

**ANTI-PROTOZOAL , ANIT-HELMINTHIC , ANTI-MALARIAL
AGENTS**

Antiprotozoal drugs

- Protozoal and helminthic infections are a major cause of disease in many parts of the world.

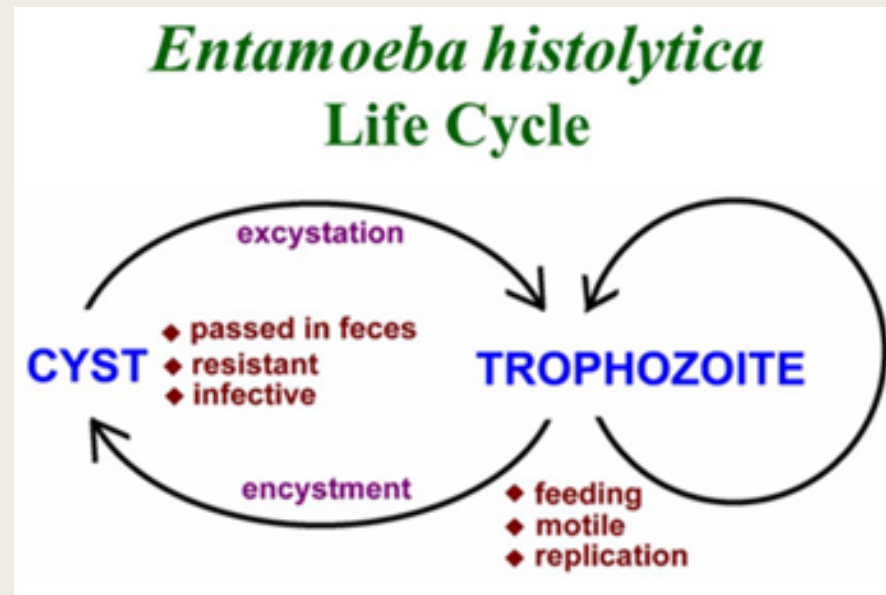
some of these diseases

- in migrant workers
- or individuals returning from an endemic area

Selected PROTOZOAL DISEASES

Amebiasis

- The protozoan *Entamoeba histolytica* causes amebiasis, an infection that is endemic in parts of the United States
- The parasite can be present in the host as either an encysted or a trophozoite form.



■ Initial ingestion of the cyst may result either in no symptoms or in severe amebic dysentery characterized by the frequent passage of bloodstained stools.

• symptom occurs after invasion of the intestinal mucosa by the actively motile and phagocytic trophozoite form of the protozoan.

- Trophozoites may spread to the liver through the portal vein and produce acute amebic hepatitis
- Many patients continue to excrete cysts for several years after recovery from the acute disease and therefore are a hazard to themselves and other persons

Entamoeba histolytica.

This organism can cause:

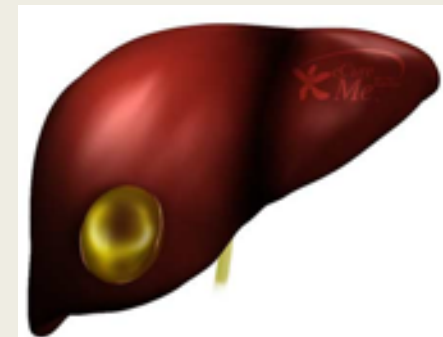
Asymptomatic intestinal infection.

Mild to moderate colitis.

Severe intestinal infection (dysentery).

Ameboma (a tumor-like mass in the intestines in amebiasis which results in a large local lesion of the bowel).

Liver abscess and other extraintestinal infection



Balantidium coli

- the largest of the protozoans that infect humans
- trophozoite form is covered with cilia, which impart mobility
- Infection is acquired through the ingestion of cyst-contaminated soil, food, or water.

Balantidium coli

- The trophozoite causes superficial necrosis or deep ulceration in the mucosa and submucosa of the large intestine
- healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea
- nutritionally stressed patients may develop severe dysentery.

Classes of oral antiprotozoal drugs

Commonly used oral antiprotozoal drugs can be generally classified into two main groups:

- *antimalarial drugs*
- *miscellaneous antiprotozoals.*

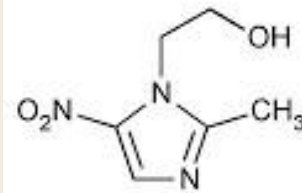
In addition to their use as antiprotozoals, some of them such as metronidazole and doxycycline are also used for treating bacterial infections.

antiprotozoals

Commonly used miscellaneous antiprotozoals include

- metronidazole,
- tinidazole and
- nifuratel.

Metronidazole

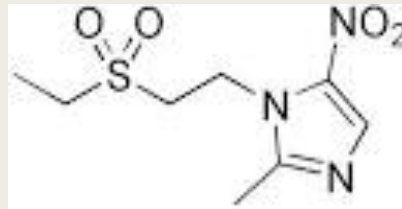


Drug of choice in the treatment of extraluminal amebiasis.

It kills trophozoites but not cysts of *E histolytica* and effectively eradicates intestinal & extraintestinal tissue infections.



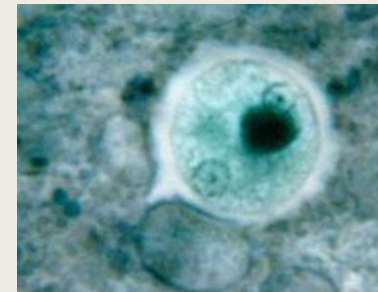
Tinidazole



Trophozoite of *Entamoeba histolytica* in intestine.

Similar activity

& better toxicity profile than metronidazole.



cysts of *E histolytica*

Metronidazole

- Metronidazole (*Flagyl, Metrogel*)
- exerts activity against most anaerobic bacteria and several protozoa.

- The drug freely penetrates protozoal and bacterial cells but not mammalian cells.

Metronidazole

- The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug.
- Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.

Clinical Uses

Amebiasis

GET GAP on the Metro with metronidazole!

Treats *Giardia*, *Entamoeba*, *Trichomonas*, *Gardnerella vaginalis*, Anaerobes (*Bacteroides*, *C difficile*). Can be used in place of amoxicillin in *H pylori* “triple therapy” in case of penicillin allergy.

Metronidazole

The drug of choice in the treatment of all tissue infections with *E histolytica*. (hepatic abscess; intestinal wall/ extraintestinal infections)

- Not effective against luminal parasites and so **must be used with a luminal amebicide to ensure eradication of the infection.** kills trophozoites but not cysts

Giardiasis

Metronidazole is the treatment of choice

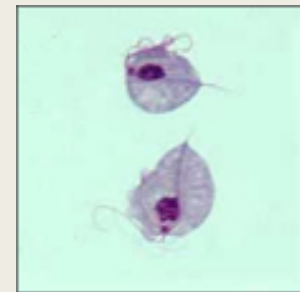
Efficacy after a single treatment is about 90%

Tinidazole is equally effective.

Trichomoniasis

Metronidazole is the treatment of choice.

A single dose of 2 g is effective.



Trichomonas vaginalis

Adverse Effects & Cautions

Common:

Nausea, headache, dry mouth, metallic taste.

Infrequent adverse effects:

vomiting, diarrhea, insomnia, weakness, dizziness,.

Rare:

Pancreatitis and severe central nervous system toxicity
Tinidazole is better tolerated.

Metronidazole is best avoided in pregnant or nursing women, although congenital abnormalities have not clearly been associated with use in humans.

Tinidazole

Tinidazole works as well as metronidazole and has many of the same side effects, but it can be given in a single dose. Whereas, nifuratel can be used as an alternative to metronidazole or tinidazole in the treatment of trichomoniasis.

Treatment of Specific Forms of Amebiasis

Asymptomatic Intestinal Infection

Asymptomatic carriers are treated with a **luminal amebicide**.

Standard luminal amebicides are:

Diloxanide furoate, Iodoquinol, and Paromomycin.

Therapy with a luminal amebicide is also required in the treatment of all other forms of amebiasis.

Amebic Colitis

Metronidazole + a luminal amebicide

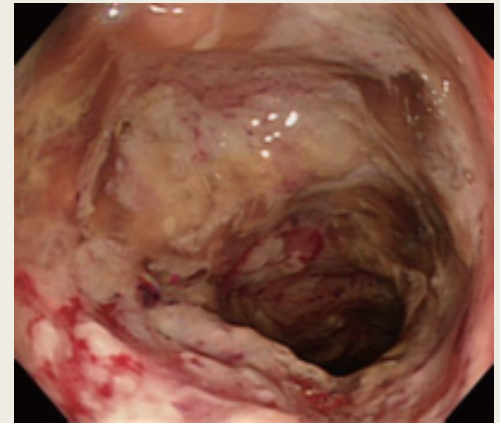
is the treatment of choice.

Tetracyclines and **erythromycin** are

alternative drugs for moderate colitis but

are not effective against extraintestinal disease.

Dehydroemetine or emetine can also be used, but are best avoided because of toxicity.

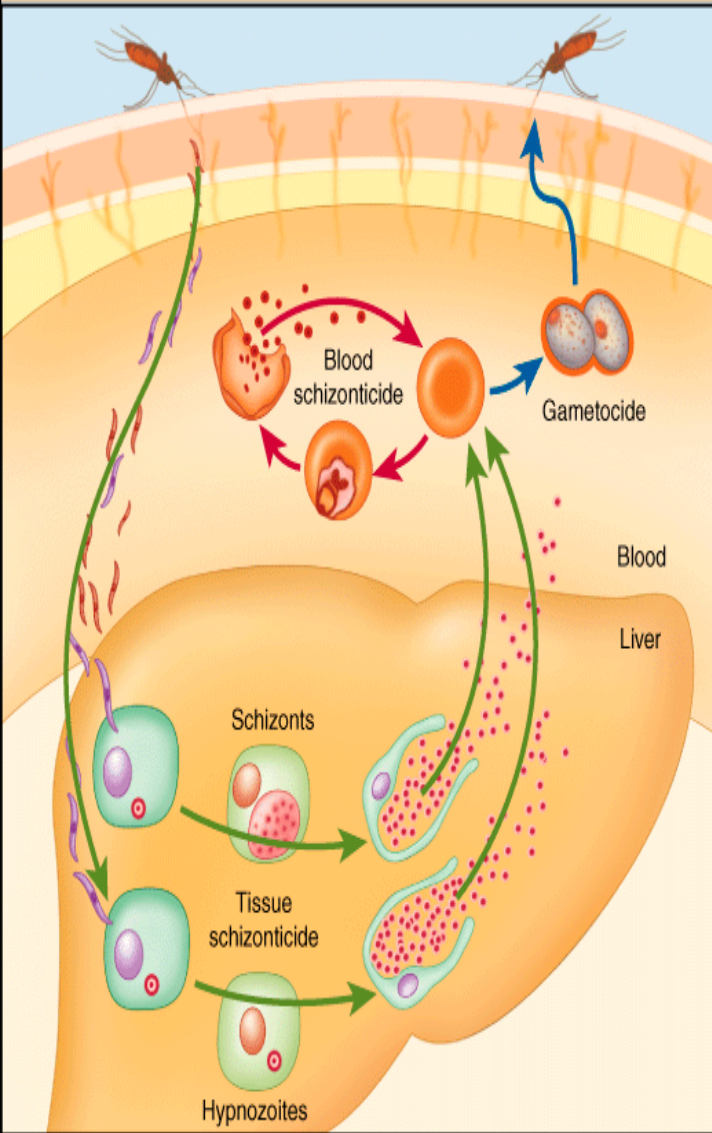


Amebic Colitis

Antimalarial Drugs

- **Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a group of single-celled microorganism) belonging to the genus Plasmodium.**

Life Cycle of Malaria Parasites



- Malaria transmitted by the bite of infected female *Anopheline* mosquitoes.
- From the mosquito salivary glands enter the circulation
- localize *in* hepatocytes to multiply, and develop
 - Asymptomatic for 5 to 15 days, depending on the *Plasmodium*
 - Tissue schizonts rupture,
 - releasing thousands of merozoites that enter the circulation, invade erythrocytes where mature schizonts form
 - Schizont-containing erythrocytes rupture, each releasing 6 to 32 merozoites this process that produces febrile attacks.

Antimalarial Drugs

■ **Chloroquine:** / Hydroxychloroquine → P. malariae, P. ovale, or P. vivax

- **Most useful agent to terminate an acute attack.**
- **Available as oral, IV, and IM preparation.**
- **Resistance develops.**
- **Causes N, headache, and is teratogenic.**

Disease-modifying antirheumatic drugs

Abbreviation: DMARD

A group of unrelated medications with immunosuppressive and antiinflammatory properties that improve symptoms and prevent further disease progression. They are commonly used to treat rheumatoid arthritis, but may also be indicated in other diseases (e.g., malignancies, psoriatic arthritis, systemic lupus erythematosus). DMARDs can be classed as either synthetic agents, which are further divided into conventional (e.g., methotrexate, hydroxychloroquine, cyclophosphamide) and targeted DMARDs (e.g., JAK inhibitors), or biologic agents (e.g., TNF inhibitors, anti-CD20).

Antimalarial Drugs

■ Quinine:

- **Oldest drug, from Cinchona tree.**
- **Many actions**
- **Toxic**
- **Still used, no resistance to its action**

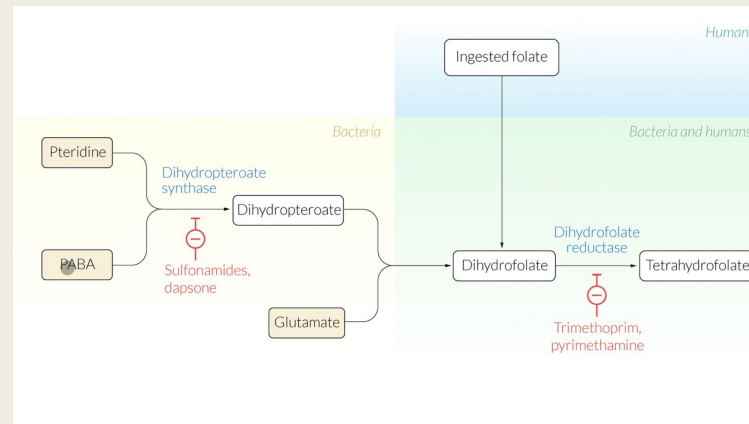
Cinchonism: a group of adverse effects including nausea, dizziness, headache, tinnitus, and visual changes.

■ Artemisinin: Artemisinin derivatives include artesunate and artemether.

- **New drug, from Sweet wormwood, الشج**

■ Doxycycline

■ Pyrimethamine



Anthelmintics

Infection by *helminths* (worms)

- May be limited solely to the intestinal lumen
- May involve a complex process with migration of the adult or immature worm through the body before localization in a particular tissue.

helminths have either

- a simple cycle of egg deposition and development of the egg to produce a mature worm,
- others must progress through one or more hosts and one or more morphological stages, each metabolically distinct from the other, before emerging as an adult

Pathogenic helminths can be divided into the following

- *cestodes* (flatworms),
- *nematodes* (roundworms),
- *trematodes* (flukes)
- *Acanthocephala* (thorny-headed worms).

CESTODES : general properties

- Flat worms, tape-like, Segmented parasites
- Length range from mm to meters
- Scolex (Head) provided with suckers, Hooks +/-
- Adult worms are in Gastrointestinal tract
- Digestive tract is absent, absorb nutrients from body wall
- Hermaphrodites, Reproductive system, Excretory & Nervous systems present
- complete chain of segments known as *strobila*, Segment – **Proglottid**
- Life span – 5 to 25 years



Nematode

the roundworms

- The body of a nematode is long and narrow, resembling a tiny thread in many cases, and this is the origin of the group's name
- Most living roundworms are microscopic, On the other hand, one species of parasitic nematode can reach 13 meters in length



Trematodes

الديدان المثقوبة

- Trematode infections occur worldwide.
- Trematodes, also called flukes, cause various clinical infections in humans.
- The parasites are so named because of their conspicuous suckers, the organs of attachment

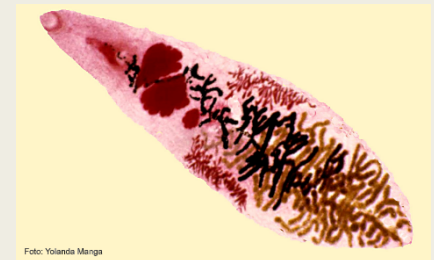
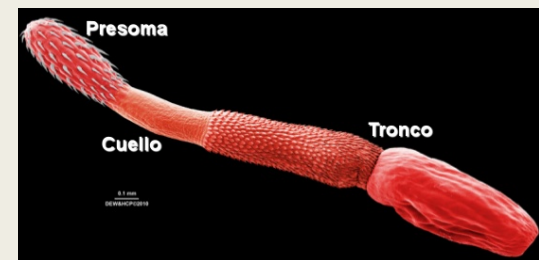


Foto: Yolanda Manga

مشوكات الرأس

Acanthocephala

- Thorny-headed worms, are parasites that live in the gut of vertebrates and - earlier in their life cycle - within invertebrates.
- Acanthocephalans lack a mouth or alimentary canal. Adult stages live in the intestines of their host and uptake nutrients which have been digested by the host, directly, through their body surface.



Anthelmintics

- are drugs that act either locally to expel worms from the gastrointestinal tract or systemically to eradicate adult helminths or developmental forms that invade organs and tissues

Most available anthelmintic drugs exert their antiparasitic effects by interference with

- (1) energy metabolism,
- (2) neuromuscular coordination,
- (3) microtubular function,
- (4) cellular permeability.

TREATMENT FOR INFECTIONS CAUSED BY NEMATODES (Round worms)

Mebendazole”Vermox”:

- Widely used, wide spectrum, safe drug.

- Threadworm: *Enterobius*

vermicularis, simple treatment:

single dose, can be repeated after 3 weeks.

Hockworm: *Ankylostomiasis*:

2tablets*3days.

Roundworm: *Ascaris lumbricoidis*

Piperazine

- Prolonged treatment and might need a purgative
- Piperazine (Vermizine) contains a heterocyclic ring that lacks a carboxyl group.

Piperazine

- It acts on the musculature of the helminths to cause reversible flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. this results in expulsion of the worm.
- Piperazine acts as an agonist at gated chloride channels on the parasite muscle.

Diethylcarbamazine

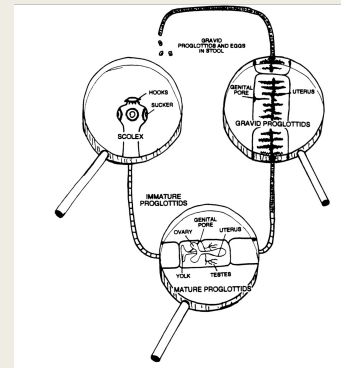
- It interferes with the metabolism of arachidonic acid and blocks the production of prostaglandins,
- resulting in capillary vasoconstriction and impairment of the passage of the microfilaria

TREATMENT FOR INFECTIONS CAUSED BY CESTODES (Tapeworms)

Niclosamide

- Niclosamide is a chlorinated salicylamide that inhibits the production of energy derived from anaerobic metabolism
- Inhibition of anaerobic incorporation of inorganic phosphate into ATP is detrimental to the parasite

Niclosamide



- The drug affects the scolex and proximal segments of the cestodes,
- resulting in detachment of the scolex from the intestinal wall and eventual evacuation of the cestodes from the intestine by the normal peristaltic action of the host's bowel.

TREATMENT FOR INFECTIONS CAUSED BY TREMATODES (Flukes)

Praziquantel

- The neuromuscular effects of praziquantel (Biltricide) appear to increase parasite motility leading to spastic paralysis.
- The drug increases calcium permeability through parasite-specific ion channels, so that the muscle cells of the parasite accumulate calcium

Praziquantel

- This action is followed by exposure of hitherto masked tegmental antigens, lipid anchored protein, and actin.
- Insertion of the drug into the fluke's lipid bilayer causes conformational changes, rendering the fluke susceptible to antibody- and complement-mediated assault.