TREATMENT GUIDELINES

Treatment of Malaria (Guidelines For Clinicians)

If you wish to share your clinical experience, please contact us at: malaria@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 (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 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

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 (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 $\geq$ 5%) are considered to have manifestations of more severe disease and should be treated aggressively with parenteral antimalarial therapy.

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 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 (or toll free 855-856-4713) Monday – Friday, 9:00 am to 5:00 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 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 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) po given initially, followed by 310 mg base (=400 mg salt) po 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 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 8am to 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 three treatment regimens for chloroquine-resistant *P. vivax* infections are quinine sulfate plus doxycycline or tetracycline, **or**, Atovaquone-proguanil, **or** mefloquine. These three treatment options are equally recommended.

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 recommends a primaquine phosphate dose of 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 8 years old, doxycycline and tetracycline are generally not indicated; therefore, for chloroquine-resistant *P. vivax,* mefloquine is the recommended treatment. If it 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 pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, prompt treatment with either 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 mefloquine 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 and artemether-lumefantrine are classified as a pregnancy category C medications and are generally 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 or artemether-lumefantrine 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 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 regardless of the species of malaria seen on the blood smear. Oral antimalarial drugs are not recommended for the initial treatment of severe malaria. 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 may be started.

Since 1991, quinidine gluconate has been the only parenterally administered antimalarial drug available in the United States. 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). 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). At least 24 hours of quinidine gluconate infusion (or 3 intermittent doses) are recommended; once the parasite density is < 1% and the patient can take oral medication, the patient can complete the treatment course with an oral regimen such as oral quinine at the same dosage for uncomplicated malaria (for a combined treatment course of quinidine/quinine for 7 days for malaria acquired in Southeast Asia and 3 days for malaria acquired elsewhere). Other oral regimens such as atovaquone-proguanil or artemether-lumefantrine may be used instead of an oral quinine based regimen.

Initial (including loading) doses of parenteral 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.

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 (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 so a baseline EKG should be obtained before initiating therapy. Quinidine should be administered in an intensive care setting with continuous cardiac and frequent blood pressure monitoring. At the dosages required for the treatment of falciparum malaria, quinidine gluconate may cause ventricular arrhythmia, hypotension, hypoglycemia, and prolongation of the QTc interval. 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. 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. Because there is less evidence 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. Consulting a cardiologist and a physician with experience in treating malaria is advised when treating malaria patients in the United States with quinidine gluconate. Glucose must be monitored closely as quinidine- (or quinine-) induced hyperinsulinemic hypoglycemia can occur.

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 in U.S. health care facilities, hospital drug services need to maintain or add quinidine gluconate injection to formularies. If quinidine gluconate injection 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 or the Eli Lilly Company directly by telephone (1-800-821-0538).

If quinidine is unavailable, or in patients with adverse effects or contraindications to quinidine, or in patients with a parasitemia >10% of baseline at 48 hours after initiation of IV quinidine, parenteral artesunate is available as an investigational new drug through CDC. If both quinidine and artesunate can be obtained in similar time frames the treating physician may choose either option. To obtain artesunate for the treatment of severe malaria or for assistance in diagnosing or managing patients with malaria, health care professionals can contact CDC's malaria hotline (770-488-7788, or toll-free 855-856-4713 Monday-Friday 9am to 5pm 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. 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, acute respiratory distress syndrome, or renal complications exist. Exchange transfusion is thought to have beneficial effects by removing infected red cells, improving the rheological properties of blood, and reducing toxic factors such as parasite-derived toxins, harmful metabolites, and cytokines. 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.