Malaria

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General Concepts

Clinical Manifestations

Initially patients have fever, chills, sweating, headache, weakness, and other symptoms mimicking a "viral syndrome." Later, severe disease may develop, with an abnormal level of consciousness, severe anemia, renal failure, and multisystem failure.

Classification

Plasmodia are protozoa. Only the species *Plasmodium falciparum*, *P vivax*, *P malariae*, and *P ovale* are usually infectious for humans. Of these, *P falciparum* is the most dangerous.

Structure and Life Cycle

In nature, uninucleate sporozoites in the salivary glands of infected mosquitoes are injected into a human host when the mosquito feeds. The sporozoites rapidly invade liver parenchymal cells, where they mature into liverstage schizonts, which burst to release 2,000 to 40,000 uninucleate merozoites. In *P vivax* and *P ovale* infections, maturation of the schizont may be delayed for 1 to 2 years. Each merozoite can infect a red blood cell. Within the red cell, the merozoite matures either into a uninucleate gametocyte-the sexual stage, infectious for *Anopheles* mosquitoes-or, over 48 to 72 hours, into an erythrocyticstage schizont containing 10 to 36 merozoites. Rupture of the schizont releases these merozoites, which infect other red cells. If a vector mosquito ingests gametocytes, the gametocytes develop in the mosquito gut to gametes, which undergo fertilization and mature in 2 to 3 weeks to sporozoites.

Pathogenesis

The fever and chills of malaria are associated with the rupture of erythrocyticstage schizonts. In severe falciparum malaria, parasitized red cells may obstruct capillaries and
postcapillary venules, leading to local hypoxia and the release of toxic cellular products. Obstruction of the microcirculation in the brain (cerebral malaria) and in other vital organs is thought to be responsible for severe complications. Cytokines (e.g., tumor necrosis factor) are also felt to be involved, but at present their role is unclear.

**Host Defenses**

Both innate and acquired immunity occur. Innate immunity consists of various traits of erythrocytes that discourage infection. The sicklecell trait protects against the development of severe *P falciparum* malaria, and the absence of Duffy antigen prevents infection by *P vivax*. Recurrent infections lead to the development of humoral and cellular immune responses against all *Plasmodium* stages. Acquired immunity does not prevent reinfection but does reduce the severity of disease.

**Epidemiology**

Malaria is distributed worldwide throughout the tropics and subtropics.

**Diagnosis**

Diagnosis depends primarily on the identification of plasmodia in thick and thin blood smears.

**Control**

**Treatment:** The widespread resistance of *P falciparum* to chloroquine complicates treatment of falciparum malaria. Alternative drugs such as mefloquine, pyrimethamine/sulfadoxine (FansidarR), quinine, quindine, halofantrine and artemisinin derivatives (qinghaosu) are used. Chloroquine remains highly effective against *P malariae* and *P ovale* malaria, and against *P vivax* everywhere except Papua New Guinea and parts of Indonesia, where significant resistance has developed. Disease caused by *P vivax* and *P ovale* requires primaquine to eradicate latent liver forms of the parasite.

**Prevention:** Malaria may be prevented by chemoprophylaxis and personal protective measures against the mosquito vector and by communitywide measures to control the vector. Exposure to nightfeeding *Anopheles* mosquitoes is reduced by using protective clothing, insect repellents, insecticides, insecticide-impregnated bed nets, etc. Mosquitoes may be reduced by destroying breeding places and by application of insecticides. Vaccines are being developed.
**INTRODUCTION**

Malaria has been a major disease of humankind for thousands of years. It is referred to in numerous biblical passages and in the writings of Hippocrates. Although drugs are available for treatment, malaria is still considered by many to be the most important infectious disease of humans: there are approximately 200 million to 500 million new cases each year in the world, and the disease is the direct cause of 1 million to 2.5 million deaths per year.

Malaria is caused by protozoa of the genus *Plasmodium*. Four species cause disease in humans: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Other species of plasmodia infect reptiles, birds and other mammals. Malaria is spread to humans by the bite of female mosquitoes of the genus *Anopheles*.

**Clinical Manifestations**

The most characteristic symptom of malaria is fever. Other common symptoms include chills, headache, myalgias, nausea, and vomiting. Diarrhea, abdominal pain, and cough are occasionally seen. As the disease progresses, some patients may develop the classic malaria paroxysm with bouts of illness alternating with symptomfree periods (Fig. 83-1). The malaria paroxysm comprises three successive stages. The first is a 15-to-60 minute cold stage characterized by shivering and a feeling of cold. Next comes the 2-to-6 hour hot stage, in which there is fever, sometimes reaching 41°C, flushed, dry skin, and often headache, nausea, and vomiting. Finally, there is the 2-to-4 hour sweating stage during which the fever drops rapidly and the patient sweats. In all types of malaria the periodic febrile response is caused by rupture of mature schizonts. In *P. vivax* and *P. ovale* malaria, a brood of schizonts matures every 48 hr, so the periodicity of fever is tertian ("tertian malaria"), whereas in *P. malariae* disease, fever occurs every 72 hours ("quartan malaria"). The fever in falciparum malaria may occur every 48 hr, but is usually irregular, showing no distinct periodicity. These classic fever patterns are usually not seen early in the course of malaria, and therefore the absence of periodic, synchronized fevers does not rule out a diagnosis of malaria.
Physical findings in malaria are nonspecific and offer little aid in diagnosis. In many cases there may be no positive findings other than fever. Splenomegaly is common but may not be apparent early in disease. Hepatomegaly, jaundice, hypotension and abdominal tenderness may also be seen. Malaria does not cause lymphadenopathy and is not associated with a rash.

A variety of laboratory abnormalities may be seen in a case of uncomplicated malaria. These include normochromic, normocytic anemia, thrombocytopenia, leukocytosis or leukopenia, hypoglycemia, hyponatremia, elevated liver and renal function tests, proteinuria, and laboratory evidence of disseminated intravascular coagulation (although clinically important bleeding is rare). Eosinophilia is not seen. Patients with complicated malaria occasionally show evidence of massive intravascular hemolysis with hemoglobinemia and hemoglobinuria.

If the diagnosis of malaria is missed or delayed, especially with *P falciparum* infection, potentially fatal complicated malaria may develop. The most frequent and serious complications of malaria are cerebral malaria and severe anemia. Cerebral malaria is defined as any abnormality of mental status in a person with malaria and has a case
fatality rate of 15 to 50 percent. Other complications include: hyperparasitemia (more than 3 to 5 percent of the erythrocytes parasitized); severe hypoglycemia; lactic acidosis; prolonged hyperthermia; shock; pulmonary, cardiac, hepatic, or renal dysfunction; seizures; spontaneous bleeding; or highoutput diarrhea or vomiting. These manifestations are associated with poor prognosis. Persons at increased risk of severe disease from malaria include older persons, children, pregnant women, nonimmune persons and those with underlying chronic illness. Other complications of malaria infection include gram-negative sepsis, aspiration pneumonia and splenic rupture.

Classification

Only four species of the protozoan genus *Plasmodium* usually infect humans: *P falciparum, P vivax, P malariae,* and *P ovale* (Fig. 83-2). *P falciparum* and *P vivax* account for the vast majority of cases. *P falciparum* causes the most severe disease.

**FIGURE 83-2 Blood stages of Plasmodium.** Column A, *Plasmodium vivax; B, P ovale; C, P malariae; D, P falciparum.* Row 1, young trophozoites (ring forms); 2, growing trophozoites; 3, mature trophozoites; 4, mature schizonts; 5, macrogametocytes; 6, microgametocytes. (From Strickland GT: Hunter's Tropical Medicine. 6th Ed. WB Saunders, Philadelphia, 1984, with permission.)
Structure and Life Cycle

Like many protozoa, plasmodia pass through a number of stages in the course of their two-host life cycle. The stage infective for humans is the uninucleate, lancet-shaped sporozoite (approximately 1 X 7 µm). Sporozoites are produced by sexual reproduction in the midgut of vector anopheline mosquitoes and migrate to the salivary gland. When an infected *Anopheles* mosquito bites a human, she may inject sporozoites along with saliva into small blood vessels (Fig. 83-3). Sporozoites are thought to enter liver parenchymal cells within 30 minutes of inoculation. In the liver cell, the parasite develops into a spherical, multinucleate liverstage schizont which contains 2,000 to 40,000 uninucleate merozoites. This process of enormous amplification is called exoerythrocytic schizogony. This exoerythrocytic or liver phase of the disease usually takes between 5 and 21 days, depending on the species of *plasmodium*. However, in *P. vivax* and *P. ovale* infections, maturation of liverstage schizonts may be delayed for as long as 1 to 2 years. These quiescent liver-phase parasites are called hypnozoites.

Regardless of the time required for development, the mature schizonts eventually rupture, releasing thousands of uninucleate merozoites into the bloodstream. Each merozoite can infect a red blood cell. Within the red cell, the merozoite develops to form either an...
erythrocytic stage (blood-stage) schizont (by the process of erythrocytic schizogony) or a spherical or bananashaped, uninucleate gametocyte. The mature erythrocytic stage schizont contains 8 to 36 merozoites, each 5 to 10 µm long, which are released into the blood when the schizont ruptures. These merozoites proceed to infect another generation of erythrocytes. The time required for erythrocytic schizogonyy which determines the interval between the release of successive generations of merozoites varies with the species of *Plasmodium* and is responsible for the classic periodicity of fever in malaria (Fig 83-1).

The gametocyte, which is the sexual stage of the *Plasmodium*, is infectious for mosquitoes that ingest it while feeding. Within the mosquito, gametocytes develop into female and male gametes (macrogametes and microgametes, respectively), which undergo fertilization and then develop over 2 to 3 weeks into sporozoites that can infect humans. The delay between infection of a mosquito and maturation of sporozoites means that female mosquitoes must live a minimum of 2 to 3 weeks to be able to transmit malaria. This fact is important in malaria control efforts.

**Pathogenesis**

Clinical illness is caused by the erythrocytic stage of the parasite. No disease is associated with sporozoites, the developing liver stage of the parasite, the merozoites released from the liver, or gametocytes.

The first symptoms and signs of malaria are associated with the rupture of erythrocytes when erythrocytic stage schizonts mature. This release of parasite material presumably triggers a host immune response. The cytokines, reactive oxygen intermediates, and other cellular products released during the immune response play a prominent role in pathogenesis, and are probably responsible for the fever, chills, sweats, weakness, and other systemic symptoms associated with malaria. In the case of *falciparum* malaria (the form that causes most deaths), infected erythrocytes adhere to the endothelium of capillaries and postcapillary venules, leading to obstruction of the microcirculation and local tissue anoxia. In the brain this causes cerebral malaria (Fig. 83-4); in the kidneys it may cause acute tubular necrosis and renal failure; and in the intestines it can cause ischemia and ulceration, leading to gastrointestinal bleeding and to bacteremia secondary to the entry of intestinal bacteria into the systemic circulation. The severity of malaria-associated anemia tends to be related to the degree of parasitemia. The pathogenesis of this anemia appears to be multifactorial. Hemolysis or phagocytosis of parasitized erythrocytes and ineffective erythropoiesis are the most important factors, and phagocytosis of uninfected erythrocytes and an autoimmune hemolytic anemia have also been implicated. Massive intravascular hemolysis leading to hemoglobinuria and renal failure is referred to as blackwater fever. It was described more frequently in the past than currently. Hemolysis may also occur after the use of certain antimalarials (especially primaquine) in patients with glucose 6phosphate dehydrogenase deficiency.
**FIGURE 83-4** Light micrograph of a cerebral capillary blocked with parasitized erythrocytes. This specimen is from a patient with cerebral malaria. (From Aikawa M: Morphological changes in erythrocytes induced by malarial parasites. Biol Cell 64:174, 1988, with permission.)

**Host Defenses**

Susceptibility to malaria infection and disease is regulated by hereditary and acquired factors (Fig 83-5). It now seems clear that the sickle cell trait (which is the cause of sicklecell anemia) developed as a balanced polymorphism to protect against serious *P falciparum* disease. Although individuals with sickle cell anemia or the sickle cell trait are as easily infected with malaria parasites as normal individuals, they rarely exhibit malaria disease because *P falciparum* develops poorly in their erythrocytes. The virtual absence of *P vivax* infections in many areas of Africa is explained by the fact that most blacks do not have Duffy bloodgroup antigens, which apparently function as erythrocyte surface receptors for *P vivax* merozoites; without the Duffy antigen, the parasites cannot invade. Malaria parasites do not develop well in ovalocytes, and it has been suggested that ovalocytosis, which is quite common in some malarious areas, such as New Guinea, may reduce the incidence of malaria. Some investigators have suggested that glucose 6phosphate dehydrogenase deficiency, as well as a number of other hemoglobinopathies
(including the thalassemias and hemoglobin E), also protect against malaria infection, but the evidence for these associations is less compelling.

FIGURE 83-5 Host defense against malaria. (Adapted from Miller LH, Howard RJ, Carter R et al: Research toward malaria vaccines. Science 234:1350, 1986, with permission.)

Acquired immunity can also protect against malaria infection and the development of malaria disease. In malarious areas, both the prevalence and severity of malaria infections decrease with age. However, in contrast to many viral infections, multiple infections with malaria do not confer longlasting, sterile protective immunity. Virtually all adults in malarious areas suffer repeated malaria infections. Individuals who are repeatedly exposed to malaria develop antibodies against many sporozoite, liver-stage, blood-stage, and sexual-stage malaria antigens. It is thought that antibodies acting against sporozoites, liver-stage and blood-stage organisms are responsible for the decreased susceptibility to malaria infection and disease seen in adults in malarious areas, and that antibodies against the sexual stages of plasmodia may reduce malaria transmission. Additional work also suggests that the naturally acquired immunity includes the release of cytokines that act against all stages of the parasite, and also a cytotoxic T cell response directed at liver stages of the parasite.

Acquired antibody-mediated immunity is apparently transferred from mother to fetus across the placenta. This passively transferred immunity is lost within 6 to 9 months, as is
the immunity in adults if they leave a malarious area and are no longer exposed to plasmodia. Pregnant women, particularly primigravidas, are more susceptible to malaria infections and serious disease.

**Epidemiology**

Malaria is transmitted primarily by the bite of infected anopheline mosquitoes. It can also be transmitted by inoculation of infected blood and congenitally. Anophelines feed at night and their breeding sites are primarily in rural areas. The greatest risk of malaria is therefore from dusk to dawn in rural areas. In many malaria-endemic areas, there is little or no risk in urban areas. However, urban transmission is common in some parts of the world, especially Africa.

Malaria was once transmitted in many parts of the world, for example, as far north as North Dakota in the United States. Due both to environmental changes and to eradication campaigns conducted in the years after World War II, endemic malaria transmission has been eliminated from many areas, including the United States and Europe. The disease is still widely transmitted in the tropics and subtropics (Fig. 83-6). In these areas malaria transmission may be endemic, occurring predictably every year, or it may be epidemic, occurring sporadically when conditions are correct. Endemic transmission of malaria may be yearround or seasonal. In some areas of Africa, 90 to 100 percent of children less than 5 years old have malaria parasites circulating in their blood all the time. Because naturally acquired immunity develops with increasing exposure, in endemic areas malaria disease is primarily found in children. In epidemic areas, on the other hand, naturally acquired immunity falls off between epidemics, and malaria therefore affects all age groups during epidemics.
Approximately 1,000 cases of malaria are reported each year in the United States in returning travelers. Of the 1016 imported cases reported in 1991, the majority were acquired in Africa (466 cases) and India (221 cases). *P. vivax* accounted for 43% of the cases and *P. falciparum* for 39%. The risk to travelers of acquiring *P. falciparum* is greatest in Africa. This is because it is the most prevalent species there, malaria transmission is much more intense there than in other parts of the world, and there is significant risk in urban areas.

*Anopheles* mosquitoes capable of transmitting malaria are found in a number of areas of the United States. Local transmission may therefore occur when these mosquitoes feed upon malarial infected individuals, generally immigrants from malaria-endemic areas. Local transmission has recently occurred in southern California, New Jersey, New York City, and Houston, Texas. Malaria may also occur when infected mosquitoes are transported into non-endemic areas, such as by airplanes or ships.

In the late 1950s and early 1960s, it was thought that malaria could be eradicated through the widespread use of insecticides such as DDT and by treatment of cases with chloroquine. Eradication is no longer thought possible, however, because of the development of drug resistance by both the mosquito and the parasite, and because of deteriorating social and economic conditions in many malaria-endemic countries. These
changes have resulted in a dramatic increase in the incidence of malaria in many parts of the world, and an increase in malaria-related mortality in some of these areas.

**Diagnosis**

In the United States, many of the deaths from malaria are the result of delayed diagnosis and treatment because the health care provider did not suspect malaria. The diagnosis of malaria requires a high index of suspicion; malaria should be considered in any individual who has a fever and has visited an endemic area for malaria, received a blood transfusion, or used intravenous drugs. Although 95 percent of individuals infected with malaria develop their primary illness within 6 weeks of exposure, some may have primary attacks up to a year after exposure, and relapses of malaria can occur up to 2-3 years after exposure. Therefore, individuals having a febrile illness and a history of exposure in the last 2-3 years should be evaluated for malaria.

Definitive diagnosis of malaria generally requires direct observation of malaria parasites in Giemsa-stained thick and thin blood smears (Fig. 83-2). Thick blood smears are more difficult to interpret than thin blood smears but they are much more sensitive, as more blood is examined. Thin blood smears, in which parasites are seen within erythrocytes, are used to determine the species of the infecting parasite. The presence of diagnostic forms can vary markedly with the stage of the life cycle, especially early in disease. In falciparum malaria, most organisms are not present in the peripheral blood because they are sequestered in the microvascular tissue of internal organs. If malaria is suspected, blood smears should be examined every 6 to 12 hr for at least 2 days. New diagnostic methods include a rapid antigen-capture dipstick test and a technique for detecting parasites with a fluorescent stain. Both of these tests are fast, easy to perform and are highly sensitive and specific.

Other diagnostic methods include assays to detect malaria antibodies and antigens, and polymerase chain reaction/DNA and RNA probe techniques. These techniques are used primarily in epidemiologic studies and immunization trials and rarely in the diagnosis of individual patients.

**Control**

The principles of medical management of malaria reflect the fact that falciparum malaria can progress rapidly to a life-threatening state and that complications can occur even after the initiation of therapy. They are: (1) early recognition of infection due to *P. falciparum*; (2) rapid institution of appropriate therapy; (3) recognition and therapy of complications; and (4) monitoring of clinical and parasitologic response to therapy.
Malaria therapy is complicated by the fact that parasites may be present in the blood and the liver and that different drugs are required to eradicate each. Drugs which kill malaria parasites in the blood are called bloodstage schizonticides and those that kill them in the liver are called tissue schizonticides. A clinical cure refers to the elimination of parasites from the blood, which will relieve the signs and symptoms of disease. A radical cure is the eradication of all parasites from the body, both blood and liver. In cases of *P. falciparum* and *P. malariae*, which do not have latent liver forms (hypnozoites), an effective dose of a blood schizonticide to which the parasite is sensitive should lead to radical cure. In cases of *P. vivax* and *P. ovale* malaria, which do form hypnozoites, radical cure requires therapy with both a blood schizonticide and a tissue schizonticide.

Recurrence of malaria infections after treatment is due either to recrudescence or to relapse. Recrudescence occurs when the blood schizonticide does not eliminate all parasites from the blood stream, either because the dose was inadequate or because the parasite is resistant to the drug. Relapse occurs in *P. vivax* and *P. ovale* infections after the delayed development of liver-stage parasites that have not been treated adequately with a tissue schizonticide.

Resistance of malaria parasites to antimalarials may be complete or relative; relative resistance can be overcome by raising the dose of the antimalarial.
The choice of blood schizonticide depends upon the clinical condition of the patient, infecting species and possibility of drug resistance. Parenteral therapy is reserved for patients unable to take medications by mouth and for those with complicated malaria.

Chloroquine-resistant *P. falciparum* is widespread and currently exists in all malarious areas of the world except Mexico, Central America, the Caribbean and parts of the Middle East.

*P. falciparum* resistant to multiple drugs is most prevalent in S.E. Asia but is also present in Africa and Brazil. Chloroquine-resistant *P. vivax* is prevalent on the island of New Guinea. Primaquine-resistant *P. vivax* is most prevalent in S.E. Asia and Oceania and is reported from other areas. Drug resistance has not been reported for *P. ovale* or *P. malariae*.

If ever in doubt as to infecting species or presence of resistance, clinicians should assume the infection to be chloroquine-resistant *P. falciparum*. Such therapy will cover all malaria species, although side effects may be more common.

The response to antimalarial therapy is monitored both clinically and by examining repeated blood films. Blood smears should be continued daily in all malaria patients until parasites are no longer detected. In severe or complicated malaria, parasitemia should be evaluated twice daily. Parasitemia should decrease by 75% and clinical status improve within 48 hr after initiating therapy. If not, drug resistance, inadequate drug levels or the presence of clinical complications should be suspected.

### Treatment of Specific Infections

**Uncomplicated, chloroquine-sensitive infections**

All patients with uncomplicated *P. malariae*, *P. ovale*, and *P. vivax* and *P. falciparum* from chloroquine sensitive areas (see above and Fig 83-6) should be treated with oral chloroquine. The drug is highly effective, well tolerated and inexpensive.

**Uncomplicated, chloroquine-resistant *P. falciparum***

Therapy of chloroquine-resistant *P. falciparum* is complicated and depends primarily on area of disease acquisition. Patients with uncomplicated disease acquired in areas of chloroquine resistance can be treated with one of several regimens effective against chloroquine-resistant parasites. In the United States, two regimens are used primarily: (1) mefloquine alone, or (2) quinine, plus doxycycline or pyrimethamine/sulfadoxine (Fansidar®). Other effective drugs include halofantrine, artemisinin (qinghaosu) derivatives, and clindamycin. Halofantrine and artemisinin are used widely overseas but are not currently available in the U.S.

**Uncomplicated, chloroquine-resistant *P. vivax***
Chloroquine-resistant *P. vivax* is highly prevalent on the island of New Guinea (Papua New Guinea and Irian Jaya, Indonesia) and may be present elsewhere. Recent studies in Indonesia have shown halofantrine, and chloroquine plus primaquine to be highly effective against these resistant strains. Although not specifically tested, the above regimens for chloroquine-resistant *P. falciparum* should also be effective.

**Complicated infections**

Severe or complicated malaria is a medical emergency. It is caused almost exclusively by *P. falciparum*. Patients with complicated malaria (see Clinical Manifestations above) should be treated with intravenous antimalarials and in an intensive care unit whenever possible. The drugs of choice are intravenous quinidine or quinine (IV quinine no longer available in the U.S.). Patients on these regimens must be observed closely for signs of hypotension or myocardial conduction abnormalities. Therapeutic plasma levels are 5 to 15 µg/ml for quinine and 5 to 10 µg/ml for quinidine. Oral quinine, plus doxycycline or FansidarR, is substituted as soon as there is clinical improvement. If acquired in an area of chloroquine-sensitive parasites, parenteral chloroquine may also be given. Artemisinin compounds show promise for therapy of severe malaria because they decrease parasitemia faster than all other antimalarials.

Any complicated *P. malariae, P. vivax, or P. ovale* infection should be treated in the same way as a complicated *P. falciparum* infection, since mixed infections are common.

**Radical cure of *P. vivax* and *P. ovale* infections**

For infections due to *P. vivax* or *P. ovale*, primaquine should be given after therapy of the blood-stage infection to eradicate hypnozoites of these species and prevent relapses. *P. vivax* with decreased sensitivity to primaquine is prevalent in SE Asia and Oceania, where up to 30% of cases relapse after the standard regimen of 15 mg/day primaquine base for 14 days, and is reported from other areas. Resistance is usually relative and most initial failures respond to 30 mg/day for 14 days. Primaquine should be used with caution in persons who are G6PD deficient due to its potential to cause severe hemolysis.

**Ancillary Therapy and Treatment of Complications**

Supportive care and therapy of malaria complications may be as critical as choosing the correct antimalarial. Clinicians should monitor patients for complications (see Clinical Manifestations) and treat them as they occur.

Hyperthermia should be treated with cooling blankets and antipyretics. Proper fluid management is essential to prevent renal failure or pulmonary edema. If oliguric renal failure persists after fluid status is corrected, the patient is treated like other patients in the oliguric stage of acute tubular necrosis. Pulmonary edema, which may present like the adult respiratory distress syndrome (ARDS), is an uncommon but frequently fatal complication of severe *P. falciparum* infection. It is treated by careful fluid management and application of the principles used in treating ARDS. Transfusion of erythrocytes may
be necessary for severe anemia. Seizures are frequent with cerebral malaria and should be
treated with standard anticonvulsants. Corticosteroids are of no benefit in the therapy of
cerebral malaria. Hyperparasitemia may be treated with exchange transfusion. Exchange
transfusion is generally reserved for individuals with more than 15 percent parasitemia or
more than 5 percent parasitemia with cerebral malaria or other severe manifestation.
Plasma glucose levels should be monitored regularly and hypoglycemia treated if it
occurs. Aspiration pneumonia may occur when unconscious cerebral malaria patients
suffer seizures and vomiting. Aspiration is prevented by controlling seizures and by
attention to general airway management in the unconscious patient. Gramnegative
bacteremia is a frequent accompaniment of severe *P. falciparum* infection. Gramnegative
organisms probably enter the circulation in areas of the bowel wall that are ischemic as a
result of microcirculatory obstruction by parasitized erythrocytes. Any patient who is not
responding to antimalarial therapy as expected should be investigated for bacteremia.
Hypotension and shock may complicate severe malaria. If these occur, treatable causes
should be considered, including Gramnegative sepsis, gastrointestinal hemorrhage,
hypovolemia, and splenic rupture. Splenic rupture is seen infrequently but is one of the
few fatal complications of vivax malaria.

Recent studies have found a strong association between sustained lactic acidosis and poor
outcome in severe malaria. Until further work defines the role of specific interventions
(e.g., sodium dichloroacetate and sodium bicarbonate) in reversing lactic acidosis in
severe malaria, treatment must be aimed at the correction of defects in oxygenation and
tissue perfusion and metabolic abnormalities such as hypoglycemia.

**Special Conditions**

Malaria during pregnancy presents a unique problem. Pregnant women are at higher risk
of developing severe and fatal malaria. Hyperparasitemia, hypoglycemia and pulmonary
edema are more common in pregnant women with *P. falciparum* infections. Pregnant
women should be treated promptly with appropriate doses of antimalarials. Quinine does
not appear to induce labor as was once thought. Pregnant women with chloroquine-
sensitive *P. vivax* infections should be treated with chloroquine to eliminate the
erythrocyticstage infection and then placed on weekly chloroquine to prevent relapse, as
the safety of primaquine in pregnancy is not known.

**Prevention of Malaria**

Individuals with little or no previous exposure who develop malaria may rapidly progress
to severe, often fatal disease. Most cases of malaria in Americans can be prevented by
chemoprophylaxis and by avoiding the mosquito vector.

The female *Anopheles* mosquito feeds from dusk until dawn. During these hours,
individuals should avoid contact with the mosquito by wearing protective clothing, using
an insect repellent containing N,N-diethyltoluamide (DEET), staying in screened areas
and spraying these areas with pyrethrumincontaining insecticides, and by sleeping under
insecticide-impregnated bednets.
Travelers to endemic areas should be advised not only on avoiding the mosquito vector but also on chemoprophylaxis. It must be emphasized that chemoprophylaxis is not one hundred percent effective; regardless of prophylaxis, malaria must be considered in the differential diagnosis of any febrile illness in an individual who has been in an area endemic for malaria within the last 2-3 years.

Chemoprophylaxis is designed to kill the parasite after it has gained access to the body but before it leads to the rupture of host RBCs, which causes the symptoms of malaria. Drugs may accomplish this by attacking the parasite in either the liver or the blood. Causal chemoprophylaxis refers to killing the parasite in the liver before it gains access to the blood. Suppressive chemoprophylaxis is accomplished by drugs which attack asexual parasites in the blood. Most antimalarial drugs attack parasites in the blood and are therefore suppressive chemoprophylactics. Primaquine is the only antimalarial drug currently available which reliably kills liver stage organisms.

The choice of a chemoprophylactic regimen depends on several factors: the health of the individual (including factors such as pregnancy, age, and chronic illness); the risk and types of malaria in the areas to be visited; and the presence of drug resistant \( P \text{ falciparum} \).

Chloroquine is the recommended chemoprophylactic for those travelling to areas where plasmodia are still chloroquine sensitive (Mexico, Central America, Haiti, the Dominican Republic, and the Middle East). There are very few contraindications to chloroquine. Most travellers, however, visit areas where there is chloroquine resistance and other drugs, generally with greater toxicity, must be used. For most of these travelers, mefloquine is the drug of choice and doxycycline is as acceptable alternative. Extensive mefloquine resistance makes doxycycline the drug of choice for those visiting the borders of Thailand. Chloroquine plus proguanil (proguanil is not available in the U.S.) is another possible regimen for chloroquine-resistant areas, but this regimen is much less effective than mefloquine or doxycycline. Recent work also suggests that primaquine, apparently acting against liver-stage organisms, is as effective as mefloquine and doxycycline for chemoprophylaxis in areas of chloroquine resistance.

Prophylaxis with chloroquine or mefloquine should begin 2 weeks before entering the malarious area (to ensure tolerance to the drug and to provide adequate blood levels) and should continue throughout the stay in the area and for 4 weeks after leaving. Doxycycline should be started 1 to 2 days before travel to a malarious area and should be taken daily during the stay in the area and for 4 weeks after leaving. Taking the drugs after leaving the malarious area is referred to as terminal prophylaxis and is necessary to kill organisms which emerge from the liver after the person returns home. When there has been a significant risk of exposure to \( P \text{ vivax} \) or \( P \text{ ovale} \), primaquine should be taken for 14 days after returning home to eliminate remaining liver stage parasites. Primaquine may be taken any time during the 4 weeks in which the blood schizonticide is being taken. See Table 83-1 for drug dosages.
Control in Populations

Control of malaria is difficult and requires the sustained effort of many individuals from many disciplines (Fig. 83-8). It is much more easily accomplished in some areas of the world than others. Control can be extremely difficult in areas where the *Anopheles* vector is numerous, longlived, and feeds only on humans.
Transmission of malaria requires the presence of three factors: (1) malaria-infected humans carrying gametocytes that are infective to mosquitoes, (2) *Anopheles* mosquitoes that live long enough for the malaria parasites to develop within them to the infective sporozoite stage, and (3) infected mosquitoes that bite noninfected humans. Malaria control can be applied at each of these points: by treating human malaria infections and thereby reducing or eliminating the number of infected humans that mosquitoes feed on, by eliminating or reducing the numbers of *Anopheles* mosquitoes, by shortening the life span of mosquitoes to less than that required for the parasite to develop, or by providing alternative hosts for the mosquitoes to feed on.

There have been numerous efforts to reduce transmission by treating infected humans with drugs that render them noninfectious to mosquitoes. The success of these efforts is unclear.

Major efforts are under way to develop vaccines against malaria. Vaccines may be directed against any of the multiple stages of the organism's life cycle. Some vaccines attempt to prevent or diminish disease in the individual by inducing immune responses against sporozoites, liverstage parasites, or erythrocyticstage parasites, or by preventing the release of cellular products thought to be involved in pathogenesis. Other vaccines
attempt to block transmission to others by inducing antibodies or cytokines that attack gametocytes, or antibodies that prevent development of the extracellular stages within mosquitoes. Several vaccines are currently undergoing evaluation in clinical trials. Recently noteworthy is SPf66, a synthetic vaccine produced in Colombia which contains peptides from the organism's blood and sporozoite stages. Although initial results were promising, subsequent clinical trials have reported protective efficacies of only about 30% against first clinical episodes of *P. falciparum*. Further evaluation is needed to define the role of this vaccine in reducing the morbidity and mortality from malaria in various settings.

A second approach in malaria control is to reduce transmission by eliminating mosquitoes—primarily by eliminating breeding places such as lagoons and swamps or by killing the larvae in these breeding places. This approach has been quite successful in some parts of the world, particularly in areas where malaria transmission is not intense. Transmission can also be reduced by the use of insecticide-impregnated bednets. Several studies have shown the effectiveness of these bednets in reducing the morbidity from malaria in areas of intense transmission.

Another approach is to treat dwellings with residual insecticides, such as DDT, that shorten the lifespan of mosquitoes, thereby reducing the chance that they will live long enough to transmit malaria. This approach has been quite successful in some parts of the world, but has had significant problems because of the development of mosquitoes resistant to insecticides.

In some areas of the world where malaria vectors prefer animals, such as cows, to humans, the introduction of these animals has reduced malaria transmission.

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