CHAPTER 21

Malaria Diagnosis and Treatment

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GENERAL CONSIDERATIONS

Malaria is preventable by taking chemoprophylaxis and using mosquito avoidance measures (Chapter 6). However, healthcare providers should be knowledgeable about the work-up of malaria, as it is not uncommon for a returned traveler to present with fever. When a patient presents with fever, healthcare providers working in malaria-free areas might not consider malaria in the differential diagnosis, especially since this disease can mimic other illnesses, such as influenza or gastroenteritis. However, undiagnosed and untreated malaria can progress rapidly to death. Therefore, healthcare workers must obtain a travel history from patients who present with fever. All febrile patients who have traveled to a malaria-endemic area should be rapidly evaluated for malaria. Patients at risk for malaria most commonly come from one of the following groups:

1. Visitors, immigrants, and refugees from a malaria-endemic area
2. Travelers, regardless of duration of stay (e.g., tourist, business traveler, expatriate), especially first- and second-generation immigrants returning to their countries of origin to visit friends and relatives
3. Military personnel assigned abroad.

Other groups in which malaria infrequently occurs include:

1. Recipients of blood transfusions or organ or tissue transplant
2. Infants of mothers who have lived or traveled in an endemic area (congenital infections)
3. Injection drug users (parenteral transmission)
4. Residents of non-endemic areas where local transmission might occur from undiagnosed imported infections. For example, Greece and Jamaica, both malaria non-endemic, had outbreaks originating from imported cases of malaria between 2011-2013 and 2006-2011, respectively.

ETIOLOGY

Malaria is a vector-borne protozoan parasite infection spread from person to person in endemic areas by female mosquitoes of the genus *Anopheles*. Four species of malaria regularly cause disease in humans, including *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. *P. knowlesi*, a cause of malaria in long-tailed macaques, also naturally infects humans in Southeast Asia, most notably in Malaysia.

PRESENTATION

Epidemiology

In 2013 there were approximately 198 million cases of malaria worldwide, and 500,000 deaths, mostly in children in sub-Saharan Africa. Malaria is endemic in most tropical areas

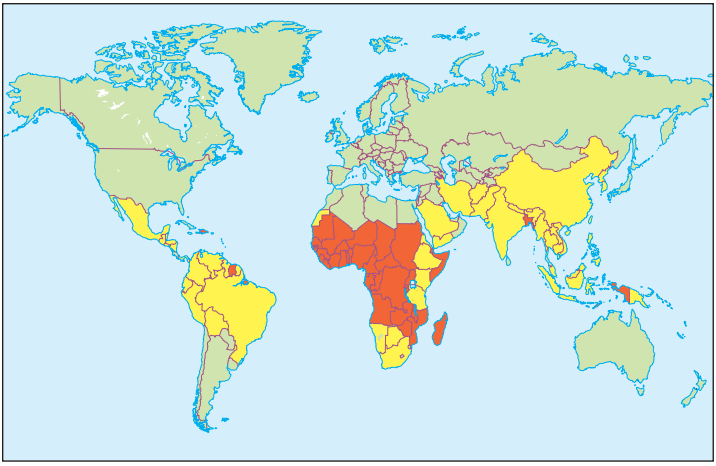

Fig. 21.1 Malaria-endemic countries shown in red (malaria everywhere) and yellow (malaria in select areas) (CDC 2014).

of the world (**Fig. 21.1**). Transmission of malaria can vary within a country and is affected by multiple factors, such as season, altitude, and urbanization. Migration and travel can potentially introduce malaria to previously malaria-free areas where the mosquito vector is present. Drug resistance is an increasing problem. Chloroquine-resistant *P. falciparum* is widespread, and there are very few areas (e.g., Central America west of the Panama Canal, the Dominican Republic, and Haiti) where chloroquine can still effectively treat *falciparum* malaria. Multidrug-resistant *P. falciparum* is present in parts of Southeast Asia, and chloroquine-resistant *P. vivax* is found in parts of Indonesia and Papua New Guinea. Resistance to sulfadoxine-pyrimethamine (Fansidar®) is also widespread.

Malaria endemicity and antimalarial drug resistance can change over time, so healthcare providers should always refer to the most up-to-date information when giving advice to a traveler or when managing malaria. A list of countries and their malaria-related information can be found in "Health Information for International Travel" (the "Yellow Book"), a publication prepared by the Centers for Disease Control and Prevention (CDC) and available online (http://www.cdc.gov/travel/). Reports from the field by way of returned travelers, the news media, and other nonmedical news sources should be confirmed by checking official postings from the CDC (www.cdc.gov/travel or www.CDC.gov/malaria) and World Health Organization (http://www.who.int).

PATHOGENESIS

Natural Life Cycle

After inoculation of the malaria parasites (sporozoites) during feeding by a female anopheline mosquito, the sporozoites invade the liver parenchymal cells within minutes, and then replicate during an asymptomatic incubation period (pre-erythrocytic schizogony) that can last between 1 and 3 weeks but can be as long as a year (*P. vivax*). Relapsing species, *P. vivax* and *P. ovale*, can form hypnozoites in the liver, a dormant stage that can cause relapses weeks to months after the initial infection. Eventually, the hepatic schizonts rupture and parasites (merozoites) are released into the bloodstream, where red blood cells are rapidly infected (erythrocytic stage) (**Fig. 21.2**).

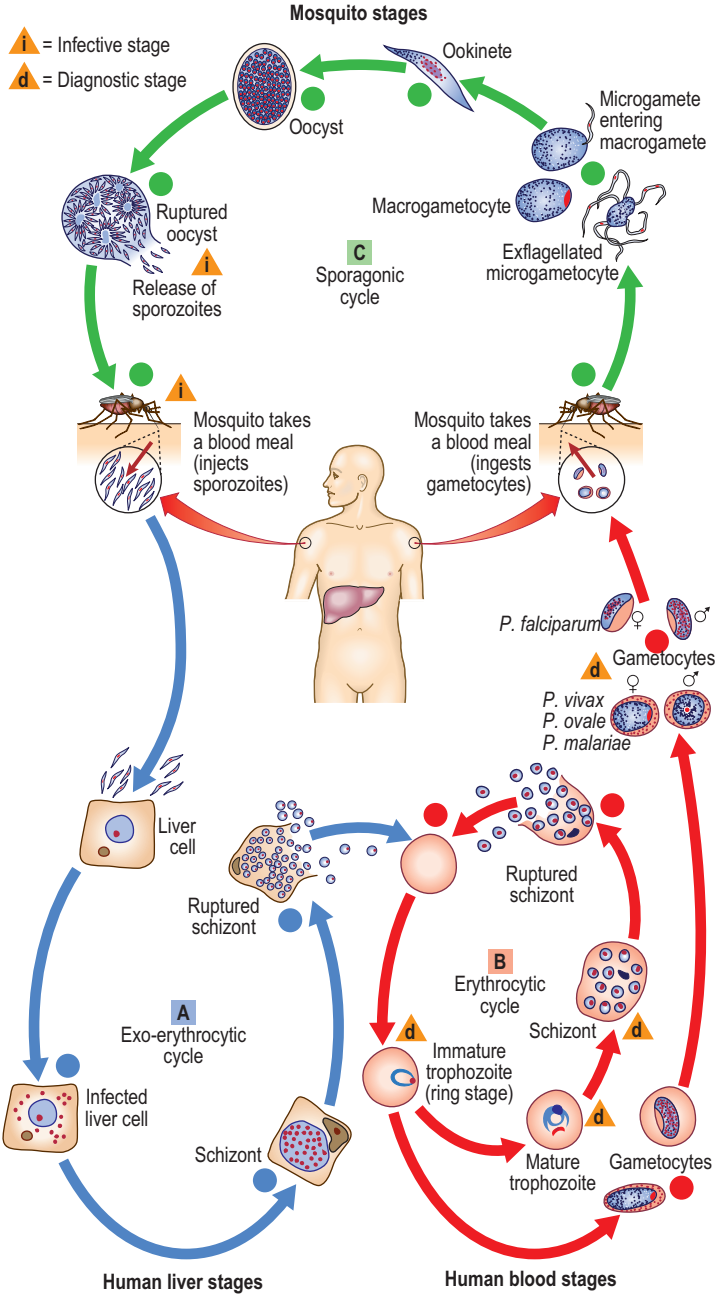

Fig. 21.2 **Life cycle of *Plasmodium* parasite (CDC).**

1. The merozoites mature in infected red cells, and early stages are called trophozoites, resembling signet rings. The blood-stage infection causes the symptoms and signs of malaria.
2. Most trophozoites undergo asexual division within the red cells to form a schizont, or ball of new merozoites. During this process, the erythrocyte's hemoglobin is consumed. Eventually the cell bursts, liberating new merozoites that invade new red cells. For *P. falciparum*, *P. vivax*, and *P. ovale*, the duration of the asexual life cycle is 48 hours, for *P. malariae* 72 hours, and for *P. knowlesi* 24 hours.
3. After asexual reproduction some merozoites will develop into sexual forms of the parasite called gametocytes. These transmissible stages are ingested by another feeding anopheline mosquito, fuse in the mosquito's midgut to form a zygote, develop in the wall of the gut, and then migrate to the mosquito's salivary gland to complete the cycle.

Pathophysiology

Each of the species has a variable incubation period (the interval between infection and the onset of clinical illness). Incubation periods can be as short as 1 week (rare) or between 2 and 4 weeks (more common), but they can be much longer for vivax or ovale malaria or if the infection is suppressed by partial adherence to chemoprophylaxis. The erythrocytic stage of the infection is associated with spiking fevers and chills, but relapsing fever is not necessarily seen. Fever and illness are caused by the release of proinflammatory cytokines (particularly tumor necrosis factor) and other inflammatory mediators. Cytokines are responsible for many features of severe malaria, but microvascular obstruction is the primary pathologic process. The pathology of severe falciparum malaria is associated with the sequestration of infected red cells in the microvasculature of vital organs. Thus, the pathologies of sepsis and severe malaria are different.

Falciparum malaria may progress rapidly to parasitize a large number of erythrocytes, with severe systemic consequences of multiple organ failure and death unless treated immediately. *P. falciparum* infections are potentially lethal for several reasons:

1. Each blood-stage schizont liberates up to 32 merozoites when it ruptures, potentially infecting many red blood cells quickly.
2. *P. falciparum* causing severe malaria parasitizes circulating red cells of all ages (in contrast to *P. vivax*, which tends to infect young cells only, and *P. malariae*, which has a predilection for older cells).
3. Erythrocytes containing mature forms of *P. falciparum* stick to the endothelium of capillaries and post-capillary venules (cytoadherence). The resulting sequestration results from the interaction between antigenically variant parasite-derived adhesive proteins expressed on the surface of infected erythrocytes and specific receptors on the vascular endothelium. In addition, the deformability of both parasitized and uninfected erythrocytes is markedly reduced in severe malaria. The subsequent interference with microcirculatory flow and regional metabolism is most evident in the brain, resulting in cerebral malaria, but also occurs in the other vital organs. Sequestration accounts for the frequently observed discrepancy between the peripheral parasite count and disease severity and also explains the relative rarity with which mature trophozoites and schizonts are seen in the peripheral blood in falciparum malaria.

Although malaria can be severe with *P. vivax*, *P. ovale*, and *P. malariae* infections, clinical attacks are less likely to be fatal because cytoadherence and sequestration do not occur with these species of malaria. For *P. vivax* and *P. ovale* infections, the hypnozoite, or dormant, stage can cause relapses weeks to months after the initial infection.

Immunity to Malaria

The immune response to malaria infections is incomplete, and frequent repeated attacks are required to induce a degree of protective immunity, which is rapidly lost if the individual leaves the endemic area. Acquired immunity is specific for both the species of malaria and the particular strain(s) causing the infection. The development of immunity to *P. falciparum*

is gained at the expense of a high mortality in children living in areas of heavy transmission. For this reason, severe malaria is a disease of childhood in these areas, and adults who have gained protective immunity are less likely to develop severe manifestations, so long as they continue to be exposed via more infected mosquito bites. Without this boosting effect, immunity will wane in time. Thus, in contrast to adult residents of areas of heavy malaria transmission, non-immune travelers—including immigrants—of all ages coming from areas without malaria to malaria-endemic areas are vulnerable to developing severe and potentially fatal infections.

CLINICAL FEATURES

The symptoms and signs of malaria are nonspecific and are most commonly fever, chills, myalgias, and headache. Malaria may present as febrile seizures in children or coma (cerebral malaria). It may be mistaken for infectious hepatitis when jaundice is prominent, for pneumonia when there is respiratory distress, or for enteric infections with fever, vomiting, abdominal pain, and diarrhea. Furthermore, malaria may exist in a patient with other acute travel-related illnesses. Therefore, clinicians should suspect and test for malaria in *all febrile patients* who traveled to a malaria-endemic area.

Malaria is typically classified as either uncomplicated or severe. Indicators for severe malaria are listed in **Table 21.1**. Patients need to have only one of these indicators to have severe malaria; however, patients with severe malaria usually meet multiple criteria.

Hyperparasitemia is defined as more than 5% erythrocytes parasitized. All patients with malaria should have their percent parasitemia calculated at the time of diagnosis, as it is not uncommon for hyperparasitemia to be the only factor that categorizes the patient as having severe malaria requiring parenteral medicine; early initiation of parenteral treatment prior to the development of clinical complications can improve the chances of prompt and complete recovery.

Cerebral malaria can present with either focal or generalized neurologic features, most commonly, altered mental status, seizures (especially in children), or coma. It must be distinguished from other causes of fever and altered consciousness (e.g., bacterial or viral meningoencephalitis).

Acute kidney injury results from acute tubular necrosis. Some patients may develop brisk hemolysis and hemoglobinuric renal failure ("blackwater fever").

Acute respiratory distress syndrome (ARDS), defined as respiratory distress from pulmonary inflammation and characterized by severe hypoxemia with bilateral pulmonary infiltrates on radiograph, is associated with a high mortality. ARDS can occur with all species of

TABLE 21.1 Criteria for Severe Malaria

Malaria is severe if one or more of the following is present:

- Acidosis
- Acute respiratory distress syndrome
- Seizures
- Disseminated intravascular congestion
- Hyperparasitemia (>5%)
- Hypoglycemia
- Impaired consciousness
- Jaundice
- Acute kidney injury or macroscopic hemoglobinuria
- Severe anemia (Hb < 7 g/dL)
- Shock

malaria. Respiratory distress in patients with malaria can also be due to metabolic acidosis, iatrogenic volume overload from overly aggressive fluid resuscitation resulting in pulmonary edema, transfusion-related lung injury, and secondary nosocomial pneumonia.

Glucose levels fall in severe malaria infections as a result of increased metabolic demands by the host and parasites, and decreased gluconeogenesis. Hypoglycemia most commonly develops in women in late pregnancy and children with severe malaria, which is hazardous to the viability of the pregnancy. It is usually accompanied by lactic acidosis. Quinine stimulates pancreatic insulin secretion and is an important cause of hypoglycemia.

Severe anemia is defined as hemoglobin levels <7 g/dL. The hematocrit falls rapidly in severe malaria because of the accelerated clearance of both parasitized and unparasitized erythrocytes. The anemia is compounded by bone marrow dyserythropoiesis.

Another poor prognostic indicator is disseminated intravascular coagulation that presents as abnormal bleeding (e.g., petechiae, ecchymosis, bleeding from intravenous lines), thrombocytopenia, and abnormal clotting or coagulation laboratory values. Some degree of thrombocytopenia (at or even below 100,000/μL) is usually seen in all symptomatic malaria cases. Thrombocytopenia alone is not a criterion for severe malaria.

Patients with severe malarial infections are more vulnerable to bacterial infections, such as aspiration pneumonia and spontaneous septicemia with Gram-negative bacteria (particularly nontyphoidal salmonellae), especially in children.

Chronic malaria can manifest in residents of highly endemic areas who, through repeated infections, have developed some degree of immunity, resulting in few to no symptoms despite having parasites in their blood. This asymptomatic parasitemia is a major cause of chronic anemia, particularly in young children. Splenomegaly is also a reflection of repeated malaria attacks in children in endemic areas. Splenic rupture occasionally occurs as a complication of *P. vivax* infection in adults. Hyperreactive malarial splenomegaly (or "tropical splenomegaly syndrome") is sometimes seen in adults in endemic areas and presents as hepatosplenomegaly, anemia, abnormal immunologic findings, and immunosuppression. This appears to reflect an exaggerated immune response to repeated infection. Nephrotic syndrome may develop in children chronically infected with *P. malariae* ("quartan nephropathy").

LABORATORY DIAGNOSIS

The diagnosis of malaria is best made by the identification of malaria parasites on the peripheral blood smear. Preparation of thick and thin smears should be done immediately for any febrile patient living in or returning from a malarious area. Because parasitemia waxes and wanes with the parasite's life cycle, these smears should be performed at least three times, 12-24 hours apart, to achieve acceptable negative predictive value. Although Giemsa stains of the blood smear are preferred for determining speciation of the parasite, the modified Wright's stain used for the routine processing of blood smears in clinical hematology laboratories is adequate. Field's stain may also be used. Both thick and thin smears are first screened at low magnification, then examined using a 100× oil immersion objective for at least 300 fields, because symptoms of malaria can occur at lower parasite densities in nonimmune individuals.

Thick smears are much more sensitive than thin smears, but provide less information regarding the species and infection burden. The thick smear is first examined for presence of parasites. If parasites are present, the thin smear is used to determine the species of parasite, and the percent parasitemia, that is, the percentage of red blood cells infected. To quantify malaria parasites, between 500 and 2000 red blood cells should be examined. Both the species of malaria and the percent parasitemia are key pieces of information when selecting therapeutic options.

The CDC offers training workshops and web-based training on malaria diagnosis for laboratory personnel throughout the United States. DPDx also allows telediagnosis, where outside laboratories can email digital images of their microscopy findings to the CDC and receive same-day feedback from CDC staff (http://www.cdc.gov/dpdx/contact.html).

Rapid Diagnostic Test (RDT)

Immunochromatographic strip assays detect malarial antigens in finger-stick blood samples using test strips or cards impregnated with specific antibodies. These are based either on detection of *P. falciparum* histidine-rich protein 2 (HRP-2) or parasite lactate dehydrogenase isoenzymes or aldolase. Unlike microscopy, which requires a microscope and trained technician, RDTs can be used in places without a skilled microscopist. Only the BinaxNOW® Malaria Test is approved by the US Food and Drug Administration (FDA) for use in the United States. Disadvantages include the cost of the test kits, the inability to determine species of malaria and parasite load, and the potential lack of sensitivity at very low parasitemias. Therefore, use of RDTs should be reserved for situations where quality microscopy is not immediately available and should be followed as soon as possible by microscopy to confirm the results, determine the species, and calculate the parasitemia. Also, HRP-2 may persist in the blood for a number of weeks after an infection has been treated, so use of this test is not recommended to diagnose malaria in a symptomatic patient who has already received a treatment course of antimalarials. However, if a retrospective diagnosis is needed in an asymptomatic patient who treated him- or herself with antimalarials, the persistent positivity of the PfHRP-2 test is helpful.

Polymerase Chain Reaction (PCR)

PCR currently has limited use for the acute management of malaria: it is not widely available, and results are not timely. The advantage of PCR, however, is its ability to detect very low sub-microscopic parasitemias and to identify species; therefore, it can be used following microscopy to confirm the malaria species. All malaria cases diagnosed in the United States should have PCR confirmation of species. This service is available at the CDC free of charge (www.CDC.gov/malaria).

Serology

Measuring malaria antibodies in the blood via indirect fluorescent antibody testing can determine whether infection occurred in the past but will not distinguish between recent or remote infection; thus it is not useful in the acute diagnosis of malaria. Serology may be useful for screening blood donors following diagnosis of transfusion-induced malaria or to confirm the diagnosis retrospectively in a patient who has been treated.

TREATMENT

In choosing which treatment course of antimalarials to give to those with laboratory-confirmed malaria, it is important to distinguish between uncomplicated versus severe malaria, to identify the species of malaria, and to identify where the malaria was acquired to assess the potential for drug resistance. Drug choice may also be affected by availability and licensing of the drug, which varies by country. Travelers who took any malaria prophylaxis should not be treated with the same class of antimalarial drug used for prophylaxis.

Uncomplicated Malaria

Most patients with uncomplicated disease can be treated with oral medications. Parenteral treatment should be used for patients who are vomiting, those with severe disease, or infants under 1 year old. Patients with a diagnosis of uncomplicated *P. falciparum* malaria should not go home unaccompanied, since deterioration can occur after treatment has started. Malaria due to *P. ovale* or *P. vivax*, which can cause relapses, should be treated with two medicines: an antimalarial for the acute infection and primaquine to prevent relapses. Administer the first dose of antimalarial drug(s) as soon as the diagnosis is made, and observe the patient. If vomiting occurs within 30 minutes, readminister the full dose (often after an antiemetic); if it occurs between 30 and 60 minutes, readminister half the dose (repeat the full dose if atovaquone-proguanil). If parenteral therapy must be used, change to oral therapy when the patient is alert and able to swallow. Follow the clinical status of the patient regularly until the individual has improved. Most patients will start to feel better and become

afebrile 24-48 hours after starting appropriate therapy. Following the level of parasitemia can be useful to assess patients who are not clinically improving. **Tables 21.2** and **21.3** present the regimens recommended for treatment of uncomplicated malaria.

Antimalarial Drugs for Uncomplicated Malaria

Artemisinin-Based Combination Therapies (ACTs)

Artemisinin (qinghaosu) and its derivatives (artesunate, artemether, dihydroartemisinin) are the most rapidly effective of all antimalarials. They are active against all malaria species. Artemisinin derivatives are used in combination with a drug with a slower rate of elimination to increase efficacy, reduce transmission of the infection, and provide mutual protection from drug resistance. Artemether-lumefantrine (Coartem®, Riamet®) is a highly effective, well-tolerated, fixed combination drug for use in both children and adults. Reliable absorption of this lipophilic drug is dependent on coadministration with food containing fat. Currently, artemether-lumefantrine is the only ACT approved by the FDA for use in the United States. Other ACTs in use in other countries include artesunate-mefloquine, artesunate-amodiaquine, artesunate-sulfadoxine-pyrimethamine, and dihydroartemisinin-piperaquine.

Atovaquone-Proguanil

A fixed dose combination of atovaquone and proguanil (Malarone® and generic) can be used to treat all species of malaria. Atovaquone-proguanil is available as an adult tablet (250 mg/100 mg) and as a pediatric tablet (62.5 mg/25 mg). The medication should be taken with food or drink with fat to enhance absorption. It is very well tolerated, and adverse effects are rare. In the event of vomiting within 60 minutes after dosing, the dose should be repeated. Atovaquone should never be given alone, as resistant mutations arise commonly in approximately one-third of patients receiving the drug.

Chloroquine

Chloroquine-resistant falciparum malaria is present in most areas with falciparum malaria, so this drug should not be used for the treatment of *P. falciparum* infections, with the exception of infections that were acquired in Latin American countries west of the Panama Canal, Haiti, and the Dominican Republic. Chloroquine can be used for nonfalciparum malaria. Chloroquine resistance in *P. vivax* has been reported from parts of Indonesia and Papua New Guinea. In such cases, the guidelines for treating uncomplicated falciparum malaria should be followed and primaquine given in addition.

Mefloquine

Mefloquine (Lariam® and generic) can be used to treat uncomplicated malaria caused by all species. At treatment doses, the risk of side effects from mefloquine increases. Mefloquine-resistant *P. falciparum* parasites are found on the eastern border of Myanmar (Burma) and adjacent parts of China, Laos, and Thailand; the western border of Thailand and adjacent parts of Cambodia and Laos; and southern Vietnam.

Primaquine

Primaquine is the only antimalarial that effectively kills the dormant hypnozoites of *P. vivax* and *P. ovale*. When treating vivax or ovale, primaquine must be given in addition to the course of antimalarials for the acute infection. A severe hemolytic reaction to primaquine can occur in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency; therefore, prior to receiving primaquine for the first time, all patients must be tested and found to have normal G6PD activity.

Drugs No Longer Recommended

Sulfadoxine-pyrimethamine (SP; Fansidar®): strains of falciparum and vivax malaria resistant to sulfadoxine-pyrimethamine are widespread, therefore SP should not be used for treating acute malaria. However, SP continues to have some niche uses such as when used in the intermittent preventive treatment of malaria in pregnancy in highly endemic areas.

TABLE 21.2 Treatment of Uncomplicated Malaria Due to Presumed Chloroquine-Resistant Infections Including if the Species Has Not Yet Been Identified

Recommended treatments (if patient had been on antimalarials for prophylaxis, DO NOT use same antimalarial)

Artemether-lumefantrine (20/120 mg artemether and lumefantrine)

One dose at hours 0, 8, 24, 36, 48, and 60 according to body weight. Administer with food or drink containing fat.

Body weight (kg)	Tablets per dose
5-14	1
15-24	2
25-34	3
>34	4

Artesunate-amodiaquine (available as 25/67.5 mg, 50/135 mg, or 100/270 mg of artesunate and amodiaquine)

4 mg/kg artesunate and 10 mg base/kg amodiaquine once a day for 3 days

Artesunate-mefloquine (separate tablets of 50 mg artesunate and 250 mg mefloquine)

4 mg/kg artesunate once a day for 3 days and mefloquine 25 mg base/kg split over 2 days (15 mg/kg day 1, 10 mg/kg day 2) or 3 days (8.3 mg/kg daily)

Atovaquone-proguanil (Malarone or generic) (adult tablet: 250/100 mg atovaquone and proguanil; pediatric tablet: 62.5/25 mg atovoquone and proguanil)

Adult dosing: 4 adult tablets as a single daily dose for 3 days

Pediatric dosing:

Body Weight (kg)	Tablets per Dose
5-8	2 pediatric tablets
9-10	3 pediatric tablets
11-20	1 adult tablet
21-30	2 adult tablets
31-40	3 adult tablets
>41	4 adult tablets

Dihydroartemisinin plus piperaquine (40/320 mg dihydroartemisinin and piperaquine)

4 mg/kg dihydroartemisinin and 18 mg/kg piperaquine once daily for 3 days

Quinine + doxycycline

Adults: quinine 650 mg (salt) three times a day for 3 days (7 days for infections from Southeast Asia) and doxycycline 100 mg (base) twice a day for 7 days

Pediatric (for children 8 years and older): quinine 10 mg salt/kg three times a day for 3 days (7 days for infections from Southeast Asia) and doxycycline 2.2 mg base/kg twice a day for 7 days

Quinine + clindamycin

Adults: quinine 650 mg (salt) three times a day for 3 days (7 days for infections from Southeast Asia) and clindamycin 20 mg base/kg per day, divided three times a day for 7 days

Pediatric: quinine 10 mg salt/kg three times a day for 3 days (7 days for infections from Southeast Asia) and clindamycin 20 mg base/kg per day, divided three times a day for 7 days

Quinine + tetracycline

Adults: quinine 650 mg (salt) three times a day for 3 days (7 days for infections from Southeast Asia) and tetracycline 250 mg four times a day for 7 days

Pediatric (for children 8 years and older): quinine 10 mg salt/kg three times a day for 3 days (7 days for infections from Southeast Asia) and tetracycline 25 mg/kg per day divided four times a day for 7 days

TABLE 21.3 Treatment of Uncomplicated Malaria Acquired in Areas Without Chloroquine Resistance

Select any option from Table 21.2 or

Chloroquine

Adults: 1000 mg at time 0, followed by 500 mg at 6, 24, and 48 h

Pediatric: 16.7 mg/kg at time 0, followed by 8.3 mg/kg at 6, 24, and 48 h

For patients with *P. vivax* or *P. ovale*, in addition to acute treatment as described above, confirm absence of G6PD deficiency in patient, and give

Primaquine

Adults: 52.6 mg (salt) per day for 14 days

Pediatric: 0.9 mg salt/kg per day for 14 days

G6PD, Glucose 6-phosphate dehydrogenase.

TABLE 21.4 Treatment of Severe Malaria

Immediate treatment with *one* of the following:

Artesunate (US clinicians can call the CDC to inquire about acquiring artesunate at 770-488-7100)

2.4 mg/kg IV at 0, 12, 24, and 48 h

On completion of artesunate, a follow-on antimalarial drug (either atovaquone-proguanil, doxycycline, clindamycin, or mefloquine) must be administered to complete treatment.

Quinine dihydrochloride

20 mg salt/kg loading dose IV in 5% dextrose or 0.9% saline over 4 h; then maintenance dose of 10 mg salt/kg (infusion rate should not exceed 5 mg salt/kg/h) 3 times a day.

After at least 24 h of parenteral therapy with quinine, and when patient can tolerate oral medications, give a full oral treatment course with one of the drugs listed in Table 21.2.

Quinidine gluconate (if parenteral quinidine is not available, or intolerance to quinidine is observed, US clinicians can call the CDC to inquire about acquiring artesunate at 770-488-7100)

Initial dose of 10 mg salt/kg IV infusion over 1-2 h, followed by maintenance dose of 0.02 mg salt/kg/min for at least 24 h. Once parasite density <1% and patient is able to tolerate oral medications, treatment can be completed with an oral regimen. Quinidine can have cardiotoxic adverse effects, so the electrocardiogram must be monitored continuously, and the infusion slowed or stopped if the QTc interval is prolonged by more than 25%.

IV quinidine should be coupled with doxycycline, clindamycin, or tetracycline, as described in Table 21.2.

Halofantrine (Halfan®): halofantrine is not recommended because it prolongs atrioventricular depolarization and ventricular repolarization and has been associated with sudden cardiac death.

Severe Malaria

Severe falciparum malaria is a serious disease with high mortality that requires admission to the intensive care unit (ICU) and the advice of a specialist. Cerebral malaria has a treated mortality of 15-20%. Concurrent meningitis should be considered for all comatose malaria patients. Intravenous antimalarials (**Table 21.4**) should be given as soon as possible after diagnosis and continued until the parasitemia is less than 1% and the patient is able to tolerate oral medicines. There are several intravenous antimalarial options, including artesunate,

quinine, and quinidine; the choice of which to use will ultimately depend on availability. For example, in the United States, currently quinidine gluconate is the only FDA-approved parenteral medicine available for the treatment of severe malaria. Parenteral artesunate has been demonstrated to be superior to quinine; two large randomized multicenter trials in East Asia and Africa showed a reduction in mortality in severe malaria patients treated with artesunate compared with quinine. In the United States, parenteral artesunate is available under an investigational new drug protocol registered with the FDA and may be procured from CDC if the patient meets inclusion criteria, as determined by CDC clinicians. To request intravenous artesunate, US clinicians are encouraged to contact the CDC for consultation (telephone number listed on www.CDC.gov/malaria).

Careful hemodynamic monitoring and attention to fluid balance are critical to ensure adequate cardiac output and urine flow while avoiding overhydration.

Hemodialysis should be instituted if indicated. Renal function typically returns slowly to normal after several days or weeks.

The blood glucose level should be checked regularly, particularly in cerebral malaria patients or pregnant women treated with quinine.

Sudden unexplained deterioration in a patient with severe falciparum malaria can be due to hypoglycemia, ARDS, or supervening bacterial septicemia and will ultimately require supportive management.

After an extensive review of the available evidence, exchange transfusion was not found to have any benefit in the outcome of severe malaria. There have been no randomized controlled clinical trials to assess its efficacy, and there is a low likelihood of such trials ever occurring. Furthermore, the rapidity with which exchange transfusion can reduce parasitemia is comparable to that of artemisinins. Therefore, the use of exchange transfusion is no longer recommended in the management of severe malaria.

The use of steroids or heparin is contraindicated as adjunctive treatment of cerebral and other severe forms of falciparum malaria.

Radical Cure of *P. vivax* or *P. ovale* Malaria

In cases of *P. vivax* or *P. ovale* malaria, when the person is not returning shortly to an endemic malarious area, "radical cure" therapy with 14 days of primaquine phosphate (**Table 21.3**) should be started at the time of the last dose of chloroquine, after G6PD deficiency has been excluded. This is done to kill latent malarial parasites in the liver (hypnozoites) and thus prevent future relapses (Chapter 6). There is little evidence of true *P. vivax* resistance to primaquine. Rather, primaquine failure has been reported in patients with decreased activity of the hepatic isoenzyme cytochrome P450 (CYP) 2D6, an isoenzyme involved in drug metabolism believed to be required for primaquine efficacy.

Prevention of Malaria in Travelers

The best management of malaria is through prevention (Chapter 6), by taking measures such as using mosquito repellants and taking chemoprophylaxis. Although there have been promising developments, a useful vaccine available for large-scale deployment in travelers is still thought to be 5-10 years away.

Travelers who reject the advice to take prophylaxis, who choose a sub-optimal 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 bring a reliable supply of a full treatment course of antimalarials. If they are diagnosed with malaria, they will have immediate access to this treatment regimen, which is unlikely to be counterfeit and will not deplete local resources. Although empiric clinical diagnosis and self-treatment are discouraged, in rare instances when access to medical care is not available and the traveler develops a febrile illness consistent with malaria, the reliable medication can be self-administered presumptively. Travelers

should be advised that this self-treatment 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 and artemether-lumefantrine. 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 medication by travelers not taking atovaquone-proguanil for prophylaxis.

SPECIAL THERAPEUTIC CONSIDERATIONS

Malaria during Pregnancy

Falciparum malaria in non-immune pregnant women carries a high fetal and maternal mortality. The placenta is a site of preferential sequestration of infected red cells. This reservoir of developing parasites interferes with utero-placental function. In endemic areas, the main adverse effects of malaria in pregnancy are low birth weight and maternal anemia; the primigravida is at greatest risk. There are insufficient data on the safety and efficacy of many antimalarials in pregnancy. Therefore if a woman of childbearing age is diagnosed with malaria, clinicians should always ask if she might be pregnant in order to select the most appropriate antimalarial. Treatment of malarial infections in pregnant women should be started in the hospital, since complications are more likely to arise. The use of primaquine, doxycycline, or tetracycline is contraindicated in pregnancy.

Severe malaria should be treated in the same way as for nonpregnant patients. Hypoglycemia is particularly common in pregnant women receiving quinine. Fetal monitoring is essential (if available), as fetal distress is extremely common in malaria and urgent delivery may be necessary to save the baby.

For uncomplicated disease acquired in areas with chloroquine-resistant *P. falciparum*, quinine sulfate plus clindamycin or mefloquine alone can be used during all trimesters of pregnancy. There are insufficient data and unresolved concerns over the use of artemisinin derivatives in the first trimester. However, for the second and third trimesters, there are published reports of >1000 pregnant women, mainly in the second and third trimesters, who have received an artemisinin derivative and have been effectively treated with no adverse outcome for mother or fetus. An artemisinin-combination drug is recommended for the second and third trimesters by the WHO. In the United States, however, artemether-lumefantrine is not yet approved by the FDA for use during any trimester of pregnancy.

It is recommended that a pregnant returned traveler presenting with an episode of acute vivax or ovale malaria should be given a treatment course of antimalarials (options include chloroquine, quinine plus clindamycin, mefloquine, or ACT where approved by local drug authorities), and then should start weekly chloroquine prophylaxis (500 mg salt) until after delivery. Primaquine therapy for a radical cure should be deferred until after delivery, once G6PD has been excluded in both the woman and her infant if she is breastfeeding.

Malaria in Infancy and Childhood

For newborns of mothers with malaria or history of malaria during pregnancy, congenitally transmitted malaria is rare. In these infants, it is best to be vigilant for fever in the first month of life, to do immediate blood smears if fever occurs, and to give appropriate antimalarials once a malaria diagnosis is established. It is not unusual for newborns to present with a transient parasitemia in the first 7 days of life. If a newborn in a non-endemic area is found to have congenital *P. vivax* or *P. ovale*, no primaquine is needed after the initial antimalarial treatment because they do not have hypnozoites. Hypnozoites are formed only from sporozoites acquired from a mosquito bite (**Fig. 21.2**). In congenital malaria, parasites are acquired at the erythrocytic stage of the life cycle from maternal blood. Newborns of mothers who have some degree of immunity to malaria may receive some temporary protection from maternal antibodies.

Among children, the initial attacks of falciparum malaria are often severe and sometimes fatal. Seizures are common, and sudden death may occur. Children are less likely than adults

to develop acute kidney injury, acute respiratory distress, or jaundice, but they are more likely to develop seizures, lactic acidosis, hypoglycemia, and severe anemia. Approximately 10% of children surviving cerebral malaria will have a residual neurological deficit (usually hemiplegia). In 50% of cases this resolves, and in 25% there is partial improvement, but 25% do not recover. More subtle residual deficits may be more common. Children with severe malaria should be admitted to an ICU and treated with parenteral antimalarials (**Table 21.4**). In all comatose children, other causes of concurrent meningitis could be considered. For uncomplicated malaria, although infants <12 months of age are usually able to take oral medications, there is some concern of adequate gut absorption, so parenteral antimalarials are preferred. If oral antimalarials are given, but there is doubt that the dose was retained, or the medication was regurgitated, parenteral treatment may be necessary.

Malaria in Patients with Chronic Diseases

It is recommended that for any patient with chronic conditions or taking medications, healthcare providers should refer to the most up-to-date drug reference for potential contraindications to or drug interactions with antimalarials. For example, patients with human immunodeficiency virus infection may be more susceptible to malaria than non-infected individuals, and there are several interactions between antiretrovirals and antimalarials. Concerns of drug interaction should not delay treatment; treatment should be initiated with the treatment least likely to cause interaction.

General Points

Clinicians should report confirmed malaria cases to their respective public health authorities. The National Malaria Surveillance System collects epidemiological and clinical information on malaria cases diagnosed in the United States. In addition, the CDC is conducting surveillance for emerging antimalarial drug resistance. For all cases of malaria diagnosed in the United States, a sample of the original diagnostic blood sample should be sent to the CDC for both species confirmation by PCR and drug resistance testing. These services are available free of charge (http://www.cdc.gov/malaria/features/ars.html/). Patients traveling to malaria-endemic areas should be advised to seek immediate medical attention if they develop fever in order to avoid a delay in diagnosis and treatment. Healthcare providers who need assistance with the diagnosis or management of malaria may call the CDC Malaria Hotline at 770-488-7788 (Monday-Friday, 8:00 a.m.-4:30 p.m., Eastern Standard Time). A CDC Malaria Branch clinician may be consulted outside those hours at 770-488-7100.

COMMONLY ENCOUNTERED PRACTICAL PROBLEMS

Errors of Diagnosis

A. Malaria was not considered in the differential diagnosis because:
   1. Travel history was not taken in a febrile patient. **Take travel history in all patients presenting with fever.**
   2. Malaria symptoms were ascribed to other more common diseases such as influenza or enteric infections. **Suspect and test for malaria in all febrile patients who have traveled to a malaria-endemic area.**
   3. Infection occurred months after leaving an endemic area. **Relapses of vivax or ovale malaria can present late, so obtain travel history in the past year.**
   4. Patient took malaria chemoprophylaxis. **While rare, it is still possible for the patient to get malaria. Malabsorption of chemoprophylactic drugs may also occur from vomiting, diarrhea, or not consuming foods with fat when taking atovaquone-proguanil.**

B. Blood smears for malaria with same-day results are unavailable because a skilled microscopist or pathologist is not available on site after hours, or smears are sent to an off-site laboratory. **Send patients to the nearest health facility with on-site blood smears for malaria.**

C. A rapid diagnostic test (RDT) is done to diagnose or rule out malaria without a follow-up blood smear. **Immediately follow an RDT with a blood smear to confirm findings, determine species, and quantify parasitemia.**
D. Antibody testing is ordered to diagnose acute malaria infection. **Blood smears, not antibody testing, are used to diagnose acute malaria infection.**
E. False-negative blood smear or RDT:
   1. Inexperienced staff processing and reading slides, or administering RDTs. **Skilled staff should be available, and if not, refer patients to the nearest hospital with this capability. US clinicians or laboratories needing immediate assistance can call the CDC for telediagnosis.**
   2. For microscopy, failure to examine at least 300 fields. **At least 300 fields should be examined to achieve good sensitivity for even low-level parasitemias.**
   3. Very low density parasitemias below the threshold of sensitivity for microscopy or RDT. **At least three negative malaria smears spaced 12-24 hours apart are needed to rule out malaria. If doubt of the diagnosis exists, PCR can be done provided results are available in a timely manner.**
F. False-positive blood smear or RDT.
   1. Platelets, dirt, or accumulations of stain are misinterpreted as malaria parasites. **If unsure of blood smear reading, obtain diagnostic assistance immediately from a reference laboratory. US laboratories can ask for assistance from either the state laboratories or the CDC.**
   2. PfHRP-2 may persist from a recently cured infection. **Obtain a good history of any recent malaria infection and treatment when RDT is being done.**
G. Misidentification of malaria species. *P. ovale* and *P. vivax* can be difficult to distinguish if microscopist is inexperienced. Unrecognized *P. falciparum* or missed in a "mixed" infection (i.e., *P. falciparum* plus another species) has serious consequences considering its drug resistance. **If unsure about species of malaria, diagnostic assistance should be sought. For US laboratories, all cases of malaria should be PCR confirmed; the CDC can provide assistance with determining malaria species.**

Errors of Management

A. Empiric treatment with antimalarials without laboratory testing. **Always do malaria smears to diagnose malaria prior to treatment and to determine species of malaria and percent parasitemia to help select the appropriate antimalarial course.**
B. Failure to admit patients with *P. falciparum*, anyone with signs of severe malaria, young children, and pregnant women. **These patients should be admitted.**
C. Failure to quantify parasitemia. Patients with parasitemias >5% will require treatment for severe malaria. Also, comparison of pre- and post-treatment parasitemia may help gauge response to treatment.
D. False conclusion that a low parasitemia indicates uncomplicated infection. **Patients with low parasitemia, especially non-immune patients, can present with signs of severe infection.**
E. Not treating asymptomatic parasitemia in a semi-immune individual. **The parasitemia still needs treatment with effective antimalarials.**

Therapeutic Dilemmas (Always Seek Expert Advice)

A. Patient has either severe malaria or uncomplicated malaria with nausea and vomiting, is unable to tolerate oral medications, and intravenous antimalarials are unavailable:
   1. For patients with uncomplicated malaria, unable to tolerate oral medications, give antiemetic and acetaminophen suppositories and retry oral antimalarials.
   2. In the United States, if intravenous quinidine is unavailable, clinicians can call the CDC at 770-488-7100 to request release of parenteral artesunate.
   3. Call nearby facilities for parenteral antimalarials.

B. Patient develops severe hemolytic anemia and "blackwater fever" while receiving parenteral quinine or quinidine:
   1. Continue the drugs and transfuse as necessary; if acute kidney injury develops, consider hemodialysis.

C. Patient with severe falciparum malaria, treated with recommended course of antimalarials, has persistent signs of severe malaria despite a 0% parasitemia.
   1. Do not extend the antimalarial course, as all parasites have been killed. The clinical sequelae of severe malaria such as ARDS or altered mental status may persist despite completing antimalarials.

D. Microscopic examination of repeat blood slides may suggest poor response to the antimalarial drug regimen (defined as <75% reduction from baseline parasitemia by day three of treatment or persistence of any asexual parasitemia by day 7) *or* the patient returns within a few weeks with another acute episode:
   1. Ensure adherence to treatment and consider decreased absorption resulting from acute illness, vomiting, or failure to take artemether-lumefantrine or atovaquone-proguanil with food containing fat.
   2. Gametocytes of *P. falciparum* are not eliminated by commonly used drug regimens and therefore may persist on smear despite treatment. These are not harmful to the patient, and no further treatment is required. Gametocytes should not be counted in the parasitemia determination.
   3. Consider the possibility of resistance and changing to a different antimalarial, preferably an artemisinin-based combination treatment and seek specialist advice.
   4. Relapse with a nonfalciparum species may occur after treatment for falciparum malaria, indicating a misdiagnosed mixed infection. In addition to treating the acute infection, give primaquine.

FURTHER READING

Diagnosis of Malaria

CDC, Malaria Diagnosis (US), available at <http://www.cdc.gov/malaria/diagnosis_treatment/diagnosis.html>.

Treatment of Malaria

CDC, Malaria Treatment (US), available at <http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html>.

Dondorp, A., Nosten, F., Stepniewska, K., et al., South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) Group, 2005. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 366, 717–725.

Phillips, R.E., Warrell, D.A., White, N.J., et al., 1985. Intravenous quinidine for the treatment of severe malaria: clinical and pharmacokinetic studies. N. Engl. J. Med. 312, 1273–1278.

World Health Organization, 2010. Guidelines for the Treatment of Malaria, second ed. WHO, Geneva. Online. Available at <http://www.who.int/malaria/publications/atoz/9789241547925/en/>.

Management Issues in Severe Malaria

Tan, K.R., Wiegand, R.E., Arguin, P.M., 2013. Exchange transfusion for severe malaria: evidence base and literature review. Clin. Infect. Dis. 57 (7), 923–928.

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