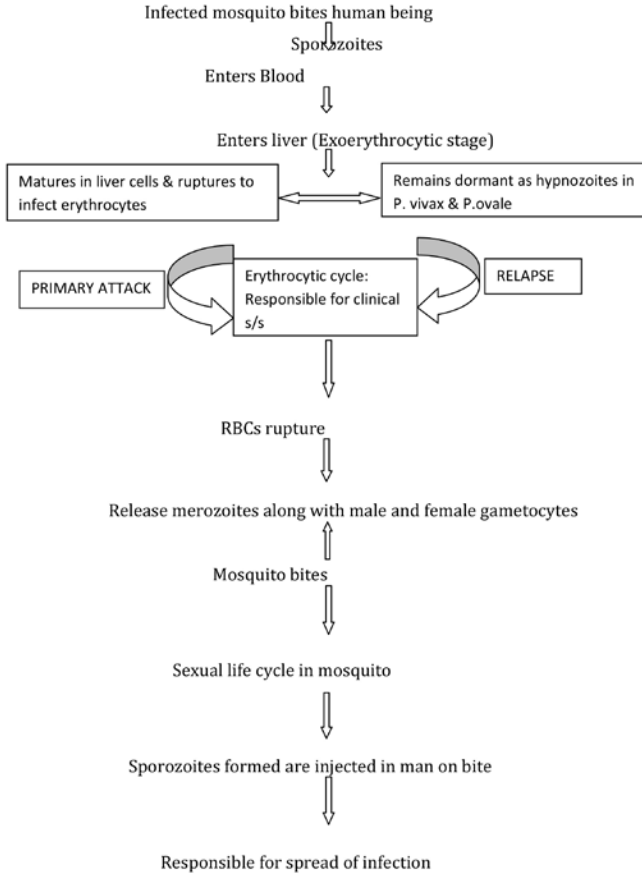
A number of alternative synthetic antimalarial drugs were deployed to both treat and prevent malaria like sulfadoxine-pyrimethamine and mefloquine.<sup>13</sup> However, resistance to these replacement therapies emerged relatively quickly. Artemisinin-based drugs emerged from China in search for new and safer antimalarials, effective in treating *falciparum* malaria. To prevent the development of resistance to artemisinin-based drugs, the World Health Organization (WHO) recommended that these drugs should be used only in combination with other antimalarials.<sup>14</sup>

**General principles:**<sup>15</sup>

- The patient's travel history should be known for selecting an effective antimalarial drug, in terms of risk of drug resistance.
- Patients with malaria should be treated immediately because *P falciparum* infections can rapidly progress to severe illness or death in as little as 1 to 2 days. Blood films should be repeated to ensure clearance of *P falciparum* parasitemia. Patients who are not responding clinically (with defervescence within 72 hours) need follow-up malaria blood films and may also require a search for other causes of fever.<sup>8</sup>
- If the species cannot be identified, the patient should be treated as if infected with *P falciparum* until the infecting species can be identified.
- Base and salt conversions for antimalarial drugs should be taken care of as they are a source of confusion resulting in treatment errors.
- Gametocytes are less susceptible to many antimalarial drugs than are asexual parasites, and their persistence in the blood in the absence of asexual parasites does not indicate drug resistance.

Antimalarial drugs can be targeted based on the life cycle (Fig.1) of the parasite. Drugs that eliminate developing or dormant liver forms are called tissue schizonticides; those that act on erythrocytic parasites are called blood schizonticides and gametocidal drugs are the ones which kill sexual stages and prevent transmission to the mosquitoes. However, there is no single agent which can lead to radical cure i.e. elimination of both hepatic and erythrocytic stages.<sup>3</sup>

Fig. 1: Life cycle of parasite:



**Treatment regimens for uncomplicated malaria:**<sup>10,11</sup>

Uncomplicated malaria	Regimen(s)
Known chloroquine-sensitive strains of <i>P. vivax</i> , <i>P. malariae</i> , <i>P. ovale</i> , <i>P. knowlesi</i> , <i>P. falciparum</i>	Chloroquine (CQ): 10 mg of base/kg stat followed by 5 mg/kg at 12, 24 and 36 h or by 10 mg/kg at 24 h & 5 mg/kg at 48h  OR  Amodiaquine (10-12 mg of base/kg qd for 3 days)
Radical treatment for <i>P. vivax</i> & <i>P. ovale</i>	In addition to chloroquine or amodiaquine, primaquine (PQ): 0.25 mg of base/kg once daily with food for 14 days to prevent relapses. In Oceania and South-East Asia: primaquine dose is 0.5 mg/kg body weight.  In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks.  PQ should not be given in severe G6PD deficiency.
Areas without Multidrug-resistant (MDR) <i>P. falciparum</i> malaria (mainly Africa)	(Artemisinin combination therapy) ACT-SP: Artesunate (4 mg/kg/day OD for 3 days) plus sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose on day 1  OR  Artesunate (4 mg/kg/day for 3 days) plus amodiaquine(10 mg/kg/day OD for 3 days)

Areas with Multidrug-resistant <i>P. falciparum</i> malaria (mainly East-Asia)	ACT-AL: Artemether-lumefantrine (1.7/12 mg/kg body weight, respectively, per dose, given twice a day for 3 days with food)  OR  Artesunate (4 mg/kg/day OD for 3 days) plus  Mefloquine (25 mg/Kg- either 8.3 mg/kg/day OD for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)
Second-line treatment/treatment of imported malaria	Either artesunate (2 mg/kg/day OD for 7 days) or quinine (10 mg/kg tid for 7 days) plus 1 of the following 3:  Tetracycline (4 mg/kg qd for 7 days)  Doxycycline (3.5 mg/kg OD for 7 days)  Clindamycin (10 mg/kg bid for 7 days)
Mixed infections ( <i>P. vivax</i> + <i>P. falciparum</i> )	Full course of ACT and primaquine 0.25 mg/kg daily for 14 days

### Treatment according to National Vector Borne Disease Control Programme (NVBDCP) in India:<sup>16</sup>

**Positive for *P.vivax*:** Same as recommended by WHO i.e. CQ for 3 days and PQ 0.25 mg/kg for 14 days

#### **Positive for *P. falciparum*:**

In North-eastern states: ACT-AL for 3 days + PQ Single dose (0.75 mg/kg body weight) on second day

In other states: Treat with ACT-SP for 3 days + PQ Single dose (0.75 mg/kg body weight) on second day

#### **Positive for mixed infections:**

In North-eastern states: ACT-AL for 3 days + PQ 0.25 mg/kg daily for 14 days

In other states: ACT-SP for 3 days + PQ 0.25 mg/kg daily for 14 days

### Treatment of *P. ovale* and *P. malariae*:

In India these species are very rarely found in few places. *P. ovale* should be treated as *P. vivax* and *P. malariae* should be treated as *P. falciparum*.

Chloroquine remains an effective choice for all *P. vivax* and *P. ovale* infections except for the infection acquired in Papua New Guinea or Indonesia.<sup>8</sup> However, any of the regimens recommended for chloroquine resistant malaria may also be used for the treatment of chloroquine sensitive malaria.

Chloroquine sensitive *P. falciparum* malaria is now found in very few areas. The World Health Organization now recommends artemisinin based combination therapy (ACT) as first line therapy for *falciparum* malaria in all tropical countries and advocates use of fixed-dose combinations.<sup>2</sup> Current ACT regimens that are well tolerated in adults and children  $\geq 5$  kg include artemether-lumefantrine (ACT-AL), artesunate-mefloquine, artesunate-amodiaquine, artesunate-sulphadoxine-pyrimethamine (ACT-SP) and dihydroartemisinin-piperaquine. Artesunate-pyronaridine has also recently completed phase III clinical trials.<sup>2</sup> ACTs have low toxicity and are considered safe for use in nonpregnant adults and children.

Quinine has a rapid onset of action and in combination with either tetracycline, doxycycline, or clindamycin, has been shown to be a very efficacious treatment option for *P. falciparum* infections acquired in regions with chloroquine-resistant strains.<sup>15</sup> The quinine and antibiotic should be started at the same time and should at least overlap by 2 days.

The tetracyclines (tetracycline and doxycycline) and clindamycin should always be used in combination with a faster-acting antimalarial drug such as quinine and never as monotherapy.<sup>15</sup> Tetracycline and doxycycline should not be given to pregnant women or to children less than 8 years of age. However, these drugs in combination with quinine can only be used when benefits outweigh the risk.<sup>8</sup>

Mefloquine is contraindicated if there is hypersensitivity to the drug, cardiac conduction abnormalities, psychiatric and seizure disorders. It should not be administered within 12 h of administration of other antimalarial agents like chloroquine, quinine, quinidine as they lead to slow elimination of mefloquine.

### Treatment of uncomplicated malaria in epidemic situations:<sup>11</sup>

It is same as discussed above. However, the 14-day anti-relapse therapy for *vivax* malaria patients should be postponed to the post-epidemic period.

### Uncomplicated malaria and pregnancy:

Known chloroquine-sensitive strains of *P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*, *P. falciparum*:

- Same treatment schedule as with non-pregnant adult patients.
- Primaquine for radical treatment in *P. vivax* & *P. ovale* should not be given during pregnancy.



- However, they should be maintained on chemoprophylactic dose of chloroquine phosphate i.e. 300 mg base (= 500 mg salt) orally once per week.
- After delivery, primaquine should be given to those, who do not have G6PD deficiency.<sup>17</sup>

Pregnancy & malaria due to *P.falciparum*:<sup>11</sup>

First trimester:

- quinine plus clindamycin to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails)

Second and third trimesters:

- ACTs are known to be effective in the country / region or artesunate plus clindamycin to be given for 7 days, or quinine plus clindamycin to be given for 7 days.

NVBDCP of India also recommends the treatment of malaria in pregnancy as recommended by WHO along with region specific ACT whenever required i.e. ACT-AL in North Eastern States and ACT-SP in other States.

**Caution** needs to be taken with Quinine as it may induce hypoglycemia. Pregnant women should not start taking quinine on an empty stomach and should eat regularly, while on quinine treatment.

The objective of treating uncomplicated malaria is to cure the infection as rapidly as possible. The number of antimalarial drug trials published has continued to increase over the years, with the result that these guidelines have a firmer evidence base than previous treatment recommendations. However, the widespread availability of cheap counterfeit drugs containing subclinical quantities of artemisinin and the marketing and use of noncombination forms of the drug have created an environment for both the development and spread of artemisinin resistance.<sup>14</sup> Although, new antimalarial drugs are in pipeline but a check should be kept on the development of resistance.

## References:

1. Cox-Singh J, Davis TM, Lee KS, Shamsul SS, Matusop A, Ratnam S et al. *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis* 2008; 46: 165-71.
2. Vinetz JM, Clain J, Bounkeua V, Eastman RT, Fidock D. *Chemotherapy of malaria*. In: Brunton LL, Chabner BA, Knollmann BC, editors. *Goodman and Gilman's: The pharmacological basis of therapeutics*. 12th Ed. New York: McGraw-Hill Medical Publishing Division; 2011. p. 1383-419.
3. Rosenthal PJ. *Antiprotozoal drugs*. In: Katzung BG, Masters SB, Trevor AJ, editors. *Basic & Clinical Pharmacology*. 11th Edn. New Delhi: Tata McGraw-Hill Education Private Limited; 2009. p. 899-922.
4. Collins WE, Jeffery GM. *Plasmodium malariae: Parasite and Disease*. *Clin. Microbiol. Rev.* October 2007; 20:579-92. doi: 10.1128/CMR.00027-07.
5. *Malaria worldwide*. Available from: [http://www.nature.com/nrmicro/journal/v4/n9\\_suppl/fig\\_tab/nrmicro1525\\_F2.html](http://www.nature.com/nrmicro/journal/v4/n9_suppl/fig_tab/nrmicro1525_F2.html). [Accessed on: 12.10.14].

6. Tangpukdee N, Duangdee C, Wilairatana P, Krudsood S. Malaria diagnosis: A Brief review. *Korean j Parasitol* 2009; 47(2):93-102. Doi:10.3347/kjp.2009.47.2.93.
7. Rosenthal PJ. Protozoal and helminthic infections. In: McPhee SJ, Papadakis MA editors. *Current medical diagnosis and treatment*. 50th Edn. New York: McGraw-Hill Medical Publishing Division; 2011. p. 1421-61.
8. *Treatment of Malaria (Guidelines For Clinicians)* [www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf](http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf) July, 2013 [Accessed on: 08.10.14].
9. *Malaria clinical presentation-Medscape reference*. Available from: <http://emedicine.medscape.com/article/221134-clinical> [Accessed on: 08.10.14].
10. White NJ, Breman JG. Malaria. In: Longo DL, Fauci AS, Kasper DL, Hayser SL, Jameson JL, Loscalzo J editors. *Harrison's Principles of Internal Medicine*. 18th Edn. New York: McGraw-Hill Medical Publishing Division; 2012. p. 1688-1705.
11. *Guidelines for the treatment of malaria – 2nd edition*. World Health Organization, 2010 Available from: <http://www.who.int/malaria/publications/atoz/9789241547925/en/> [Accessed on: 03.10.14].
12. *Antimicrobials*. In: Torok ME, Cooke FJ, Moran E. editors. *Oxford handbook of infectious diseases and microbiology*. Oxford University press Inc., New York; 2009. p. 148-9.
13. Packard RM. *The making of a tropical disease: a short history of malaria*. Baltimore: Johns Hopkins University Press, 2007.
14. Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, et al.. Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol* 2010; 8:272-80.
15. Griffith KS, Lewis LS, Mali S, Parise ME. *Treatment of Malaria in the United States: A Systematic Review*. *JAMA*. 2007; 297:2264-77. doi:10.1001/jama.297.20.2264.
16. *National Drug Policy on Malaria - 2013 – NVBDCP*. Available from: [nvbdc.gov.in/Doc/National-Drug-Policy-2013](http://nvbdc.gov.in/Doc/National-Drug-Policy-2013). [Accessed on: 01.10.14]
17. *Treatment of Malaria: Guidelines For Clinicians (United States)*. Part 3: *Alternatives for Pregnant Women and Treatment of Severe Malaria*. Available from: [http://www.cdc.gov/malaria/diagnosis\\_treatment/clinicians3.html](http://www.cdc.gov/malaria/diagnosis_treatment/clinicians3.html). [Accessed on: 01.10.14]