MALARIA

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➢ Definition:

Malaria is an infection caused infected mosquitoes **(mosquito-borne disease)**, specifically female *Anopheles* mosquitoes, infected with *Plasmodium parasite.*

Species:

Four species of Plasmodium cause human malaria:

1. *Plasmodium vivax*: Benign tertian malaria.
2. *Plasmodium ovale*: Benign tertian malaria.
3. *Plasmodium malariae*: Benign quartan malaria.
4. *Plasmodium falciparum*: Tertian or subtertian malignant malaria.

➢ Geographical distribution:

- *P. vivax*: The most widely distributed species found in tropical, subtropical and temperate areas.

- *P. ovale*: West Africa.

- *P. malariae:* Tropical Africa and Far East.

- *P. falciparum*: Africa and Far East

➢ **Life cycle:** The life cycle of malaria parasites is **heteroxenous** (alternation of generations between two hosts), where an ***asexual*** cycle occurs in man (intermediate host), and ***sexual*** cycle occurs in female Anopheles (definitive host).

1. **Definitive host:** Female *Anopheles* mosquito.

2. **Intermediate host:** Man.

3. **Reservoir host:** No. However, in *P. malariae*, chimpanzee can be affected and act as a reservoir of infection.

4. Habitat: In ***mosquito***: Gut, salivary glands.

In ***man***: Intracellular inside the liver cells and RBCs.

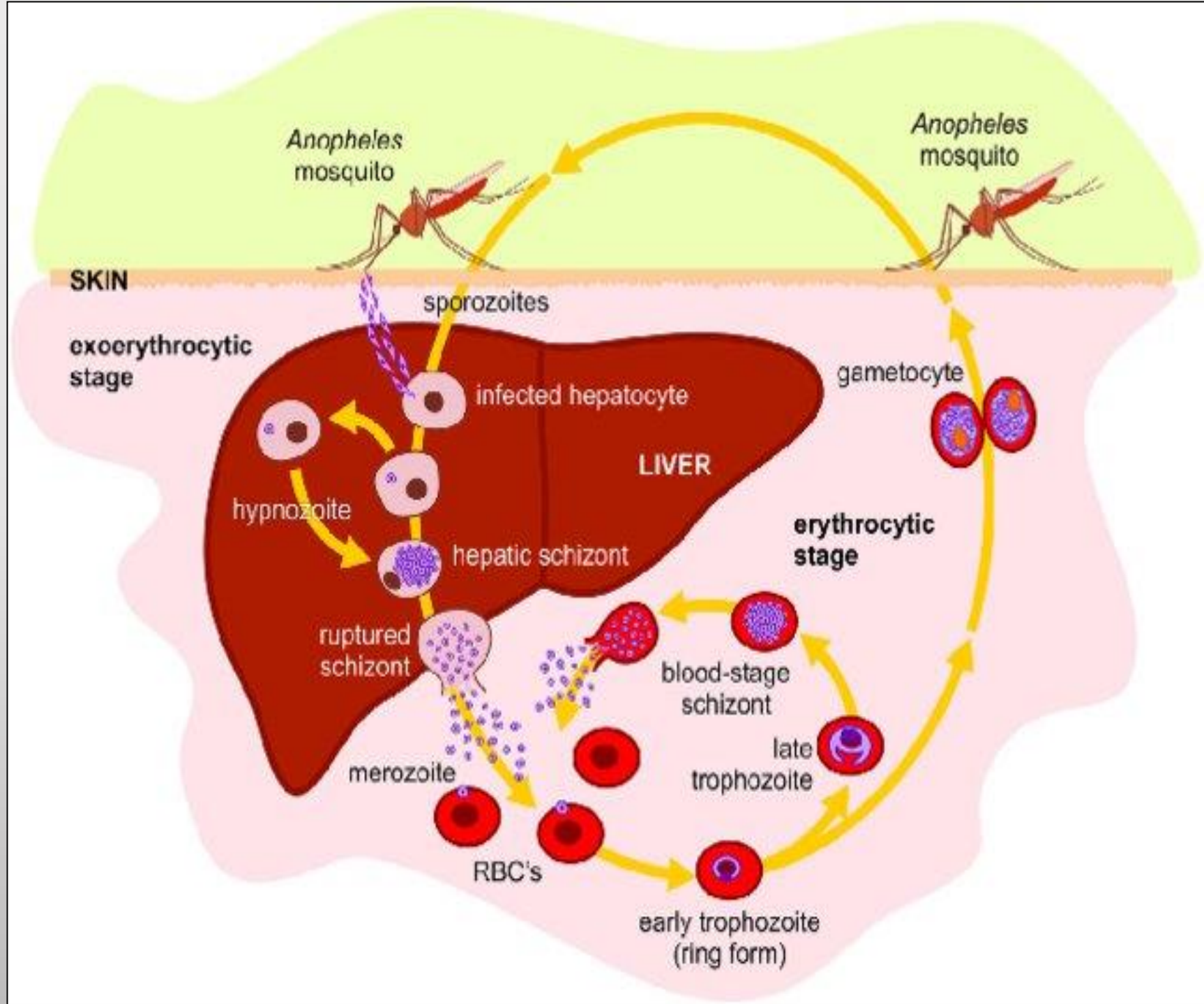
5. Infective stage: a. Sporozoites (in ***mosquito-borne*** malaria).

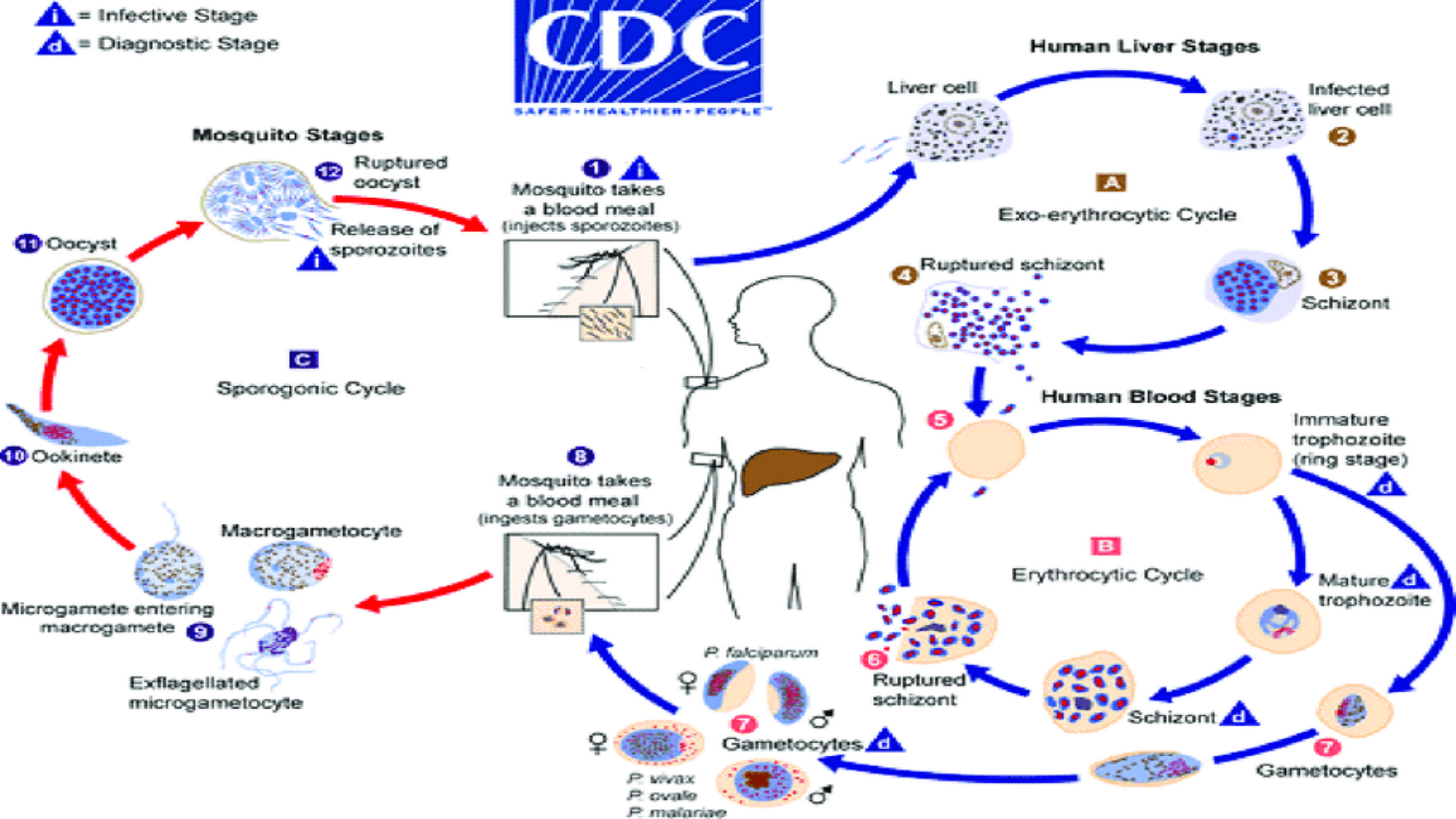
b. Merozoites and/or trophozoites (in *blood-borne* malaria).

6. Mode of infection:

1. Bite of infected female Anopheles.
2. Blood-borne transmission:
    a. Blood transfusion (whole blood and packed RBCs).
    b. Shared syringes among drug addicts.
    c. Transplacental transmission.
    d. Organ transplantation.

The asexual cycle in man: exo-erythrocytic and erythrocytic




i = Infective Stage
d = Diagnostic Stage
CDC
SAFER • HEALTHIER • PEOPLE™
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Mosquito Stages
12
Ruptured oocyst
Release of sporozoites
1
Mosquito takes a blood meal
(injects sporozoites)
11
Oocyst
C
Sporogonic Cycle
10
Ookinete
8
Mosquito takes a blood meal
(ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte
Human Blood Stages
5
Immature trophozoite (ring stage)
B
Erythrocytic Cycle
Mature trophozoite
6
Ruptured schizont
Schizont
7
Gametocytes
P. falciparum
P. vivax
P. ovale
P. malariae

➢ Pathogenicity of malaria:

The major clinical manifestations of malaria are due to the products of erythrocytic schizogony and host´s reaction to them.

I. **Destruction of parasitized RBCs**

II. **Host inflammatory response**

III. **Additional pathology associated with *P. falciparum***

➢ I. Destruction of parasitized RBCs:

Rupture of infected RBCs at the end of a schizogony cycle results in:

a. ***Tissue hypoxia*** because of reduction of blood flow by parasitized RBCs

b. ***Release of haemozoin and parasite metabolites in blood stream*** resulting in hepatosplenomegaly. The soft, large spleen becomes susceptible to spontaneous rupture and in chronic infection it becomes firm and fibrotic. Kidneys are also enlarged and congested.

c. ***Haemolytic anaemia and jaundice.***

➢ Causes of anaemia in malaria?

1. Obligatory destruction of RBCs at merogony.

2. Destruction of large number of RBCs by complement-mediated and autoimmune hemolysis.

3. Increased clearance of both parasitized and non-parasitized RBCs by the spleen.

4. Decrease erythropoiesis in bone marrow due to increased tumour necrosis factor.

5. Shortened red cell survival.

6. Failure of the host to recycle the iron bound in haemozoin pigments.

II. Host inflammatory response: Occurs as an immune response of the host to the liberated parasite metabolites and malaria pigments.

a. ***Fever*** coincides with rupture of erythrocytic schizont with release of merozoites, parasitic pigments, and residual body in the blood stream. These materials activate tissue macrophages, which in turn produce interleukin-1, tumour necrosis factor and pyrogens which cause fever.

b. ***Activation of complement and immune complexes formation*** as a result of the antigen excess situation in chronic quartan malaria may lead to the deposition of these circulating antigen-antibody complexes within renal glomeruli leading to nephrotic syndrome.

III. Additional pathology associated with *P. falciparum*:

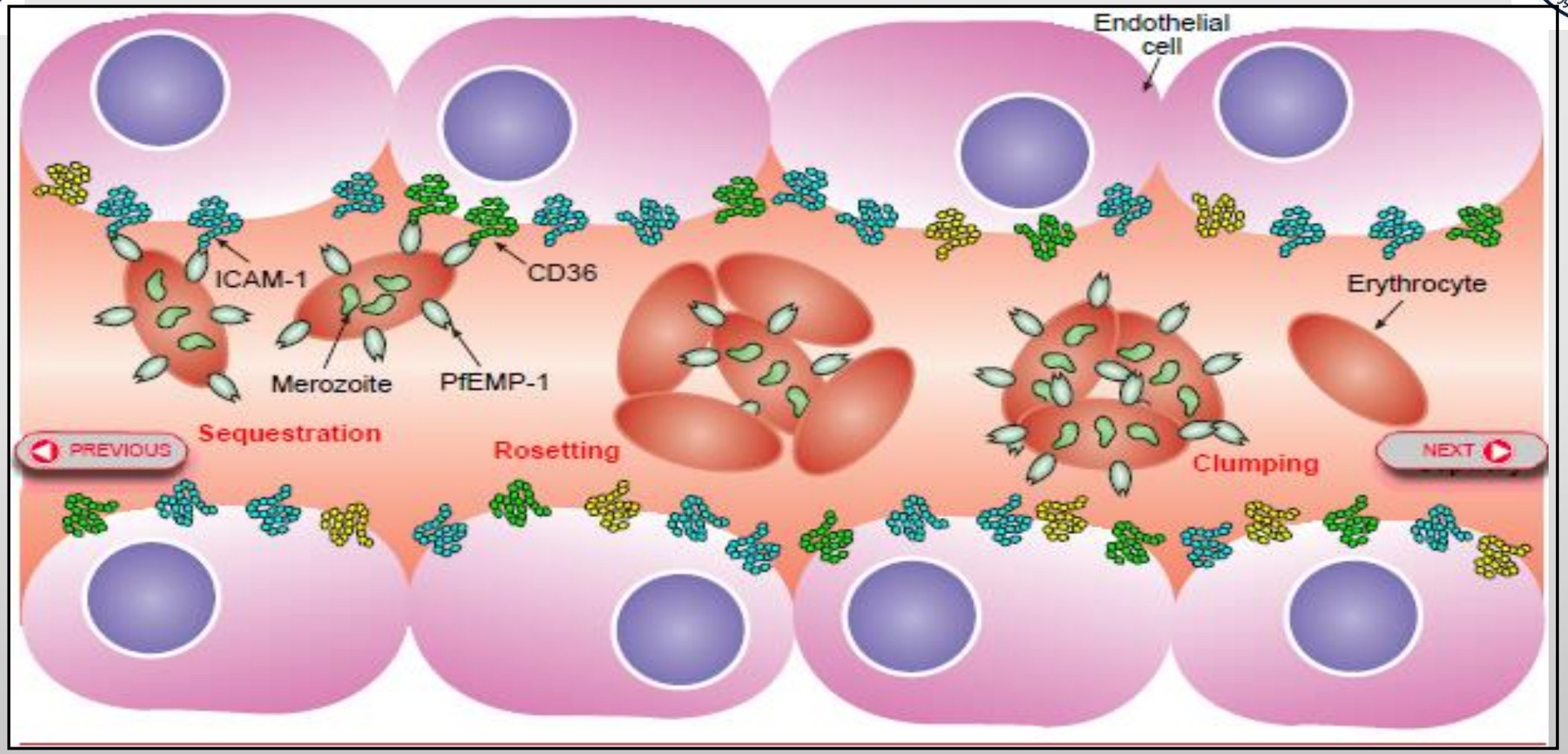
a. ***Sequestration of RBCs:*** Knobs formation on the surface of RBCs infected with late stages of parasites and the resulting increase in rigidity, lead to their adherence to receptors on the endothelium of internal capillaries, a phenomenon termed **cytoadherence**.

- Also, infected RBCs adhere to uninfected RBCs, resulting in **resetting**.

- Sequestration block blood flow, with subsequent infarctions and haemorrhage, mainly in brain and large intestine.

- erythrocytic schizogony takes place in **capillaries of internal organs** as brain, kidney, spleen, bone marrow, and intestine.

- All these factors contributing to the development of severe disease (malignant malaria


Endothelial cell
ICAM-1
CD36
Merozoite
PfEMP-1
Erythrocyte
Sequestration
Rosetting
Clumping
PREVIOUS
NEXT

b. ***Black water fever (malarial haemogloblinuria)*** due to massive intravascular haemolysis caused by anti-erythrocyte antibodies, leading to massive absorption of haemoglobin by renal tubules with its passage in urine causing haemoglobinuria (red urine). Sometimes, the haemoglobin is transformed into met-haemoglobin in the renal tubules, causing black coloured urine; black water.

c. ***Acute renal failure***, tubular necrosis from tissue anoxia.

d. ***Adrenal and retinal haemorrhage***.

e. ***Pulmonary oedema*** due to disseminated intravascular clotting.

f. ***Cardiac oedema,*** blocked capillaries and degenerated foci.

g. ***Spontaneous abortion***.

➢ Clinical picture:

1. Incubation period:

- It is the interval between the inoculation of the sporozoites into the human host and appearance of the earliest manifestation of the disease (1st paroxysm). - It represents the duration of **exo-erythrocytic cycle**.

- Patient may feel malaise, muscle pain, headache, loss of appetite and fever.

2. Malarial paroxysms: The typical picture of malaria consists of series of febrile paroxysm, followed by anaemia and splenomegaly. The febrile paroxysm occurs in 3 successive stages; cold, hot and sweating.

a. Cold stage: Intense cold and uncontrollable shivering for 15-60 minutes.

b. Hot stage: Intense heat, flushing, nausea, vomiting and severe headache, lasting for 2-6 hours.

c. Sweating stage: Decreased temperature and profuse sweating, lasting for 2- 3 hours.

The paroxysm usually begins in the early afternoon and lasts for 8-12 hours.

- It synchronizes with the **erythrocytic schizogony cycle**. With a 48-hour cycle, the fever recurs every third day; tertian malaria, and with 72-hour cycle, the fever recurs every fourth day; quartan malaria

➢ Complications:

1. ***Cerebral malaria:*** Manifested by headache, hyperpyrexia, coma and paralysis.
2. ***Black water fever:*** It is seen in patients with **repeated *P. falciparum*** infection and **inadequate treatment** with quinine. Clinical manifestations include vomiting, with passage of dark red or black urine. This condition may be complicated with acute renal failure and circulatory collapse

3. Algid malaria: Characterized by **peripheral circulatory failure**, rap pulse, low blood pressure, cold wet skin and profound shock. There may be severe abdominal pain, vomiting (gastric type), watery diarrhea (choleric type), or passage of blood in feces (dysenteric type).

4. Septicaemic malaria: It is characterized by high continuous fever with **dissemination of parasite to various organs**, causing multiorgan failure.

5. Recurrence of malarial attack:

a. Relapse: It is the recurrence of clinical manifestations of malaria and the reappearance of peripheral parasitaemia months or years after subsidence of a previous attack, in the absence of a new mosquito bite.

- **Species:** Relapse occurs in ***P. vivax*** and ***P. ovale*** (infections last up to 4 years).

- **Cause:** It is due to activation of the dormant **hypnozoites** initiating exo-erythrocytic schizogony, with the production of erythrotropic merozoites.

- Can be **prevented** by giving primaquine to eradicate hypnozoites.

b. Recrudescence: It is a recurrence of clinical attack of malaria, few weeks or many years after apparent clinical cure, without re-infection.

- Species: Recrudescence can occur in **all Plasmodium** species, but it is more common in ***P. falciparum*** (up to 2 years) and ***P. malariae*** (up to 40 years).

- **Causes**: It results from the persistence of some erythrocytic parasites at a sub-clinical level, which start to multiply to reach significant numbers.

-causes:

a. Incomplete anti-malarial therapy.

b. Anti-malarial drug resistance.

c. Changes of the surface antigens (antigenic variation) of the parasites resulting in evasion of the host immune response.

d. Splenectomy or immunosuppression.

- Can be **prevented** by adequate drug therapy or use of new antimalarial drugs in case of drug resistance.

➢ Diagnosis:

I- Clinical diagnosis: In endemic areas, malaria must be suspected in all cases of typical malarial paroxysm or fever.

II- Laboratory diagnosis:

1. Parasitic diagnosis: Examination of thin and/or thick Leishman or Geimsa stained **blood smears**.

- All **erythrocytic stages** can be detected in peripheral blood except in ***P. falciparum***, only **ring** form alone or with **gametocytes** can be detected.

2. Therapeutic diagnosis: The **non-subsidence** of the febrile paroxysms after the administration of anti-malarial drug for 3 days, means that the case is **not malaria.**

3. Serodiagnosis:

a. **Circulating antibodies** can be detected by IHA, IFA and ELISA.

b. **Circulating antigens** can be detected by ELISA.

c. **Rapid immunochromatographic test** for detection of malaria antigens by using a dipstick impregnated with specific monoclonal antibodies.

4. Molecular diagnosis.

5. Haematological diagnosis: Anaemia and reticulocytosis.

6. Biochemical diagnosis:

- Hypergammaglobulinemia and low albumin level.

- Hyperglycemia or hypoglycemia.

- Hyperkalemia.

➢ **Treatment: I. General and supportive measures:** Given to treat symptoms and complications, e.g. antipyretics, fluids and electrolytes replacement and blood transfusion.

II. Antimalarial drugs: A. Treatment of uncomplicated malaria:

1. Suppressive treatment (Erythrocytic schizonticides): These drugs act on the erythrocytic stages, e.g. 4-aminoquinoline as **chloroquine**, quinine, and atebrine.

2. Prophylactic treatment (Tissue schizonticides): These drugs act on the exoerythrocytic stages, e.g. 8-aminoquinolines as **primaquine**.

3. Radical treatment: Two drugs are given to eradicate plasmodia, one acting on the erythrocytic stages, to improve the symptoms (**chloroquine**), and another one acting on the exoerythrocytic stages to prevent relapse (**primaquine**).

B. Treatment of complicated falciparum malaria:

1. Chloroquine-sensitive falciparum malaria: Treated with chloroquine along with primaquine.

2. Chloroquine-resistant falciparum malaria: Artemisinin combined therapy (ACT) should be used.

➢ Prevention and control:

1. Mass treatment of infected cases.

2. Mosquito control.

3. ***Chemoprophylaxis***: It is used to prevent erythrocytic infections by giving one of the tissue schizonticides. Primaquine is given for healthy individuals, one day before visiting a malaria-endemic area and continued for 4 weeks after the last exposure.

4. ***Vaccination***: nowadays; there is no malaria vaccine. Many vaccines are being tested, and the most effective vaccine will attack the parasite at each stage of its life cycle: sporozoites can by blocked by antibodies, T-cell-mediated immunity can block liver stage, blood stage can easily targeted, and finally transmission can be blocked by targeting gametocytes.

MCQ 1: Which *Plasmodium* species is most widely distributed?

a. Plasmodium malariae

b. Plasmodium vivax

c. Plasmodium gallinaceum

d. Plasmodium falciparum

e. Plasmodium ovale

MCQ 2: Which stage induces relapse of malaria attack when activated?

a. Merozoites

b. Trophozoites

c. Sporozoites

d. Schizont

e. Hypnozoites

Discussion & Feedback

10 minutes