Malaria

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EPIDEMOLOGY

Malaria is a global parasitic disease caused by four species of *Plasmodium*: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Approximately 40% of the world’s population live in malaria-endemic areas, and an estimated 300–500 million cases occur annually. The majority of deaths occur in infants and children (WHO Special Programme for Research and Training in Tropical Diseases Web site: http://www.who.int/tdr/diseases/malaria/direction.htm). Progress in the diagnosis and treatment of malaria has been hampered by its prevalence mainly in impoverished areas of the world, limiting patient access to health care and funds for research. Malaria was eradicated in the United States during the 1950s via a combination of mosquito control programs and aggressive antimalarial treatment of infected individuals (1). However, cases in the United States continue to be reported annually. Most cases are described in recent immigrants, but rarely cases occur through blood transfusions, congenital transmission, or cryptic transmission in patients without identifiable exposure to malaria (2).

PLASMODIUM LIFE CYCLE

*Plasmodium* is a unicellular protozoan in the order Kinetoplastida, which also includes the pathogenic parasites *Toxoplasma* and *Trypanosoma*. *Plasmodium* requires an insect host, the Anopheles mosquito, and a mammalian host during the sexual and asexual life cycle stages, respectively. *Plasmodium* species exhibit restricted host specificity, such that species causing human malaria are unable to survive in nonhuman hosts. Conversely, *Plasmodium* species infecting other mammals are not capable of causing human disease. This host range limitation facilitated the eradication of malaria in previously endemic areas of the United States as no animal reservoirs persisted after *Plasmodium* was eliminated from the human population.

On entry into the human circulatory system via the bite of an infected mosquito, *Plasmodium* sporozoites rapidly attach to and enter hepatocytes. During this hepatic or exo-erythrocytic stage, sporozoites undergo asexual reproduction within hepatocytes over 5–15 days, ultimately lysing the host cell to release merozoites into the bloodstream. A proportion of *P. vivax* and *P. ovale* sporozoites do not replicate but remain inert as hypnozoites within hepatocytes, retaining the ability to reactivate and cause
relapses months or even years after initial infection. Such forms are responsible for clinical disease long after an individual has left an endemic area and may cause congenital malaria in offspring of women experiencing unsuspected reactivations during pregnancy. In contrast, *P. falciparum* and *P. malariae* do not maintain liver latency and do not cause disease recrudescence after acute infection. However, *P. malariae* has been reported to persist at low levels in the bloodstream for years and thus may cause congenital malaria in children born to asymptomatic mothers (1,3).

Once liberated from hepatocytes into the bloodstream, merozoites rapidly invade circulating erythrocytes. *P. vivax* utilizes the Duffy blood group antigen as a receptor (4), whereas the receptors utilized by the other *Plasmodium* species remain undetermined. *P. vivax* and *P. ovale* infect only reticulocytes; *P. malariae* infects only old red blood cells (RBCs), thus limiting the degree of parasitemia and severity of clinical disease associated with these infections. In contrast, *P. falciparum* is capable of infecting erythrocytes of any age, reaching high parasitemias, and often causing life-threatening disease. After entering the erythrocyte, intraerythrocytic parasites undergo further asexual replication, filling and eventually rupturing the host RBC. The intraerythrocytic life cycle is characteristically 48–72 hours, depending on the *Plasmodium* species. These cycles of synchronized erythrocyte lysis are responsible for the classically described quotidian and tertian fevers experienced in clinical malaria. Clinical disease resolves with antimalarial treatment or the development of strain-specific antibodies. However, these antibodies do not protect against reinfection, thus allowing patients in endemic areas to experience multiple episodes of clinical malaria throughout their lives (1,3).

Finally, some intraerythrocytic parasites develop into sexual gametocytes. When ingested by a mosquito feeding on the human host, the gametocytes undergo sexual reproduction in the mosquito gut to form diploid zygotes that mature and undergo meiosis into haploid sporozoites, which are again capable of infecting humans. Each species of *Plasmodium* forms a morphologically distinctive gametocyte. In patients from geographic areas harboring multiple *Plasmodium* species, definitive diagnosis of the species infecting a given human patient requires identification of the gametocyte on a blood smear. Research laboratories are capable of performing species-specific polymerase chain reaction (PCR) from whole blood, but this technique is not commercially available (5,6).

**CLINICAL MANIFESTATIONS: ADULTS AND CHILDREN**

Acute malaria manifests during the erythrocytic phase of infection. Symptoms in immunologically naïve hosts are initially nonspecific and include fevers, rigors, headache, myalgias, lethargy, abdominal pain, and vomiting. In children, symptoms may present acutely and in a rapidly progressive fashion with seizures, hypoglycemia, severe anemia, and hypotension. The physical examination may reveal hepatosplenomegaly, but despite hemolysis, jaundice is not frequently observed. Cerebral malaria, characterized by unarousable coma caused by sludging of parasitized erythrocytes in cerebral capillaries, is a severe complication of falciparum malaria and is fatal if untreated.

In contrast, partially immune hosts (i.e., patients living in malaria-endemic areas) may have asymptomatic circulating parasitemia. Others may have intermittent fevers without localizing signs or severe disease. In these cases, interpretation of positive