ANTIMALARIAL AGENTS
Protozoal Infections

Parasitic protozoa: live in or on humans

- Malaria
- Leishmaniasis
- Amebiasis
- Giardiasis
- Trichomoniasis
Malaria

- Caused by *Plasmodium* protozoa – 4 different species

- **Cause:** the bite of an infected adult female anopheline mosquito

- Also transmitted by infected individuals via blood transfusion, congenitally, or infected needles by drug abusers
Malarial Parasite (*Plasmodium*)

**Two interdependent life cycles**

- **Sexual cycle:** occurs in the mosquito
- **Asexual cycle:** occurs in the human

- Knowledge of the life cycles is essential in understanding antimalarial drug treatment
- Drugs are effective only during the asexual cycle
Malaria is one of the most widespread diseases caused by protozoan parasite of the genus, *Plasmodium*. These parasites spend an asexual phase in man and sexual phase in female anopheles mosquito. Malaria is caused by four species of one-cell protozoan of the *Plasmodium* genus: *P. falciparum, P. vivax, P. malariae* and *P. ovale*. No antimalarial drug is effective against all four species.
Plasmodium Life Cycle

Asexual cycle: two phases

- **Exoerythrocytic phase**
  - Occurs “outside” the erythrocyte
  - Also known as the tissue phase

- **Erythrocytic phase**
  - Occurs “inside” the erythrocyte
  - Also known as the blood phase

Erythrocytes = RBCs
FEMALE ANOPHELES MOSQUITO

SPOROZOITES [salivary glands of insect]

Oocysts

(Stomach epithelium)

Zygotes

Insect bite

Fertilization (Stomach)

HUMAN

Primary Schizonts (Liver)

MEROZOITES (Liver)

(Pre-erythrocytic stage)

Secondary Schizonts (Liver)

MEROZOITES (blood)

Erythrocytic stage

Merozoites release

Entering into erythrocytes

Erythrocyte rupture

Female gametocytes

Male gametocytes

Female gametocytes

Multiplication and development of merozoites or gametocytes

Antigens

Chills, Fever

Insect bite

Gut wall

Oocysts

(Zymoderm)
Antimalarial agents are chemically classified as

- **Cinchona alkaloids**: eg. Quinine, Cinchonine.
- **4- Amino quinolines**: eg. Chloroquine, Amodiaquine, Hydroxychloroquine.
- **8 - Amino quinolines**: eg. Bulaquine, Primaquine, Pamaquine.
- **9- Amino acridine**: eg. Mepacrine.
- **Biguanides**: eg. Proguanil, Cycloguanil.
- **Pyrimidine analogue**: eg. Pyrimethamine.
- **Polycyclics**: eg. Doxycycline, Halofantrine.
- **Newer antimalarial agents**: eg. Artemisinin, Fosmidomycin.
- **Sesquiterpene lactones**: eg. Arteether, Arteemether, Artesunate.
- **Miscellaneous**: eg. Metaloamine, Sulphadoxine, Mefloquine.
Chloroquine (Cadiquin, Melubrin)

7-Chloro-4- {[4- (diethylamino) -1-methyl butyl] amino} quinoline
Cinchona alkaloids

(R)- (6-Methoxy quinolin-4-yl) (2S, 4S, 8R)-8-vinyl quinuclidin-2-yl methanol
Antimalarials: Mechanism of Action

4-Aminoquinoline derivatives: chloroquine and hydroxychloroquine

- Bind to parasite nucleoproteins and interfere with protein synthesis; also alter pH within the parasite
- Interfere with parasite’s ability to metabolize and use erythrocyte hemoglobin
- Effective only during the erythrocytic phase
Antimalarials: 
Mechanism of Action

4-Aminoquinoline derivatives: quinine and Mefloquine (Lariam)

- Alter pH within the parasite
- Interfere with parasite’s ability to metabolize and use erythrocyte hemoglobin
- Effective only during the erythrocytic phase
Antimalarials:
Mechanism of Action

Diaminopyrimidines (pyrimethamine (Daraprim) & trimethoprim)

- Inhibit protein synthesis essential for growth and survival
- Only effective during the erythrocytic phase
- These drugs may be used with sulfadoxine or dapsone or synergistic effects
Antimalarials: Mechanism of Action

- **Primaquine**
  - Only exoerythrocytic drug (works in both phases)
  - Binds and alters parasitic DNA

- **Sulfonamides, tetracyclines, clindamycin**
  - Used in combination with antimalarials to increase protozoacidal effects
Antimalarials

Adverse Effects

- Many adverse effects for the various drugs

- Primarily gastrointestinal: nausea, vomiting, diarrhea, anorexia, and abdominal pain