### Malaria

### Fever of unknown origin in Togo – Malaria or Typhoid until proven otherwise!

### Disease

Infection with malaria parasites may result in a wide variety of symptoms, ranging from absent or very mild symptoms to severe disease and even death. Malaria disease can be categorized as [uncomplicated](http://www.cdc.gov/malaria/about/disease.html#uncomplicated) or [severe (complicated)](http://www.cdc.gov/malaria/about/disease.html#severe). In general, malaria is a curable disease if diagnosed and treated promptly and correctly.

All the clinical symptoms associated with malaria are caused by the asexual erythrocytic or blood stage parasites. When the parasite develops in the erythrocyte, numerous known and unknown waste substances such as hemozoin pigment and other toxic factors accumulate in the infected red blood cell. These are dumped into the bloodstream when the infected cells lyse and release invasive merozoites. The hemozoin and other toxic factors such as glucose phosphate isomerase (GPI) stimulate macrophages and other cells to produce cytokines and other soluble factors which act to produce fever and rigors and probably influence other severe pathophysiology associated with malaria.

Plasmodium falciparum-infected erythrocytes, particularly those with mature trophozoites, adhere to the vascular endothelium of venular blood vessel walls and do not freely circulate in the blood. When this sequestration of infected erythrocytes occurs in the vessels of the brain it is believed to be a factor in causing the severe disease syndrome known as cerebral malaria, which is associated with high mortality.

#### Incubation Period

Following the infective bite by the [Anopheles mosquito](http://www.cdc.gov/malaria/about/biology/mosquitoes/), a period of time (the "incubation period") goes by before the first symptoms appear. The incubation period in most cases varies from 7 to 30 days. The shorter periods are observed most frequently with P. falciparum and the longer ones with P. malariae.

Antimalarial drugs taken for prophylaxis by travelers can delay the appearance of malaria symptoms by weeks or months, long after the traveler has left the malaria-endemic area. (This can happen particularly with P. vivax and P. ovale, both of which can produce dormant liver stage parasites; the liver stages may reactivate and cause disease months after the infective mosquito bite.)

Such long delays between exposure and development of symptoms can result in misdiagnosis or delayed diagnosis because of reduced clinical suspicion by the health-care provider. Returned travelers should always remind their health-care providers of any travel in areas where malaria occurs during the past 12 months.

#### Uncomplicated Malaria

The classical (but rarely observed) malaria attack lasts 6-10 hours. It consists of

* A cold stage (sensation of cold, shivering)
* A hot stage (fever, headaches, vomiting; seizures in young children)
* A sweating stage (sweats, return to normal temperature, tiredness)

Classically (but infrequently observed) the attacks occur every second day with the "tertian" parasites (P. falciparum, P. vivax, and P. ovale) and every third day with the "quartan" parasite (P. malariae).

**More commonly, the patient presents with a combination of the following symptoms:**

* Fever
* Chills
* Sweats
* Headaches
* Nausea and vomiting
* Body aches
* General malaise

More commonly, the patient presents with a combination of the following symptoms: In countries where cases of malaria are infrequent, these symptoms may be attributed to influenza, a cold, or other common infections, especially if malaria is not suspected. **Conversely, in countries where malaria is frequent, residents often recognize the symptoms as malaria and treat themselves without seeking diagnostic confirmation (presumptive treatment).**

**Physical findings may include:**

* Elevated temperatures
* Perspiration
* Weakness
* Enlarged spleen
* Mild jaundice
* Enlargement of the liver
* Increased respiratory rate

[Diagnosis](http://www.cdc.gov/malaria/diagnosis_treatment/diagnosis.html) of malaria depends on the demonstration of parasites in the blood, usually by microscopy. Additional laboratory findings may include mild anemia, mild decrease in blood platelets (thrombocytopenia), elevation of bilirubin, and elevation of aminotransferases.

#### Severe Malaria

Severe malaria occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria include

* Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities
* Severe anemia due to hemolysis (destruction of the red blood cells)
* Hemoglobinuria (hemoglobin in the urine) due to hemolysis
* Acute respiratory distress syndrome (ARDS), an inflammatory reaction in the lungs that inhibits oxygen exchange, which may occur even after the parasite counts have decreased in response to treatment
* Abnormalities in blood coagulation
* Low blood pressure caused by cardiovascular collapse
* Acute kidney failure
* Hyperparasitemia, where more than 5% of the red blood cells are infected by malaria parasites
* Metabolic acidosis (excessive acidity in the blood and tissue fluids), often in association with hypoglycemia
* Hypoglycemia (low blood glucose). Hypoglycemia may also occur in pregnant women with uncomplicated malaria, or after treatment with quinine.

**Severe malaria is a medical emergency and should be treated urgently and aggressively.**

#### Malaria Relapses

In P. vivax and P. ovale infections, patients having recovered from the first episode of illness may suffer several additional attacks ("relapses") after months or even years without symptoms. Relapses occur because P. vivax and P. ovale have dormant liver stage parasites (["hypnozoites"](http://www.cdc.gov/malaria/about/biology/index.html)) that may reactivate. Treatment to reduce the chance of such relapses is available and should follow treatment of the first attack.

#### Other Manifestations of Malaria

* Neurologic defects may occasionally persist following cerebral malaria, especially in children. Such defects include trouble with movements (ataxia), palsies, speech difficulties, deafness, and blindness.
* Recurrent infections with P. falciparum may result in severe anemia. This occurs especially in young children in tropical Africa with frequent infections that are inadequately treated.
* [Malaria during pregnancy](http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm#pregnancy) (especially P. falciparum) may cause severe disease in the mother, and may lead to premature delivery or delivery of a low-birth-weight baby.
* On rare occasions, P. vivax malaria can cause rupture of the spleen.
* Nephrotic syndrome (a chronic, severe kidney disease) can result from chronic or repeated infections with P. malariae.
* Hyperreactive malarial splenomegaly (also called "tropical splenomegaly syndrome") occurs infrequently and is attributed to an abnormal immune response to repeated malarial infections. The disease is marked by a very enlarged spleen and liver, abnormal immunologic findings, anemia, and a susceptibility to other infections (such as skin or respiratory infections).

Diagnosis

Travelers who have symptoms of malaria should seek medical evaluation as soon as possible. Physicians should consider malaria in any patient with a febrile illness who has recently returned from a malaria-endemic country.

Smear microscopy remains the gold standard for malaria diagnosis. Microscopy can also be used to determine the species of malaria parasite and quantify the parasitemia—both of which are necessary pieces of information for providing the most appropriate treatment. Microscopy results should be available within a few hours. It is an unacceptable practice to send these tests to an offsite laboratory or batch them with results provided days later.

Various test kits are available to detect antigens derived from malaria parasites. Such immunologic (immunochromatographic) tests most often use a dipstick or cassette format and provide results in 2–15 minutes. These rapid diagnostic tests (RDTs) offer a useful alternative to microscopy in situations where reliable microscopic diagnosis is not available. Although RDTs can detect malaria parasites within minutes, they cannot determine the species or quantify parasitemia. In addition, positive and negative results must always be confirmed by microscopy. The Food and Drug Administration (FDA) has approved one RDT for use in the United States by hospital and commercial laboratories, not by individual clinicians or by patients themselves. This RDT, called BinaxNOW Malaria test, is produced by Inverness Medical Professional Diagnostics, located in Scarborough, Maine.

PCR tests are also available for detecting malaria parasites; however, none are FDA-approved. Although these tests are slightly more sensitive than routine microscopy, results are not usually available as quickly as microscopy results should be, thus limiting the utility of this test for acute diagnosis. PCR testing is most useful for definitively identifying the species of malaria parasite and detecting mixed infections. Species confirmation by PCR is available at the CDC malaria laboratory.

In sub-Saharan Africa, clinical over-diagnosis and the rate of false-positive tests for malaria may be high. Travelers to this region should be warned they may be diagnosed with malaria incorrectly, even though they are taking a reliable antimalarial regimen. In such cases, acutely ill travelers should be advised to seek the best available medical services and follow the treatment offered locally (except the use of halofantrine, which is not recommended; see below) but not to stop their chemoprophylaxis regimen.

Treatment

Malaria can be treated effectively early in the course of the disease, but delay of appropriate therapy can have serious or even fatal consequences. Travelers who have symptoms of malaria should be advised to seek medical evaluation as soon as possible. Specific treatment options depend on the species of malaria, the likelihood of drug resistance (based on where the infection was acquired), the age of the patient, pregnancy status, and the severity of infection.

**See attached treatment regimen for Togo 2011 using Coartem.**

Detailed CDC recommendations for malaria treatment can be found at [www.cdc.gov/malaria/diagnosis\_treatment/treatment.html](http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html).

Medications that are not used in the United States for the treatment of malaria, such as halofantrine, are widely available overseas. CDC does not recommend halofantrine for treatment because of cardiac adverse events, including deaths, which have been documented after treatment. These adverse events have occurred in people with and without preexisting cardiac problems and both in the presence and absence of other antimalarial drugs (such as mefloquine).

Travelers who reject the advice to take prophylaxis, who choose a suboptimal drug regimen (such as chloroquine in an area with chloroquine-resistant P. falciparum), or who require a less-than-optimal drug regimen for medical reasons are at increased risk for acquiring malaria and needing prompt treatment while overseas. In addition, some travelers who are taking effective prophylaxis but who will be in remote areas may decide, in consultation with their travel health provider, to take along a reliable supply of a full course of an approved malaria treatment regimen. In the event that they are diagnosed with malaria, they will have immediate access to this treatment regimen, which if acquired in their home country is unlikely to be counterfeit and will not deplete local resources. In rare instances when access to medical care is not available and the traveler develops a febrile illness consistent with malaria, the reliable supply medication can be self-administered presumptively. Travelers should be advised that this self-treatment of a possible malarial infection is only a temporary measure and that prompt medical evaluation is imperative.

Two malaria treatment regimens can be prescribed as a reliable supply: atovaquone-proguanil (MALARONE) and artemether-lumefantrin (COARTEM). The use of the same or related drugs that have been taken for prophylaxis is not recommended to treat malaria. For example, atovaquone-proguanil may be used as a reliable supply regimen by travelers not taking atovaquone-proguanil for prophylaxis.

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. As a 2nd line alternative for treatment, hydroxychloroquine may be given instead. 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.

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 no 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.

#### Malaria Facts

#### Malaria in the United States

* On average, 1500 cases of malaria are reported every year in the United States, even though malaria has been eradicated in this country since the early 1950's.
* First- and second-generation immigrants from malaria-endemic countries returning to their "home" countries to visit friends and relatives tend not to use appropriate malaria prevention measures and thus are more likely to become infected with malaria.
* Between 1957 and 2009, in the United States, 63 outbreaks of locally transmitted mosquito-borne malaria have occurred; in such outbreaks, local mosquitoes become infected by biting persons carrying malaria parasites (acquired in endemic areas) and then transmit malaria to local residents.
* Of the species of Anopheles mosquitoes found in the United States, the three species that were responsible for malaria transmission prior to elimination (Anopheles quadrimaculatus in the east, An. freeborni in the west, and An. albimanus in the Caribbean) are still widely prevalent; thus there is a constant risk that malaria could be reintroduced in the United States.
* During 1963-2009, 96 cases of transfusion-transmitted malaria were reported in the United States; approximately two thirds of these cases could have been prevented if the implicated donors had been deferred according to established guidelines.

#### Malaria Worldwide

* 3.3 billion people (half the world’s population) live in areas at risk of malaria transmission in 109 countries and territories.
* 35 countries (30 in sub-Saharan Africa and 5 in Asia) account for 98% of global malaria deaths.
* WHO estimates that in 2008 malaria caused 190 - 311 million clinical episodes, and 708,000 - 1,003,000 deaths.
* 89% of the malaria deaths worldwide occur in Africa.
* Malaria is the 5th cause of death from infectious diseases worldwide (after respiratory infections, HIV/AIDS, diarrheal diseases, and tuberculosis).
* Malaria is the 2nd leading cause of death from infectious diseases in Africa, after HIV/AIDS.

#### Biology, Pathology, Epidemiology

* Among the malaria species that infect humans, Plasmodium vivax and P. ovale can develop dormant liver stages that can reactivate after symptomless intervals of up to 2 (P. vivax) to 4 years (P. ovale).
* [Pregnant women](http://www.cdc.gov/malaria/malaria_worldwide/reduction/iptp.html) have increased susceptibility to Plasmodium falciparum malaria; in malaria-endemic countries, P. falciparum contributes to 8-14% of low birth weight, which in turn decreases the chance of a baby’s survival.
* After a single sporozoite (the parasite form inoculated by the female mosquito) of Plasmodium falciparum invades a liver cell, the parasite grows in 6 days and produces 30,000-40,000 daughter cells (merozoites), which are released into the blood when the liver cell ruptures. In the blood, after a single merozoite invades a red blood cell, the parasite grows in 48 hours and produces 8-24 daughter cells, which are released into the blood when the red blood cell ruptures.
* Under the microscope, Plasmodium knowlesi can resemble either P. falciparum or P. malariae.  Thus PCR is often required to confirm infection.

**Malaria Treatment Regimen**

**Coartem** is a fixed dose oral combination of artemether (20 mg), an artemisinin derivative, and lumefantrinef (120 mg), two anti-malarials.   Coartem is specifically indicated for the treatment of acute, uncomplicated malaria infections due to Plasmodium falciparum in patients of 5 kg bodyweight and above. Coartem is supplied as a tablet designed for oral administration. Coartem tablets should be taken with food. In the event the patient is unable to swallow the tablets, such as infants and children, the tablets may be crushed and mixed with a small amount of water. The recommended initial dose of the drug is as follows:

**Adults (Aged 16 years and above)** 🡪 **4 Tabs PO BID x 3days = 24 tablets**

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above. The tablets should be administered the following way: 4 tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets). *For patients weighing less than 35 kg, see the dosage for pediatrics.*

**Pediatrics (Below 16 years of age)**

**5-15 kg bodyweight** 🡪 1 Tab PO BID x 3days = 6 tablets 🡪 1 tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) for the following two days.
**15-25 kg bodyweight** 🡪2 tabs PO BID x 3days = 12 tablets 🡪 2 tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) for the following two days.
**25-35 kg bodyweight** 🡪 3 tabs PO BID x 3days = 18 tablets 🡪 3 tablets as an initial dose, three tablets again after 8 hours and then three tablets twice daily (morning and evening) for the following two days
**35 kg bodyweight and above** 🡪 4 tabs PO BID x 3days = 24 tablets 🡪 *Same as adult dose*