



# TREATMENT GUIDELINES

## Treatment of Malaria (Guidelines for Clinicians)

### Treatment Table

The Treatment Table is available in PDF format at <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>

### Reporting

We encourage clinicians to report all cases of laboratory-confirmed malaria to help CDC's surveillance efforts. Refer to our information on the Malaria Case Surveillance Report Form (<http://www.cdc.gov/malaria/report.html>).

### Evaluation and Diagnosis

Because malaria cases are seen relatively rarely in North America, misdiagnosis by clinicians and laboratorians has been a commonly documented problem in published reports. However, malaria may be a common illness in areas where it is transmitted and therefore the diagnosis of malaria should routinely be considered for any febrile person who has traveled to an area with known malaria transmission in the past several months preceding symptom onset.

Symptoms of malaria are generally non-specific and most commonly consist of fever, malaise, weakness, gastrointestinal complaints (nausea, vomiting, diarrhea), neurologic complaints (dizziness, confusion, disorientation, coma), headache, back pain, myalgia, chills, and/or cough. The diagnosis of malaria should also be considered in any person with fever of unknown origin regardless of travel history.

Patients suspected of having malaria infection should be urgently evaluated. Treatment for malaria should not be initiated until the diagnosis has been confirmed by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory confirmation, usually by microscopy).

Laboratory diagnosis of malaria can be made through microscopic examination of thick and thin blood smears. Thick blood smears are more sensitive in detecting malaria parasites because the blood is more concentrated allowing for a greater volume of blood to be examined; however, thick smears are more difficult to read. Thin smears aid in parasite species identification and quantification. Blood films need to be read immediately; off-hours, qualified personnel who can perform this function should be on-call. A negative blood smear makes the diagnosis of malaria unlikely. However, because non-immune individuals may be symptomatic at very low parasite densities that initially may be undetectable by blood smear, blood smears should be repeated every 12–24 hours for a total of 3 sets. If all 3 are negative, the diagnosis of malaria has been essentially ruled out.

After malaria parasites are detected on a blood smear, the parasite density should then be estimated. The parasite density can be estimated by looking at a monolayer of red blood cells (RBCs) on the thin smear using the oil immersion objective at 100x. The slide should be examined where the RBCs are more or less touching (approximately 400 RBCs per field). The parasite density can then be estimated from the percentage of infected RBCs, after counting 500 to 2000 RBCs.

In addition to microscopy, other laboratory diagnostic tests are available. Several antigen detection tests (rapid diagnostic tests or RDTs) using a "dipstick" or cassette format exist, but only one is approved for general diagnostic use in the United States. RDTs can more rapidly determine that the patient is infected with malaria, but they cannot confirm the species or the parasitemia. Laboratories that do not provide in-house on-the-spot microscopy services should maintain a stock of malaria RDTs so that they will be able to perform malaria diagnostic testing when urgently needed.

Parasite nucleic acid detection using polymerase chain reaction (PCR) is more sensitive and specific than microscopy but can be performed only in reference laboratories and so results are not often available quickly enough for routine diagnosis. However, PCR is a very useful tool for confirmation of species and detecting of drug resistance mutations. CDC offers malaria drug resistance testing for all malaria diagnosed in the United States free of charge. Serologic tests, also performed in reference laboratories, can be used to assess past malaria experience but not current infection by malaria parasites. Your state health department or the CDC can be contacted for more information on utilizing one of these tests.

## **Treatment: General Approach**

It is preferable that treatment for malaria should not be initiated until the diagnosis has been established by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory diagnosis).

Once the diagnosis of malaria has been made, appropriate antimalarial treatment must be initiated immediately. Treatment should be guided by three main factors:

- The infecting *Plasmodium* species
- The clinical status of the patient
- The drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired and the previous use of antimalarial medicines

**The infecting *Plasmodium* species:** Determination of the infecting *Plasmodium* species for treatment purposes is important for three main reasons. Firstly, *P. falciparum* and *P. knowlesi* infections can cause rapidly progressive severe illness or death while the other species, *P. vivax*, *P. ovale*, or *P. malariae*, are less likely to cause severe manifestations. Secondly, *P. vivax* and *P. ovale* infections also require treatment for the hypnozoite forms that remain dormant in the liver and can cause a relapsing infection. Finally, *P. falciparum* and *P. vivax* species have different drug resistance patterns in differing geographic regions. For *P. falciparum* and *P. knowlesi* infections, the urgent initiation of appropriate therapy is especially critical.

**The clinical status of the patient:** Patients diagnosed with malaria are generally categorized as having either uncomplicated or severe malaria. Patients diagnosed with uncomplicated malaria can be effectively treated with oral antimalarials. However, patients who have one or more of the following clinical criteria are considered to have manifestations

of more severe disease and should be treated aggressively with parenteral antimalarial therapy: impaired consciousness/coma, severe normocytic anemia [hemoglobin < 7], renal failure, acute respiratory distress syndrome, hypotension, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%.

**The drug susceptibility of the infecting parasites:** Finally, knowledge of the geographic area where the infection was acquired provides information on the likelihood of drug resistance of the infecting parasite and enables the treating clinician to choose an appropriate drug or drug combination and treatment course. In addition, if a malaria infection occurred despite use of a medicine for chemoprophylaxis, that medicine should not be a part of the treatment regimen. If the diagnosis of malaria is suspected and cannot be confirmed, or if the diagnosis of malaria is confirmed but species determination is not possible, antimalarial treatment effective against chloroquine-resistant *P. falciparum* must be initiated immediately.

Malaria is a nationally notifiable disease and all cases should be reported to your state health department, which are forwarded on to CDC.

CDC clinicians are on call 24 hours to provide advice to clinicians on the diagnosis and treatment of malaria and can be reached through the Malaria Hotline 770-488-7788 (or toll free 855-856-4713) Monday–Friday, 9am–5pm. Off-hours, weekends, and federal holidays, call 770-488-7100 and ask to have the malaria clinician on call to be paged.

The three-page Treatment Guidelines table (<http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>) can be used as a guide for treatment of malaria in the United States. The drug or drug combinations recommended for treatment are listed in bold on the first line of each box in the adult and pediatric “drug and dose” columns. Each drug and its recommended dose are then listed individually on the lines below in the same box. It is important to note that the base/salt conversions for antimalarials are a continual source of confusion and can contribute to treatment errors. In this treatment table (where appropriate), the antimalarial dose is expressed in base with the salt equivalency noted in parentheses.

After initiation of treatment, the patient's clinical and parasitologic status should be monitored. In infections with *P. falciparum* or suspected chloroquine-resistant *P. vivax*, blood smears should be made to confirm adequate parasitologic response to treatment (decrease in parasite density).

## **Treatment: Uncomplicated Malaria**

### ***P. falciparum* or Species Not Identified – Acquired in Areas Without Chloroquine Resistance**

For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include Central America west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East, patients can be treated with oral chloroquine. A chloroquine dose of 600 mg base (=1,000 mg salt) should be given initially, followed by 300 mg base (=500 mg salt) at 6, 24, and 48 hours after the initial dose for a total chloroquine dose of 1,500 mg base (=2,500 mg salt). Alternatively, hydroxychloroquine may be used at a dose of 620 mg base (=800 mg salt) by mouth given initially, followed by 310 mg base (=400 mg salt) by

mouth at 6, 24, and 48 hours after the initial dose for a total hydroxychloroquine dose of 1,550 mg base (=2,000 mg salt).

In addition, any of the regimens listed below for the treatment of chloroquine-resistant malaria may be used for the treatment of chloroquine-sensitive malaria. Prompt initiation of an effective regimen is vitally important and so using any one of the effective regimens that readily at hand would be the preferred strategy.

### ***P. falciparum* or Species Not Identified – Acquired in Areas With Chloroquine Resistance**

For *P. falciparum* infections acquired in areas with chloroquine resistance, four treatment options are available. The first two treatment options are atovaquone-proguanil (Malarone) **or** artemether-lumefantrine (Coartem). These are fixed dose combination medicines that can be used for non-pregnant adult and pediatric patients. Both of these options are very efficacious. Quinine sulfate plus doxycycline, tetracycline, or clindamycin is the next treatment option. For the quinine sulfate combination options, quinine sulfate plus either doxycycline or tetracycline is generally preferred to quinine sulfate plus clindamycin because there are more data on the efficacy of quinine plus doxycycline or tetracycline. Quinine treatment should continue for 7 days for infections acquired in Southeast Asia and for 3 days for infections acquired in Africa or South America. The fourth option, mefloquine, is associated with rare but potentially severe neuropsychiatric reactions when used at treatment doses. We recommend this fourth option only when the other options cannot be used.

For pediatric patients, the treatment options are the same as for adults except the drug dose is adjusted by patient weight. The pediatric dose should never exceed the recommended adult dose. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine. If unable to provide pediatric doses of quinine, consider one of the other three options.

If using a quinine-based regimen for children less than eight years old, doxycycline and tetracycline are generally not indicated; therefore, quinine can be given alone for a full 7 days regardless of where the infection was acquired or given in combination with clindamycin as recommended above. In rare instances, doxycycline or tetracycline can be used in combination with quinine in children less than eight years old if other treatment options are not available or are not tolerated, and the benefit of adding doxycycline or tetracycline is judged to outweigh the risk.

If infections initially attributed to "species not identified" are subsequently diagnosed as being due to *P. vivax* or *P. ovale*, additional treatment with primaquine or tafenoquine should be administered (see *P. vivax* and *P. ovale*, below).

### ***P. malariae* and *P. knowlesi***

There has been no widespread evidence of chloroquine resistance in *P. malariae* and *P. knowlesi* species; therefore, chloroquine (or hydroxychloroquine) may still be used for both of these infections. In addition, any of the regimens listed above for the treatment of chloroquine-resistant malaria may be used for the treatment of *P. malariae* and *P. knowlesi* infections.

### ***P. vivax* and *P. ovale***

Chloroquine (or hydroxychloroquine) remains an effective choice for all *P. vivax* and *P. ovale* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia. The regimens listed for the treatment of *P. falciparum* are also effective and may be used. Reports have confirmed a high prevalence of chloroquine-resistant *P. vivax* in these two specific areas. Rare cases of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine. If the patient does not respond to chloroquine, treatment should be changed to one of the two regimens recommended for chloroquine-resistant *P. vivax* infections, and your state health department and the CDC should be notified (CDC Malaria Hotline: (770) 488-7788 Monday–Friday 9am–5pm EST; (770) 488-7100 after hours, weekends, and holidays).

Persons acquiring *P. vivax* infections in Papua New Guinea or Indonesia should initially be treated with a regimen recommended for chloroquine-resistant *P. vivax* infections. The three treatment regimens for chloroquine-resistant *P. vivax* infections are quinine sulfate plus doxycycline or tetracycline, **or**, Atovaquone-proguanil, or if other options are not available, mefloquine.

In addition to requiring blood stage treatment, infections with *P. vivax* and *P. ovale* can relapse due to hypnozoites that remain dormant in the liver. To eradicate the hypnozoites, patients should be treated with either primaquine phosphate or tafenoquine. Tafenoquine can be used in those 16 years old and over, and is given as a single dose of 300 mg by mouth. If primaquine phosphate is used, CDC recommends a dose of 30 mg (base) by mouth daily for 14 days. Because both primaquine and tafenoquine can cause hemolytic anemia in persons with glucose-6-phosphate-dehydrogenase (G6PD) deficiency, persons must be tested for G6PD deficiency using a quantitative test prior to starting primaquine treatment. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given at the dose of 45 mg (base) by mouth one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine and tafenoquine must not be used during pregnancy. Tafenoquine must not be used in children less than 16 years old, or in those with a history of a psychotic disorder.

For pediatric patients greater than 8 years old, the treatment options, with the exception of tafenoquine, are the same as for adults except the drug dose is adjusted by patient weight. The pediatric dose should never exceed the recommended adult dose. For children less than 8 years old, doxycycline and tetracycline are generally not indicated; therefore other treatment options should be used. For pediatric patients <5kg, mefloquine is the only option. If mefloquine is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead. Primaquine should be given to pediatric patients only after they have been screened for G6PD deficiency.

### **Alternatives for Pregnant Women**

Malaria infection in pregnant women is associated with high risks of both maternal and perinatal morbidity and mortality. While the mechanism is poorly understood, pregnant women have a reduced immune response and therefore less effectively clear malaria infections. In addition, malaria parasites sequester and replicate in the placenta. Pregnant women are three times more likely to develop severe disease than non-pregnant women acquiring infections from the same area. Malaria infection during pregnancy can lead to

miscarriage, premature delivery, low birth weight, congenital infection, and/or perinatal death.

For pregnant women diagnosed with uncomplicated malaria caused by *P. malariae*, *P. vivax*, *P. ovale*, or chloroquine-sensitive *P. falciparum* infection, prompt treatment with chloroquine (treatment schedule as with non-pregnant adult patients) is recommended. Alternatively, hydroxychloroquine may be given instead. For women in their second or third trimesters, artemether-lumefantrine is an additional option. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, women in their second and third trimesters can be treated with artemether lumefantrine, and for all trimesters, mefloquine or a combination of quinine sulfate and clindamycin is recommended. Quinine treatment should continue for 7 days for infections acquired in Southeast Asia and for 3 days for infections acquired elsewhere; clindamycin treatment should continue for 7 days regardless of where the infection was acquired. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. vivax* infection, prompt treatment with artemether-lumefantrine (second and third trimesters) or mefloquine (all trimesters) is recommended.

Doxycycline and tetracycline are generally not indicated for use in pregnant women. However, in rare instances, doxycycline or tetracycline can be used in combination with quinine if other treatment options are not available or are not being tolerated, and the benefit of adding doxycycline or tetracycline is judged to outweigh the risks.

According to its U.S. labels, atovaquone/proguanil is not indicated for use in pregnant women because there are no adequate, well-controlled studies in pregnant women. However, for pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

For *P. vivax* or *P. ovale* infections, primaquine phosphate and tafenoquine for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* or *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300mg base (=500 mg salt) by mouth once per week. After delivery, pregnant patients with *P. vivax* or *P. ovale* infections who do not have G6PD deficiency, subsequent treatment with primaquine phosphate or tafenoquine is needed, but will depend on breastfeeding. If not breastfeeding, either drug can be used. For women who are breastfeeding infants with normal G6PD activity, primaquine phosphate can be given. Tafenoquine is not recommended during breastfeeding. Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy as described below.

### **Treatment: Severe Malaria**

Patients who are considered to have manifestations of more severe disease should be treated aggressively with parenteral antimalarial therapy regardless of the species of malaria seen on the blood smear. If severe malaria is strongly suspected but a laboratory diagnosis cannot be made at that time, blood should be collected for diagnostic testing as soon as it is available and parenteral antimalarial drugs should be started.

All patients with severe malaria, regardless of infecting species, should be treated with intravenous (IV) artesunate. Clinicians caring for patients with suspected severe malaria

should call CDC to obtain IV artesunate. The CDC Malaria Hotline (770-488-7788, or toll-free 855-856-4713) is available Monday–Friday 9am–5pm EST. Outside those hours, providers should call 770-488-7100 and ask to speak with a malaria expert.

Severe malaria can progress rapidly and must be treated as soon as possible. While timely delivery of IV artesunate is anticipated, health-care providers can consider treating the patient with an oral antimalarial while waiting for IV artesunate to arrive. Health-care providers will need to decide the most feasible route to administer the drug for patients unable to tolerate an oral antimalarial. For example, if this intolerance is due to nausea and vomiting, an anti-emetic preceding the antimalarial may help. For comatose patients, a nasogastric tube can be considered.

One of the antimalarials listed below can be administered. IV clindamycin and IV tetracyclines such as doxycycline are not recommended. These drugs are slow-acting antimalarials that would not take effect until well after 24 hours, and they are not effective antimalarials for treatment of severe malaria when used alone.

- Artemether/lumefantrine (Coartem®): 1 tablet=20 mg artemether and 120 mg lumefantrine. Give initial dose, then if still needed, follow with second dose 8 hours later.
  - 5–14 kg: 1 tablet per dose
  - 15–24 kg: 2 tablets per dose
  - 25–34 kg: 3 tablets per dose
  - ≥35 kg: 4 tablets per dose
- Atovaquone/proguanil (Malarone®): Adult (250 mg atovaquone/100 mg proguanil) and pediatric (62.5 mg atovaquone/25 mg proguanil) formulations are available.
  - Adults: 4 adult tablets as one dose
  - Children (≥5 kg only): Dosing based on weight
    - 5–8 kg: 2 peds tabs
    - 9–10 kg: 3 peds tabs
    - 11–20 kg: 1 adult tab
    - 21–30 kg: 2 adult tabs
    - 31–40 kg: 3 adult tabs
    - >40 kg: 4 adult tabs
- Quinine: Adults: 650 mg (salt) every 8 hours. Children: 10 mg (salt)/kg every 8 hours.
- Mefloquine (because of a risk of severe neuropsychiatric adverse events at treatment doses, mefloquine should only be used if atovaquone/proguanil or quinine is not available, and based on health-care provider judgement that treatment is needed prior to the arrival of IV artesunate): Adults: 750 mg salt, initially, then 500 mg salt 6–12 hours after initial dose. Children: 15 mg salt/kg, initially, then 10 mg salt/kg 6–12 hours after initial dose.

When IV artesunate arrives, discontinue the oral medication. The dosing of IV artesunate is as follows:

- Adults and children ≥20 kg: 2.4 mg/kg at 0 hour, 12 hours, and 24 hours; and 48 hours
- Children <20 kg: 3.0 mg/kg at 0 hour, 12 hours, and 24 hours; and 48 hours

After the course of IV artesunate is completed, a follow-on drug must be administered. Options include the following:

- Artemether/lumefantrine (Coartem®): 1 tablet=20 mg artemether and 120 mg lumefantrine. A 3-day treatment schedule with a total of 6 oral doses as follows: initial dose, second dose 8 hours later, then 1 dose twice a day for the following 2 days. Dosing as above.
- Atovaquone/proguanil (Malarone®): One dose daily for 3 days. Dosing as above.
- Doxycycline:
  - Adults: 100 mg twice a day for 7 days.
  - Children (8 years or older): 2 mg/kg twice a day for 7 days.
  - Children under 8 years of age or pregnant women should instead receive clindamycin 20 mg base/kg/day divided three times a day for 7 days.
- Mefloquine (because of a risk of severe neuropsychiatric adverse events at treatment doses, mefloquine should only be used if other options are not available):
  - Adults: 750 mg salt, initially, then 500 mg salt 6–12 hours after initial dose.
  - Children: 15 mg salt/kg, initially, 10 mg salt/kg 6–12 hours after initial dose.

For those patients who still cannot tolerate oral medications after completing artesunate treatment, several treatment options are available, depending on the patient's clinical and parasitological status. The most suitable course of treatment should be selected by the attending clinicians in consultation with CDC. Potential options include the following:

- Continue IV artesunate, 1 dose daily (see above for dosing) not to exceed a total course of 7 days.
- Switch to treatment with IV doxycycline (7 days) or IV clindamycin (7 days), dosing as above.

IV artesunate is safe in infants, children, and pregnant women in the second and third trimesters. There are limited clinical data on women taking IV artesunate in the first trimester of pregnancy; no harmful effects have been observed. Given that severe malaria is life threatening for pregnant women and their fetuses, and the lack of other treatment options for severe malaria in the United States, the benefits of treatment with IV artesunate outweigh the risks and IV artesunate should not be withheld. The only contraindication to IV artesunate is known allergy to IV artemisinins.

IV artesunate is well tolerated. While rare, delayed post-artemisinin hemolytic anemia has been noted in published case reports following treatment of severe malaria with IV artesunate in other non-endemic countries. Persons treated for severe malaria with IV artesunate should be monitored for up to 4 weeks after that treatment for evidence of hemolytic anemia. Persons with higher parasitemia seem to have a higher likelihood of delayed hemolytic anemia after treatment with IV artesunate. Depending on the amount of hemolysis, transfusion may be needed.

Previously, CDC recommended that exchange transfusion be considered for certain severely ill persons. However, exchange transfusion had not been proven beneficial in an adequately powered randomized controlled trial. In 2013 CDC conducted an analysis of cases of severe malaria treated with exchange transfusion and was unable to demonstrate a survival benefit of the procedure. CDC no longer recommends the use of exchange transfusion as an adjunct procedure for the treatment of severe malaria.