Guidelines for Treatment of Malaria in the United States

(Based on drugs currently available for use in the United States – April 1, 2019)

CDC Malaria Hotline: (770) 488-7788 or (855) 856-4713 (toll-free) Monday–Friday 9am–5pm EST - (770) 488-7100 after hours, weekends, and holidays

<table>
<tr><th>Clinical Diagnosis/
Plasmodium species</th><th>Region Infection Acquired</th><th>Recommended Drug and Adult Dose[1]</th><th>Recommended Drug and Pediatric Dose[1]
Pediatric dose should NEVER exceed adult dose</th></tr>
<tr><td rowspan="4">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 or tafenoquine</td><td rowspan="4">Chloroquine-resistant or unknown resistance[2]
(All malarious regions except those specified as chloroquine-sensitive listed in the box below.)</td><td>A. Atovaquone-proguanil (Malarone™)[3,4]
Adult tab = 250 mg atovaquone/ 100 mg proguanil
4 adult tabs po qd x 3 days</td><td>A. Atovaquone-proguanil (Malarone™)[3,4]
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</td></tr>
<tr><td colspan="2">B. Artemether-lumefantrine (Coartem™)[3,5]
1 tablet = 20mg artemether/ 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</td></tr>
<tr><td>C. Quinine sulfate[6] plus one of the following: Doxycycline[7], Tetracycline[7], or Clindamycin
Quinine sulfate: 542 mg base (=650 mg salt) po tid x 3 or 7 days[8]
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</td><td>C. Quinine sulfate[6] plus one of the following: Doxycycline[7], Tetracycline[7] or Clindamycin
Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days[8]
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</td></tr>
<tr><td>D. Mefloquine[9]
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</td><td>D. Mefloquine[9]
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</td></tr>
</table>

[1] If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead.

[2] 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.

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

[4] Not recommended in pregnancy or in infants weighing < 5kg. However, 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.

[5] Can be used in second and third trimesters of pregnancy. Can be used in first trimester of pregnancy if no other drug options are available. Not recommended in infants weighing <5 kg.

[6] 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.

[7] Not recommended in pregnancy or in children <8 years old. 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.

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

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

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Uncomplicated malaria/ ***P. falciparum*** or ***Species not identified***	**Chloroquine-sensitive**[10] (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**[10]	**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**[10] Note: for suspected chloroquine-resistant *P. vivax*, see row below	**Chloroquine phosphate plus either Primaquine phosphate or Tafenoquine (Krintafel™)**[11,12] **Chloroquine phosphate:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days **Tafenoquine:** 300 mg po x 1 dose **OR** **Hydroxychloroquine plus Primaquine phosphate**[11,12] **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days **Tafenoquine:** 300 mg po x 1 dose	**Chloroquine phosphate plus Primaquine phosphate**[11,12] **Chloroquine phosphate:** Treatment as above **Primaquine phosphate:** 0.5mg base/kg po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate**[11,12] **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 0.5mg base/kg po qd x 14 days **Tafenoquine (Krintafel™)**[11,12] can be used instead of primaquine in children 16 years and older: 300 mg po x 1 dose
Uncomplicated malaria/ ***P. vivax***	**Chloroquine-resistant**[13] (Papua New Guinea and Indonesia)	**A. Quinine sulfate plus either Doxycycline**[7] **or Tetracycline**[7] **plus either Primaquine phosphate or Tafenoquine (Krintafel™)**[11,12] **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate or Tafenoquine:** Treatment as above	**A. Quinine sulfate plus either Doxycycline**[7] **or Tetracycline**[7] **plus Primaquine phosphate**[11,12] **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above **Tafenoquine (Krintafel™)**[11,12] can be used instead of primaquine in children 16 years and older: 300 mg po x 1 dose
		B. Atovaquone-proguanil plus either Primaquine phosphate or Tafenoquine (Krintafel™)[11,12] **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate or Tafenoquine:** Treatment as above	**B. Atovaquone-proguanil plus Primaquine phosphate**[11,12] **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above **Tafenoquine (Krintafel™)**[11,12] can be used instead of primaquine in children 16 years and older: 300 mg po x 1 dose
		C. Mefloquine plus either Primaquine phosphate or Tafenoquine (Krintafel™)[11,12] **Mefloquine:** Treatment as above **Primaquine phosphate or Tafenoquine:** Treatment as above	**C. Mefloquine plus Primaquine phosphate**[11,12] **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above **Tafenoquine (Krintafel™)**[11,12] can be used instead of primaquine in children 16 years and older: 300 mg po x 1 dose
Uncomplicated malaria: alternatives for pregnant women[12]	**Chloroquine-sensitive** (see sections above for regions with chloroquine-sensitive malaria species)	**Chloroquine phosphate:** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	Not applicable

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	Chloroquine-resistant (see sections above for regions with chloroquine resistant malaria species**)**	**Artemether-lumefantrine (Coartem™)[3,5]:** Treatment as above if in second or third trimesters **OR for all trimesters: Quinine sulfate plus Clindamycin:** Treatment as above **OR Mefloquine:** Treatment as above	Not applicable

[10] When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available. Note that if treating P vivax or P. ovale infections, primaquine or tafenoquine (after quantitative testing to rule out G6PD deficiency) should also be given.

[11] Primaquine and tafenoquine kill any dormant hypnozoites in the liver, thus prevent relapses of *P. vivax* and *P. ovale* infections. Because primaquine and tafenoquine can cause hemolytic anemia in G6PD-deficient persons, **quantitative G6PD testing** must occur prior to starting treatment with these drugs. For persons with borderline G6PD deficiency, 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.

[12] Primaquine and tafenoquine must not be used 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 or tafenoquine. Primaquine can be used during breastfeeding if the infant is found to have normal G6PD levels. Tafenoquine is not recommended in breastfeeding women.

[13] 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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Severe malaria [14,15,16]	**All regions**	**Intravenous (IV) Artesunate** ***available under an expanded access investigational new drug (IND) protocol (Call CDC):*** Give 2.4 mg/kg per dose. Administer one dose at 0, 12, 24, and 48 hours for a total of four doses. **AND** **Follow artesunate by one of the following: Artemether-lumefantrine (Coartem™), Atovaquone-proguanil (Malarone™), Doxycycline (Clindamycin in pregnant women), or if no other options, Mefloquine** **Artemether-lumefantrine (Coartem™):** Treatment as above. **Atovaquone-proguanil (Malarone):** Treatment as above. **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. **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. **If needed, give interim treatment until IV artesunate arrives (if oral medications are not tolerated, consider administration via nasogastric tube or after an antiemetic):** **Artemether-lumefantrine (Coartem™):** Treatment as above. **Atovaquone-proguanil (Malarone™)** Treatment as above. **Quinine sulfate** Dosing as above. **Mefloquine** Use if other options are not available. Dosing as above.	**IV Artesunate** ***available under an expanded IND protocol (Call CDC)*** For children ≥20kg: Give 2.4 mg/kg per dose. Administer one dose at 0, 12, 24, and 48 hours for a total of four doses. For children <20kg: Give 3.0 mg/kg per dose. Administer one dose at 0, 12, 24, and 48 hours for a total of four doses. **AND** **Follow artesunate by one of the following: Artemether-lumefantrine (Coartem™), Atovaquone-proguanil (Malarone™), Doxycycline (Clindamycin in children <8 years old), or if no other options, Mefloquine** **Artemether-lumefantrine (Coartem™):** Treatment as above. **Atovaquone-proguanil (Malarone):** Treatment as above. **Doxycycline (children ≥\8 years old):** 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. **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. **If needed, give interim treatment until IV artesunate arrives (if oral medications are not tolerated, consider administration via nasogastric tube or after an antiemetic :** **Artemether-lumefantrine (Coartem™):** Treatment as above. **Atovaquone-proguanil (Malarone™)** Treatment as above. **Quinine sulfate** Dosing as above. **Mefloquine** Use if other options are not available. Dosing as above.

[14] 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. The parasite density can be estimated from the percentage of infected RBCs by examining the thin smear slide under oil immersion magnification where the RBCs are more or less touching (approximately 400 RBCs per field), and should be monitored every 12 hours. Severe malaria is most often caused by *P. falciparum.*

[15] All patients with severe malaria should be treated with IV artesunate. Call CDC for IV artesunate.

[16] Exchange transfusion is no longer recommended based on a systematic review of the literature and analysis of US malaria surveillance data showing no added benefit in severe malaria.