Malaria: An Overview

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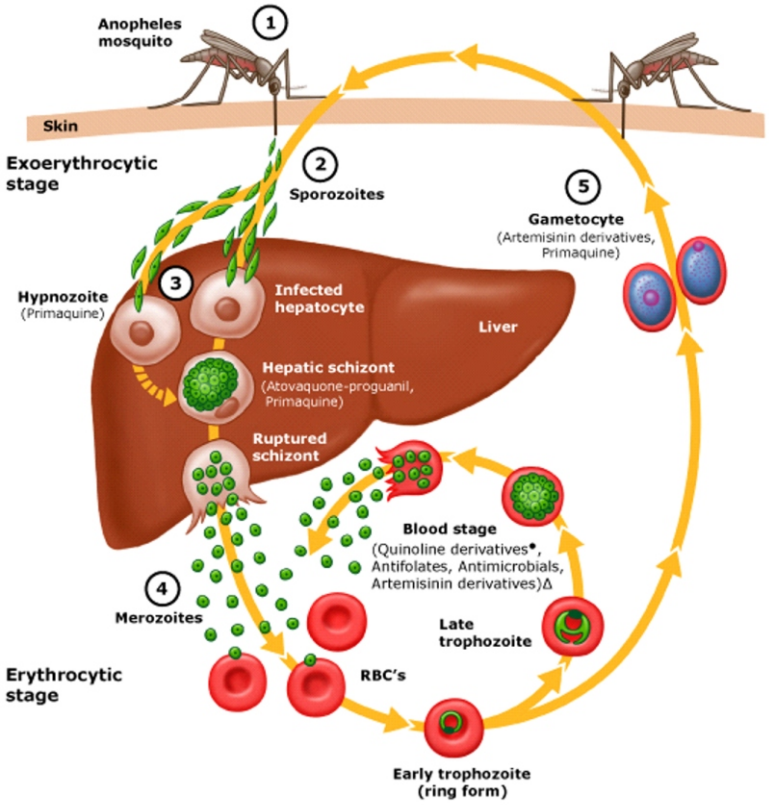
Species
Human malaria is a parasitic infection caused by different species of the plasmodium parasite:-

- *Plasmodium falciparum* – Causes >90% of infections in Sub-Saharan Africa, present in tropical and temperate zones. Severe disease common.
- *P.vivax* – Tropical and temperate zones, absent in West Africa. Severe disease less common.
- *P.ovale* – Tropical, epidemic in West Africa. Severe disease uncommon.
- *P.malariae* – Tropical, isolated pockets. Severe disease rare.
- *P.knowlesi* – Southeast Asia. Severe disease can occur.

Lifecycle of Plasmodium
Understanding the pathogenesis of malaria requires investigation of mechanisms of parasite invasion and host defense. The parasite life cycle illustrates the interplay between parasite and host.



Exoerythrocytic (asymptomatic stage):
Step 1: Plasmodium sporozoites are transmitted by the bite of an infected Anopheline mosquito.
Step 2: The sporozoites travel through the bloodstream of the host to the liver and invade the hepatocytes. They then divide until schizonts are formed containing thousands of daughter merozoites.
Step 3: In the setting of *P.vivax* and *P.ovale* infection, some parasites remain dormant in the liver as hypnozoites and can cause late relapse by reactivating after many months. In the setting of *P. falciparum* and *P. malariae* infection, hypnozoite parasites do not develop in the liver. However, *P.malariae* can cause very late relapse due to subpatent infection that can become symptomatic years later.

Erythrocytic (Symptomatic) Stage – After 12 – 14 days:

Step 4: asexual phase

- The hepatic schizont ruptures and releases merozoites. The merozoites invade the red blood cells and mature from *ring forms* ⟶ *trophozoites* ⟶ *schizonts*. They burst open and release the merozoites and pro-inflammatory cytokines. The haemolysis of the red cells causes anaemia. The red cell remnants are phagocytized by the macrophages in the blood and stimulate the immune response. The pro-inflammatory cytokines cause fever and raise the CRP level. The raised CRP correlates directly with the parasitaemia. TNF suppresses haemopoiesis and causes anaemia.

- Within the red cells the parasites mature and feed on the haemoglobin ⟶ the breakdown products are stored as haemozoin (a polarizable crystal). Intracellular parasites and haemozoin decrease the deformability of red cells resulting in haemolysis or splenic clearance ⟶ anaemia and eventually splenomegaly. The parasite cannot feed on abnormal haemoglobin e.g. HbAS and thalassemia. These patients are more resistant to malaria.

- Within the red cell the parasite derives energy from anaerobic glycolysis. Glucose is changed to lactic acid. This contributes to hypoglycaemia and lactic acidosis seen in severe malaria.

- The maturing *P.falciparum* parasite induces the formation of sticky knobs on the red cell surface. These knobs bind to receptors on endothelium of capillaries, venules and placenta ⟶ sequestration and accumulation of red cells ⟶ partial blood flow obstruction, accumulation of high levels of parasites, endothelial damage and inflammation.

- Although sequestration can be demonstrated in any organ of a patient with *P.falciparum*, the most catastrophic clinical manifestation of sequestration is cerebral malaria, renal failure and DIC. Infected red cells stick to uninfected red cells and form rosettes that further clog the microcirculation ⟶ hypoxia.

- Endothelial breakdown leads to the release of tissue factor ⟶ activation of clotting ⟶ low platelet count. Consumption of platelets in the microvascular sequestration also leads to a low platelet count.

Step 5: sexual phase

- Most released merozoites infect new red cells and a few differentiate into gametocytes which circulate until they are ingested by a mosquito.

Clinical Manifestations

1. **Uncomplicated Malaria**

- Febrile illness with a history of exposure.
- Physical findings may include anaemia, a palpable spleen and mild jaundice (breakdown of haem released from red cells).
- Laboratory findings may demonstrate parasitaemia <5%, anaemia, low platelet counts, raised bilirubin, mild coagulopathy and a raised CRP.

2. **Complicated Malaria**

- Generally defined as acute malaria with hyperparasitaemia >5% and major signs of organ dysfunction.
- Usually due to *Plasmodium falciparum*.
- Features of complicated malaria may include cerebral malaria, hypoglycaemia, acidosis, liver dysfunction, renal impairment, non-cardiogenic pulmonary oedema and anaemia.
- Laboratory findings:
  * Parasitaemia >5% - usually *P.falciparum.*
  * Anaemia, low platelet count.
  * Positive D-Dimer, prolonged PT and PTT.
  * Raised liver enzymes, hypoglycaemia, acidosis.
  * Raised CRP.
  * Renal Impairment.

Diagnostic tools

1. **Microscopic detection**

- Light microscopy is the gold standard for diagnosis of malaria. It permits determination of the infecting species as well as the quantification of parasitaemia. It also facilitates monitoring of the response to therapy.
- At least three smears at different time intervals should be submitted before the diagnosis can be excluded.

2. **Rapid diagnostic tests – (RDT)**

- RDT for malaria generally employ immunochromatographic lateral flow technology, in which the blood sample migrates across the surface of a nitrocellulose membrane containing stripes of antibodies specific for different epitopes of a target antigen along with a control antibody.

3. **Fluorescence microscopy**

- If the thin and thick smears are negative a QBC Malaria test (fluorescence microscopy-based) can be performed.
- The test has a superior sensitivity compared to a thick smear.

4. **Molecular Technologies**

- PCR tests are available. They are limited by factors including the need for specialised equipment, turnaround time and cost.
- PCR is not currently recommended as a first line test.
- The PCR is able to differentiate between the four main Plasmodium species.

Immunity
- Individuals living in endemic areas appear to develop partial immunity to malaria following repeated infections. The degree of protective immunity appears to be proportional to transmission intensity. Humoral immunity requires ongoing parasite antigen stimulation; individuals who leave endemic areas appear to lose some humoral protection.
- Duffy blood group – these antigens are necessary for the invasion by *P.vivax*.
- Abnormal haemoglobins can inhibit growth of the parasite in the red cells.

Prevention of malaria:-

Groups at high risk for severe malaria in endemic areas include:
- Children (6-36 months) who may develop severe illness.
- Pregnant women who are at risk of delivering low birth newborns.
- Older age groups will become more susceptible due to decreasing immunity.
- Travellers (non-immune individuals).
- Post splenectomy patients.
- Immunocompromised individuals.·

1. Mosquito bite prevention
- Avoid outdoor exposure between dusk and dawn (when anopheles mosquitoes feed).
- Wear clothing that reduces the amount of exposed skin.
- Wear insect repellent.
- Sleeping under bed nets treated with insecticides.
- Stay in well screened / air-conditioned rooms.

2. Chemoprophylaxis
Use the CDC guidelines for risk assessment of the area: http://www.cdc.gov/malaria/map/
- **Atovaquone-proguanil (Malanil®)**
  * One tablet daily. Start 1-2 days before exposure. Give for 7 days after last exposure.
  * Paediatric dose: 11 -20kg 1 paediatric tablet daily; 21 -30kg 2 paediatric tablets daily; 31 -40kg 3 paediatric tablets daily, >40kg 1 adult tablet daily.
  * Targets the liver stage of infection.
  * Side effects mild e.g. GIT upset, headache, insomnia, rash.
  * Contraindicated in pregnancy, kidney failure (creatinine clearance <30ml / min), children <5kg and patients on warfarin.
- **Mefloquine (Lariam®)**
  * One tablet weekly. Start a minimum of 1 week before exposure.
  * Give 4 weeks after last exposure.
  * Can be used in pregnant women.
  * Not recommended for children who are less than 3 months old or weigh less than 5kg.
  * Paediatric dose: 5 -20kg ¼ tablet; 21 -30kg ½ tablet; 31-45kg ¾ tablet; >45kg adult dose).
  * Targets the asexual stage of infection.
  * Contraindicated as prevention of malaria in *P.falciparum* resistant areas (Thailand, Cambodian border, parts of China, Burma and Vietnam).
  * Side effects mostly mild e.g. GIT upset, headaches, difficulty concentrating, mood swings and strange dreams. Only 5% experience disabling neuropsychiatric effect and must stop the drug. Most adverse effects occur with the first 3 doses.
  * Contraindications:
    - History of seizure or major psychiatric disorders and a recent history of depression or anxiety.
    - Associated with bradycardia and QT interval prolongation, use with caution in cardiac patients.
- **Doxycycline**
  * One tablet (100mg) daily. Start 1-2 days before exposure. Give 4 weeks after last exposure.
  * Targets the asexual phase of infection.
  * Contraindicated in pregnancy and children <8years.
  * Side effects – photosensitivity; Candida vaginitis.

Treatment of uncomplicated *P.falciparum* malaria (Chloroquine resistant or unknown resistance)

1. Artemisinin combination therapy (Coartem® ⟶ Artemether-lumefantrine)
- The best current treatment for uncomplicated *P.falciparum* malaria.
- Patients should receive an initial dose, followed by the second dose 8 hours later, then 1 dose p.o bid for the following 2 days.
- Dose according to weight: 5 - 14.9kg 1 tablet per dose, 15 - 24.9kg 2 tablets per dose, 25 - 24.9kg 3 tablets per dose; ≥35kg 4 tablets per dose.
- Drug has been studied in patients weighing less than 65kg and thus is not yet registered for use in patients weighing >65kg.
- Potent against all stages of asexual forms of malaria resulting in rapid clearance and activity against gametocytes.
- Low side-effect profile, so the drug of choice in uncomplicated malaria.
- Must not be used during the first trimester of pregnancy.
- Resistance has been documented in Thailand.

2. Atovaquone – proguanil (Malanil ®)
- Not to be used for treatment if it was taken as prophylaxis.
- No severe side effects.
- Must not be used during pregnancy.
- 5-8kg 2 paeds tablets p.o once daily x3days.

- 9 -10kg 3 paeds tablets p.o once daily x3days.
- 11 -20kg 1 adult tablet p.o per day x3days.
- 21 – 30kg 2 adult tablets p.o per day x3days.
- >40kg 4 adult tablets p.o per day x3days.

3. **Quinine sulphate plus one of the following: Doxycycline or Clindamycin**
- Quinine it is not recommended as first line therapy in uncomplicated malaria because of severe side effects such as hypoglycaemia and tinnitus.
- Effective and generally given for 3 days.
- For malaria acquired in SE Asia and for all travellers from non-endemic areas treat for 7 days.
- Dose is 2 tablets (600mg) every 8 hours. Paediatric dose is 10mg per kg every 8 hours for 7 days.
- Can be used during the first trimester of pregnancy in combination with Clindamycin (10mg per kg per day for 7 days).
- Doxycycline dose 200mg daily for 7 days (use in combination with quinine).

Treatment of uncomplicated non - *P.falciparum* malaria

1. **Chloroquine**
- Chloroquine 600mg immediately followed by 300mg orally at 6, 24 and 48 hours.
- *P.vivax* and *P.ovale* must also receive Primaquine after Chloroquine at a dose of 15mg orally once daily for 14 days to eradicate the hypnozoite phase in the liver.
- Primaquine is contraindicated in children <1 year old.

2. **Chloroquine resistant *P.vivax***
- Mefloquine or Malanil ® plus Primaquine.
- Quinine and doxycycline plus Primaquine.

Treatment of complicated malaria

1. **Quinine (parenteral) plus Doxycycline or Clindamycin**
- Quinine loading dose: quinine dihydrochloride salt 20mg/kg by IV infusion over 4 hours in 5% dextrose saline.
- Maintenance dose: Eight hours after the start of the loading dose, give 10mg/kg quinine dihydrochloride salt infusion over
- 4 - 6 hours, repeated every 8 hours until patient can take oral quinine. Total duration of treatment 7 – 10 days.
- Paediatric dose same as adult dose.

2. **Artesunate**
- Various artemisinin derivatives have been used in the treatment of severe malaria, including artemether, artemisinin, artemotil and artesunate. Randomized trials comparing artesunate and quinine from South-East Asia show clear evidence of benefit with artesunate. In a multi-centre trial, which enrolled 1461 patients (including 202 children < 15 years old), mortality was reduced by 34.7% in the artesunate group when compared to the quinine group. The results of this and smaller trials are consistent and suggest that artesunate is the treatment of choice for adults with severe malaria.
- For adults, artesunate 2.4 mg/kg IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment.

Reference

UpToDate: Topic 5709 Version 7.0, Topic 5722 Version 11.0, Topic 468 Version 7.0, Topic 4812 Version 12.0, Topic 5704 Version 10.0, Topic 5667 Version 20.0
Guidelines for the treatment of malaria. Second edition 2010. World Health Organization.

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