Malaria

- Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. (P. *falciparum*, P. *vivax*, P. *malariae* and P. *ovale*)
- The parasite is transmitted to humans through the bite of a female Anopheles mosquito.
- P. falciparum is the most dangerous species, causing an acute, rapidly fulminating disease that is characterized by **persistent high fever, orthostatic hypotension, and massive erythrocytosis**
- P. falciparum infection can lead to capillary obstruction and death if treatment is not instituted promptly.
- Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment of P. falciparum.

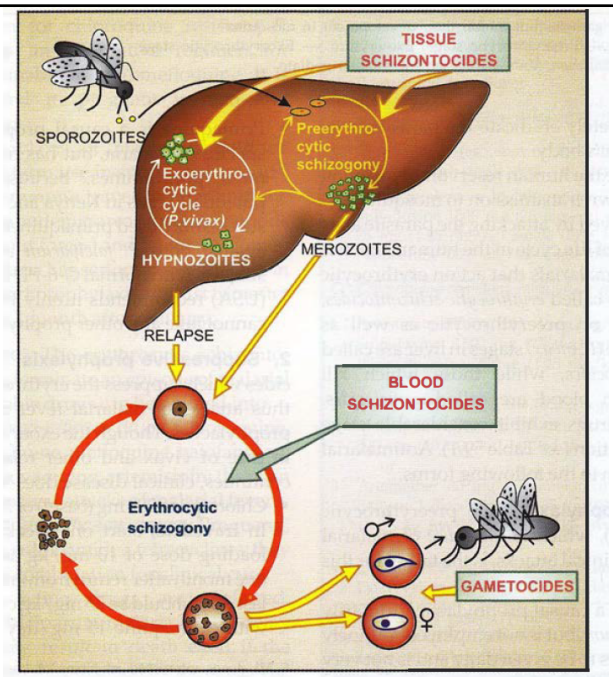
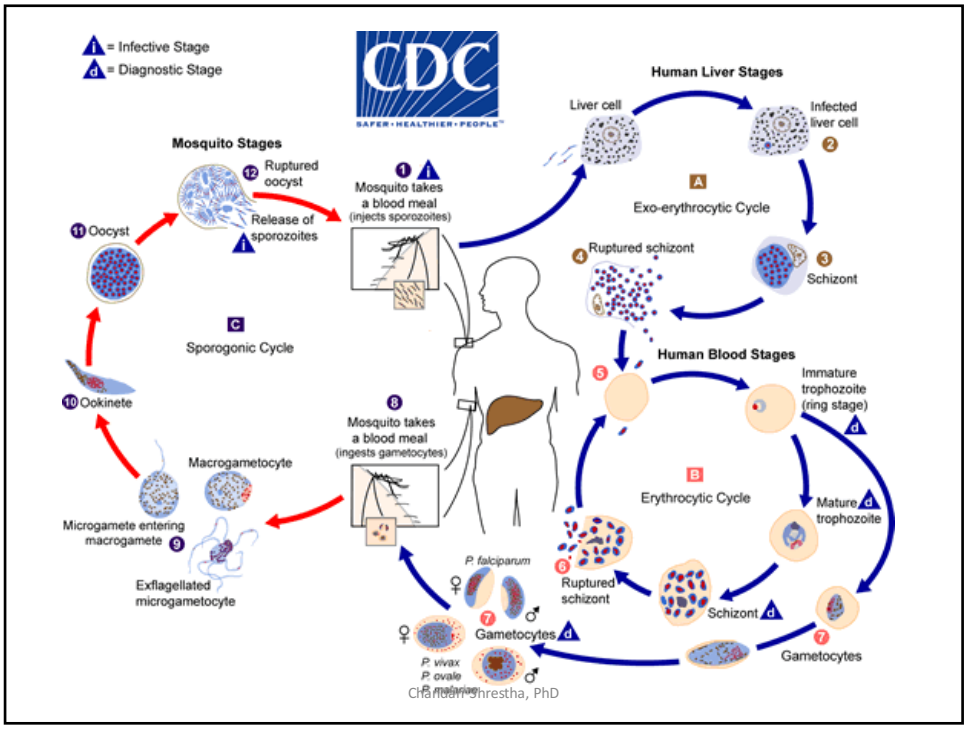


Fig. 59.1: The life cycle of malarial parasite in man. Stages and forms of the parasite at which different types of antimalarial drugs act are indicated.



Antimalarial drugs

- These are drugs used for prophylaxis, treatment and prevention of relapses of malaria.
- The aims of using drugs in relation to malarial infection are
  1. To prevent and treat clinical attack of malaria.
  2. To completely eradicate the parasite from the patient's body.
  3. To reduce the human reservoir of infection - cut down transmission to mosquito.
- These are achieved by attacking the parasite at its various stages of life cycle in the human host

Classification

1. *4-Aminoquinolines*	Chloroquine, Amodiaquine, Piperaquine.	8. *Tetracyclines*	Tetracycline, Doxycycline
2. *Quinoline-methanol*	Mefloquine.	9. *Sesquiterpine lactones*	Artesunate, Artemether Arteether
3. *Cinchona alkaloid*	Quinine, Quinidine	10. *Amino alcohols*	Halofantrine, Lumefantrine
4. *Biguanides*	Proguanil (Chloroguanide) Chlorproguanil	11. *Mannich base*	Pyronaridine
5. *Diaminopyrimidines*	Pyrimethamine	12. *Naphthoquinone*	Atovaquone
6. *8-Aminoquinoline*	Primaquine, Bulaquine		
7. *Sulfonamides and sulfone*	Sulfadoxine Sulfamethopyrazine Dapsone		

Prophylaxis: chloroquine, mefloquine, doxycycline, proguanil (erythrocytic stage)

Classification based on stage of parasite they affect

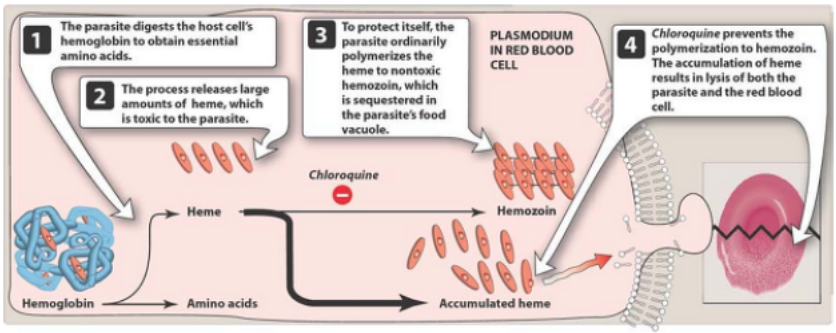
1. **Tissue schizonticidal agent**: proguanil, primaquine and pyrimethamine
2. **Blood schizonticidal agent**: chloroquine, quinine, mefloquine, artimisinin, atovaquone
3. **Gametocidal agent**: Artimisinin, primaquine against all species; chloroquine and quinine against P vivax.z

Chloroquine: blood schizonticides

- It is a rapidly acting erythrocytic schizontocide against all species of plasmodia except P. Falciparam (efflux pump)
- controls most clinical attacks in 1-2 days with disappearance of parasites from peripheral blood in 1-3 days.

MOA

- Binds to heme and Inhibit polymerization of toxic haeme (Hematin) to nontoxic parasite pigment (Hemozoin).
- free haeme or haeme-quinine complex damages parasite membranes and kills it.
- Other antimalarial drugs having similar MOA: quinine, mefloquine, lumefantrine, Amodiaquine.



In the acidic vacuole of Plasmodia:

- Haemoglobin → Haeme (toxic) → Hemozoin (non-toxic)
- Chlorquine (weak base) → Concentrated in acidic vacuole of parasite → Binds to haeme → Drug-haeme complex (prevents formation of hemozoin) → Damages plasmodial membrane

Chloroquine: blood schizonticides

Adverse effect

- Low. Nausea, vomiting, anorexia, epigastric pain, uneasiness, headache.
- Parenteral: hypotension, cardiac depression, CNS toxicity
- Prolonged use of high dose: retinal damage

Can be used during pregnancy

Chloroquine resistance→ P. falciparum (efflux system)

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Chloroquine

Uses

1. Chloroquine is the drug of choice for clinical cure and suppressive prophylaxis of all types of malaria, except that caused by resistant P. falciparum.
2. Extraintestinal amoebiasis.
3. Rheumatoid arthritis.
4. Discoid lupus erythematosus-very effective; less valuable in SLE.
5. Lepra reactions.
6. Photogenic reactions.
7. Infectious mononucleosis: affords symptomatic relief.

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Quinine: blood schizonticides

- Quinine is an erythrocytic schizontocide for all species of plasmodia; less effective and more toxic than chloroquine.
- Quinine is used orally for uncomplicated chloroquine-resistant malaria, and i.v. for complicated/ cerebral malaria
- **MOA**: similar to chloroquine
- **Adverse effect**: high and dose related; 8-10 g taken in a single dose may be fatal.

Cinchonism: A large single dose or higher therapeutic doses taken for a few days produce a syndrome called cinchonism.

- ringing in ears, nausea, vomiting, headache, mental confusion, vertigo, difficulty in hearing and visual Defects. Diarrhoea, flushing and marked perspiration may also appear. The syndrome subsides completely if the drug is stopped.

Primaquine: Tissue schizonticide

- eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale).
- The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thus interrupting the transmission of the disease.
- Primaquine is not effective against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as chloroquine, quinine, mefloquine, or pyrimethamine.

MOA

- This is not completely understood.
- Metabolites of primaquine are believed to act as oxidants that are responsible for the schizonticidal action.

Adverse effects:

- low incidence, abdominal pain, g.i. upset, weakness or uneasiness in chest
- toxic after large doses: haemolysis, tachypnoea, methaemoglobinaemia, and cyanosis.

Primaquine is contraindicated during pregnancy and G6P deficiency (hemolytic anemia)

All Plasmodium species may develop resistance to primaquine.

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Artemisinin: Blood schizonticide

- Artemisinin is derived from the qinghaosu plant, which has been used in Chinese medicine.
- Artemisinin is available for the treatment of severe, multidrug-resistant P. falciparum malaria.

MOA

Its antimalarial action involves the production of free radicals within the plasmodium food vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocytes. It is also believed to covalently bind to and damage specific malarial proteins.

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Adverse effect

- Nausea, vomiting, abdominal pain, itching and drug fever.
- Abnormal bleeding, dark urine, S-T segment changes, Q-T prolongation, first degree A-V block, transient reticulopenia and leucopenia have been noted but subside when the patient improves or drug is stopped.

Uses

1. uncomplicated chloroquine/ multidrug-resistant falciparum malaria → oral
2. severe and complicated falciparum malaria → parenteral

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Atovaquone: Blood schizontocide

MOA: Interfere with cytochrome electron transport in the mitochondria thus inhibit ATP production in mitochondria

Adverse effect: few. Skin rashes, Diarrhoea, vomiting, headache, rashes and fever, nausea,insomia

Resistance: Mutation in cytrochrome gene

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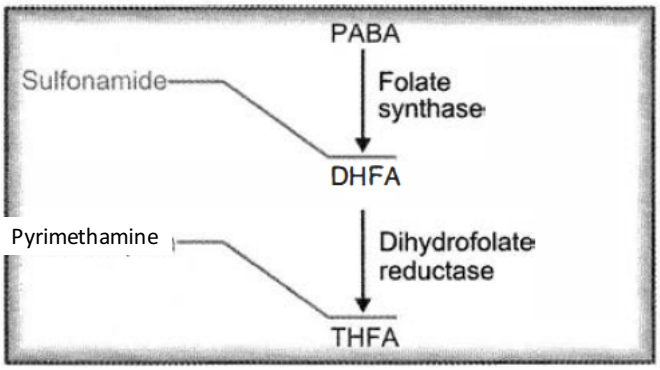
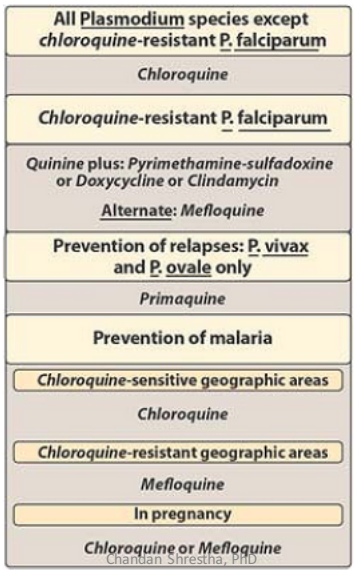
Pyrimethamine: blood schizonticide and sporontocide

- The antifolate agent pyrimethamine is frequently employed to effect a radical cure as a blood schizonticide.
- It also acts as a strong sporonticide in the mosquito's gut when the mosquito ingests it with the blood of the human host.
- Pyrimethamine inhibits plasmodial dihydrofolate reductase. Tetrahydrofolate cofactor required in the de novo biosynthesis of purines and pyrimidines and in the interconversions of certain amino acids.
- Pyrimethamine alone is effective against P. falciparum.
- In combination with a sulfonamide, it is also used against P. malariae and Toxoplasma gondii.
- If megaloblastic anemia occurs with pyrimethamine treatment, it may be reversed with leucovorin.

MOA



Treatment and prevention of malaria



Chemoprophylaxis

A. For travel to area with chloroquine-sensitive P. falciparum, P. vivax, P. malariae and P. ovale malaria

- Chloroquine phosphate is given orally. Chloroquine phosphate 500 mg (Chloroquine base 300 mg) once weekly, starts one week before entering the endemic area, continue during the stay there, and for for 4 weeks after leaving that area.

B. In areas with chloroquine resistant P. falciparum malaria

- Mefloquine 250 mg salts (228 mg base) orally, once weekly, starts one week before entering the endemic area, continue once weekly there, and for 4 weeks after leaving that area.

Or

- Doxycycline hyclate 100 mg orally daily, starts one day before entering the endemic area,

Chemoprophylaxis continue

continue daily during stay there, and daily for 4 weeks after leaving that area. Doxycycline is

Or

- Atovaquone 250 mg + proguanil 100 mg, fixed dose combination tablet is available for oral administration. One tablet daily, starts one day before entering the endemic area, continue daily during the stay there and daily for 1 weeks after leaving that area.

C. For terminal prophylaxis (Antirelapse therapy for P. vivax and P. ovale malaria)

- Primaquine 15 mg daily is started shortly before or after the person leaves the endemic area, and continued for 2 weeks.

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Chemotherapy in malaria

1. Treatment of uncomplicated malaria

a. For acute attack of P. vivax, P. ovale, P. malariae and chloroquine sensitive P. falciparum malaria:
   - Oral chloroquine is the drug of choice.
   - Chloroquine 600 mg base (10 mg/ kg) stat, followed by 300 mg base 6 hour later - first day.
   - 300 mg base- second day
   - 300 mg base - third day

b. For radical cure of P. vivax and P. ovale

chloroquine (as above)

+

Primaquine 15 mg base orally, from day 4 daily for 14 days.

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Chemotherapy in malaria continue

2. For severe or complicated P. falciparum malaria (cerebral malaria)

- Parenteral antimalarial should be administered for at least 24 h once started. Then complete the treatment with full course of oral ACT once the patients areable to take orally.
  - Artesunate
    - Dose: 2.4 mg/kg at 0 hr (i.v./i.m); repeat at 12 h and at 24 h. Then, once a day till patients is able to take oral medication.
    - If patients is able to take orally after 24 h, switch over to full course of 3 days **oral ACT.**

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Artemisinin-Based Combination Treatment (ACT regimen) for uncomplicated malaria

i. Artesunate - mefloquine
- Artesunate 100 mg BD (4 mg/kg/day) * 3 days + mefloquine 750 mg (15 mg/kg/days) on second days and 500 mg (10 mg/ kg) on third days.

ii. Artemether - lumefantrine
- Artemether (80 mg BD) + lemefantrine (480 mg BD) * 3 days.

iii. Artesunate-sulfadoxine + pyrimethamine
- Artesunate 100 mg BD (4 mg/kg/day) * 3 days + sulfadoxine 1500 mg (25 mg/ kg) and pyrimethamine 75 mg (1.25 mg/kg) single dose.

iv. Arterolane - piperaquine
- Arterolane as maleate 150 mg + piperaquine 750 mg daily * 3 days.

v. Dihydroartemisinin - piperaquine (DHA/ PPQ)
- DHA 120 mg (2 mg/kg) + piperaquine 960 mg (16 mg /kg) daily * 3 days.

vi. Artesunate - amodiaquine
- Artesunate 200 mg (4 mg/kg) +amodiaquine 600 mg (10 mg/ kg) per day * 3 days.

vii. Artesunate- pyronaridine
- Artesunate 100-200 mg (2-4 mg mg/kg) + pyronaridine 300-600 mg (6-12 mg /kg) per days * 3 days.

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