TREATMENT OF MALARIA


A. GENERAL PRINCIPLES OF MANAGEMENT
Management of malaria depends on several factors. There are three main questions which must be addressed before initiating treatment.

1. Is this infection caused by Plasmodium falciparum?
   This is critical as treatment varies according to the species of malaria. *P. falciparum* can cause life-threatening disease in non-immune persons, and should be considered a medical emergency.

2. Is this a severe or complicated infection?
   **Severe *P. falciparum* malaria is a medical emergency, and the Infectious Disease Service should be consulted immediately** This can be determined using the criteria listed below. Severe or complicated malaria, regardless of causative species, requires parenteral therapy and sometimes an exchange transfusion. While the overwhelming majority of severe infections are caused by *P. falciparum*, in rare instances, *P. vivax* can also cause severe disease, characterized by the clinical manifestations below. In addition, *P. knowlesi*, a simian malaria parasite, has emerged from countries of Southeast Asia including Thailand, Myanmar, Malaysia, the Philippines, and Singapore, and like *P. falciparum*, can cause a severe and fatal infection.

   **Criteria for Severe falciparum Malaria:**
   Asexual forms of *Plasmodium falciparum* on blood smear or compatible history plus
   Any one or more of the following features:
   - Impaired consciousness or unrousable coma with GCS <10
   - Prostration with extreme weakness
   - Severe normocytic anemia (hemoglobin <50 g/L)
   - Acute renal failure with urine output <400 mL/24 hours and serum creatinine >265 micromol/L
   - Pulmonary edema or acute respiratory distress syndrome
   - Hypoglycemia (plasma glucose <2.2 mmol/L)
   - Shock with systolic blood pressure <80 mmHg
   - Spontaneous bleeding/disseminated intravascular coagulation
   - Repeated generalized convulsions (>2 within 24 hours)
   - Acidemia/acidosis (arterial pH <7.25 or plasma bicarbonates <15 mmol/L or venous lactate >15 mmol/L)
   - Macroscopic hemoglobinuria not associated with oxidant drugs and RBC enzyme defects
   - Jaundice detected clinically or total serum bilirubin >50 micromol/L
   - Parasitemia of >5% in non-immune individuals

3. Is the organism likely to be drug resistant?
   Therapy will have to be modified accordingly. In most areas in the world where malaria is transmitted it is caused by drug resistant parasites. When in doubt treat all falciparum malaria as drug resistant. For more information on malaria risk by geographic areas please refer to the Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers 2004, Appendix I: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/04vol30/30s1/appendix1_e.html
**MALARIA (cont'd)**

### Quick Reference to Global Distribution of Drug Resistant *Plasmodium* spp.

<table>
<thead>
<tr>
<th>Chloroquine-resistant <em>P. falciparum</em></th>
<th>Multi-drug resistant <em>P. falciparum</em></th>
<th>Chloroquine-resistant <em>P. vivax</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine-resistant <em>P. falciparum</em> is found in ALL malarious areas EXCEPT in the Americas North of the Panama canal (Mexico, Hispaniola, other Central American countries) parts of the Middle East and central China</td>
<td>Multi-drug resistant (chloroquine, sulfadoxine-pyrimethamine, mefloquine) <em>P. falciparum</em> is found in Southeast Asia along the Thai borders with Myanmar (Burma) and Cambodia, focally in Vietnam, and in parts of the Amazon basin</td>
<td>Chloroquine-resistant <em>P. vivax</em> is found primarily in Papua New Guinea, Irian Jaya, Indonesia, Myanmar, Korea, the Solomon Islands. It is less problematic in countries of South America including Colombia, Brazil, Guyana, and Peru.</td>
</tr>
</tbody>
</table>

### B. MANAGEMENT OF FALCIPARUM MALARIA (AND SEVERE NON-FALCIPARUM MALARIA)

**Severe *P. falciparum* malaria is a medical emergency, and the Infectious Disease Service should be consulted immediately**

A detailed geographic history is essential to the management of malaria. *P. falciparum* malaria acquired in areas where drug resistance is known to occur should be treated as chloroquine-resistant infections. **Severe *P. falciparum* infections may have a mortality rate of 30% or higher.** These patients require immediate hospitalization and urgent intensive medical management. As a general rule, all non-immune patients with *P. falciparum* malaria, whether severe or not, should be considered for admission to hospital in order to ensure tolerance of antimalarials and to detect complications and early treatment failure.

All patients with severe infections, regardless of causative species, (including those who are pregnant in the second and third trimester), and all patients unable to tolerate oral drugs, should receive **intravenous artesunate**, which is the WHO treatment of choice for complicated malaria. Artesunate is an artemisinin derivative that results in a more rapid parasite clearance, significant reduction in mortality and hypoglycemia and is better tolerated and easier to administer than quinine injection. Pregnant women in the first trimester with severe malaria infections should receive **intravenous quinine**. If IV quinine is not readily available, the benefit of artesunate in the first trimester outweighs the risk of inadequate treatment of severe malaria in both mother and fetus. Intravenous artesunate and quinine (quinine dihydrochloride) are "Special Access" drugs in Canada, but are available at the University Health Network. During daytime hours, IV artesunate and quinine are available through the inpatient Central Pharmacy (14-3467). After hours, the on-call pharmacist should be paged to release the drug of choice from a locked depot in the Emergency Room of Toronto General Hospital.

**Falciparum malaria in pregnancy**

*P. falciparum* infection in pregnancy is associated with increased risk of severe malaria and its associated complications, particularly pulmonary edema and hypoglycaemia, as well as low birth weight, adverse fetal outcome, increased maternal anemia. Administration of appropriate antimalarial therapy should not be delayed. In the case of severe malaria in pregnancy, consultation from Infectious Disease, Tropical Diseases, and Obstetrics Services should be sought immediately.
CHEMOTHERAPY FOR SEVERE MALARIA (usually caused by *P. falciparum*)

Artesunate

*Dosing:* Artesunate 2.4 mg/kg per dose IV at 0, 12, 24, and 48 hours (total dose 9.6 mg/kg). Each dose should be administered IV push over 1-2 minutes into an established IV line. The drug is reconstituted in phosphate buffer (supplied with the drug) according to the instructions supplied. Artesunate may be mixed with 5 mL of 5% dextrose or normal saline prior to injection if desired. First dose should be administered STAT. *Once reconstituted, administer artesunate within one hour of preparation.*

*If available* a 0.8 micron hydrophilic polyethersulfone syringe filter (e.g., PharmAssure®, Supor membrane) should be used to inject the drug. The filter is inserted between the syringe and the needle.

If a suitable syringe filter is not available, do **not** delay in administering any dose of artesunate. An in-line filter is preferred but is **not** mandatory.

*Note:* Dosing is weight based; there is no maximum dose. Dose obese and pediatric patients based on actual body weight. Patients should be observed for 30 minutes following administration for signs of an allergic reaction. Dose adjustment of artesunate is not required in renal or liver dysfunction.

*plus one of the following follow-on oral agents* (to start 4-hours after last dose of IV artesunate)†:

**Malarone™ (atovaquone 250mg/proguanil 100mg) with food (preferred agent unless patient received Malarone prophylaxis, is pregnant, or has CrCl<30ml/min)**

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>4 tablets daily x 3 days</strong></td>
<td><strong>5-8 kg:</strong> 2 pediatric* tablets daily x 3 days&lt;br&gt;<strong>9-10 kg:</strong> 3 pediatric tablets daily x 3 days&lt;br&gt;<strong>11-20 kg:</strong> 1 adult tablet daily x 3 days&lt;br&gt;<strong>21-30 kg:</strong> 2 adult tablets daily x 3 days&lt;br&gt;<strong>31-40 kg:</strong> 3 adult tablets daily x 3 days</td>
</tr>
<tr>
<td></td>
<td><strong>100 mg PO bid for 7 days</strong></td>
<td><strong>2 mg/kg (to a maximum of 100 mg) bid for 7 days</strong></td>
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</tbody>
</table>

*1 pediatric tablet contains 62.5 mg atovaquone + 25 mg proguanil

*or*

**Doxycycline**

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<td></td>
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</tr>
</tbody>
</table>

*Note:* Contraindicated if age <8 years or in pregnancy.

*or*

**Clindamycin**

Only use if patient is unable to take Malarone or doxycycline or if patient is pregnant.

| Dose | 20 mg/kg/day orally, **divided** TID or QID for 7 days |

†In the rare case of a patient who is unable to tolerate oral medications following 4 doses of artesunate, artesunate can be continued daily for 7 days total, or the patient can receive a 7-day course of IV doxycycline (100 mg q12h or 2mg/kg q12h [max 100 mg] for pediatric patients) OR a 7-day course of IV clindamycin (10 mg/kg loading dose, followed by 5 mg/kg IV q8h).
MALARIA (cont'd)

CHEMOTHERAPY for SEVERE MALARIA IN FIRST TRIMESTER OF PREGNANCY OR IF OTHER CONTRAINDICATIONS TO ARTESUNATE EXISTS:

Quinine

Loading Dose:

Without an infusion pump:
quinine (base) 16.7 mg/kg [quinine dihydrochloride (salt) 20 mg/kg]
diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours
followed immediately by a maintenance dose.

If an infusion pump is available:
quinine (base) 5.8 mg/kg [quinine dihydrochloride (salt) 7 mg/kg] intravenously by infusion pump over 30 minutes followed immediately by a maintenance dose.

Note: Loading dose should not be used if patient received quinine, quinidine or mefloquine within the preceding 12 to 24 hours.

Maintenance Dose: quinine (base) 8.3 mg/kg [quinine dihydrochloride (salt) 10 mg/kg]
diluted in 10 mL/kg of isotonic fluid by intravenous infusion over 4 hours, every 8 hours. 7-days total of quinine therapy is recommended for P. falciparum infections acquired in Southeast Asia. 3-day quinine therapy is recommended for all other regions of acquisition (Africa, Latin America, etc.). In patients requiring more than 48 hours of parenteral therapy, reduce the quinine maintenance dose by one-third to one-half.

As soon as the patient is able to swallow, step down to a 3-day course of:

Malarone™ (dosing as above). Malarone™ is the preferred oral agent unless the patient received Malarone™ prophylaxis, is pregnant, or has a CrCl of less than 30 mL/min.

or oral quinine tablets (2 tablets tid; 300 mg salt/tablet) PLUS a second agent as below (doxycycline or clindamycin) to complete 3-7 days of quinine therapy and 7-days of doxycycline or clindamycin.

plus a second agent (to begin concurrently with IV quinine or immediately after):

Doxycycline

Adult Dose: 100 mg PO* q12h for 7 days

Pediatric Dose: 2 mg/kg (to a maximum of 100 mg) q12h/bid for 7 days

Note: Contraindicated if age <8 years or in pregnancy.

* The IV formulation of doxycycline is no longer available on the Canadian market. It is available through the Health Canada Special Access Program only.
or
Clindamycin (to be used in pregnancy)

*Dose:* 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of asexual parasites or oral therapy is tolerated (300 mg base PO q6h [20 mg/kg/day orally divided tid-qid] to complete a 7-day course)

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**CHEMOTHERAPY FOR UNCOMPPLICATED *P. falciparum***

Uncomplicated *P. falciparum* infections unequivocally acquired in a chloroquine-sensitive zone may be treated with chloroquine alone. Those infections that were possibly or definitely acquired in drug-resistant zones should be treated with Malarone™ (atovaquone/proguanil) **alone** or quinine **plus** a second drug. If the patient can tolerate oral quinine, then it and the second drug – either doxycycline or clindamycin - may be administered simultaneously or sequentially (start quinine first) orally. If the patient cannot tolerate oral therapy then administer the drugs parenterally.

**N.B.** When quinine is administered to a patient who has taken mefloquine or halofantrine in the previous 2 weeks, there is a risk of drug-induced cardiac arrhythmia; if possible, such patients should be monitored electrocardiographically.

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**CHLOROQUINE-SENSITIVE:**

Chloroquine Phosphate (Aralen®) 150 mg base/tablet

*Adult Dose:* 1.5 g base (10 tablets) over 3 days

*Note:* This is usually given as 2 tablets bid on days 1 and 2, and 2 tablets once on day 3.

**Chloroquine is safe in all trimesters of pregnancy; dose as above**

*Pediatric Dose:* 25 mg base/kg total over 3 days

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**CHLOROQUINE-RESISTANT:**

Malarone™ (atovaquone 250mg/proguanil 100mg) **with food**

*Adult Dose:* 4 tablets daily x 3 days

*Pediatric Dose:* 5-8 kg: 2 pediatric* tablets daily x 3 days

9-10 kg: 3 pediatric tablets daily x 3 days

11-20 kg: 1 adult tablet daily x 3 days

21-30 kg: 2 adult tablets daily x 3 days

31-40 kg: 3 adult tablets daily x 3 days

*1 pediatric tablet contains 62.5 mg atovaquone + 25 mg proguanil

*Or*

Quinine Sulfate 250 mg base/300 mg salt/tablet

*Adult Dose:* 2 tablets tid for 3-7 days (7 days if acquired in Southeast Asia)

*Pediatric Dose:* 7.5 mg base/kg (maximum 500 mg base) tid for 7 days

**plus one of** (either concurrently with quinine or immediately after)

Doxycycline

*Adult Dose:* 100 mg PO bid for 7 days;
MALARIA (cont’d)

Pediatric Dose: 2 mg/kg (to a maximum of 100 mg) tid for 7 days

Note: Contraindicated if age <8 years or in pregnancy.

or

Clindamycin

Only use if patient is unable to take Doxycycline or if patient is pregnant.

Adult Dose: 300 mg base PO q6h for 7 days

Pediatric Dose: 5 mg/kg tid for 7 days

Or (subject to future availability through the special access programme)

Co-artemether (artemether 20mg/lumefantrine 120mg) with food

The fixed dose combination of artemether (20 mg) and lumefantrine (120 mg) (Co-artemether; Coartem®) is recommended by several national and international health authorities (including the WHO) for treatment of uncomplicated malaria. Co-artemether is effective against multi-drug resistant P. falciparum and results in rapid parasite clearance and symptom resolution. Co-artemether has been recently licensed by the U.S. FDA for treatment of uncomplicated P. falciparum malaria, and may become available in Canada via the special access program in the future. The adult dosage consists of 6 doses over 3 days, and has an excellent safety and tolerability profile. It is contraindicated during pregnancy, and needs to be taken with food as lumefantrine absorption is enhanced by co-administration of fat.

Adult Dose: 4 tablets (80 mg / 480 mg) as a single dose, then 4 tablets again after 8 hours, then 4 tablets every 12 hours for 2 days

Pediatric Dose: 5-<15 kg: 1 tablet (20 mg / 120 mg) as a single dose, then 1 tablet again after 8 hours, then 1 tablet every 12 hours for 2 days

15-<25 kg: 2 tablets (40 mg / 240 mg) as a single dose, then 2 tablets again after 8 hours, then 2 tablets every 12 hours for 2 days

25-<35 kg: 3 tablets (60 mg / 360 mg) as a single dose, then 3 tablets again after 8 hours, then 3 tablets every 12 hours for 2 days

>35 kg: As per adult dose

CHEMOTHERAPY for UNCOMPLICATED CHLOROQUINE-RESISTANT falciparum MALARIA IN PREGNANCY:

Quinine (dosing as above to complete 3-7 days)

plus

Clindamycin (as above to complete 7 days)

C. ANCILLARY TREATMENT FOR SEVERE MALARIA

Many ancillary treatments have been suggested for the treatment of malaria but few have been shown to improve outcome. The use of steroids to treat severe or cerebral malaria has been associated with worse outcomes and should be avoided. In cases of complicated P. falciparum infection or hyperparasitemia (>5% parasitemia in non-immune individuals), exchange transfusion has been used on an experimental basis as a potential life-saving procedure. In all cases of severe malaria, please consult the Infectious Disease Service immediately by paging the on-call resident. Tropical Diseases consultation can be arranged by contacting Dr. Kevin Kain at 416-340-3535 or Dr. Jay Keystone at 416-340-3671 or 416-340-3675 (clinic number) or on his cellphone 416-606-5868 or through locating.
D. MANAGEMENT OF UNCOMPLICATED NON-*falciparum* MALARIA (including *P. knowlesi*)

Outside of New Guinea (Papua New Guinea and Irian Jaya), chloroquine remains the treatment of choice for malaria other than *falciparum*.

**Chloroquine Phosphate (Aralen®) 150 mg base/tablet**

*Adult Dose:* 1.5 g base (10 tablets) over 3 days  
*Note:* This is usually given as 2 tablets bid on days 1 and 2, and 2 tablets once on day 3.  
**Chloroquine is safe in all trimesters of pregnancy; dose as above**

*Pediatric Dose:* 25 mg base/kg total over 3 days

At present, chloroquine can no longer be relied upon for chemosuppression or treatment of *P. vivax* acquired in New Guinea. Expert advice from Tropical Diseases should be sought for the management of these cases.

E. PREVENTION OF RELAPSE OF MALARIA DUE TO *P. vivax* or *P. ovale*

*P. vivax* and *P. ovale* have a persistent liver phase that is responsible for relapses and is susceptible only to treatment with primaquine. None of the currently recommended chemosuppressive regimens will prevent relapses due to these two species of malaria. Relapses can occur weeks to months following initial infection, regardless of whether or not symptoms of malaria occurred. In order to reduce the risk of relapse following the treatment of symptomatic *P. vivax* or *P. ovale* infection, primaquine is indicated to provide “radical cure”. Primaquine should be initiated to overlap with the blood schizonticide agent (typically chloroquine) in radical cure.

Primaquine is not recommended for routine use to prevent relapsing malaria in the average asymptomatic returned traveller, however, primaquine is indicated empirically for persons who have had prolonged exposure in malarious areas (greater than 6 months) where *P. vivax* or *P. ovale* constitute a significant proportion of malaria cases (such Papua New Guinea and other parts of Oceania). This is referred to as presumptive anti-relapse therapy (PART). Administration of primaquine in a PART regimen should coincide with the last 2 weeks of chloroquine, mefloquine, or doxycycline prophylaxis or be initiated during the final week of atovaquone-proguanil prophylaxis.

Primaquine is well tolerated but may cause nausea and abdominal pain which may be diminished by taking the drug with food. More importantly, primaquine may cause oxidant-induced hemolytic anemia with methemoglobinemia, particularly in those with a deficiency of G6PD. Patients of Mediterranean, African, and Asian ethnic origin have a greater risk of hemolysis due to G6PD deficiency. These individuals, and preferably all potential users of the drug, should have their G6PD level measured before primaquine therapy is initiated. Primaquine is contraindicated in patients with moderate to severe deficiency. In mild variants of G6PD deficiency, primaquine has been used safely at a lower dose (0.8 mg base/kg/week; adult dose of 45 mg base once weekly for 8 weeks) for radical cure of *P. vivax* or *P. ovale* malaria, or as a PART regimen. Patients should be advised to stop their medication and report to a physician immediately if jaundice or abnormally dark or brown urine is noted.

**Primaquine use is contraindicated in pregnancy.** *P. vivax* or *P. ovale* infections occurring during pregnancy should be treated with standard doses of chloroquine. Relapses can be prevented by weekly chemosuppression with chloroquine until after delivery, when primaquine can be safely used in mothers.
with normal glucose 6-phosphate dehydrogenase (G6PD) levels. Expert advice from Tropical Diseases should be sought for cases of malaria in pregnancy.

**Primaquine (15 mg base/tablet) (Dosing is for standard radical cure or PART regimen)**

*Adult Dose:* 30 mg base/day for 14 days  
*Pediatric Dose:* 0.5 mg base/kg/day for 14 days

### BASE/SALT EQUIVALENTS OF SELECTED ANTIMALARIAL DRUGS

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Base</th>
<th>Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroquine phosphate</td>
<td>150 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>clindamycin hydrochloride</td>
<td>150 mg</td>
<td>225 mg</td>
</tr>
<tr>
<td>mefloquine</td>
<td>250 mg</td>
<td>274 mg</td>
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<tr>
<td></td>
<td>5 mg</td>
<td>5.5 mg</td>
</tr>
<tr>
<td>quinidine dihydrochloride</td>
<td>15 mg</td>
<td>18 mg</td>
</tr>
<tr>
<td></td>
<td>16.7 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>quinine sulfate</td>
<td>250 mg</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

*Prepared by:* Dr. Kevin Kain, Director, Centre for Travel and Tropical Medicine - December 2000  
*Reviewed and Updated by:* Dr. Jay Keystone, Centre for Travel and Tropical Medicine - December 2002; Dr. Andrea Boggild and Dr. Jay Keystone - October 2006; Dr. Andrea K. Boggild – December 2008; Dr. Andrea K. Boggild and Dr. Jay S. Keystone – June 2009