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Editor-in-Chief
Anupam Sachdeva

Editors
Nita Radhakrishnan
Manas Kalra

Handbook on FALCIPARUM MALARIA



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CHAPTER

2

Etiology of *Plasmodium falciparum*

Chand Wattal, Neeraj Goel

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THE CAUSATIVE ORGANISM

Malaria is caused by plasmodia-protozoa which have a complex life cycle involving both vertebrate and arthropod hosts. Among the protozoa, plasmodia are part of the Apicomplexa, and thus share apical organelles associated with the invasion of vertebrate host cells (micronemes, rhoptries, dense granules) with other Apicomplexa such as *Toxoplasma*, *Babesia*, and *Cryptosporidium*. It is suggested that the micronemes, rhoptries, and dense granules are responsible for sequential attachment to the host cell, formation of the parasitophorous vacuole, and invasion, respectively.

There are five species of *Plasmodium* that are associated with malaria infection: *P. vivax, P. falciparum, P. ovale*, *P. malariae* and *P. knowlesi*. Of these *P. vivax* is estimated to cause 80 percent of malaria infection worldwide. This species has also the widest distribution covering tropics, subtropics and temperate zones. Approximately 15 percent of the infection is caused by *P. falciparum*. It is restricted to tropics. The other 5 percent of infection are caused by *P. malariae* (sporadic distribution) and *P. ovale* (confined to central West Africa and some South Pacific islands).

Transmission

Malaria is transmitted by the bite of infected female anopheline mosquito. Two things are critical for transmission of infection: contact between humans with infectious gametocytes in their blood and competent anopheline mosquito vectors.

The anopheline vector: The most important vectors are anthropophilic anophelines competent to permit development of the parasite. Anophelines that

bite primarily animals rarely transmit human malaria. In addition, a number of anophelines are not capable of transmitting malaria even when they have been infected. Of the approximately 360 known anophelines, only about 45 have been shown to transmit malaria to humans. To maintain sustained transmission in a geographical area, new mosquitoes must be infected continuously because mosquitoes have short life spans (from 5 to 20 days), and because the extrinsic incubation period of the parasite in the mosquito is 8 to 10 days or more.

Anophelines are found worldwide except Antarctica. Female mosquitoes take blood meals to carry out egg production, and such blood meals are the link between the human and the mosquito hosts in the parasite life cycle. The successful development of the malaria parasite in the mosquito (from the "gametocyte" stage to the "sporozoite" stage) depends on several factors. The most important is ambient temperature and humidity (higher temperatures accelerate the parasite growth in the mosquito) and whether the *Anopheles* survives long enough to allow the parasite to complete its cycle in the mosquito host ("sporogonic" or "extrinsic" cycle, duration 10–18 days). Differently from the human host, the mosquito host does not suffer noticeably from the presence of the parasites.

The human reservoir: Humans are supposed to be the primary host reservoir for *P. falciparum* as well for the other species (*P. vivax*, *P. ovale*, *P. malariae.* Recently a fifth malarial species known as *P. knowlesi* has been reported been reported from forested regions of South-East Asia which is originally thought to be restricted to macaques in Southeast Asia but now is accepted to cause naturally acquired sporadic human infections in these restricted areas. In addition to suitable vectors, there must be a reservoir of parasitemic humans with sufficient numbers of gametocytes in their blood to infect the anopheline vector. Because persons with early infections have predominantly asexual-stage parasites, the human reservoir must have substantial numbers of persistently infected persons. Thus, natural mosquito-borne transmission requires a reservoir of semi-immune humans able to tolerate parasitemia (gametocytemia) for prolonged periods of time.

Other Means of Transmission of Infections

Blood-borne Transmission

Malaria may also be transmitted by the transfusion of infected donor's blood. Rarely platelets, white blood cells, bone marrow, and other tissues and organs may also transmit malaria.

Congenital malaria: In addition, some mothers transmit malaria to their children at or near the time of birth. The organism most frequently associated with congenital malaria is *P. vivax* presumably because it produces asymptomatic infection in pregnant women more frequently than *P. falciparum.*

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Life Cycle

After the bite of infected anopheline mosquito, the sporozoites travel from the salivary glands of the mosquito and within approximately 60 minutes, the sporozoites are carried via the blood to the liver hepatocytes, thus initiating the pre-erythrocytic or primary exoerythrocytic cycle. These cells divide many 1000-folds until mature tissue schizonts are formed, each containing thousands of daughter merozoites. This exoerythrocytic stage is asymptomatic. The liver schizonts rupture after 6 to 16 days in *P. falciparum*. Thousands of merozoites are released from the infected liver cells to invade red blood cells (RBCs). Once the RBCs have been invaded, the parasites continue to grow and feed on hemoglobin. The merozoite (or young trophozoite) is vacuolated, ring shaped, more or less ameboid, and uninucleate (an exception is the "headphone" rings seen primarily in *P. falciparum* infections). Within red blood cells the parasites digest red cell proteins, primarily hemoglobin. As hemoglobin is digested, the breakdown products are toxic to the parasite and, thus, hemozoin (a malarial pigment) is formed in the food vacuole (Fig. 2.1). As the nucleus begins to divide, the trophozoite is now called a developing schizont. The mature schizont contains merozoites that are subsequently released into the bloodstream.

The intracellular parasites due to maturation and multiplication may cause hypoglycemia and lactic acidosis because of anaerobic glycolysis for their energy needs. As the cell wall of infected RBCs becomes less deformable, enhanced hemolysis and increased splenic clearance of RBCs results in anemia. Red cell lysis stimulates release of pro-inflammatory cytokines, including tumor necrosis factor (TNF). TNF suppresses hematopoiesis, which also contributes to anemia. The liver and spleen enlarge over time; the spleen may become massively enlarged. Thrombocytopenia is caused by a combination of hypersplenism (i.e. increased splenic sequestration and decreased platelet survival time) and, in the case *of P. falciparum*, consumption of platelets in microvascular sequestration is the cause.

Although many merozoites are destroyed by the immune system, others immediately invade RBCs, in which a new cycle of erythrocytic schizogony begins.

After several erythrocytic generations, few of the merozoites (asexual forms) change into the male and female gametocytes (sexual forms). The stimulus for such changes in still not completely clear.

In *P. falciparum* infections, the RBC membrane develops certain adherence factors (parasites proteins) and becomes sticky. *Plasmodium falciparum*-infected erythrocytes, particularly those with mature trophozoites, adhere to the vascular endothelium of venular blood vessel walls and do not freely circulate in the blood. Thus, only the ring forms and the gametocytes (occasionally mature

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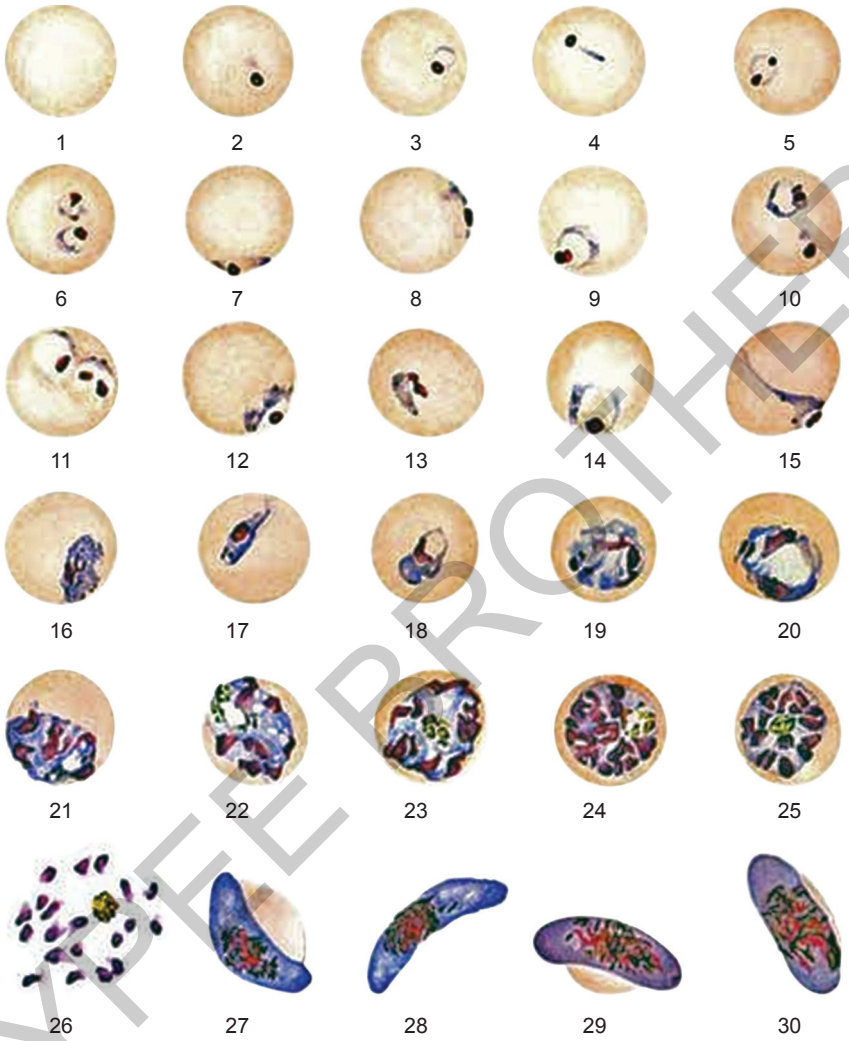

Fig. 2.1 Stages of *Plasmodium falciparum* as drawn from microscopic observation of thin blood smears

1: Normal red cell; **2–18:** Trophozoites (among these, **2–10** Correspond to ring-stag trophozoites); **19–26:** Schizonts (**26** is a ruptured schizont); **27, 28:** Mature macrogametocytes (female); **29, 30:** Mature microgametocytes (male)

Illustrations from Coatney GR, Collins WE, Warren M, Contacos PG. The Primate Malarias. Bethesda: US Department of Health, Education and Welfare; 1971.

schizonts) normally appear in the peripheral blood. When this sequestration of infected erythrocytes occurs in the vessels of the brain it is believed to be a factor in causing the severe disease syndrome known as cerebral malaria, which is associated with high mortality.

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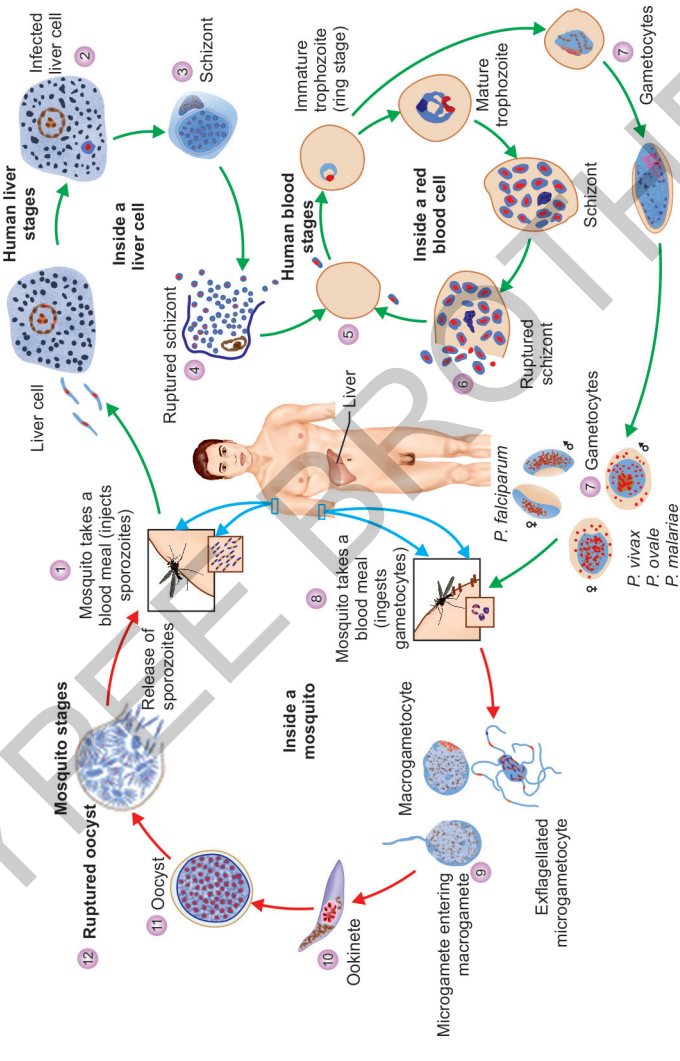

Fig. 2.2 *Plasmodium falciparum* life cycle

Source: Center for Disease Control and Prevention (CDC) Available at. *http://www.cdc.gov/malaria/about/biology*

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During *P. falciparum* infection, asexual and sexual forms circulate in the blood and when gametocytes are ingested with the vector's blood meal, they mature into gametes within the mosquito gut. The male microgametes undergo nuclear division by a process called exflagellation. The microgametes break out of the RBC, become motile, and penetrate the female macrogamete, with the fertilized stage being called the zygote. As the zygote elongates and becomes motile, it is now called the ookinete. This stage migrates to the mosquito midgut, secretes a thin wall, and grows into the oocyst, which extends into the insect's hemocele. Within days to weeks, the oocyst matures, with the development of hundreds of sporozoites. Within the mosquito the oocyst ruptures, then the sporozoites are released into the hemocele and disperse throughout the body, including the salivary glands. When the mosquito next takes a blood meal, the sporozoites are injected with saliva into the host and thus completes the malarial cycle (Fig. 2.2).

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Handbook on
FALCIPARUM MALARIA

Salient Features

- Gives all aspects of malaria from the epidemiology to preventive strategies
- A must-read book for any postgraduate from the fields of medicine, pathology, microbiology, pediatrics, community medicine, obstetrics and gynecology and a must on the desk of all physicians in the tropical countries
- It not only provides material for the postgraduates but also enough material for the practicing physicians including intensivists, involved in the treatment of critically ill patient suffering from malaria
- All-in-all a great compendium on malaria dealing with every aspects of malaria.



Anupam Sachdeva is a veteran in the field of hematology-oncology and has been treating children diagnosed with such diseases for more than 20 years. After completing his MD (Pediatrics) from Ludhiana, Punjab, India, he has been trained in Hematology-Oncology, University College Hospital, London and Royal Marsden Hospital, London, UK.

He is the Director, Pediatric Hematology-Oncology and Hematopoietic Stem Cell Transplantation Unit; the Co-Chairman, Department of Pediatrics; the Chairman, Department of Academics; and Convener Research, Sir Ganga Ram Hospital, New Delhi, India.

He was instrumental in setting up the Bone Marrow Transplantation Unit, Sir Ganga Ram Hospital, New Delhi, India. He has done more than 80 pediatric bone marrow transplants till date. He has and continues to hold various administrative posts in Indian Academy of Pediatrics (IAP). He has won innumerable awards including the prestigious Dr BC Roy Award, and he is the only pediatrician to be awarded the Silver Jubilee Research Award Category I by the President of India. He has published over 100 papers in international and national journals.



Nita Radhakrishnan has completed her MD (Pediatrics) and Fellowship in Pediatric Hematology-Oncology; and Fellowship in Bleeding and Thrombotic Diseases. She is the Consultant, Pediatric Hematology-Oncology and Bone Marrow Transplantation (BMT) Unit, Sir Ganga Ram Hospital, New Delhi, India. She has experience and interest in managing children with hematological diseases including thalassemias, aplastic anemias, bleeding disorders and leukemias as well as primary immunodeficiencies.



Manas Kalra has undergone training in Pediatric Oncology and Stem Cell Transplantation, Children's Hospital, Westmead, Australia. He is focused on leukemias, solid tumors and bone marrow transplantation in children with diseases such as thalassemias, sickle cell diseases, metabolic diseases, aplastic anemias, immunodeficiencies, leukemias and high-risk solid tumors. He is the Consultant, Pediatric Hematology-Oncology and Bone Marrow Transplantation Unit, Sir Ganga Ram Hospital, New Delhi, India.

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