Malaria, an infection caused by *Plasmodium spp.*, has affected mankind for millennia. The word malaria means 'bad air', and refers to the association between the illness and the marshes where Anopheles mosquitoes breed. It's a major problem in tropical countries where it causes an estimated 216 million cases and 655000 deaths per year.

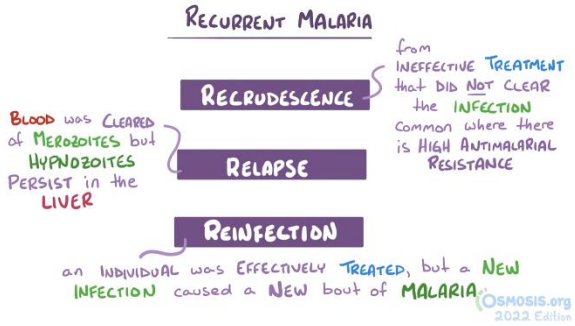
The Organisms

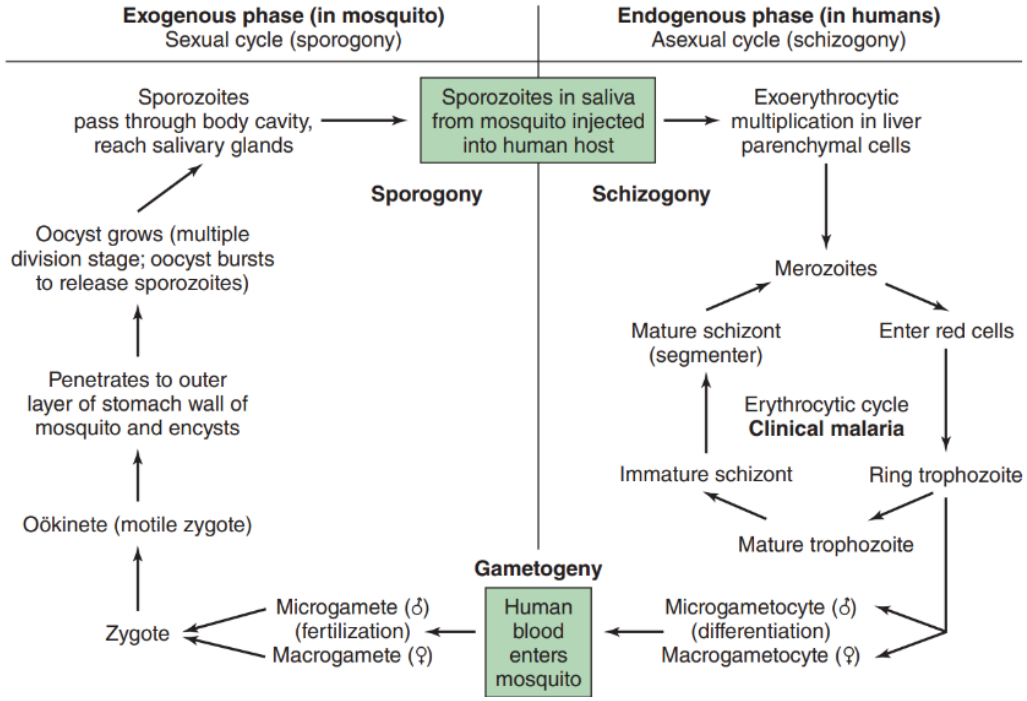
There are four main species of Plasmodium that cause malaria in humans: ***Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, and Plasmodium ovale. Plasmodium knowlesi.*** The two most common species are *P vivax and P falciparum*, with falciparum being the most pathogenic of all. Transmission to humans is by the bloodsucking bite of female ***Anopheles mosquitoes***.

Human infection results from the bite of an infected female Anopheles mosquito, through which the sporozoites are injected into the bloodstream. The sporozoites rapidly (usually within 1 hour) enter parenchymal cells of the liver, where the first stage of development in humans takes place (exoerythrocytic phase of the life cycle). Subsequently, numerous asexual progeny, the merozoites, rupture and leave the liver cells, enter the bloodstream, and invade erythrocytes. The merozoites do not return from red blood cells to liver cells.

Parasites in the red cells multiply in a species-characteristic fashion, breaking out of their host cells synchronously. This is the erythrocytic cycle, with successive broods of merozoites appearing at 48-hour intervals (*P vivax, P falciparum, and P ovale*) or every 72 hours (*P malariae*). During the erythrocytic cycles, certain merozoites enter red cells and become differentiated as male or female gametocytes.

The sexual cycle therefore begins in the vertebrate host (e.g.,Human), but for its continuation into the sporogonic phase, the gametocytes must be taken up and ingested by bloodsucking female Anopheles. *P vivax* and *P ovale* may persist as dormant forms, or hypnozoites, after the parasites have disappeared from the peripheral blood. Resurgence of an erythrocytic infection (**relapse**) occurs when merozoites from hypnozoites in the liver break out, are not phagocytosed in the bloodstream, and succeed in reestablishing a red cell infection. Without treatment, *P vivax* and *P ovale* infections may persist as periodic relapses for up to 5 years.





Pathology and Pathogenesis

The incubation period for malaria is usually between 9 and 30 days, depending on the infecting species (*P vivax and P falciparum*:10–15 days, but it may be weeks or months. *P.malariae* about 28 days).

Five Plasmodium species cause human infection:

• ***P. falciparum*** can invade RBCs of all ages, may be drug-resistant, and is responsible for most severe, life-threatening infections. It does not produce dormant liver stages (hypnozoites) or cause relapse.

[P falciparum invades red cells of all ages, including the erythropoietic stem cells in bone marrow, so parasitemia may be very high. P falciparum also causes parasitized red cells to adhere to the endothelial lining of blood vessels, with resulting obstruction, thrombosis, and local ischemia. *P falciparum* infections are therefore far more serious than the others, with a much higher rate of severe and frequently fatal complications (cerebral malaria, malarial hyperpyrexia, gastrointestinal disorders, algid malaria, blackwater fever). Consideration of malaria in the differential diagnosis in patients with a suggestive presentation and history of travel to an endemic area is critical because delays in therapy can lead to severe illness or death with falciparum malaria.]

• ***P. vivax*** **and** ***P. ovale*** cause clinically similar, milder infections. They produce hypnozoites and may cause relapse months after the initial infection.

• ***P. malariae*** rarely causes acute illness in normal hosts, does not produce hypnozoites, but may persist in the bloodstream for years.

• ***Plasmodium knowlesi*** causes malaria in macaques and has recently been recognized as a cause of human malaria in South East Asia. Microscopically, it resembles *P. malariae* but can cause fatal disease (like *P. falciparum*).

Mixed infections may occur in 5–7% of patients.

Normocytic anemia of variable severity may be detected. During the paroxysms, there may be transient leukocytosis; subsequently, leukopenia develops, with a relative increase in large mononuclear cells. Liver function tests may give abnormal results during attacks but revert to normal with treatment or spontaneous recovery. In severe *P falciparum* infections, renal damage may cause oliguria and the appearance of casts, protein, and red cells in the urine.

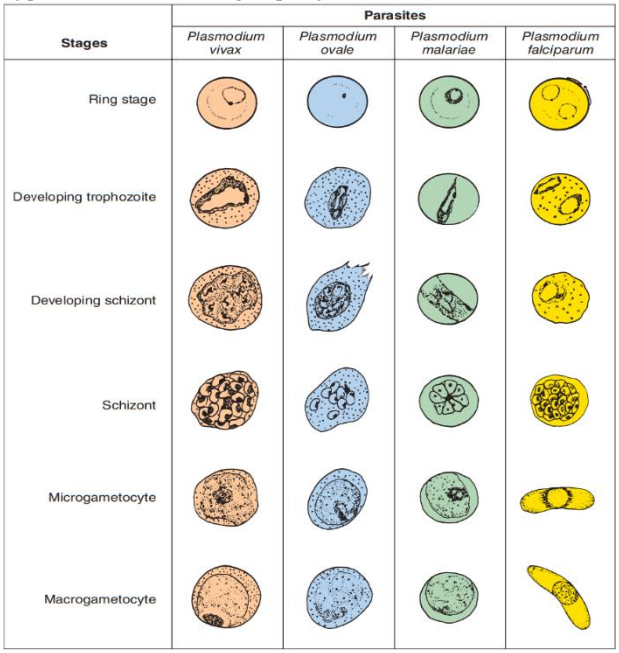
Periodic paroxysms of malaria are closely related to events in the bloodstream. An initial chill, lasting from 15 minutes to 1 hour, begins as a synchronously dividing generation of parasites rupture their host red cells and escape into the blood. Nausea, vomiting, and headache are common at this time. The succeeding febrile stage, lasting several hours, is characterized by a spiking fever that frequently reaches 40°C or more. During this stage, the parasites invade new red cells. The third, or sweating, stage concludes the episode. The fever subsides, and the patient falls asleep and later awakes feeling relatively well. In the early stages of infection, the cycles are frequently asynchronous and the fever patern is irregular; later, paroxysms may recur at regular 48- or 72-hour intervals, although P falciparum pyrexia may last 8 hours or longer and may exceed 41°C. As the disease progresses, splenomegaly and, to a lesser extent, hepatomegaly appear. A normocytic anemia also develops, particularly in P falciparum infections.

Laboratory diagnosis

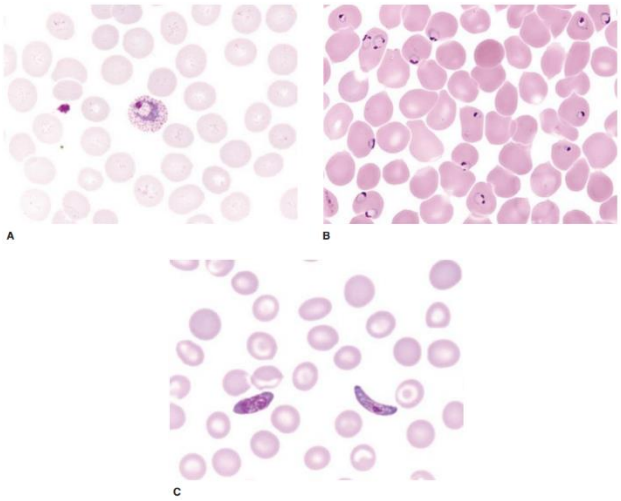
• Thick and thin blood smears, stained with Field's stain or Giemsa stain, examined under light microscopy.

• Malaria dipstick tests. These detect plasmodial lactate dehydrogenase (LDH)

• hemolytic anemia, thrombocytopenia (common), uremia, hyperbilirubinemia, coagulopathy.



Morphologic characteristics of developmental stages of malarial parasites ***in the red blood cell****. Note cytoplasmic Schüffner dots and enlarged host cells in* ***Plasmodium vivax*** *and* ***Plasmodium ovale*** *infections, the band-shaped trophozoite often seen in* ***Plasmodium malariae*** *infection, and the small, often multiply infected rings and the banana-shaped gametocytes in* ***Plasmodium falciparum*** *infections. Rings and gametocytes are typically seen in peripheral blood smears from patients with* ***Plasmodium falciparum infections.***



*Distinguishing features between the two most common malarial parasites: **A**: Plasmodium vivax trophozoite inside a red blood cell with Schüffner dots. **B**: Double rings and **C**: banana-shaped gametocytes are typically seen in P falciparum infections.*

Treatment

• Antimalarials —remain the mainstay of therapy, but successful treatment is threatened by increasing drug resistance.

The main classes of drugs are: • quinoline derivatives (chloroquine, quinine, mefloquine, halofantrine);

• ribosomal inhibitors (clindamycin);

• artemisinin derivates (artemisinin, artemether, artemotil, artesunate); artemisinin derivatives are the treatment of choice and show rapid parasite clearance, and have low toxicity and limited resistance (in South East Asia).

• Supportive therapy—good supportive therapy, with careful management in severe malaria. Exchange transfusion may be helpful in hyperparasitemia.

Prevention

Chemoprophylaxis, taken rigorously, is efficacious in reducing the incidence of malaria in travellers.

1. An apparently fatigued but alert 38-year-old woman has spent 6 months as a teacher in a rural Thailand village school. Her chief complaints include frequent headaches, occasional nausea and vomiting, and periodic fever. You suspect malaria and indeed find parasites in red blood cells in a thin blood smear. To rule out the dangerous falciparum form of malaria, which one of the following choices is NOT consistent with a diagnosis of Plasmodium falciparum malaria based on a microscopic examination of the blood smear?

a) Red blood cells containing trophozoites with Schuffner's dots
b) Red blood cells containing >1 parasite per RBC
c) Banana-shaped or crescent-shaped gametocytes
d) Parasites within normal-sized red blood cells
e) Parasites with double nuclei

2. Given a diagnosis of uncomplicated Plasmodium falciparum malaria for the patient in Question 1, which one of the following treatment regimens is appropriate where chloroquine-resistance is known?

a) Oral artemisinin-based combination therapy (ACT)
b) Oral chloroquine
c) Intravenous chloroquine
d) Oral proguanil
e) Intravenous quinidine

3. Given a diagnosis of Plasmodium falciparum, you should tell the patient in Question 1 that (select one)

a) Relapse occurs with Plasmodium vivax and Plasmodium ovale, not Plasmodium falciparum and therefore no treatment for hypnozoites is necessary.
b) Primaquine is used to prevent relapse of Plasmodium falciparum.
c) Returning to the tropics would be dangerous because hypersensitivity to the parasite may have developed.
d) The use of insecticide treated bednets in endemic areas is not necessary since she already had malaria.
e) It is not necessary for her to take antimalarials when traveling in endemic areas.

Answers: 1.A 2.A 3.A

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	Plasmodium vivax	*Plasmodium falciparum*	*Plasmodium malariae*	*Plasmodium ovale*
Parasitized red cells	Enlarged, pale. Fine stippling (Schüffner dots). Primarily invades reticulocytes, young red cells	Not enlarged. Coarse stippling (Maurer's clefts). Invades all red cells regardless of age	Not enlarged. No stippling (except with special stains). Primarily invades older red cells	Enlarged, pale. Schüffner dots conspicuous. Cells often oval, fimbriated, or crenated
Ring stage trophozoites	Large rings (1/3–1/2 red cell diameter). Usually one chromatin granule; ring delicate	Small rings (1/5 red cell diameter). Often two granules; multiple infections common; ring delicate, may adhere to red cells	Large rings (1/3 red cell diameter). Usually one chromatin granule; ring thick	Large rings (1/3 red cell diameter). Usually one chromatin granule; ring thick
Pigment in developing trophozoites	Fine; light brown; scattered	Coarse; black; few clumps	Coarse; dark brown; scattered clumps; abundant	Coarse; dark yellow-brown; scattered
Older trophozoites	Very pleomorphic	Compact and rounded[a]	Occasional band forms	Compact and rounded
Mature schizonts (segmenters)	More than 12 merozoites (14–24)	Usually more than 12 merozoites (8–32). Very rare in peripheral blood[a]	Fewer than 12 large merozoites (6–12). Often in rosette	Fewer than 12 large merozoites (6–12). Often in rosette
Gametocytes	Round or oval	Crescentic	Round or oval	Round or oval
Distribution in peripheral blood	All forms	Only rings and crescents (gametocytes)[a]	All forms	All forms