Treatment of dysentery and amebiasis

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- **Team note << purple**
- **Imp points >> Red**

Dysentery

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

Causes of Dysentery

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 or Intravenous fluid therapy.**
- **Antimicrobial agents should not be given untill stool analysis is done.**

Amebiasis

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

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)*.**
- **Hepatic abscess, and other extra-intestinal diseases.**

Life Cycle

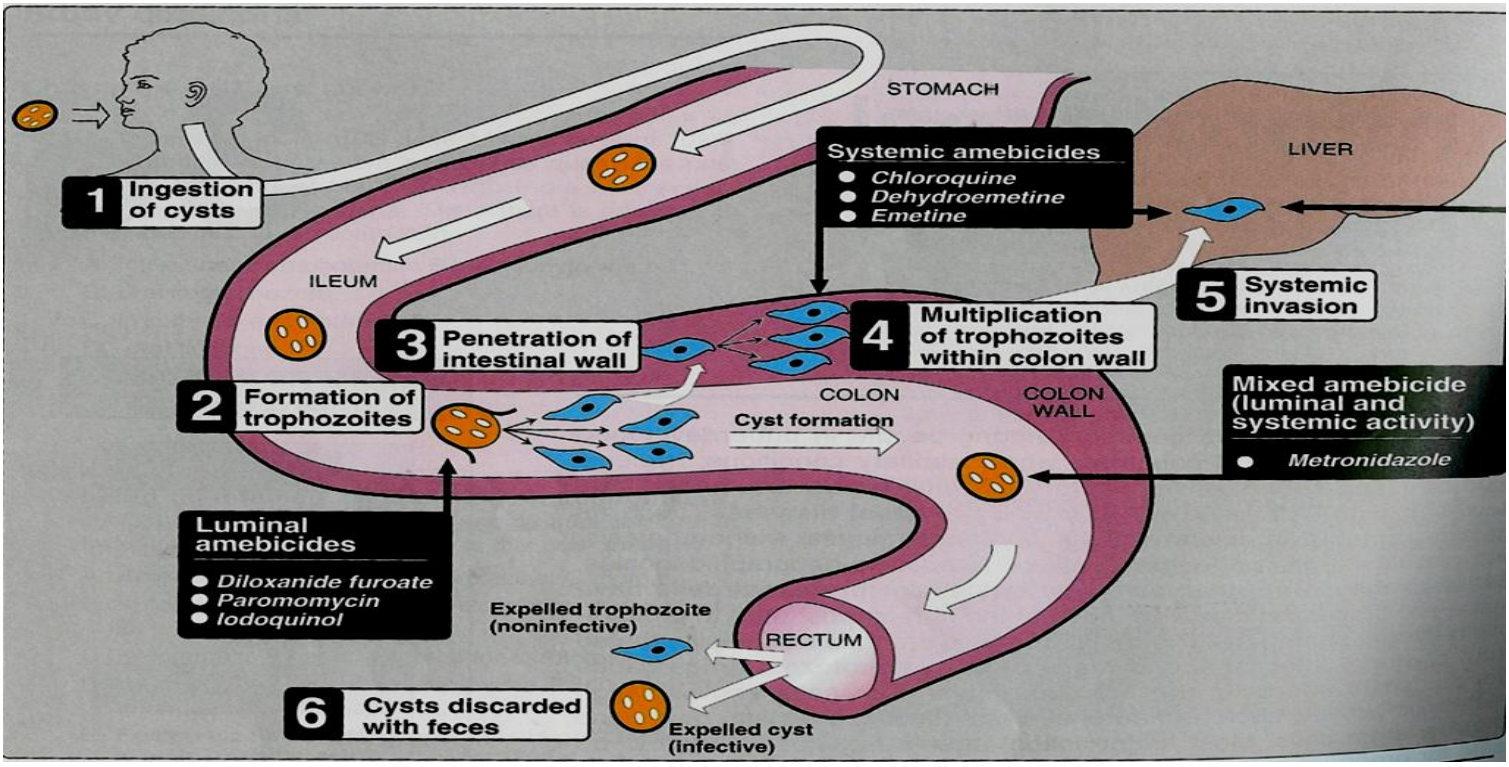
***Entamoeba histolytica* exists in two forms:**

1. Cysts (infective stage):

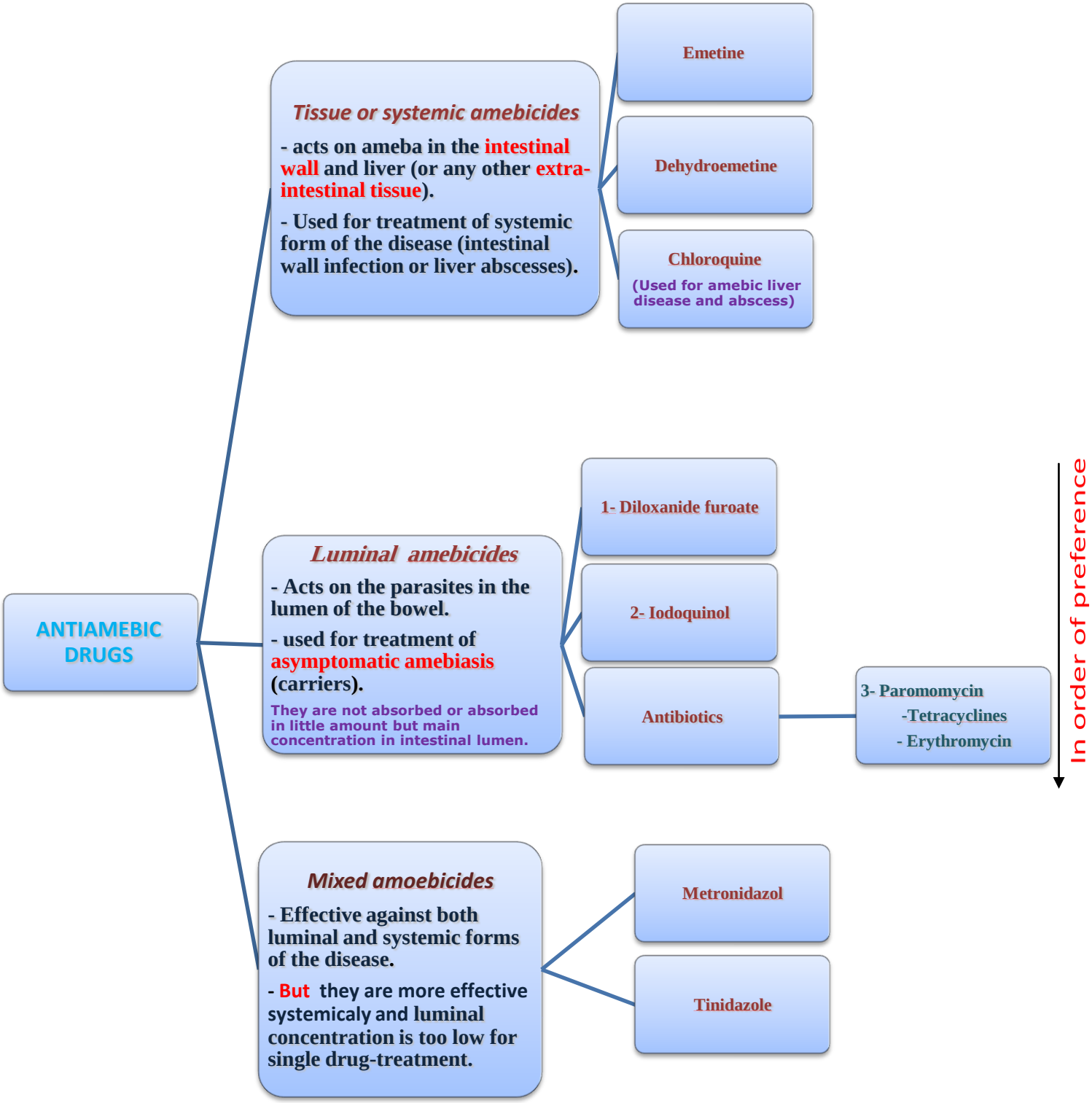
- **can survive outside the human body.**
- **When ingested, liberate trophozoites in the lumen of the intestine.**

2. Trophozoites (non-infective; invasive stage):

- **Multiply and feed on intestinal bacterial flora.**
- **They may invade and ulcerate wall of large intestine, or may migrate to liver or other tissues.**



Treatment of Amebic dysentery



Mixed amoebicides

1- Metronidazole :

-Drug of choice for intestinal & extra-intestinal amoebiasis.

-Acts on trophozoites. Has no effect on cysts.

- MOA:

Nitro group of metronidazole is reduced by protozoan and gives

cytotoxic reduced product

this product binds to DNA and proteins resulting into parasite death.

[DNA and protein damage]

Pharmacokinetics :

-Given orally or IV.
-Absorption is rapid & complete.
- Due to rapid absorption from GIT, *not reliably effective against luminal parasites as a single therapy*
-Wide distribution to all tissues and body fluids (CSF, saliva, milk).
-Plasma half life is 8 h
-Metabolized in liver by mixed function oxidase followed by glucouroidation.
-Excreted in urine.
-Clearance is decreased in liver impairment

Clinical uses :

-Extra-luminal amoebiasis: is the drug of choice in all tissue amebiasis (*should be combined with luminal amebicide*).

-Giardiasis

-Trichomoniasis

-Broad spectrum of anaerobic bacteria e.g.:

+ Helicobacter pylori infection

+ Pseudo-membranous colitis *by Clostridium difficile* [associated with antibiotic use]

Adverse effects :

* * GIT:
-Dry mouth, metallic taste
-Nausea, vomiting, diarrhea(*NVD*)
-Oral Thrush (Moniliasis, yeast infection).
* * CNS: *Neurotoxicological effect*
-Insomnia, dizziness
-peripheral neuropathy, paresthesia
-encephalopathy, convulsion (due to *IV infusion, rare*).
-Dysuria =dark urine.
-Neutropenia =decrease neutrophils
-Disulfiram-like effect if taken with alcohol.

Drug interactions:

Enzyme inhibitors *(cimetidine, ketoconazole= antifungal drug)*

↑duration of action of metronidazole

Enzyme Inducers *(phenytoin & phenobarbitone). anti epileptic drug*

↓*duration of action of metronidazole*

--Metronidazole itself inhibits CYP family 2C9 & 3A4 lead to :

+ increases anticoagulant effect of warfarin.

+ Increases lithium toxicity.

CONTRAINDICATIONS / PRECAUTIONS:

- Pregnancy and nursing women.
- Alcohol intake
- CNS diseases
- Severe hepatic & renal disease

Disulfiram is a drug used in treatment of alcohol abuse . the main MOA is prevents alcohol metabolism → accumlation of acetaldehyde → abdominal distress, nausea, vomiting, flushing, or headache, tachycardia, hyperventilation.
Metronidazole has Disulfiram like -effect When is given with alcohol

2- Tinidazole

Tinidazole has similar activity to metronidazole BUT has :

-longer duration of action (12-14h) SO a simpler dosing regimen (جرعات أقل)

- better toxicity profile than metronidazole.

- no effect against aneorbic bacteria.

Tissue or systemic amebicides

1- Emetine and dehydroemetine

-Emetine is an alkaloid derived from ipeca while dehydroemetine is a synthetic analog .

MOA :

-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.

(impacted by first-pass metabolism and others)

-Given preferably subcutaneously but could be given by IM, NEVER I.V. (it can cause cardiotoxicity so not given by IV)

-Has long plasma half life about 5 days.

-Metabolized & Excreted slowly via kidney so they have 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).

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).

So in case of acute amoebic dysentery :
1st choice is Metronidazole then dehydroemetine (has less side effect than emetine)

Adverse Effects :

-Dehydroemetine is less toxic than emetine
-pain at site of injection, abscesses.
-GIT: nausea, vomiting, diarrhea.
-Serious toxicities: ***cardiotoxicity***
Hypotension, cardiac arrhythmias, heart failure

Caution:

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

2- Chloroquine :

- Anti-malarial drug
- Used in combination with metronidazole or dehydroemetine and luminal amebicide for amebic liver diseases.

Adverse effects :

- pruritus is common (Itch)
- Nausea, vomiting, abdominal pain, anorexia.
- Blurring of vision.
- Hemolysis in G6PD deficient patients
- Agranulocytosis
- imparid hearing, alopecia (صلع), hypotension .

Luminal amoebicides

1- Diloxanide furoate

-Ester of diloxanide + furoic acid .

-Given orally.

-It splits in the intestine, most of diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine (90%).

-The unabsorbed diloxanide is the amoebicidal agent (10%). (small percentage but highly effective)

-Direct amoebicidal action against luminal forms

-*Not active against trophozoites in intestinal wall or extra-intestinal tissues*. Only luminal

-Mechanism of action is unknown

Clinical uses:

-Drug of choice for asymptomatic intestinal infection.

-For complete eradication of amebic infections given along with tissue amebicides. (e.g Metro. , Chloroquine , dehydroemetine)

Adverse Effects:

Flatulence , Nausea, vomiting, abdominal cramps.

No serious adverse effects

Contraindications:

- Pregnancy

- Children (less than 2 years).

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 :

-luminal 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 (^{131}I *uptake).*

(impaired measurement of Thyroid test if Iodoquinol is taken)

-Iodoquinol should be used with caution in patients with optic neuropathy, renal or thyroid disease.

-discontinued if it produces persistent diarrhea or signs of iodine toxicity *(dermatitis, urticaria, pruritus, fever).*

3- Paromomycin Sulphate

-Aminoglycoside antibiotic.
-It is given orally
-Not significantly absorbed from GIT
-Effective against luminal forms of ameba

MOA

-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.
→ Ameba feed on intestinal normal flora. By killing NF,ameba won't find anything to eat

-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

4- Tetracyclines

-Very weak direct amoebicidal action.

-Acts mainly *indirectly* on bacterial normal flora.

-Used in severe cases of amoebic dysentery not responding to metronidazole combined with dehydroemetine.

Bacillary dysentery

Treated by:

- **Fluoroquinolones such as ciprofloxacin (drug of choice)**
- **Cotrimoxazole (trimethoprim- sulfamethoxazole)**

✓ Ciprofloxacin

- active against a variety of gram-positive and gram-negative bacteria.
- block bacterial DNA synthesis.
- Used in treatment of :
  Bacterial diarrhoea (caused by shigella, salmonella,and E coli).
  Urinary tract infections , Respiratory tract infections , Soft tissues, bones, and joint infections

✓ Cotrimoxazole

- Cotrimoxazole is combination of sulphamethoxazole and trimethoprim,
- Mechanism of Action of sulphamethoxazole and trimethoprim :

PABA (1) → Dihydrofolic acid (2) → Tetrahydrofolic acid → Purines → DNA

**1: Sulphamethoxazole 2: Trimethoprim they inhibit DNA formation

MOA of Cotrimoxazole: inhibition of DNA synthesis

1) Sulphamethoxazole
-Cotrimoxazole is combination of sulphamethoxazole and trimethoprim, unlike humans, bacteria cannot use exogenous folate but must synthesize it from PABA.
-Sulfonamides are structural analogs of PABA [so they compete with PABA] → they inhibit dihydropteroate synthase and folate production.
-Sulfonamides inhibit both gram –positive and gram- negative bacteria such as shigella, E.Coli and others.
Adverse effects:
-Fever, skin rashes,**.[Hypersensitivity]**
-Nausea, vomiting, diarrhoea
-Stevens –johnson syndrome (uncommon, but serious and potentially fatal type of skin and mucus membrane eruption).
-Stomatitis,, hemolytic or aplastic anemia.
-It precipitate in urine and cause crystaluria, hematuria, or obstruction.

2) Trimethoprim
-MOA: an inhibitor of dihydrofolate reductase provide. Combined with sulpha -→ synergistic activity because of sequential inhibition of folate synthesis
-ADR's:
Megaloblastic anemia, leucopenia,
Agranulocytosis.

SUMMARY

- **Maintain *fluid* intake (oral rehydration therapy or Intravenous fluid therapy).**
- **asymptomatic luminal amebiasis is treated by luminal amebicides (diloxanide furoate, or paromomycin or Diloxanide).**
- **Intestinal and extra-intestinal amebiasis is treated by tissue amebicides (metronidazole is drug of choice usually being given first, followed by luminal amebicides to ensure complete eradication).**
- **Ciprofloxacin is the drug of choice in bacillary dysentery.**

Summary for treatment of amebiasis:

Asymptomatic cyst carriers	*Iodoquinol* or *Paromycin* or *Diloxanide furoate*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *Iodoquinol* or *Paromycin* or *Diloxanide furoate*
Amebic liver absess	*Chloroquine* plus *Metronidazole* or *Emetine*

Table 53–4. Treatment of amebiasis.[1]

Clinical Setting	Drugs of Choice and Adult Dosage	Alternative Drugs and Adult Dosage
Asymptomatic intestinal infection	Luminal agent: Diloxanide furoate,[2] 500 mg 3 times daily for 10 days *or–* Iodoquinol, 650 mg 3 times daily for 21 days *or–* Paromomycin, 10 mg/kg 3 times daily for 7 days	
Mild to moderate intestinal infection	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *plus–* Luminal agent (see above)	Luminal agent (see above) *plus either–* Tetracycline, 250 mg 3 times daily for 10 days *or–* Erythromycin, 500 mg 4 times daily for 10 days
Severe intestinal infection	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *plus–* Luminal agent (see above)	Luminal agent (see above) *plus either–* Tetracycline, 250 mg 3 times daily for 10 days *or–* Dehydroemetine[3] or emetine,[2] 1 mg/kg SC or IM for 3–5 days
Hepatic abscess, ameboma, and other extraintestinal disease	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *plus–* Luminal agent (see above)	Dehydroemetine[3] or emetine,[2] 1 mg/kg SC or IM for 8–10 days, followed by (liver abscess only) chloroquine, 500 mg twice daily for 2 days, then 500 mg daily for 21 days *plus–* Luminal agent (see above)