Guidelines for Treatment of Malaria in the United States

(Based on drugs currently available for use in the United States – updated May 18, 2009)

CDC Malaria Hotline: (770) 488-7788 Monday-Friday 8 am to 4:30 pm EST – (770) 488-7100 after hours, weekends and holidays

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/ ***P. falciparum*** or Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P ovale:* see *P. vivax* and *P ovale* (below) re. treatment with primaquine	**Chloroquine-resistant or unknown resistance**[1] (All malarious regions except those specified as chloroquine-sensitive listed in the box below. Middle Eastern countries with chloroquine-resistant *P. falciparum* include Iran, Oman, Saudi Arabia, and Yemen. Of note, infections acquired in the Newly Independent States of the former Soviet Union and Korea to date have been uniformly caused by *P. vivax* and should therefore be treated as chloroquine-sensitive infections.)	**A. Atovaquone-proguanil (Malarone™)**[2] **Adult tab = 250 mg atovaquone/ 100 mg proguanil** 4 adult tabs po qd x 3 days	**A. Atovaquone-proguanil (Malarone™)**[2] **Adult tab = 250 mg atovaquone/ 100 mg proguanil** **Peds tab = 62.5 mg atovaquone/ 25 mg proguanil** 5 - 8kg: 2 peds tabs po qd x 3 d 9-10kg: 3 peds tabs po qd x 3 d 11-20kg: 1adult tab po qd x 3 d 21-30kg: 2 adult tabs po qd x 3d 31-40kg: 3 adult tabs po qd x 3d > 40 kg: 4 adult tabs po qd x 3d
		B. Artemether-lumefantrine (Coartem™)[2] **1 tablet = 20mg artemether and 120 mg lumefantrine** A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose po bid for the following 2 days. 5 - <15 kg: 1 tablet per dose 15 - <25 kg: 2 tablets per dose 25 - <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin **Quinine sulfate:** 542 mg base (=650 mg salt)[3] po tid x 3 or 7 days[4] **Doxycycline:** 100 mg po bid x 7 days **Tetracycline:** 250 mg po qid x 7 days **Clindamycin:** 20 mg base/kg/day po divided tid x 7 days	**C. Quinine sulfate**[3] **plus one of the following: Doxycycline**[5]**, Tetracycline**[5] **or Clindamycin** **Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days[4] **Doxycycline:** 2.2 mg/kg po every 12 hours x 7 days **Tetracycline:** 25 mg/kg/day po divided qid x 7 days **Clindamycin:** 20 mg base/kg/day po divided tid x 7 days
		D. Mefloquine (Lariam™ and generics)[6] 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6-12 hours after initial dose Total dose= 1,250 mg salt	**D. Mefloquine (Lariam™ and generics)**[6] 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6-12 hours after initial dose. Total dose= 25 mg salt/kg

[1] NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[2] Take with with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose.

[3] US manufactured quinine sulfate capsule is in a 324mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine.

[4] For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[5] Doxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with 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.

[6] Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.

[7] Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg 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.

[8] NOTE: There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax.* High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. 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 outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

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Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose	Recommended Drug and Pediatric Dose *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/ *P. falciparum* or ***Species not identified***	**Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	**Chloroquine phosphate (Aralen™ and generics)** 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours Total dose: 1,500 mg base (=2,500 mg salt) **OR** **Hydroxychloroquine (Plaquenil™ and generics)** 620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours Total dose: 1,550 mg base (=2,000 mg salt)	**Chloroquine phosphate (Aralen™ and generics)** 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg **OR** **Hydroxychloroquine (Plaquenil™ and generics)** 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg
Uncomplicated malaria/ *P. malariae or P. knowlesi*	**All regions**	**Chloroquine phosphate:** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	**Chloroquine phosphate:** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above
Uncomplicated malaria/ *P. vivax* or ***P. ovale***	**All regions** Note: for suspected chloroquine-resistant *P. vivax,* see row below	**Chloroquine phosphate plus Primaquine phosphate[7]** **Chloroquine phosphate:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate[7]** **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days	**Chloroquine phosphate plus Primaquine phosphate[7]** **Chloroquine phosphate:** Treatment as above **Primaquine:** 0.5mg base/kg po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate[7]** **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 0.5mg base/kg po qd x 14 days
Uncomplicated malaria/ *P. vivax*	**Chloroquine-resistant[8]** (Papua New Guinea and Indonesia)	**A. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate[7]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above	**A. Quinine sulfate plus either Doxycycline[5] or Tetracycline[5] plus Primaquine phosphate[7]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above
		B. Atovaquone-proguanil plus Primaquine phosphate **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above	**B. Atovaquone-proguanil plus Primaquine phosphate** **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above
		C. Mefloquine plus Primaquine phosphate[7] **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above	**C. Mefloquine plus Primaquine phosphate[7]** **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above
Uncomplicated malaria: alternatives for pregnant women[9,10,11,12]	**Chloroquine-sensitive** (see uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	Not applicable
	Chloroquine resistant *P. falciparum*[1] (see sections above for regions with chloroquine resistant ***P. falciparum*****)**	**Quinine sulfate plus Clindamycin** **Quinine sulfate:** Treatment as above **Clindamycin:** Treatment as above	Not applicable
	Chloroquine-resistant *P. vivax* (see uncomplicated malaria sections above for regions with chloroquine-resistant ***P. vivax*****)**	**Quinine sulfate** **Quinine sulfate:** 650 mg[3] salt po tid x 7 days	Not applicable

[9] For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[10] Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. 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.

[11] Because of a possible association with mefloquine treatment during pregnancy and an increase in stillbirths, mefloquine is generally not recommended for treatment in pregnant women. However, mefloquine may be used if it is the only treatment option available and if the potential benefit is judged to outweigh the potential risks.

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Severe malaria[13,14,15,16]	**All regions**	**Quinidine gluconate[14] plus one of the following: Doxycycline, Tetracycline, or Clindamycin** **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America. **Doxycycline:** Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hours and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by one of the following: Atovaquone-proguanil (Malarone™), Doxycycline (Clindamycin in pregnant women), or Mefloquine**	**Quinidine gluconate[14] plus one of the following: Doxycycline[4], Tetracycline[4], or Clindamycin** **Quinidine gluconate:** Same mg/kg dosing and recommendations as for adults. **Doxycycline:** Treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hours and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by one of the following: Atovaquone-proguanil (Malarone™), Clindamycin, or Mefloquine**

[12] For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

[13] Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology 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. Severe malaria is most often caused by *P. falciparum*.

[14] Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

[15] Consider exchange transfusion if the parasite density (i.e. parasitemia) is > 10% OR if the patient has altered mental status, non-volume overload pulmonary edema, or renal complications. The parasite density can be estimated by examining a monolayer of red blood cells (RBCs) on the thin smear under oil immersion magnification. 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 and should be monitored every 12 hours. Exchange transfusion should be continued until the parasite density is <1% (usually requires 8-10 units). IV quinidine administration should not be delayed for an exchange transfusion and can be given concurrently throughout the exchange transfusion.

[16] Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.