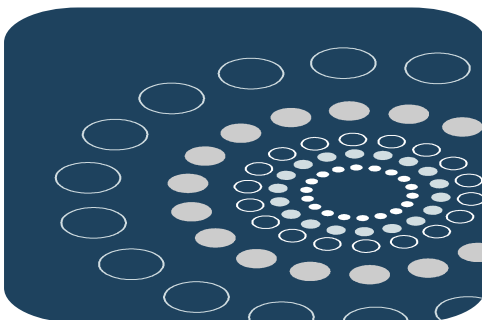
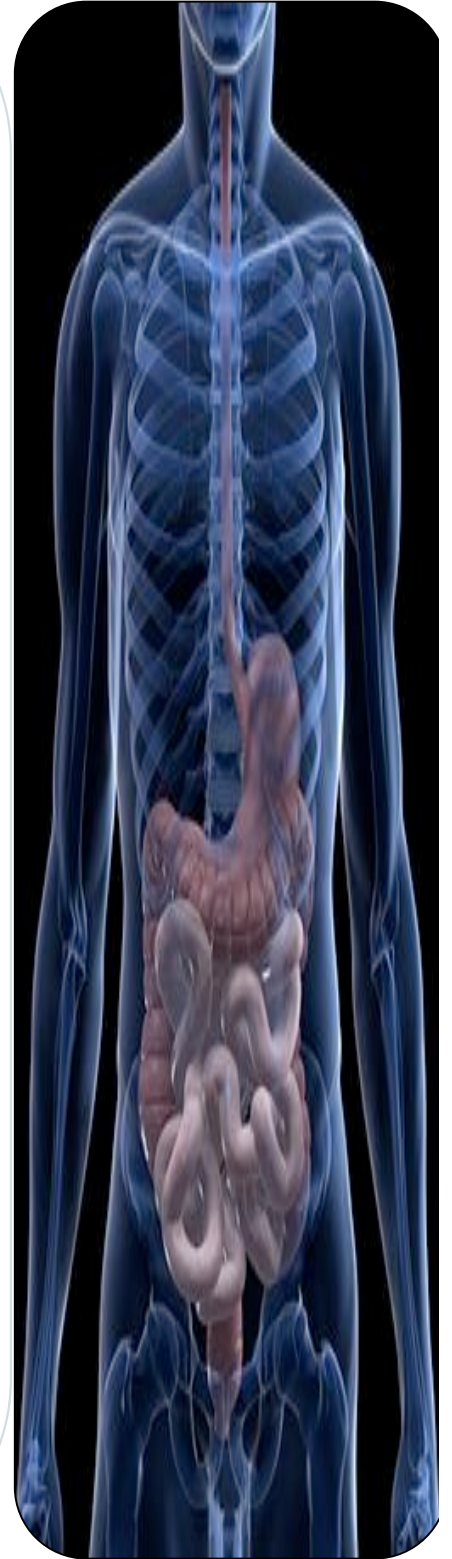


Pharmacology

**Treatment of dysentery
and amebiasis**



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+ Introduction :

Dysentery → is an inflammatory disorder of the intestine, that results in severe diarrhea containing mucus and/or blood in the feces with fever and abdominal pain.

DYSENTERY RESULTS FROM VIRAL INFECTIONS, BACTERIAL INFECTIONS, OR PARASITIC INFESTATIONS

THE TWO MOST COMMON CAUSES ARE :

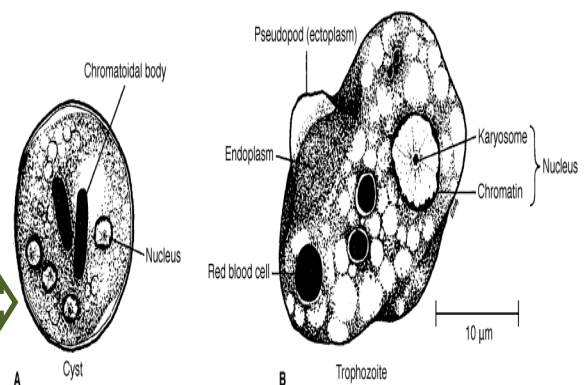
- **Amebic dysentery** (protozoal infection mainly by *Entameba Histolytica*).
- **Bacillary dysentery** (bacterial infection mainly by *shigella*).

TREATMENT OF DYSENTERY :

- Maintain **Fluid intake** using oral rehydration therapy or Intravenous fluid therapy. (*The first line of treatment because the patient may die from sever dehydration*)
- **Antimicrobial agents** should **not** be given until stool analysis is done (*empiric therapy* should be started after sample of stool taken for analysis).

+ AMOEBIASIS :

- ✓ Amebiasis is a protozoal infection of the intestinal tract that occurs due to ingestion of foods or water contaminated with **cysts of *Entameba Histolytica***. (pathologic type)
- ✓ The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery.



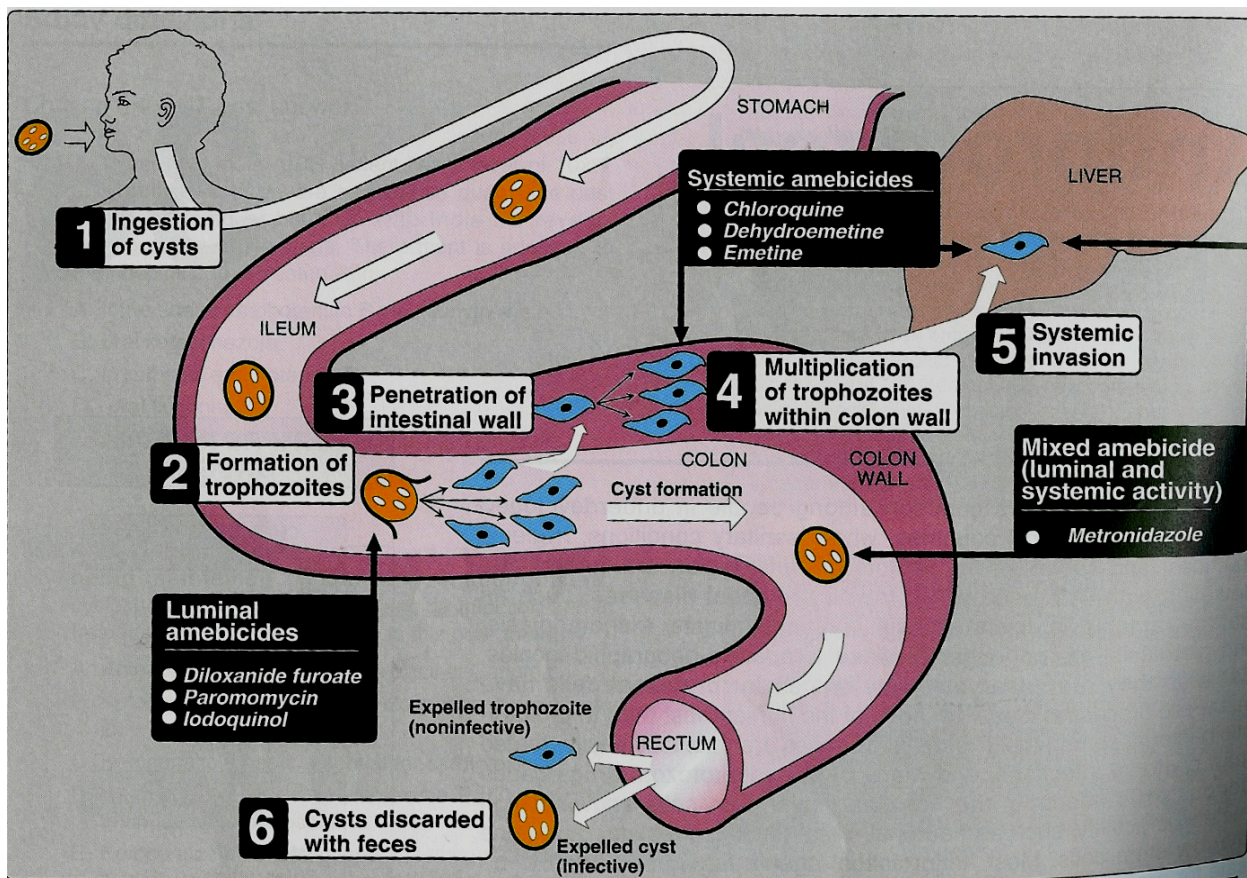
The picture shows : *Entameba Histolytica*
Cyst : Infective Stage
Trophozoite : Non-infective stage
(Invasive stage)

Clinical presentations :

- **Asymptomatic intestinal infection** (*Carriers, passing cysts in stool*)
- **Mild to moderate intestinal disease** (*colitis*)
- **Severe intestinal infection** (*amoebic dysentery*)
- **Ameboma** (*localized granulomatous lesion of colon*).
- **Extra-intestinal diseases**, e.g. Hepatic abscess.

Life Cycle:

- Cysts ingestion in contaminated food or water.** } **Pre-infection period**
Liberation of trophozoites in the colon.
Invasion & penetration of intestinal wall. } **Intestinal infection**
Multiplication of trophozoites within colon wall.
Systemic invasion to liver. } **Extra-intestinal infection**
Cyst formation in rectum and excretion in feces.



ANTIAMEBIC DRUGS :

A-Luminal Amebicides :

*Acts on the parasites in the **lumen of the bowel**.

*Used for treatment of asymptomatic amebiasis (carriers).

*Drugs Include :

1. **Diloxanide furoate**
2. **Iodoquinol**
3. **Antibiotics** } **Paromomycin and Tetracyclin**

*used to eradicate cysts of *E histolytica* after treatment of invasive disease.

1. Diloxanide furoate:

- Ester of diloxanide + furoic acid
- Given orally.
- It splits in the intestine, **most of diloxanide is absorbed**, conjugated to form a glucuronide which is **excreted in urine (90%)**.
- The **unabsorbed diloxanide is the amoebicidal agent (10%)**.
- Direct amoebicidal action against luminal forms.
- **NOT active against trophozoites in (intestinal wall or extra-intestinal tissues)**
- Mechanism of action is **unknown**
- **Drug of choice for asymptomatic intestinal infection (drug of choice in cysts passers)**.
- **For complete eradication** of amebic infections **given along with** tissue amebicides eg **metronidazole**.

Adverse Effects:

- Flatulence
- Nausea, vomiting, abdominal cramps.
- **No** serious adverse effects

Contraindications:

- Pregnancy (Because it crosses the placenta)
- Children (less than 2 years).

Because it is highly absorbed in the body, It has high side effect on the fetus and children

2. Iodoquinol :

- Is given orally
- **Not absorbed (90%), excreted in feces.**
- 10% enter circulation, excreted as glucouronide in urine.
- Mechanism of action is **unknown**
- effective against the **luminal trophozoites.**

Uses :

uminal amoebicide for **asymptomatic amebiasis.**

Adverse Effects :

- **GIT: Nausea, vomiting, diarrhea.**
 - **Peripheral neuropathy including optic neuritis**
 - **Enlargement of the thyroid gland.**
 - **Iodine sensitivity**
 - **interference with thyroid function tests (increase protein-bound serum iodine, decrease in measured (¹³¹I uptake).**
- ❖ Iodoquinol should be used with caution in patients with **optic neuropathy, renal or thyroid disease.** (b/c of the side effect)
- ❖ **discontinued** if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever).

These side effect because interference with thyroid function because it has iodine with it components .

3. Paromomycin:

- **Aminoglycoside antibiotic.**
- It is given orally and **Not absorbed from GIT**
- Effective against luminal forms of ameba
- Small amount absorbed is excreted unchanged in urine (*may accumulate with renal insufficiency*)

Mechanism of action :

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

Uses:

in chronic amebiasis to eliminate cysts , in cysts passers (Dilaxonide and iodoquinol are best for this purpose)

Adverse Effects :

Gastrointestinal distress and diarrhea.

WE are usually use Aminoglycosides I.V in Bacterial infection because it can't be absorbed in small intestine, but here the cysts present in the lumen so we use it orally.

Safe in pregnancy

4-TETRACYCLINES :

- Very weak direct amoebicidal action.
- Acts mainly indirectly on bacterial flora.
- Used in severe cases of amoebic dysentery not responding to metronidazole combined with dehydroemetine.

B-Tissue or systemic amebicides :

-Acts on ameba in the intestinal wall and liver (or any other extra-intestinal tissue).

-Used for treatment of systemic form of the disease (invasive amebiasis)
e.g:(intestinal wall infection or liver abscesses).

Drugs Include :

1. Metronidazole
2. Tinidazole
3. Emetine and dehydroemetine
4. Chloroquine (liver only)

1.Metronidazole:

- **Tissue** amoebicide.
- Acts on **trophozoites**.
- Does **not** eradicate cysts from intestines
- **Drug of choice for treating invasive amebic infections (intestinal & extra-intestinal).**

Mechanism of action :

Inhibits DNA replication

Pharmacokinatic :

- 1-Given orally or IV.
- 2-Absorption is rapid and complete.
- 3-Wide distribution to all tissues and body fluids (CSF, saliva, **milk**)
- 4-Plasma half life is (8 h)
- 5-Metabolized in liver by mixed function oxidase followed by glucuronidation (**consider drug interactions**).
- 6-Excreted in urine.
- 7-Clearance is decreased in liver impairment

*We prefer to combine
it with luminal
amebicide*

Clinical uses :

- **Extra-luminal amoebiasis:** is the drug of choice in all tissue amebiasis (*should be combined with luminal amebicide*)
- **Giardiasis** (cause by *G. lamblia* & common in children)
- **Trichomoniasis**
- **Broad spectrum of anaerobic bacteria e.g.,**
 - **Helicobacter pylori infection**
 - Pseudo-membranous colitis (*Clostridium difficile*).

It is a sexually transmitted disease, and is caused by the single-celled protozoan parasite *Trichomonas vaginalis* is a common cause of vaginitis

Adverse effects :

1-GIT:

- Dry mouth, metallic taste
- Nausea, vomiting
- **Oral Thrush** (Moniliasis, yeast infection).

2-CNS: Neurotoxicological effect

- Insomnia, dizziness
- **peripheral neuropathy, paresthesia**
- encephalopathy, convulsion (*IV infusion, rare*).

Due to killed the normal flora found in buccal cavity to allow fungal infection

3-Dysuria : dark urine.

4-Neutropenia (decrease the numbers of neutrophils in the serum)

5-Disulfiram-like effect (if taken with alcohol):

Combining metronidazole and alcohol causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia, hyperventilation



Drug interaction:

Metronidazole inhibits Cytochrome p450, so it will increase the effect of other drugs:

- increases anticoagulant effect of **warfarin**.
- Increases **lithium toxicity**.

Also it is affected by :

- Enzyme **inhibitors** (*cimetidine, ketoconazole*) increase duration of action of metronidazole
- **Inducers** (*phenytoin and phenobarbitone*) decrease duration of action of metronidazole.

CONTRAINDICATIONS / PRECAUTIONS:

- Pregnancy and **breast feeding women**
- CNS diseases (b/c of side effects)
- **Alcohol intake** (b/c of side effects)
- **Severe hepatic disease** (b/c of metabolism)
- **Severe renal disease** (b/c of excretion)

2. Tinidazole

Tinidazole has similar activity to metronidazole but **better potency**

Advantages of tinidazole:

- 1- has longer duration of action (12-14h), so the frequency of administration will be less
- 2- a simpler dosing regimen
- 3- a better toxicity profile than metronidazole
(Well tolerated in Children)

3- Emetine and dehydroemetine

- **Emetine** is an alkaloid derived from ipecac while **dehydroemetine** is a synthetic analog.
- Both are effective against (**tissue trophozoites of E. histolytica**) causing **irreversible block of protein synthesis**.
- Because of major toxicity concerns **they have been almost completely replaced by metronidazole**

Pharmacokinetics :

- Have erratic oral absorption.
- Given preferably subcutaneously but could be given by IM, **NEVER I.V.**
- Has long plasma half life about 5 days.
- Metabolized & excreted slowly via kidney so they have a **cumulative effect**.
- Should not be used for more than 10 days (usually 3-5 days) why? b/c of the **cumulative effect**.
* **dehydroemetine is preferable due to less toxicity (3-5 days)**.

Uses :

- 1- **Amoebic liver abscess.**
- 2- **Intestinal wall infections.**
- 3- Severe forms of amebiasis **acute amoebic dysentery**

Adverse Effects :

Dehydroemetine is less toxic than emetine

- GIT: nausea, vomiting, diarrhea.
- **Serious toxicities: cardiotoxicity**
 - Hypotension
 - cardiac arrhythmias
 - heart failure

Precaution :

The drug should **not** be used in patients with **cardiac or renal disease**, in **young children**, or in **pregnancy**

4- Chloroquine:

Use to treat extra-intestinal amebiasis
Specially in the liver
(highly concentrated in the liver)

- **Anti-malarial drug**
- Used in combination with metronidazole or dehydroemetine and luminal amebicide for **amebic liver diseases**.
- **Now NOT commonly used in amebiasis.**

Adverse effects

- pruritus is common
- Nausea, vomiting, abdominal pain, anorexia.
- Blurring of vision.
- **Hemolysis in G6PD deficient patients**

Summary for treatment of amebiasis

Asymptomatic dysentery (cyst carriers)	Luminal amebicides Diloxanide, iodoquinol or Paromomycin
Amebic colitis and dysentery ameboma, and extra-intestinal disease	Metronidazole or tinidazole followed by luminal amebicides
Hepatic abscess	Metronidazole, tinidazole, chloroquine or dehydroemetine

✚ Bacillary dysentery :

Treated by :

1-Fluoroquinolones e.g: *Ciprofloxacin*

Active against a variety of BOTH gram-positive and gram-negative bacteria (**board spectrum**)

- Mechanism of action :
 - **Block bacterial DNA synthesis.**
- Used in treatment of :
 - Bacterial diarrhea (caused by shigella, salmonella and E coli).
 - Urinary tract infections
 - Respiratory tract infections
 - Soft tissues, bones, and joint infections
- Side effects:
 - Arthropathy (damage of growing cartilage).
 - GIT disorders (nausea, vomiting, diarrhea).
 - CNS disorders (headache, dizziness).
 - CVS disorder (prolonged QT interval)
 - Phototoxicity.
 - Liver toxicity.
- Contraindication :
 - **Children, pregnancy**, nursing mother
 - Epilepsy
 - Arrhythmias.
 - Should not be combined with antacids, divalent cations

2-Cotrimoxazole (trimethoprim and sulfamethoxazole) :

- Uses:
 - Commonly used in **travelers diarrhea**.
- Contraindication:
 - **Children or patient allergic to sulpha drugs**

3-Ceftriaxone (penatrally) and cefixime (oral): (3dr gen cephalosporin)

- **Ceftriaxone** Third-generation cephalosporin with broad-spectrum, gram-negative activity. It acts by inhibiting cell wall synthesis
- **Cefixime** Third-generation oral cephalosporin with broad activity against gram-negative bacteria.

BOTH are safe and effective

SUMMARY

- Maintain ***fluid*** intake (oral rehydration therapy or Intravenous fluid therapy).
- asymptomatic luminal amebiasis is treated by luminal amebicides (**diloxanide, or iodoquinol or paromomycin**).
- **Metronidazole** is the mainstay of therapy for invasive amebiasis (**followed by luminal amebicides to prevent relapse**).
- Chloroquine has also been used for patients with hepatic amebiasis.
- Dehydroemetine is useful but not preferable due to CVS toxicity
- **Ciprofloxacin** is the drug of choice in bacillary dysentery. In children and pregnancy, **ceftriaxone** or **cefixime** is the choice.