

# Athar Batch



## Pharmacology

Lecture: 36

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# Chemotherapy for Amebiasis

Pharmacology and Toxicology

General Pharmacology

Second Year Medical Students

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**Textbook:** Chapter 46 (uploaded to OneDrive)



# Amebiasis

a unicellular eukaryote.

- **Amebic dysentery:** infection of the **intestinal tract** caused by *Entamoeba histolytica* a protozoal parasite.

ameba is a very common cause of food poisoning in the under-developed world like the middle east.

- **Fecal-oral** due to the contaminated food or water with ameba and the ingestion of this contaminated source.

- **Intestinal or systemic** the majority of the cases are intestinal but it can be extended to be systemic, by being translocated to other extra-intestinal sites and cause systemic invasive infections as well.

- **Asymptomatic - mild diarrhea - fulminating dysentery – systemic** won't show any symptoms "carrier only"

- **Therapy is indicated for both asymptomatic carriers and ill patients** even the asymptomatic patients will continue to be contagious and able to transmit the infections.

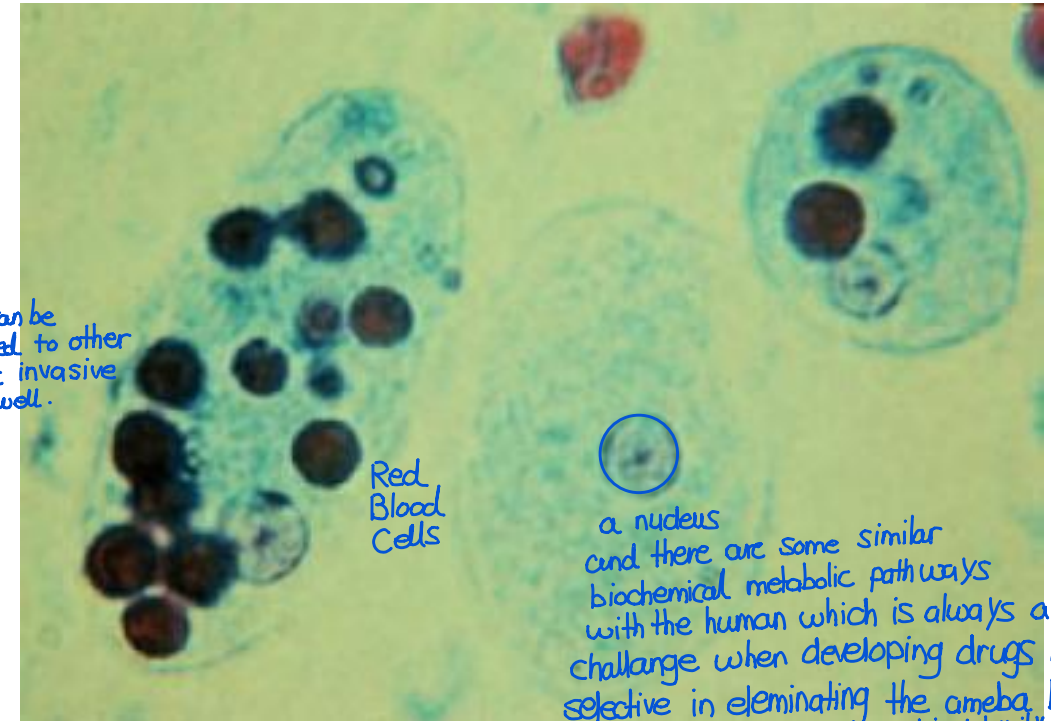
severe advanced form of gastroenteritis.  
\* heavy, severe diarrhea.  
\* bloody diarrhea.  
\* dehydration.

- **Therapy: luminal, systemic or mixed amebicides** only to treat the systemic ameba.

أهم واحد

drugs that can target both the luminal and the systemic ameba.

only effective against the gastrointestinal ameba, that only presents within the gastrointestinal tract.



a nucleus and there are some similar biochemical metabolic pathways with the human which is always a challenge when developing drugs are selective in eliminating the ameba but having minimal toxicity to the human.

Trichrome stain of *Entamoeba histolytica* trophozoites in amebiasis. Two diagnostic characteristics are observed. Two trophozoites have ingested erythrocytes, and all 3 have nuclei with small, centrally located karyosomes.

Medscape

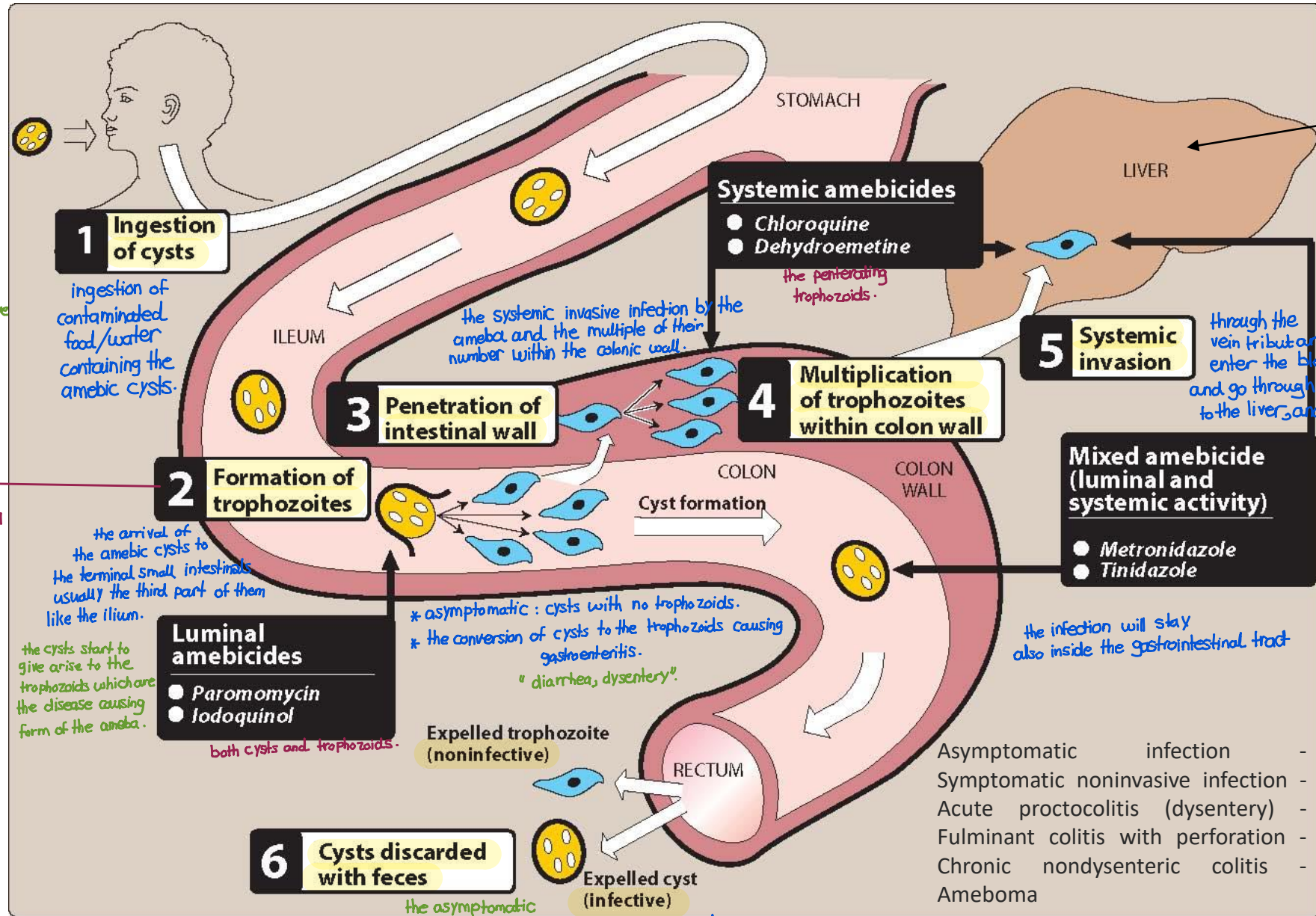




Remember that the major route is the fecal-oral route.

**Ameba's Forms**  
 - cystic form.  
 - trophozooid form "the infective form".

the amebic cysts have 4 nudei meaning that they divide to form 4 trophozooids.



**1 Ingestion of cysts**  
 ingestion of contaminated food/water containing the amebic cysts.

**2 Formation of trophozoites**  
 the arrival of the amebic cysts to the terminal small intestinals usually the third part of them like the ilium.

**3 Penetration of intestinal wall**  
 the systemic invasive infection by the ameba and the multiple of their number within the colonic wall.

**4 Multiplication of trophozoites within colon wall**  
 the penetrating trophozooids.

**5 Systemic invasion**  
 through the vein tributaries, they enter the bloodstream and go through the portal circulation to the liver, and they stay in the liver causing amebic abscess.

**Luminal amebicides**  
 ● Paromomycin  
 ● Iodoquinol  
 both cysts and trophozooids.

**Systemic amebicides**  
 ● Chloroquine  
 ● Dehydroemetine

**Mixed amebicide (luminal and systemic activity)**  
 ● Metronidazole  
 ● Tinidazole

**6 Cysts discarded with feces**  
 the asymptomatic patients will still to discard the cysts thus they need to be treated.

Exelled cyst (infective)  
 if it touches a food then the cycle will continue to occur.

Amebic liver abscess is the most common manifestation of invasive amebiasis

the amebic liver abscess is the most common manifestation of invasive systemic amebiasis.

both the systemic and the luminal infections.

- Asymptomatic infection
- Symptomatic noninvasive infection
- Acute proctocolitis (dysentery)
- Fulminant colitis with perforation
- Chronic nondysenteric colitis
- Ameboma





# Mixed Amebicides

## AMEBIASIS

*Chloroquine* ARALEN

*Dehydroemetine* DEHYDROEMETINE

*Iodoquinol* YODOXIN

→ *Metronidazole* FLAGYL

*Paromomycin* HUMATIN

→ *Tinidazole* TINDAMAX



# Metronidazole

have the same chemical family as the imidazole.

- Nitroimidazole *has a nitro group which has a very important function in its mechanism of action.*

- The mixed amebicide of choice

- Other important uses of metronidazole:

1. Giardia lamblia infection *another parasitic infection of the gastrointestinal tract.*

2. Trichomonas vaginalis *causes vaginal infections in women.*

3. Anaerobic cocci and anaerobic gram-negative bacilli (bacteria) *antibacterial activity.*

*when treating a patient empirically, metronidazole is usually part of the treatment.*

4. Treatment of peptic ulcer disease (bacteria)

5. Treatment of pseudomembranous colitis caused by *C. difficile* (bacteria) *after the prolonged use of the third generation of cephalosporins or clindamycin.*

*\* the two effective drugs to treat Clostridium difficile is the use of the oral vancomycin or the use of the metronidazole.*



*as we said before that one of the complications of using the broad-spectrum drugs is the distribution of the normal flora leading to super infections like the pseudomembranous colitis*



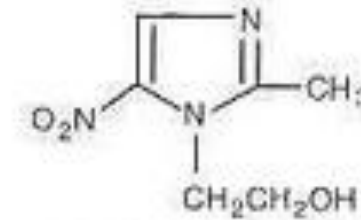
The amebic cells are also engaged in energy production metabolism that are similar to the human pathways, and go also under the ORRs which is the last stage of ATP production.



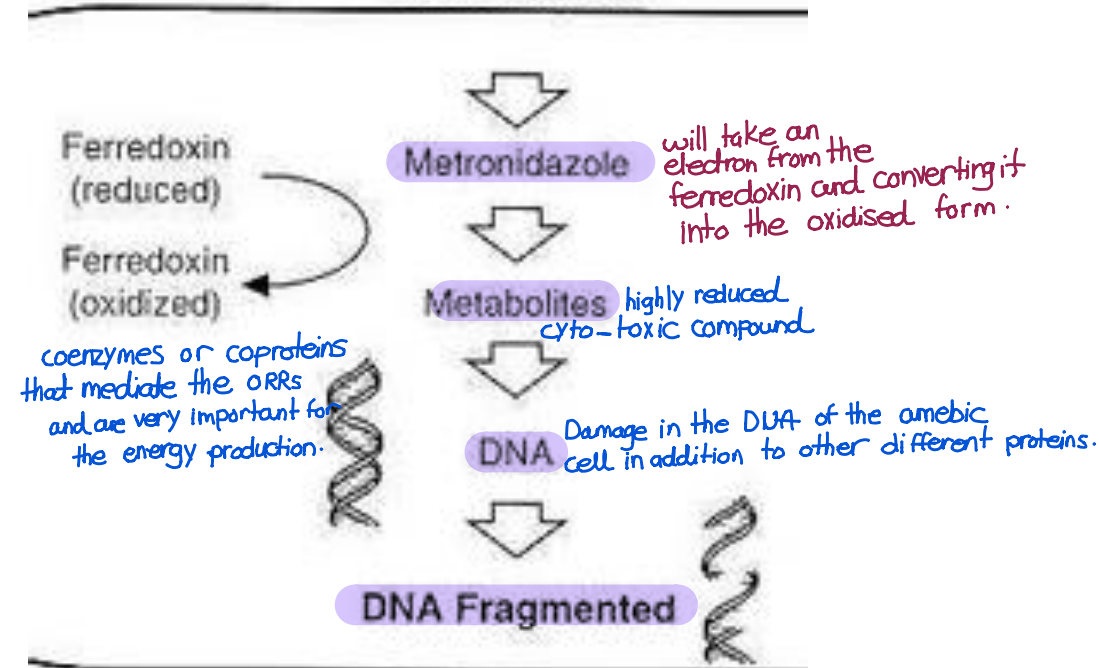
# Metronidazole

## Mechanism of action

- Ameba has ferredoxin-like, low-redox-potential, **electron transport proteins**
- **Nitro group of metronidazole is able to serve as an electron acceptor** *strong and like to take electrons from other substances.*
- **This forms reduced cytotoxic compounds that bind to proteins and DNA**
- Ameoba **cell death**



Metronidazole

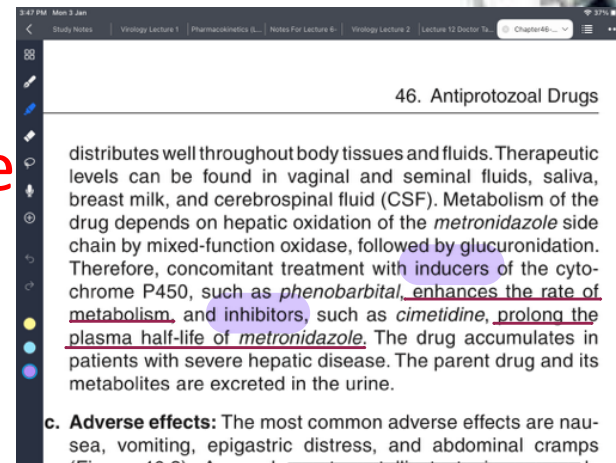




# Metronidazole

## Pharmacokinetics

- Completely absorbed after oral administration. *this is why we use oral metronidazole to treat luminal and systemic amebic infection.*
- Distributes very well
- Metabolized hepatically: mixed-function oxidation and glucuronidation
- What happens when you give CYP450 inducers? Inhibitors?
- Excreted renally *in the urine.*



IV metronidazole  
*for certain types of infections.*





# Metronidazole

is usually a well-tolerated drug but comes with some adverse effects that are usually mild.

they are annoying adverse effects but are on the safe side.

## Adverse effects

- N/V, epigastric distress, and abdominal cramps
- Metallic taste
- Oral moniliasis
- Neurotoxicity (dizziness, vertigo, and numbness or paresthesia)

neural damage especially to the inner ear.

peripheral neuropathy

a burning or prickling "tingling" sensation.

a serious adverse effect but not common.



Nausea



GI disturbance



Metallic taste



# Tinidazole

- Second-generation nitroimidazole
- Similar to metronidazole in spectrum of activity, absorption, adverse effects, and drug interactions
- Used for treatment of amebiasis, amebic liver abscess, giardiasis, and trichomoniasis
- More expensive.



# How is metronidazole used?

*metronidazole is more effective in eliminating systemic ameba in comparison with the luminal ameba.*

For the treatment of amebiasis:

*Combination with*

- Administered with a luminal amebicide (e.g., iodoquinol or paromomycin)  
*that only targets ameba located within the gastrointestinal tract.*
- Combination provides cure rates of greater than 90%.



# Luminal Amebicides

## AMEBIASIS

*Chloroquine* ARALEN

*Dehydroemetine* DEHYDROEMETINE

→ *Iodoquinol* YODOXIN

*Metronidazole* FLAGYL

→ *Paromomycin* HUMATIN

*Tinidazole* TINDAMAX

for treatment of the asymptomatic colonization state

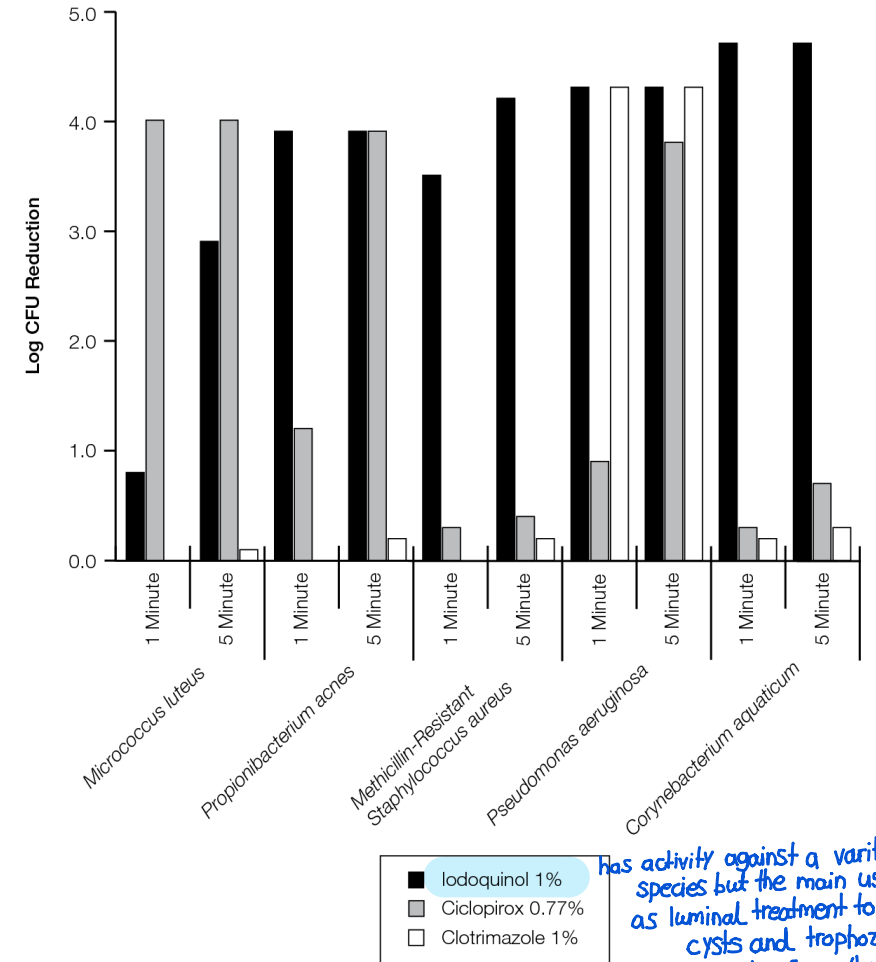




# Iodoquinol

antibiotics that are effective in treating the UTIs and RTIs.

- halogenated 8-hydroxyquinolone
- Amebicidal
- Effective against luminal trophozoites and cysts *but is usually given in combination with the metronidazole.*
- Can cause dose-related neuropathy *especially when iodoquinol is used for long periods of time.*
- For short courses only.

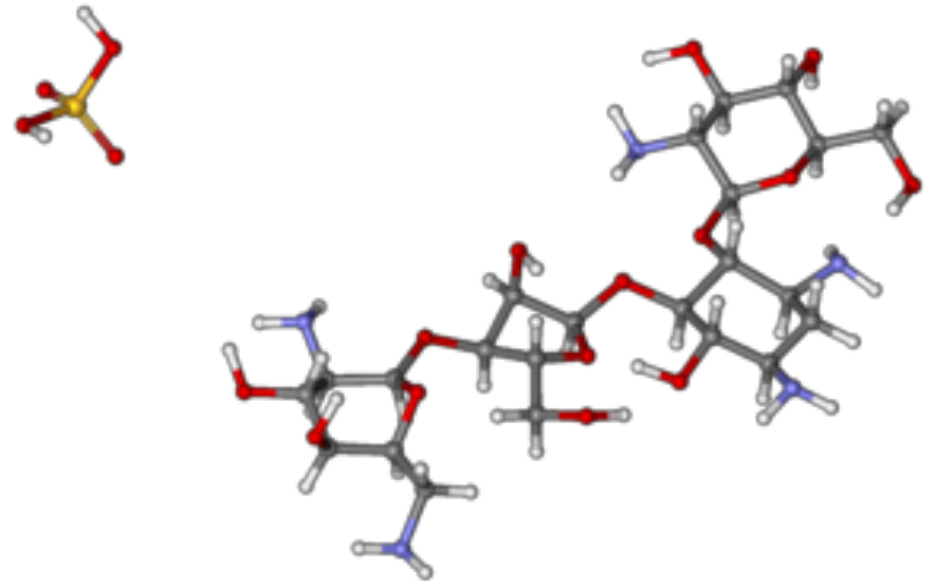


has activity against a variety of species but the main use of it is as luminal treatment to eradicate cysts and trophozooids of the ameba from the GIT.



# Paromomycin

- aminoglycoside antibiotic
- Amebicidal
- Only effective against luminal *E. histolytica*
- Can also be used for giardiasis





# Systemic Amebicides

## AMEBIASIS

→ **Chloroquine** ARALEN

→ **Dehydroemetine** DEHYDROEMETINE

**Iodoquinol** YODOXIN

**Metronidazole** FLAGYL

**Paromomycin** HUMATIN

**Tinidazole** TINDAMAX

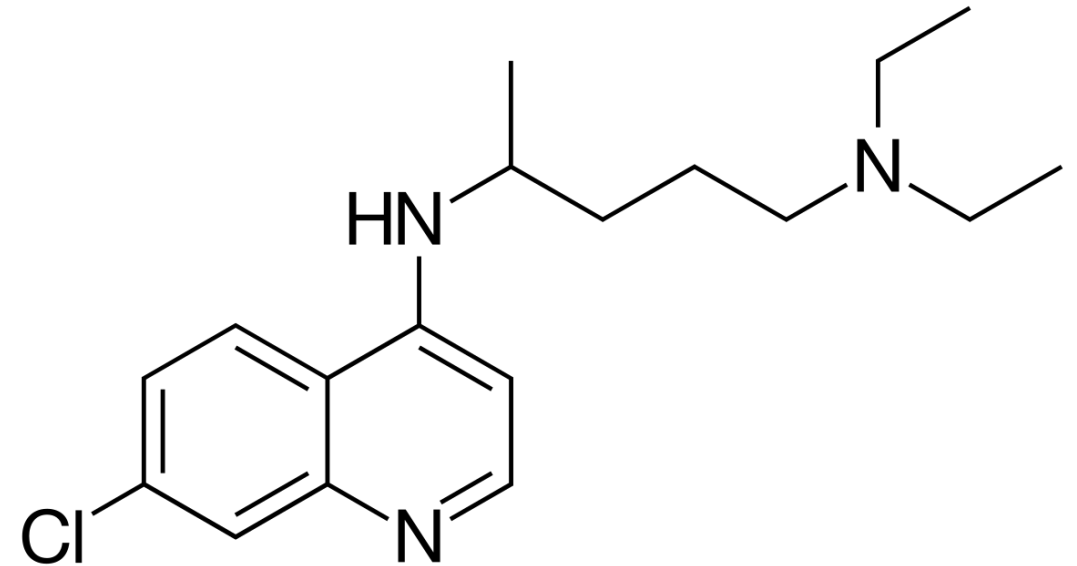


# Chloroquine

it was developed as an anti-malaria drug and still is the main drug against malaria around the world.

one of the drugs that were used to treat covid-19 or an infection with SARS-CoV-2.

- Used in combination with metronidazole
- eliminates trophozoites in liver abscesses
- Has a potent antimalarial activity







# Dehydroemetine

*the second or third line to treat systemic amebiasis.*

- Is an alternative agent for the treatment of amebiasis
- Has largely been replaced by metronidazole
- Drug inhibits protein synthesis by blocking chain elongation



# Summary of Antiameoba Agents

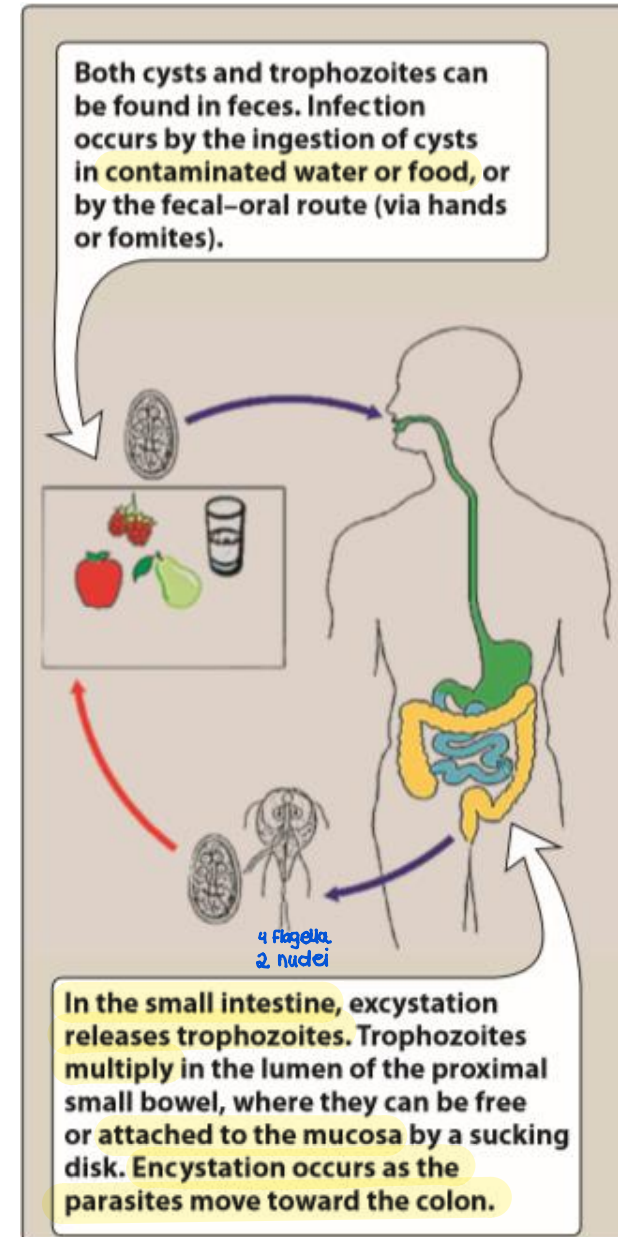
CLINICAL SYNDROME	DRUG
<b>Asymptomatic cyst carriers</b> <i>developing multiple cysts within the GIT that can be shed through feces and be transmitted to other people.</i>	<b>Iodoquinol</b> or <b>paromomycin</b> <i>luminal anti-ameba.</i>
<b>Diarrhea/dysentery</b> <b>Extraintestinal</b> <i>systemic invasion</i>	<b>Metronidazole</b> plus <b>iodoquinol</b> or <b>paromomycin</b> <i>this combination in order to ensure more than 90% of eradication of cysts and trophozoites from the gastrointestinal tract.</i>
<b>Amebic liver abscess</b> <i>يعني أناني جزء طاع على الكبد            وفي جزء خسر في الأمعاء عشان            هو المكان الأساسي لوجدها</i>	<b>Metronidazole</b> (or tinidazole) plus <b>iodoquinol</b> or <b>paromomycin</b>

*chloroquinolones with combination of metronidazole to treat serious amebic liver abscesses*



# Giardia Lamblia

- the most commonly diagnosed intestinal parasite in the United States
- two life cycle stages:
  - binucleate trophozoite (four flagella)
  - four-nucleate cyst (drug-resistant)
- Fecal-oral





# Treatment of Giardiasis

- The treatment of choice is oral metronidazole for 5 days.
- An alternative is a single dose of tinidazole, (effective as metronidazole)
- Nitazoxanide (3-day course of oral therapy)
- Albendazole
- Paromomycin





# Toxoplasmosis

- Caused by *T. gondii* usually infects people with immunocompromised state like the AIDs patients.
- Transmitted through raw, inadequately cooked infected meat, or accidentally ingest oocysts from cat feces.
- An infected pregnant woman can transmit *T. gondii* to her fetus. can cross the placenta into the fetus causing congenital anomalies.
- The treatment of choice: *sulfadiazine* and *pyrimethamine*.
- Alternatives: *Pyrimethamine* with *clindamycin* or the combination of *trimethoprim* and *sulfamethoxazole*
- *Trimethoprim/sulfamethoxazole* is used for prophylaxis against toxoplasmosis in immunocompromised patients.

pregnant women shouldn't come across cats unless those cats are being vaccinated against toxoplasmosis