Chemotherapy

Drugs Used in Protozoal Infections

What are protozoa?

- **Protozoa** are single-celled organisms that can cause disease in humans.
- They are different from bacteria, fungi, and worms.
- Many protozoal diseases are common in tropical and subtropical regions, but some occur worldwide.

Important protozoal diseases include:

- Malaria
- Amoebiasis
- Giardiasis
- Trichomoniasis
- Leishmaniasis
- Toxoplasmosis
- Trypanosomiasis
- The drugs used against these infections are called **antiprotozoal drugs**.

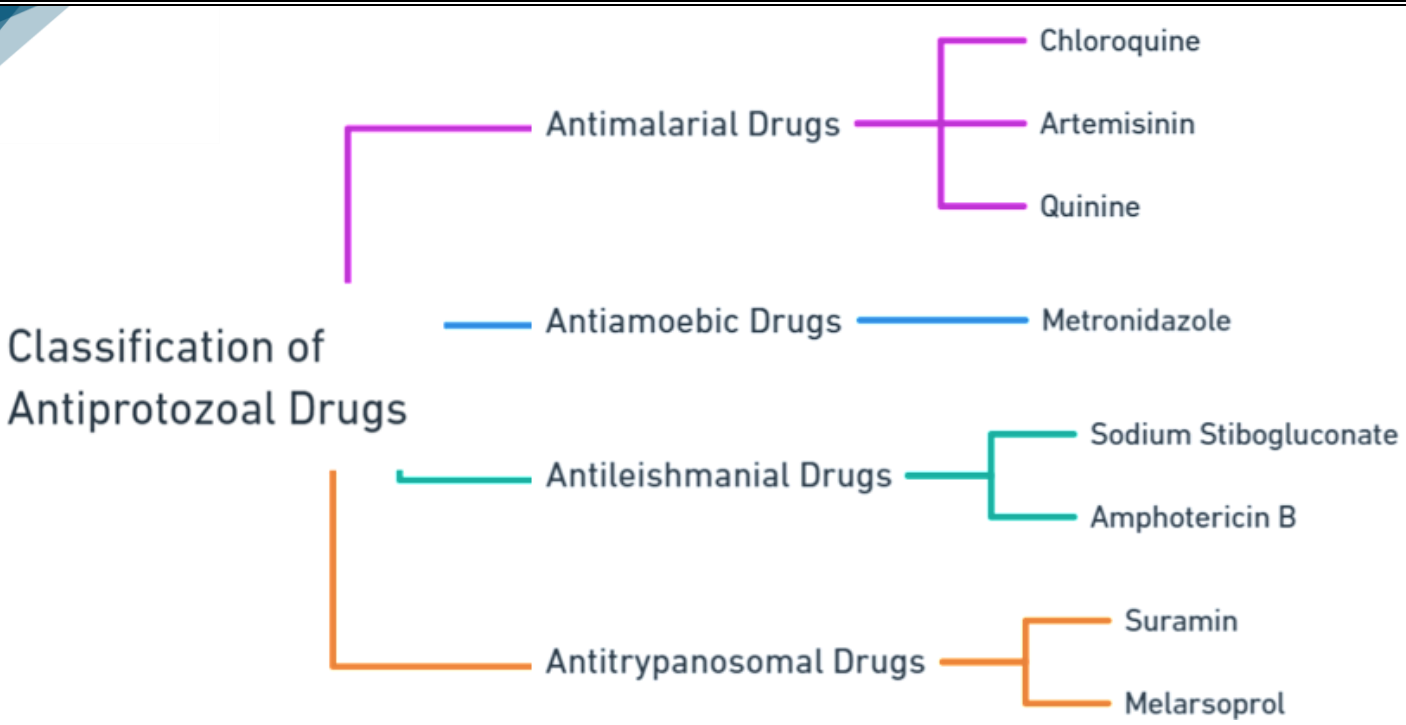
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General principles of antiprotozoal therapy

- **When treating protozoal infections, the doctor considers:**
  - Which protozoa is causing the disease
  - Where the parasite lives in the body
  - Whether the infection is mild or severe
  - Patient factors such as age, pregnancy, liver disease, kidney disease, and immune status
  - Drug resistance in that area
  - Protozoa are eukaryotic cells, like human cells.
  - Because of this, it is often harder to find drugs that kill protozoa without harming human cells.
  - That is why many antiprotozoal drugs can have important adverse effects.

Classification of antiprotozoal drugs

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1. Antimalarial Drugs

A. Chloroquine

MOA:

1. Passive diffusion into parasite-infected RBC and accumulation in acidic food vacuole (ion trapping).
2. Inhibits polymerization of ferriprotoporphyrin IX (heme) → prevents conversion to hemozoin.
3. Free heme + chloroquine–heme complex → lipid peroxidation and membrane damage.
4. Interferes with parasite proteolysis of hemoglobin and vacuolar function.

Resistance:

1. Mutation in *PfCRT* (K76T) → enhanced efflux of chloroquine from food vacuole.
2. *PfMDR1* polymorphisms → altered drug transport and reduced accumulation.
3. Changes in vacuolar pH and ion homeostasis → decreased drug trapping.
4. Net effect: insufficient heme toxicity to kill parasite.

B. Artemisinin

MOA:

1. Activation by Fe^{2+} from heme inside parasite digestive vacuole.
2. Cleavage of endoperoxide bridge → formation of reactive oxygen/carbon-centered radicals.
3. Alkylation of parasite proteins (e.g., PfATP6, membrane proteins).
4. Disruption of mitochondrial and membrane integrity → rapid parasite death.

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Resistance:

1. Mutations in *K13* gene → reduced hemoglobin uptake and heme availability.
2. Induction of dormant ring-stage forms → temporary growth arrest.
3. Upregulation of stress response pathways (protein repair, ubiquitination).
4. Delayed parasite clearance rather than complete resistance.

C. Quinine

MOA:

1. Accumulates in food vacuole of parasite.
2. Inhibits heme detoxification → accumulation of toxic ferriprotoporphyrin IX.
3. Interferes with DNA replication and transcription at higher concentrations.
4. Disrupts parasite metabolism and membrane stability.

Resistance:

1. Mutations in *PfMDR1* → reduced drug accumulation.
2. Increased efflux and altered transporter activity.
3. Partial cross-resistance with chloroquine mechanisms.
4. Changes in vacuolar environment affecting drug action.

2. Antiamoebic Drugs

A. Metronidazole

MOA:

1. Passive diffusion into anaerobic protozoa.
2. Reduction of nitro group by ferredoxin-linked pathways.
3. Formation of reactive nitro radical anions.
4. DNA strand breakage, helix destabilization, inhibition of nucleic acid synthesis.

Resistance:

1. Decreased activity of pyruvate:ferredoxin oxidoreductase.
2. Reduced expression of nitroreductases → less drug activation.
3. Increased intracellular oxygen → scavenges radicals.
4. Enhanced DNA repair mechanisms.

3. Antileishmanial Drugs

A. Sodium Stibogluconate

MOA:

1. Conversion of Sb^{5+} → active Sb^{3+} inside macrophages/parasite.

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2. Inhibits trypanothione reductase → disrupts redox balance.
3. Increases reactive oxygen species → oxidative damage.
4. Inhibits glycolysis and fatty acid oxidation → ATP depletion.

Resistance:

1. Upregulation of ABC transporters (MRPA) → drug efflux.
2. Increased intracellular thiols (trypanothione, glutathione) → drug sequestration.
3. Reduced uptake via aquaglyceroporins.
4. Impaired reduction of Sb^{5+} to active Sb^{3+}.

B. Amphotericin B

MOA:

1. Binds ergosterol-like sterols in parasite membrane.
2. Formation of transmembrane pores.
3. Leakage of intracellular ions (K^+, Mg^{2+}) and metabolites.
4. Induces oxidative stress and membrane destabilization.

Resistance:

1. Altered sterol biosynthesis → reduced ergosterol content.
2. Replacement with precursor sterols → lower drug affinity.
3. Increased antioxidant defenses.
4. Changes in membrane composition reducing pore formation.

4. Antitrypanosomal Drugs (e.g., Suramin, Melarsoprol)

A. Suramin

MOA:

1. Enters parasite via receptor-mediated endocytosis.
2. Inhibits key glycolytic enzymes (e.g., glycerol-3-phosphate oxidase).
3. Disrupts ATP generation in bloodstream forms.
4. Interferes with nucleic acid and protein metabolism.

Resistance:

1. Loss or mutation of surface receptors (e.g., ISG75).
2. Reduced endocytosis → decreased drug uptake.
3. Altered intracellular trafficking to lysosomes.
4. Metabolic adaptation reducing dependence on inhibited pathways.

B. Melarsoprol

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MOA:

1. Converted to melarsen oxide (active form).
2. Forms stable adduct with trypanothione.
3. Inhibits trypanothione reductase → oxidative stress.
4. Inactivates sulfhydryl-containing enzymes → energy failure.

Resistance:

1. Mutation/loss of *TbAQP2* transporter → reduced drug uptake.
2. Increased thiol production → detoxification.
3. Enhanced efflux mechanisms.
4. Altered redox pathways reducing drug impact.

Drugs Used in the Treatment of Helminthiasis

Basic idea

- Helminths are parasitic worms.
- They are larger and more complex than protozoa.
- They may live in the intestine, blood, lymphatics, liver, lungs, muscles, or other tissues.

Main groups of helminths:

- Nematodes (roundworms)
- Cestodes (tapeworms)
- Trematodes (flukes)
- **Treatment of helminthiasis is important because worms may cause:**
  - Malnutrition
  - Intestinal obstruction
  - Anemia
  - Tissue damage
  - Allergic reactions
  - Chronic inflammation
  - Organ dysfunction

Classification of antihelminthic drugs

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