Malaria

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March 09
Introduction

Malaria, one of major killer diseases, is caused by protozoa of the genus *Plasmodium*.

Four species cause disease in humans:
- *P. falciparum*,
- *P. vivax*,
- *P. ovale* and
- *P. malariae*.

*P. falciparum* is world wide common and causes the most severe disease, and remains firmly entrenched as a leading cause of morbidity and mortality in humans.

Approximately 300-500 million clinical episodes and 2.7 million deaths are attributed to *P. falciparum* infections each year and with the emergence of widespread drug-resistant parasite populations and insecticide-resistant mosquitoes, this situation is predicted to worsen.

Malaria spread from man to man by the bite of female mosquitoes of the genus *Anopheles*. 
The word ‘malaria’ comes from the Italian word that literally mean as bad air ‘mal=bad, aria=air’. Since, Italian writers thought that the disease was caused by offensive vapors emanating from “tiberia marshes”.

In 1880, Laveran demonstrated live parasites in blood taken form a fever patient. Later in 1885 – 1886, Golgi demonstrated the erythrocytic schizogony of *P. falciparum* and *P. vivax*.

Romanowsky introduced the staining method of malarial parasite in 1882. Ross worked out the mosquito cycle in 1898 on suggestive theory of Manson. The theory of mosquito transmission was proved by Manson in 1900.
Epidemiology Geographic distribution

- The disease is widely distributed in the tropics and subtropics.
- The highest transmission is found in Africa, followed by countries in South America and South-east Asia. More than 90% of all malaria cases occur in sub-Saharan Africa.
- Two-thirds of the remainder is concentrated in six countries in decreasing order of prevalence: India, Brazil, Srilanka, Vietnam, Colombia, and Solomon Islands.
- *P. vivax* and *P. ovale* are traditionally thought to occupy complementary niches, with *P. ovale* predominating in Sub-Saharan Africa and *P. vivax* in the other areas.
Risk factors

- Persons most vulnerable are those with no or little protective immunity against the disease. In areas with high transmission (such as Africa, south of the Sahara), the most vulnerable groups are:
  - Young children, who have not yet developed immunity to malaria
  - **Pregnant women**, whose immunity is decreased by pregnancy, especially during the first and second trimester
  - Travelers or immigrants coming from areas with little or no malaria transmission, who lack immunity.
  - Refugees
  - Displaced persons
  - Laborers entering endemic areas
Bangladesh situation

- Malaria is a major public health problem in Bangladesh and the situation has been worsening in the recent years.
- Of the two prevalent species *P. falciparum* and *P. vivax*, the former by far is the most predominant.
- A majority of malaria cases are reported from 13 districts, out of the total 64 districts in the country.
- Endemic transmission of malaria may be year round or seasonal.
Taxonomy

❖ **Phylum - Myzozoa,**
   - **Class - Aconoidasida,**
   - **Order - Hemosporida,**
     - **Family - Plasmodiidae,**
     - **Genus - Plasmodium,**
❖ **Species -** (There 120 species of which following 4 infects man):
   - P. falciparum, P. vivax, P. ovale and P. malariae
Clinical Classification

1. Parasites belonging to this genus possess a life cycle, which shows an alteration of generation accompanied by alteration of host.

2. Asexual cycle occurs intracellularly within RBC of vertebrate host and sexual cycle occurs in invertebrate host.

3. Gametogony starts inside the RBC of vertebrate host and completed in mosquito.

4. Sporozoite forms in blood sucking mosquito.
The malarial parasite passes its life cycle into two different hosts; man, and female anopheline mosquito.

Man is an intermediate host, as the parasite reproduces by asexual method in man; mosquito is the definitive host, where sexual method of reproduction occurs.
Morphological stages in human

- This small single-cell organism has three to four different forms; *Gametocyte, sporozoite, merozoites and schizonts.*

- The **gametocyte** is the reproductive form that infects the mosquito. When the mosquito sucks blood containing gametocytes, these pass into the **salivary glands** of the mosquito, where they develop into a new form, the **sporozoite.**

- The **sporozoite** is the infective form that can be passed on to man when the mosquito bites, injecting its saliva into the tiny blood vessels. The sporozoite travels with the blood to the liver and enters the liver cells. In the liver cells, some of the sporozoites divide (tachysporozoites) and become thousands of merozoites.

- The **merozoites** are released from the liver to the blood, where they enter into red blood corpuscles. Some of these turn into ring-formed trophozoites. This split again to form schizonts.

- **Schizonts** burst the red blood corpuscles at a certain moment, releasing the merozoites. This release coincides with the violent rises in temperature during the attacks seen in malaria.
Morphological stages in mosquito

✔ Following stages are found in mosquitoes:
  – Microgamete,
  – Macrogamete,
  – Zygote,
  – Ookinete,
  – Oocyst containing sporozoites.
Life cycle
Definitive host: Female anopheles mosquito
Intermediate host: Man
Life cycle stages:
- In Man - Gametocyte, sporozoite, merozoites and schizonts,
- In mosquito - microgamete, macrogamete, zygote, ookinete, oocyst containing sporozoites
Types life cycle: Pre-erythrocytic cycle, Erythrocytic cycle, Sexual cycle
Infective form for man: Sporozoites
Route of infection: Through bite of infected female anopheles mosquito.
Site of localization: Liver and RBC
## Time extent of life cycle of different Plasmodium

<table>
<thead>
<tr>
<th>Species</th>
<th>Pre-erythrocytic cycle</th>
<th>Erythrocytic cycle</th>
<th>Sexual cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. vivax</em></td>
<td>8 days</td>
<td>48 hours</td>
<td>8-9 days</td>
</tr>
<tr>
<td><em>P. falciparum</em></td>
<td>5-7 days</td>
<td>24-48 hours</td>
<td>9-10 days</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>9 days</td>
<td>48 hours</td>
<td>14 days</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>15-16 days</td>
<td>72 hours</td>
<td>15-20 days</td>
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</table>
Transmission

- **Vector borne transmission**: VL is transmitted to man by the bite of infected female sand fly. Once the vector is infected, it remains infective throughout its life time and capable of infecting several persons.

- **Direct transmission**: Due to contamination of the bite wound. Accidental inoculation of parasite during laboratory work results in leishmaniasis. Transmission by blood transfusion is also recorded.

- **Congenital transmission**: Rarely occurs. Transmission of infection to fetus in uterus may occur due to placental defect.
Virulence factors

- Malaria parasite *P. falciparum*, one of the world's most devastating pathogens, has an astonishing array of sequences and genes, that play key roles in pathogenesis and immune evasion.
- We must understand the functions of these elements if the chronicity and unpredictable virulence of Plasmodium is to be explained. The complete sequence of the 14 linear chromosomes that comprise the *P. falciparum* genome has recently been determined.
- It is perhaps not surprising for such a successful pathogen that these studies have revealed that a high proportion of the 5,300 predicted genes encode proteins known or predicted to play a role in pathogenic processes, such as invasion of red blood cells, cytoadherence and immune evasion.
Virulence factors

- The adhesion of parasite-infected red blood cells to vascular endothelium leads to sequestration of *P. falciparum* in the deep microvasculature of various tissues and organs, and is associated with certain severe disease outcomes. A parasite protein inserted into the infected red blood cell surface, known as *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), is considered to be a key adhesive ligand mediating sequestration.

- In a process known as ‘antigenic variation,’ clonal *P. falciparum* parasites can vary the type of PfEMP1 molecule they express, to avoid antibody-mediated clearance. Intriguingly, different PfEMP1 ligands mediate adherence to different receptors on endothelial cells, including the scavenger receptor CD36, chondroitin sulfate A and intracellular adhesion molecule-1 (ICAM-1).

- In some instances, parasite populations with a predisposition to adhere to certain receptors are more commonly associated with certain disease outcomes, such as cerebral and placental malaria. Although the precise role of parasite-receptor interactions in determining disease severity remains to be understood. *P. falciparum* infections are persistent and this chronicity is promoted by antigenic variation at the infected red blood cell surface. Proteins of the repetitive interspersed family (rifins) are also expressed at the surface of infected red blood cells and like PfEMP1, these also undergo antigenic variation.
The fever and chills of malaria are associated with the rupture of erythrocytic stage schizonts. No disease is associated with sporozoites, the merozoites or gametocytes.

This release of parasite material presumably triggers a host immune response. The cytokines (e.g., tumor necrosis factor, IL-1 and IL 10), reactive oxygen intermediates and other cellular products released during the immune response, play a prominent role in pathogenesis. These 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; 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 black water 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.
Susceptibility to malaria infection and disease is regulated by hereditary and acquired factors. It now seems clear that the sickle cell trait (which is the cause of sickle cell 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 blood group 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 6 phosphate 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.
Immunity

- 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 long lasting, 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 plasmodium 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.

- Antibodies against the sexual stages of plasmodia may reduce malaria transmission. It is also suggested 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.
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- 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.
Clinical Features

✓ The most characteristic symptom of malaria is fever. Other common symptoms include chills, headache, myalgias, nausea, and vomiting.

✓ The malaria paroxysm comprises three successive stages.
  – The first is a 15-60 minute ‘cold stage’ characterized by shivering, and a feeling of cold.
  – Next comes the 2-6 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 2-4 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.

✓ Physical findings in malaria are nonspecific and offer little aid in diagnosis. Splenomegaly is common,. Hepatomegaly, jaundice, hypotension,. 
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 - 50 percent. Other complications include; hyperparasitemia (more than 3 - 5 percent of the erythrocytes parasitized), severe hypoglycemia, lactic acidosis, prolonged hyperthermia, shock, pulmonary, cardiac, hepatic, or renal dysfunction, seizures, spontaneous bleeding, or high output 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.
Immunological complications of malaria

✔ Hyper-reactive malarial splenomegaly, previously known as tropical splenomegaly (TSS). Persons with hyper-reactive malarial splenomegaly are immune adults in endemic area of malaria, who have gross chronic splenomegaly with over production of IgM, high level of malarial antibody, and circulating immune complexes.

✔ The patient is usually anaemic and has a reduced white cell and platelet count. It is associated with vivax and quatrain malaria, as well as falciperum malaria. The condition responds to prolonged treatment by antimalarial drugs.

✔ Malarial nephrosis: A serious complication of infection with *P. malariae*, which may progresses to renal failure. It occurs more frequently in children, and is due to deposition of antigen-antibody complexes in the glomerular basement membrane of kidneys.