Antiprotozoal and Antihilmintic Drugs

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Protozoal Infection

- Protozoal diseases, such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis.

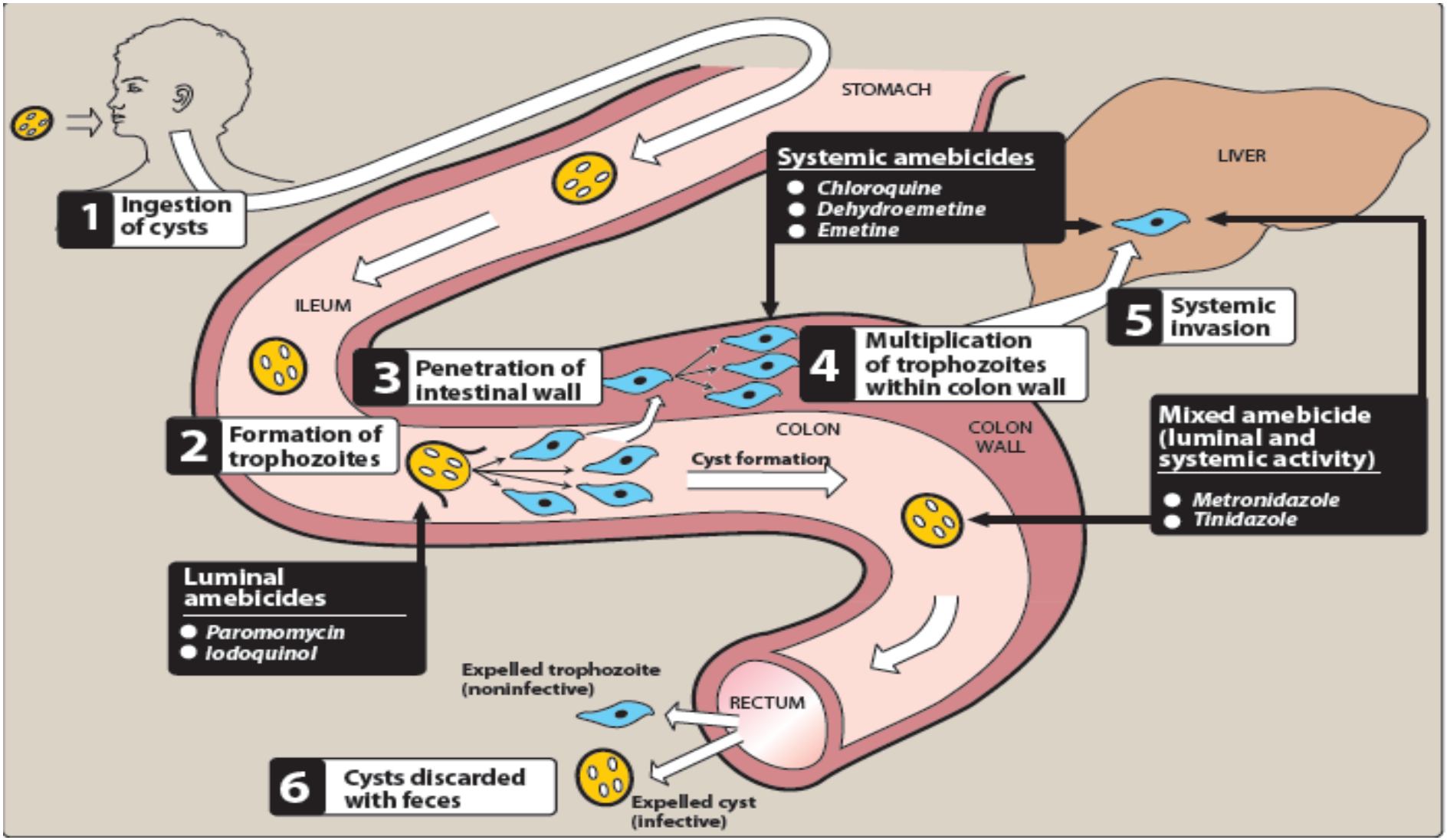
- Protozoal diseases are less easily treated than bacterial infections.
- Many of antiprotozoal drugs cause serious Toxic effects and most of them are not safe In pregnancy.

Antiprotozoal Drugs

1. Chemotherapy for amebiasis
2. Chemotherapy for malaria
3. Chemotherapy for giardiasis
4. Chemotherapy for leshmaniasis
5. Chemotherapy for toxoplasmosis
6. Chemotherapy for trypanosomiasis

Amebiasis **Amebiasis is a protozoal infection of the intestinal tract that occurs due to ingestion of foods or water contaminated with Entameba Histolytica cysts**

Life cycle of Entameaba histolytica and the sites of action of amebicidal drugs



Antiamebic Drugs

- Luminal amebicides
  - **Paromomycin,**
  - **Iodoquinol,**

- systemic amebicides “intestinal wall and the liver”
  - **Chloroquine**
  - **Emetine**
  - **Dehydroemetine**

- Mixed amebicides : both systemic and luminal
  - **Metronidazole**
  - **Tinidazole)**

Mixed amebicide

- **Metronidazole** is Drug of choice (DOC) for amebic infection
- And for infections caused by:
- Giardia lamblia
- Trichomonas vaginalis
- Anaerobic cocci, gram+ve bacilli and "**Clostridium defficil**".
- " that cause **Pseudomemberanous colitis**

It kills the trophozoites and less effective against the cyst.

Metronidazole (cont.)

- Most effective against the invasive amebae
- Less effective against the luminal amebae
- it is usually administered with a luminal amebicide, such as *iodoquinol or paromomycin*

MOA:

- Releases in the parasites toxic superoxide or hydroxyl radical forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.

Metronidazole (Kinetics)

- **Given orally or IV**
- **Well absorbed orally.**
- **Well distributed to all tissues and fluids.**
- **Metabolized by CYP450 (Inducer: phenobarbital and inhibitor cimetidine)**
- **Metabolites excreted in urine.**

Metronidazole Adverse effects: (ADRs)

- Nausea and vomiting.
- GI disturbances, metallic taste.
- Headache, dizziness , vertigo & numbness.
- Disulfiram-like effect if taken with alcohol.

Tinidazole has longer duration, simpler dosing regimen, less toxicity, than metronidazole, but is equally active.

Luminal Amebicides

*Iodoquinol *Paromomycin *diloxanide furoate

** They have a direct **amebicidal** effect to the trophozoites and cyst forms.

***Used in:

asymptomatic cyst carriers and in intestinal amebiasis.

Amebae feed on intestinal Flora so tetracycline is added to luminal amebicides to decrease major food source.

Systemic Amebicides

- **Chloroquine** :useful for treating liver abscesses, and intestinal wall

** Usually used with metronidazole and diloxanide furoate to treat and prevent liver abscess – orally for 25 days

*** Other uses: Antiamebic drug, Antimalaial and anti-inflammatory in arthritis.

Emetine and Dihydroemetine

- They inhibit protein synthesis. plant alkaloid derived from ipeca.
- Direct **amebicidal** on invasive amebae in tissue.
- Given IM.
- They should not be taken for more than 5 days

➢ **ADRs**: GIT upset very common.

Cardiotoxicity: arrhythmia and CHF

Neuromuscular weakness ,dizziness and skin rash.

EMETINE

- **Concentrated in Liver, Lungs, Spleen, Kidney, Cardiac muscle and Intestinal wall.**
- **Metabolized & Excreted slowly via kidney so it has a cumulative effect.**
- **Trace amounts could be detected in urine 1-2 month after last dose.**
- **Should not be used for more than 10 days (usually 3-5 days).**

Mechanism

- **Act on tissue trophozoites causing irreversible block of protein synthesis.**
- **Adverse Effects: GIT: nausea, vomiting, diarrhoea.**
- **Neuromuscular weakness**
- **Serious toxicities: cardiotoxicity**

  - cardiac arrhythmias,- Hypotension,- heart failure

Clinical Uses

- **Amoebic liver abscess.**
- **Intestinal wall infections.**
- **Severe forms of amebiasis acute amoebic dysentery dehydroemetine is preferable due to less toxicity (3-5 days).**

Contraindications

- **Heart disease**
- **Kidney disease**
- **Pregnancy**
- **Children**

Paromomycin Sulphate

- **Aminoglycoside, not absorbed.**
- **Effective against luminal forms of ameba**

Mechanism of action

- **Direct amebicidal action (causes leakage by its action on cell membrane of parasite).**
- **Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.**

Kinetics

- **Orally**
- **Not significantly absorbed from the GIT**
- **Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency).**

Adverse effects

- **Gastrointestinal distress and diarrhea.**

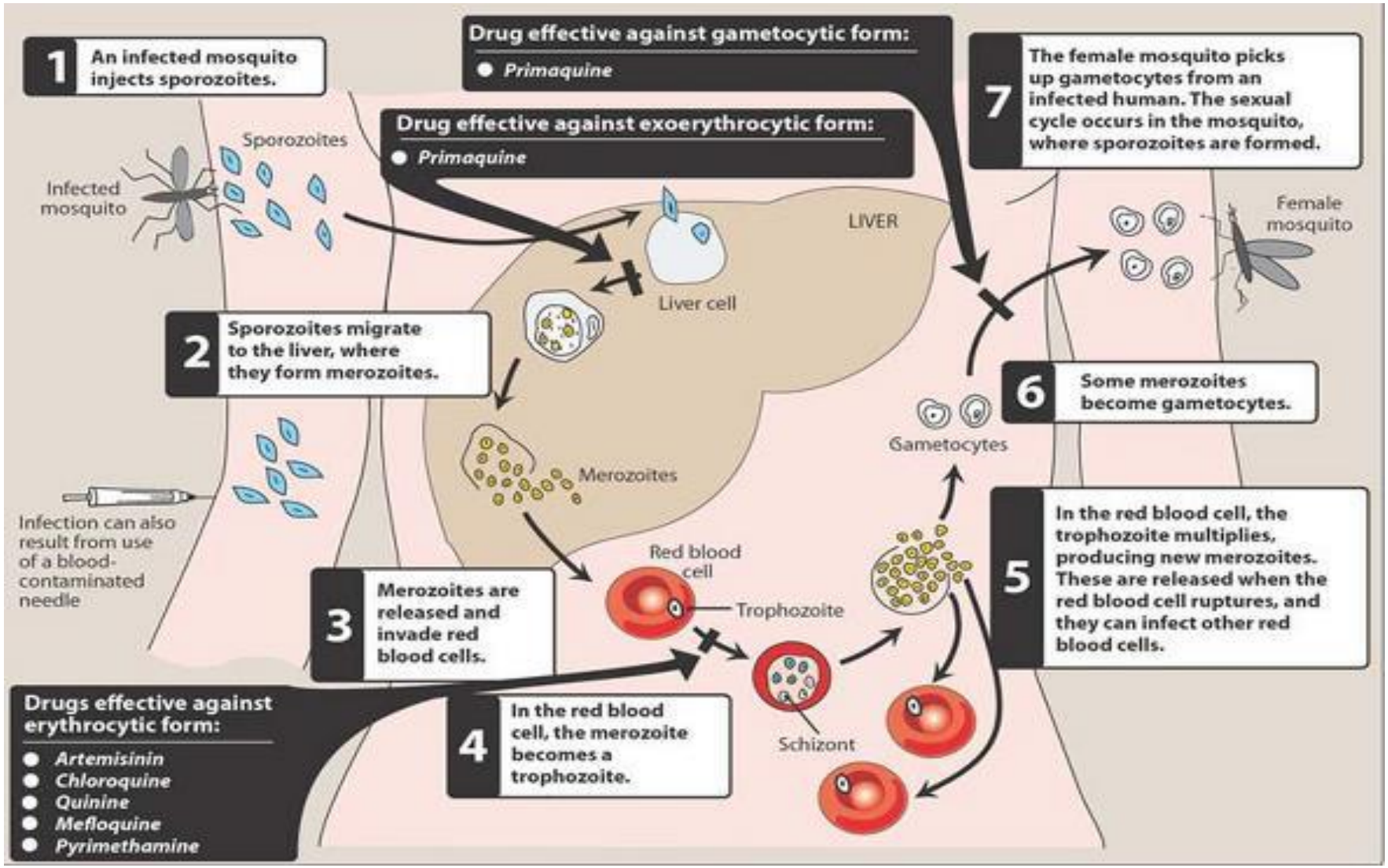
Precautions

- **Severe renal disease**
- **patients with GIT ulceration**

Summary

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *paromomycin*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *Iodoquinol* or *paromomycin*
Amebic liver absess	*Chloroquine* plus *metronidazole* and/or *diloxanide furoate*

Life cycle of malaria parasite and the sites of action of antimalarial drugs



Life cycle of Malaria

- Anopheles mosquito injects -- Plasmodium **sporozoites** into the bloodstream - to the liver form **merozoites** invades a red blood cell, becoming a **trophozoite -** released merozoites from RBCs can become **gametocytes –** to the insect becoming sporozoites again……and so on

Anti-malarial Drugs

- No drug against sporozoites is available.

a: They remain in the blood for a very short time.
b: They have very low metabolic rate , “not easily destroyed by drugs”

1:Drugs Against Exoerythrocytic Form

- **"Tissue schizonticide"**
- **Primaquine** (8-aminoquinoline)
- Also has **gametocidal** effect → prevent transmission.
- Well absorbed orally.
- May cause hemolytic anemia in G6PD deficiency ,decrease WBC and hemoglobinemia.
- C/I in pregnancy

2:Drugs Against Erythrocytic Form

- **"Blood schizonticides"**
- Clinical cure or suppression of S &S.

1. Chloroquine:

- Also has **gametocidal** effect → prevent transmission.
- Very well absorbed orally. *The drug concentrates in erythrocytes and some tissues.* 4 days of therapy to cure the disease.
- Mainly metabolized by the liver.
- The rest is eliminated unchanged in urine

Chloroquine (cont.)

- Other uses:

–Amebic hepatitis

– Giardiasis.

–rheumatoid arthritis.

❖ **ADRs:** Blurring of vision,

Yellow discoloration of skin and nails

Alopecia.

BM (Bone marrow) depression.

Mental confusion.

Arrhythmia.

2:Drugs Against Erythrocytic Form

2: Quinine:

- Blood **schizonticidal** and **gametocidal**.
- It is reserved for severe infection and for malarial strains that are resistant to other agents such as *chloroquine*.

➢ Stimulate uterine contraction C/I in pregnancy (abortion)

ADRs:

- **Cinchonism**: a syndrome causing nausea, vomiting, and vertigo
- Slight deafness,
- Haemolysis

3: Mefloquine

- Similar to chloroquine.
- Less toxic.
- Effective in most cases of chlorquine resistant malaria.
- ECG abnormalities and cardiac arrest are possible if *mefloquine is taken concurrently with quinine* or *quinidine.*

4: Artemisnin

- *It's available for the treatment of severe, multi-drug resistant P. falciparum malaria.* IV, orally and rectally
- High doses couse neurotoxicity

2:Drugs Against Erythrocytic Form

5. Pyrimethamine "Antifolate"

- inhibits plasmodial dihydrofolate reductase
- They have tissue and blood **schizonticidal** effect clinical and radical cure.

ADRs: megaloplastic anemia.

- **Combination: Pyrimethamine + sulphadoxine= Fansidar**

for : **P. malariae and Toxoplasma gondii.**

Other Protozoa

❑ Trichomoniasis and Giardiasis

Metronidazole &Tinadizole

❑ Toxoplasmosis

Pyrimethamine-sulphadoxine

Co-trimoxazole

Azithromycin

❑ Leishmaniasis

Na- stebogluconate .

Antihelmintic Drugs(AHDs)

❖ Drugs that kill or remove intestinal parasites

- **Vermicide** – to kill.
- **Vermifuge** – affect the worm in such away, they can be expelled by peristalsis or by purgatives.

➢ Purgation may be needed as $MgSO_4$ or $NaSO_4$,

➢ AHDs:

- in pregnancy ⟶ teratogenicity & GI ulceration.

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR NEMATODES

Diethylcarbamazine BANOCIDE

Ivermectin STROMECTOL

Mebendazole VERMOX

Pyrantel pamoate NEMEX

Thiabendazole MINTEZOL

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR TREMATODES

Praziquantel BILTRICIDE

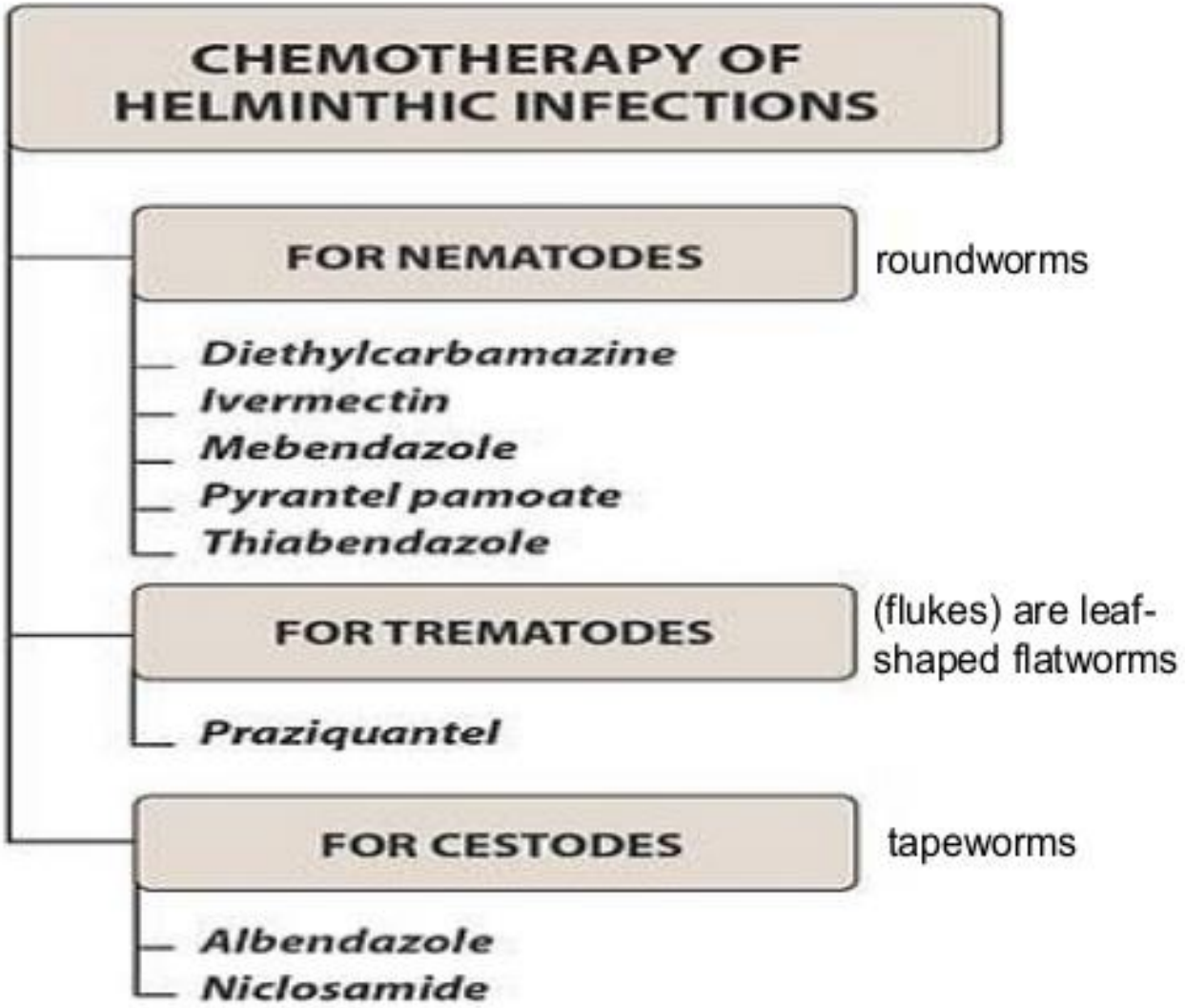
CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR CESTODES

Albendazole ALBENZA

Niclosamide NICLOCIDE

Anthelemintic Drugs

6. ANTHELMINTIC DRUGS



Antihelemintic Drugs

For Nematodes

❑ Mebendazole

- acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake
- for Nematodes
- C/I in pregnancy

❑ Pyrantel pamoate.

MOA:

It is depolarizing NM blocker, the paralyzed worm is then expelled from the host's intestinal tract.

- along with *mebendazole,* is effective in the treatment of infections caused by roundworms, pinworms, and hookworms

- **For Trematodes**

❑ **Praziquantel**

- Increase Ca+2 permeability → contracture and paralysis.
- DOC in all forms of schistosomiasis and other trematode infections

•**SE:**

- drowsiness, dizziness, malaise, and anorexia as GIT upsets
- **C/I: pregnancy and nursing mother**

- **For Cestodes**

❑ **Niclosamide**

- inhibition of the parasite's mitochondrial phosphorylation of ADP to form of ATP.
- A laxative is administered prior to oral administration of *niclosamide,* to purge the bowel of all dead segments and so preclude digestion and liberation of the ova, which may lead to cysticercosis.

THANK YOU