2- Plasmodium and Malaria

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Objectives

- Describe the morphology, life cycle, epidemiology, pathogenesis, immunity, clinical presentations, diagnosis, management and prevention of malaria

Parasitology

- The plasmodia are sporozoa in which the sexual and asexual cycles of reproduction are completed in different host species
- The sexual phase occurs within the gut of mosquitoes that subsequently transmit the parasite while feeding on a vertebrate host
- Within the red blood cells (RBCs) of the vertebrate, the plasmodia reproduce asexually; they eventually burst from the erythrocyte and invade other uninvolved RBCs. This event produces periodic fever and anemia in the host, a disease process known as malaria
- Of the many species of plasmodia, four are known to infect humans and will be considered here: *Plasmodium vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*

Life Cycle

1. The sexual cycle

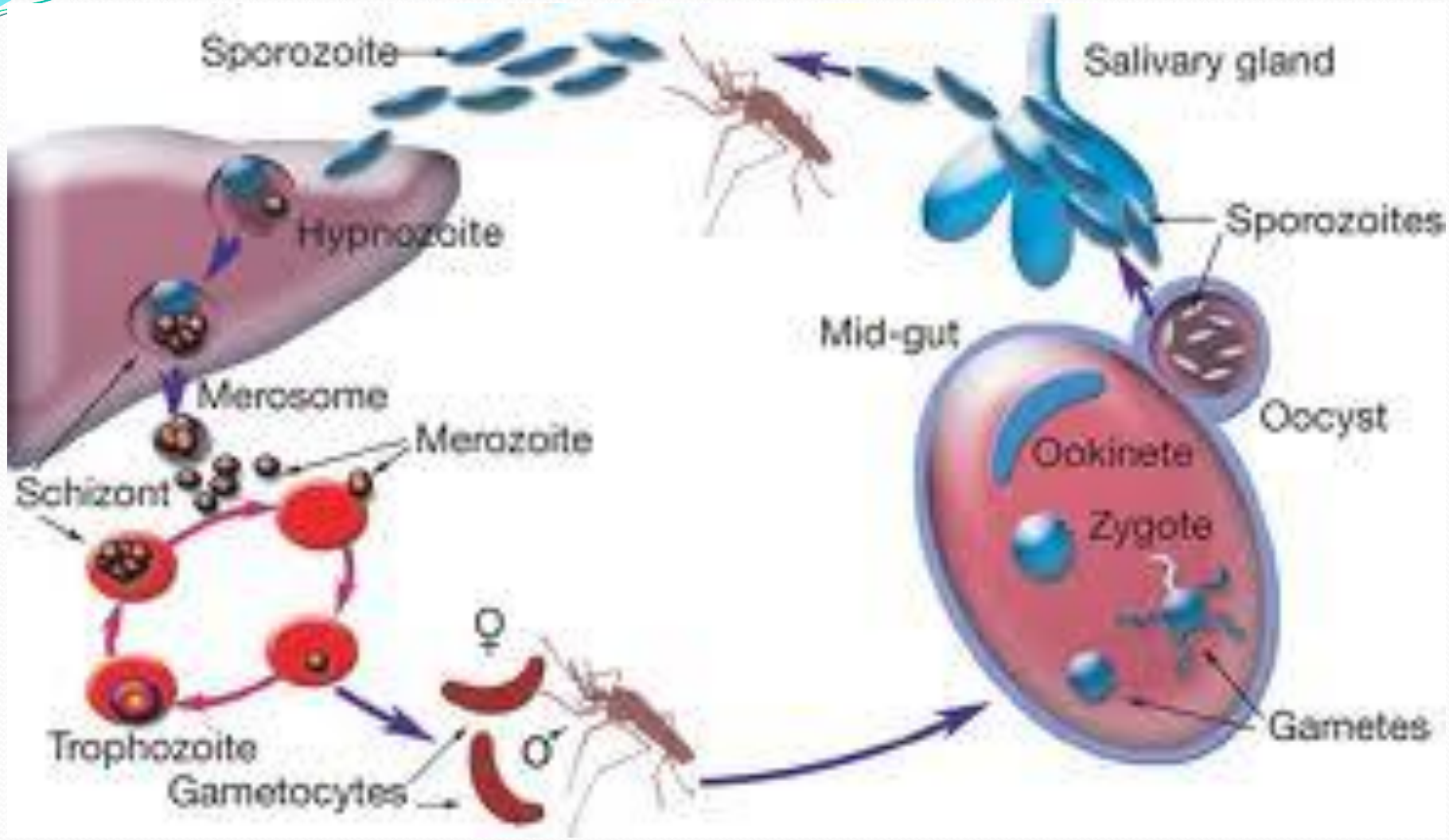
1. Begins when a female Anopheles mosquito ingests circulating male and female gametocytes while feeding on a malarious human
2. In the gut of the mosquito, the gametocytes mature and effect fertilization. The resulting zygote penetrates the mosquito's gut wall, lodges beneath the basement membrane, and vacuolates to form an oocyst
3. Within this structure, thousands of sporozoites are formed. The enlarging cyst eventually ruptures, releasing the sporozoites into the body cavity of the mosquito
4. Some penetrate the salivary glands, rendering the mosquito infectious for humans

2. The asexual cycle

1. Occurs in the human and begins when the infected Anopheles takes a blood meal from another individual
2. Sporozoites from the mosquito's salivary glands are injected into the human's subcutaneous capillaries and circulate in the peripheral blood
3. Within 1 hour they attach to and invade liver cells (hepatocytes)
4. Each sporozoites producing about 2000 to 40,000 daughter cells, or merozoites
5. One to two weeks later, the infected hepatocytes rupture, releasing merozoites into the general circulation

3. The erythrocytic phase

1. Starts with the attachment of merozoite to a specific receptor on the RBC surface
2. After attachment, the merozoite invaginates the cell membrane and is slowly endocytosed. The intracellular parasite initially appears as a ring-shaped trophozoite, which enlarges and becomes more active and irregular
3. Within a few hours, nuclear division occurs, producing the multinucleated schizont
4. Cytoplasm eventually condenses around each nucleus of the schizont to form an intraerythrocytic cluster of merozoite daughter cells
5. Infected erythrocytes rupture, releasing the merozoites and producing the first clinical manifestations of disease
6. Other daughter cells are transformed into sexual forms or gametocytes, continue to circulate in the peripheral vasculature until ingested by an appropriate mosquito

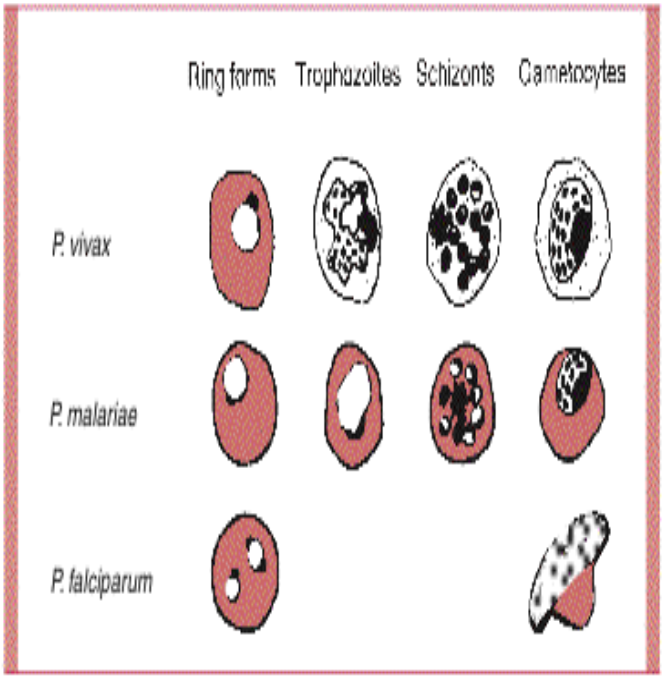

Sporozoite
Salivary gland
Hypnozoite
Sporozoites
Mid-gut
Merosome
Merozoite
Oocyst
Ookinete
Schizont
Zygote
♀
Trophozoite
♂
Gametocytes
Gametes

Morphology

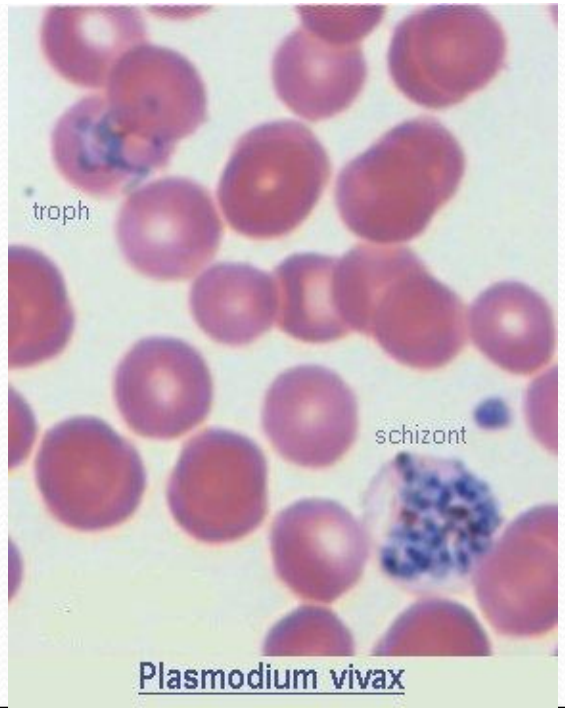
- The morphology of the stained intraerythrocytic parasites shows three characteristic features:

1. red nuclear chromatin
2. blue cytoplasm
3. brownish-black malarial pigment, or hemozoin

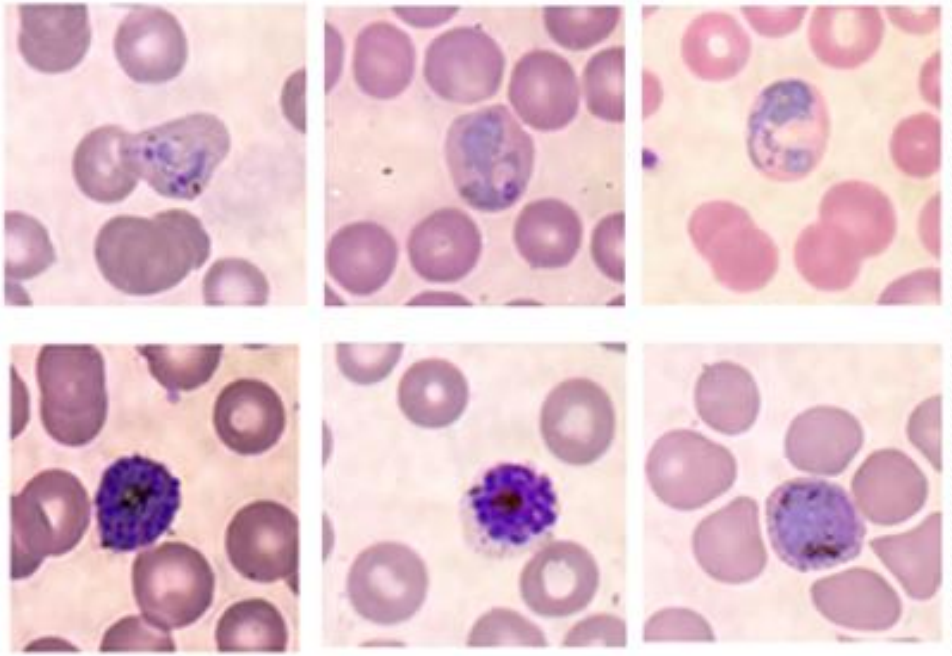
- The change in the shape of the cytoplasm and the division of the chromatin at different stages of parasite development are obvious
- Gametocytes can be differentiated from the asexual forms by their large size and lack of nuclear division



Examples of erythrocytic stages of malarial parasites. Note: Trophozoite and schizont forms of *Plasmodium falciparum* occur in visceral capillaries rather than in blood. Male and female gametophytes show distinctive morphologic differences.



Plasmodium vivax



Epidemiology

- Malaria has a worldwide distribution . *P. vivax* is the most widely distributed of the four species, and together with the uncommon *P. malariae*, is found primarily in temperate and subtropical areas. *P. falciparum* is the dominant organism of the tropics. *P. ovale* is rare and found principally in Africa
- In hyperendemic areas transmission is usually constant, and disease manifestations are moderated by the development of immunity
- Mortality is largely restricted to infants and to nonimmune adults who migrate into the region

Pathogenesis

1. Fever

- The hallmark of malaria, appears to be initiated by the process of RBC rupture that leads to the liberation of a new generation of merozoites (sporulation)
- The resulting fever is irregular and periodic. Because temperatures in excess of 40° C destroy mature parasites, a single population eventually emerges, sporulation is synchronized, and fever occurs in distinct paroxysms at 48hour or, in the case of *P. malariae*, 72-hour intervals

2. Anemia

- Parasitized erythrocytes are phagocytosed by a stimulated reticuloendothelial system or are destroyed at the time of sporulation
- Depression of marrow function, sequestration of erythrocytes within the enlarging spleen, and accelerated clearance of nonparasitized cells all appear to contribute to the anemia
- Intravascular hemolysis, although uncommon, may occur, particularly in falciparum malaria. When hemolysis is massive, hemoglobinuria develops, resulting in the production of dark urine. This process in conjunction with malaria is known as blackwater fever

3. Circulatory Changes

- The high fever results in significant vasodilatation. In falciparum malaria, vasodilatation leads to a decrease in the effective circulating blood volume and hypotension
- The intense parasitemias *P. falciparum* is capable of producing adhesion of infected RBCs to the endothelium of visceral capillaries can impair the microcirculation and precipitate tissue hypoxia, lactic acidosis, and hypoglycemia. Although all deep tissues are involved, the brain is the most intensely affected

4. Thrombocytopenia

- Is common in malaria and appears to be related to both splenic pooling and a shortened platelet lifespan

5. Acute transient glomerulonephritis in *falciparum* malaria and progressive renal disease in chronic *P. malariae* malaria. These phenomena probably result from the host immune response, with deposition of immune complexes in the glomeruli

Immunity

- Once infected, the host quickly mounts a species- and strain-specific immunologic response that typically limits parasite multiplication and moderates the clinical manifestations of disease
- Without eliminating the infection. A prolonged recovery period marked by recurrent exacerbations in both symptoms and number of erythrocytic parasites follows
- With time, these recrudescences become less severe and less frequent, eventually stopping altogether

Clinical Manifestations

- The incubation period between the bite of the mosquito and the onset of disease is approximately 2 weeks
- The clinical manifestations vary with the species but typically include chills, fever, splenomegaly, and anemia
- The hallmark of disease is the malarial paroxysm. This manifestation begins with a cold stage, which persists for 20 to 60 minutes. During this time, the patient experiences continuous rigors and feels cold. With the consequent increase in body temperature, the rigors cease and vasodilatation commences, ushering in a hot stage. The temperature continues to rise for 3 to 8 hours, reaching a maximum of 40 to 41.7° C before it begins to fall. The wet stage consists of a decrease in fever and profuse sweating. It leaves the patient exhausted but otherwise well until the onset of the next paroxysm

- In falciparum malaria, capillary blockage can lead to several serious complications
- When the central nervous system is involved (cerebral malaria), the patient may develop delirium, convulsions, paralysis, coma, and rapid death
- When splanchnic capillaries are involved, the patient may experience vomiting, abdominal pain, and diarrhea with or without bloody stools
- Jaundice and acute renal failure are also common in severe illness
- Most deaths occur within 3 days

Diagnosis

- Malarial parasites can be demonstrated in stained smears of the peripheral blood in virtually all symptomatic patients. Blood are stained with Wright or Giemsa stain and examined for the presence of erythrocytic parasites. Thick smears, where erythrocytes are lysed with water concentrate the parasites and allow detection of mild parasitemia
- Simple, specific card antigen detection procedures are now available. The most widely used test, ParaSight F, detects a protein (HRP2) excreted by *P. falciparum* within minutes. The test can be performed under field conditions and has a sensitivity more than 95%. A second rapid test, OptiMAL, detects parasite lactate dehydrogenase, and, unlike ParaSight F, can distinguish between *P. falciparum* and *P. vivax*
- Serologic tests are offered at large reference laboratories but are used primarily for epidemiologic purposes

Treatment

- The indications for treatment rest on two factors:

1. The first is the infecting species of Plasmodium
2. The second is the immune status of the afflicted patient

- Falciparum malaria is potentially lethal in nonimmune individuals such as new immigrants or travelers to a malarious area and immunosuppressed indigenous individuals such as pregnant women. These individuals must be treated emergently
- The complete treatment of malaria requires the destruction of the erythrocytic schizont, the hepatic schizont, and the erythrocytic gametocyte

- **Termination of Acute Attack**

1. Several agents can destroy asexual erythrocytic parasites. Chloroquine, has been the most commonly used
2. Chloroquine-resistant strains of *P. falciparum* are now widespread in Africa and Southeast Asia
3. Other agents include quinine/quinidin

- **Radical Cure**

  In *P. vivax* and *P. ovale* infections, hepatic schizonts persist and must be destroyed to prevent reseeding of circulating erythrocytes with consequent relapse. Primaquine, is used for this purpose

Prevention

1. Personal Protection

In endemic areas, mosquito contact can be minimized with the use of house screens, insecticide within rooms, and/ or insecticide-impregnated mosquito netting around beds. Those who must be outside from dusk to dawn, the period of mosquito feeding, should apply insect repellent and wear clothing with long sleeves and pants. In addition, it is possible to suppress clinical manifestations of infection with a weekly dose of chloroquine

2. General

Malaria control measures have been directed toward reducing the infected human and mosquito populations to below the critical level necessary for sustained transmission of disease. The techniques employed include those mentioned previously, treatment of febrile patients with effective antimalarial agents, chemical or physical disruption of mosquito breeding areas, and use of residual insecticide sprays

3. Chemoprophylaxis: anti-malria prophylaxis before travelling to endemic area

4. Vaccines

Advances in the last decade have produced the hope that an effective malaria vaccine might be within reach of medical science for the first time