



TREATMENT GUIDELINES

Treatment of Malaria (Guidelines For Clinicians)

If you wish to share your clinical experience, please contact us at: nciddpdmalaria@cdc.gov

Treatment Table

The Treatment Table is available in PDF format at

www.cdc.gov/malaria/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 (www.cdc.gov/malaria/clinicians.htm#report).

Epidemiology

Malaria continues to be one of the most important and devastating infectious diseases in developing areas of the world. Worldwide, over 40% of the population lives in areas where malaria transmission occurs (i.e., parts of Africa, Asia, the Middle East, Central and South America, Hispaniola, and Oceania).¹ It is estimated that 300-500 million cases of malaria occur each year resulting in 750,000-2 million deaths.²

While malaria transmission was successfully interrupted in the United States during the late 1940s, malaria remains a constant health threat for U.S. travelers to malarious areas and immigrants arriving from malarious areas. With approximately 27 million U.S. residents traveling each year to malarious areas, it is important for clinicians to provide pre-travel advice on malaria prevention, to remain alert to the possibility of malaria in persons returning from these areas, and to treat malaria cases promptly and effectively. While the vast majority of malaria cases diagnosed in the U.S. are imported (i.e., acquired outside of the United States and its territories), congenital infections, infections through exposure to infected blood or blood products, and infections through local mosquito-borne transmission still occur.³⁻⁶

In 2002, 1,337 cases of malaria were reported in the United States.³ *Plasmodium falciparum*, the most severe and life-threatening form of the disease was identified in over 50% of the cases. Malaria cases were reported from all 50 states with New York City (202), California (197), and Maryland (101) reporting the highest number. Of the 1,337 malaria cases, 854 occurred in U.S. civilians, all but five of which were imported.³ Of the civilian patients with imported malaria, 60% did not take any chemoprophylaxis and only 20% were compliant with a chemoprophylactic regimen recommended by the Centers for Disease Control and Prevention (CDC) for the area in which they traveled. Eighty-six percent of civilian patients with imported malaria reported symptom onset after arriving back in the United States and, for patients with *P. falciparum* infections, 80% experienced symptom onset within one month after arrival back in the United States. Overall, approximately 50% of patients required hospitalization and 8 died. Risk factors for

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fatal malaria include failure to take recommended chemoprophylaxis, refusal of or delay in seeking medical care, and misdiagnosis.⁷

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 case series.⁸⁻¹² However, malaria is a common illness in areas where it is transmitted and, therefore the diagnosis of malaria should routinely be considered for anyone 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.^{7, 13} 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).

Laboratory diagnosis of malaria can be made through microscopic examination of thick and thin blood smears.³ 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. Laboratories that have limited experience may prefer to use thin smears, which can aid in parasitic species identification. 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 48-72 hours.

After the presence of malaria parasites on a blood smear is detected, 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.¹⁴

In addition to microscopy, other laboratory diagnostic tests are available. Several antigen detection tests using a "dipstick" format exist but are not yet approved for general diagnostic use in the United States. Parasite nucleic acid detection using polymerase chain reaction (PCR) are more sensitive and specific than microscopy but can be performed only in reference laboratories and should be reserved for specific instances (e.g., back up or confirmation of microscopy). 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

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

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for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory confirmation).

Once the diagnosis of malaria has been confirmed, 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, and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired. Determination of the infecting *Plasmodium* species for treatment purposes is important for three main reasons: *P. falciparum* infections can cause rapidly progressive severe illness or death while the non-falciparum (*P. vivax*, *P. ovale*, or *P. malariae*) species rarely cause severe manifestations; *P. vivax* and *P. ovale* infections require treatment for the hypnozoite forms that remain dormant in the liver and can cause a relapsing infection; and *P. falciparum* and *P. vivax* species have different drug resistance patterns in differing geographic regions. For *P. falciparum* infections, the urgent initiation of appropriate therapy is especially critical.

The second factor affecting treatment is 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 (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of > 5%) are considered to have manifestations of more severe disease and should be treated aggressively with parenteral antimalarial therapy.¹⁵

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. 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 *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 onto the 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 Monday – Friday, 8:00 am to 4:30 pm. 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 (www.cdc.gov/malaria/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 parenthesis.

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 followed by clearance).

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Treatment: Uncomplicated Malaria

***P. falciparum* or Species Not Identified**

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 should 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). For *P. falciparum* infections acquired in areas with chloroquine-resistant strains, three treatment options are available. The first two treatment options are quinine sulfate plus doxycycline, tetracycline, or clindamycin; **or** atovaquone-proguanil (Malarone). Both or these options are very efficacious. 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 third option, mefloquine, is associated with a higher rate of severe neuropsychiatric reactions when used at treatment doses. We recommend this third option only when the quinine sulfate combination or atovaquone-proguanil 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. For children less than eight years old, doxycycline and tetracycline are generally not indicated; therefore, quinine (given alone for a full 7 days regardless of where the infection was acquired or given in combination with clindamycin as recommended above) and atovaquone-proguanil are recommended treatment options for chloroquine-resistant *P. falciparum* infections; mefloquine can be considered if these options are not available. 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 should be administered (see *P. vivax* and *P. ovale*, below).

P. malariae

There has been no widespread evidence of chloroquine resistance in *P. malariae* species; therefore, chloroquine remains the drug of choice for all *P. malariae* infections.

P. vivax* and *P. ovale

Chloroquine remains the treatment of choice for all *P. vivax* and *P. ovale* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia. Reports have confirmed a high prevalence of chloroquine-resistant *P. vivax* in these two specific areas. Rare case reports 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 8am to

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4:30pm 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 two treatment regimens for chloroquine-resistant *P. vivax* infections are quinine sulfate plus doxycycline or tetracycline, **or** mefloquine. These two treatment options are equally recommended. There are no adequate, well-controlled studies to support the use of atovaquone-proguanil to treat chloroquine-resistant *P. vivax* infections.

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 a 14-day course of primaquine phosphate. CDC has recently changed its recommendations for treating hypnozoites by increasing the recommended primaquine phosphate dose to 30 mg (base) by mouth daily for 14 days. Because primaquine can cause hemolytic anemia in persons with glucose-6-phosphate-dehydrogenase (G6PD) deficiency, persons must be screened for G6PD deficiency 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) orally 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 must not be used during pregnancy.

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 adult recommended adult dose. For children less than eight years old, doxycycline and tetracycline are generally not indicated; therefore, quinine (given alone for 7 days) or mefloquine are recommended treatment options for chloroquine-resistant *P. vivax* infections. In rare instances, doxycycline or tetracycline can be used in combination with quinine in children less than 8 years old if other treatment options are not available, are not being tolerated, and the benefit of adding doxycycline or tetracycline is judged to outweigh the risk. 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. Pregnant women are three times more likely to develop severe disease than non-pregnant women acquiring infections from the same area. In addition, malaria parasites sequester and replicate in the placenta.¹⁹ 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. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, prompt treatment with 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 in Africa or South America; 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 quinine for seven days is recommended regardless of where the infection was acquired. There are no adequate, well-controlled studies to support the addition of clindamycin to quinine when treating chloroquine-resistant *P. vivax* infections.

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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. label, atovaquone/proguanil is classified as a pregnancy category C medication and is generally not indicated for use in pregnant women because there are no adequate, well-controlled studies of atovaquone and/or proguanil hydrochloride 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. There are data on the efficacy of atovaquone/proguanil in the treatment of chloroquine-resistant *P. vivax* infections.

Mefloquine is also a pregnancy category C medication and is generally not indicated for treatment in pregnant women. Mefloquine has not been associated with an increased risk of congenital abnormalities; however, a possible association with mefloquine treatment during pregnancy and an increase in stillbirths has been reported.²⁰ CDC recommends mefloquine only when no other treatment options are available and if the potential benefit is judged to outweigh the potential risks.

For *P. vivax* or *P. ovale* infections, primaquine phosphate 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) orally once per week. After delivery, pregnant patients with *P. vivax* or *P. ovale* infections who do not have G6PD deficiency should be treated with primaquine. 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. Oral antimalarial drugs (such as oral quinine, chloroquine, or mefloquine) are not recommended for the initial treatment of severe malaria. If severe malaria is strongly suspected but the first blood smear does not demonstrate parasites, a trial of parenteral antimalarial drugs should be given.¹⁵ If there is clinical evidence of severe malaria but the blood smear is reported as *P. vivax*, *P. ovale* or *P. malariae*, the patient should be treated for falciparum malaria in case of a mixed infection or misdiagnosis.¹⁵

Since 1991, quinidine gluconate has been the only parenterally administered antimalarial drug available in the United States.¹⁶ It is recommended to give a loading dose of 6.25 mg base/kg (=10 mg salt/kg) of quinidine gluconate infused intravenously over 1-2 hours followed by a continuous infusion of 0.0125 mg base/kg/min (=0.02 mg salt/kg/min).¹⁷ An alternative regimen is an intravenous loading dose of 15mg base/kg (=24 mg salt/kg) of quinidine gluconate infused intravenously over 4 hours, followed by 7.5mg base/kg (=12mg/kg salt) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Quinidine levels should be maintained in the range of 3-8 mg/L.^{13, 14} At least 24 hours of quinidine gluconate infusion are recommended (or 3 intermittent doses); once the parasite density is < 1% and the patient can take oral medication, the patient can complete the treatment course with oral quinine at a dosage of 10 mg salt/kg every 8 hours (for a combined treatment course of quinidine/quinine for 7 days in Southeast Asia and 3 days in Africa and South America).¹⁴

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Initial (including loading) doses of parenteral quinine or quinidine do not need to be reduced in persons with renal failure. If renal failure persists or the patient does not improve clinically, the maintenance dosage should be reduced by one third to one half on the third treatment day.¹⁵

As with treatment of uncomplicated *P. falciparum*, quinidine/quinine therapy should be combined with doxycycline, tetracycline, or clindamycin. If the patient is unable to tolerate oral therapy, doxycycline hyclate (100mg every 12 hours) or clindamycin (5 mg base/kg every 8 hours) may be given intravenously until the patient can be switched to oral therapy. Rapid intravenous administration of doxycycline or clindamycin should be avoided. If the patient can tolerate oral therapy, doxycycline (100 mg every 12 hours), tetracycline (250mg every 6 hours), or clindamycin (20 mg base/kg/day divided three times per day) for 7 days are options.

Parenteral quinidine gluconate is cardiotoxic and should be administered in an intensive care setting with continuous cardiac and frequent blood pressure monitoring.^{15,17} At the dosages required for the treatment of falciparum malaria, quinidine gluconate may cause ventricular arrhythmia, hypotension, hypoglycemia, and prolongation of the QTc interval.¹⁶ The quinidine gluconate infusion should be slowed or stopped for an increase in the QRS complex by > 50%, a QTc interval > 0.6 seconds, a QTc interval that is prolonged by more than 25% of the baseline value, or hypotension unresponsive to fluid challenge.^{14,15} Because most deaths from severe malaria occur within the first 24-48 hours, the goal of a loading dose is to quickly reach therapeutic concentrations at a time when they are needed most. Recent use of other drugs that may prolong the QTc interval (e.g., quinine or mefloquine) should be considered when determining whether a patient should receive a loading dose of quinidine gluconate.¹⁶ Because there is less collected experience on which to base decisions with quinidine gluconate, recommendations for administration of a loading dose are based on experience with loading doses of quinine. A loading dose of quinidine gluconate should be given unless the patient has received more than 40 mg/kg quinine in the previous 2 days or has received mefloquine in the previous 12 hours.¹⁵ Consulting a cardiologist and a physician with experience in treating malaria is advised when treating malaria patients in the United States with quinidine gluconate. 16 Glucose must be monitored closely as quinidine- (or quinine-) induced hyperinsulinemic hypoglycemia can occur.¹⁷

With the advent of newer anti-arrhythmic agents, quinidine gluconate has been dropped from many hospital formularies and fewer clinicians have experience with the drug. To ensure the availability of quinidine gluconate in U.S. health care facilities, hospital drug services need to maintain or add quinidine gluconate to formularies. If quinidine is not available on the hospital formulary, the hospital should be able to immediately locate a nearby health care facility that stocks it. If a local source cannot be found, quinidine gluconate should be requested from the local or regional distributor. In the event that quinidine gluconate is needed acutely and is not available by the aforementioned routes, pharmacists and clinicians should contact Eli Lilly Company directly; telephone 1-800-821-0538 if calling between the hours of 7:30 am and 4:15 pm EST or 317-276-2000 (Lilly Security Station) after hours, weekends and holidays, to arrange a rapid shipment of the drug. If further assistance is needed in obtaining quinidine gluconate or in managing patients with malaria, health care professionals can contact CDC's malaria hotline (770-488-7788 Monday-Friday 8am to 4:30pm EST; 770-488-7100 after hours, weekends and holidays and ask to have the malaria clinician on-call paged.)

While exchange transfusion has not been proven beneficial in an adequately powered randomized controlled trial, it has been an option in the treatment of severe malaria since 1974.¹⁵ CDC recommends that exchange transfusion be strongly considered for persons with a parasite density of more than 10% or if complications such as cerebral malaria, non-volume overload pulmonary edema, or renal complications exist.¹⁴ Exchange transfusion is thought to have beneficial effects by removing infected red cells,

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improving the rheological properties of blood, and reducing toxic factors such as parasite derived toxins, harmful metabolites, and cytokines.¹⁸ The risks of exchange transfusion include fluid overload, febrile and allergic reactions, metabolic disturbances (e.g., hypocalcemia), red blood cell alloantibody sensitization, transmissible infection, and line sepsis. Thus, the potential benefits of exchange transfusion should be weighed against the risks. The parasite density should be monitored every 12 hours until it falls below 1%, which usually requires the exchange of 8-10 units of blood in adults.¹⁴ The technical aspects of exchange transfusion have been discussed in a review by Powell and Grima.¹⁸

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For more information, visit www.cdc.gov/malaria