MED438 ate my life

pharmacology Team 438

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Treatment of Dysentery and Amoebiasis

Objectives:

By the end of the lecture , you should know:

- To understand different causes of dysentery
- To describe different classes of drugs used in treatment of both bacillary dysentery and amebic dysentery
- To be able to describe actions, side effects of drugs for treating bacillary dysentery
- To understand the pharmacokinetics, actions, clinical applications and side effects of antiamebic drugs
- to be able to differentiate between types of antiamebic drugs; luminal amebicides, and tissue amebicide

Color index:

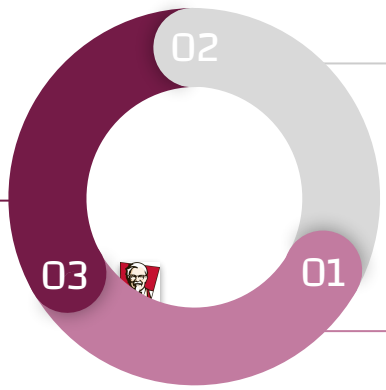
Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

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 caused by any kind of infection.

Causes of Dysentery:



Viral infection

The most common:

Bacterial infection

Bacillary dysentery
(bacterial infection mainly by shigella)

Parasitic infection

Amebic dysentery
(Protozoal infection Mainly by Entamoeba Histolytica)

Treatment:

Maintain fluid intake using oral **rehydration** therapy or intravenous fluid therapy[1].

Antidiarrheal drugs[2]

Antimicrobial agents should not be given until stool analysis is done to **specify** the etiological agent[3]

Antidiarrheal Drugs

Drug	Loperamide Common	Diphenoxylate + Atropine[4]
MOA	opioid-receptor agonist[5]	
P.K	• μ-opioid receptors **in the myenteric plexus** of the large intestine. • **Do not cross BBB**[6] • Minimal liability for addiction	• **Can cross BBB** • Has high liability for addiction • Side effects are mainly due to atropine.
C.I	Treatment should be **avoided in:** 1. presence of high fever 2. if the stool is bloody. 3. C. difficile infections They are contraindicated because they delay fecal excretion that can prolong fever, as it increases the risk of toxin retention[7] and precipitation of toxic megacolon.	

Amebiasis

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

1: oral if patient is not vomiting, IV if patient cannot handle oral. 2:work by reducing GI motility, but has no antimicrobial effect.
3: so you could treat either with antiviral, antibacterial or antiparasitic.
4:Atropine is added to diphenoxylate to increase the side effects (purposally), to avoid patients getting addicted to it.
5: morphine derivatives, morphine itself is not used due to high liability for addiction.(synergist)
6: advantage over morphine and diphenoxylate.
7: the decrease in GI motility will not allow for the was out of the causative organism, preventing the body from getting rid of it.

Entamoeba histolytica exists in two form:

Cysts (infective stage)	Trophozoites (non-infective; invasive stage)
- Can survive outside the human body. - When ingested, liberate trophozoites in the lumen of the intestine.	- Multiply and feed on intestinal bacterial flora. - They may invade and ulcerate wall of large intestine or may migrate to liver or other tissues. - In rectum, trophozoites transform to cysts and are excreted in feces.

Life cycle of Amebiasis:

Cysts ingestion in contaminated food or water → Liberation of trophozoites in the colon[1]. → Invasion[2] of intestinal wall and multiplication of trophozoites within colon wall → Systemic invasion to other organs (liver, lungs, brain) → Cyst formation in rectum and excretion in feces.

Clinical Presentation:

1. The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery
2. **Asymptomatic (Lumenal) amebiasis** = **Carriers** (passing cysts in stool)
3. **Mild to moderate** intestinal disease (colitis)
4. **Severe** intestinal infection (amoebic dysentery)
5. **Ameboma** (localized granulomatous lesion of colon)
6. **Hepatic abscess,** and other extra-intestinal disease

Antiamebic drugs:

Types	Tissue or systemic amebicides[3]	Luminal amebicides[4]
Site of Action	• Act on amoeba **in tissues** E.g. the intestinal wall and/**or other extra-intestinal tissues as liver**, brain, and lung.	• Acts on the parasites **in the lumen** of the bowel
Uses	★ Used for treatment of **systemic form of the disease (invasive amebiasis)** e.g. intestinal wall infection or liver abscesses.	★ Used for treatment of **asymptomatic** amebiasis (carriers). ★ Used to eradicate cysts of E.histolytica **after** treatment of invasive disease.
Drugs	1. Metronidazole/ tinidazole 2. Emetine / dehydroemetine 3. Chloroquine **(liver only)**	1. Diloxanide furoate 2. Iodoquinol 3. Antibiotic: a. Paromomycin b. Tetracycline

1: before invasion, the amoeba is only found in the colon, therefore at this stage (asymptomatic patients) Luminal amebicides are enough to treat.
2: once invasion occur, luminal amebicides are no longer enough alone, systemic amebicides should be used to eradicate the infection.
3: They are highly absorbable, allowing them to reach to systemic circulation and eradicate the organism from the systemic tissues. BUT they are not enough to eradicate the cysts from the intestines, thus, luminal amebicides SHOULD be administered after the systemic amebicides.
4: they are poorly absorbed, allowing them to act on the site of infection (the intestines).

A) Tissue or Systemic Amebicides

Drug	Metronidazole
M.O.A	• It is a Tissue amoebicide that **acts on trophozoites** by: ★ Inhibiting DNA replication ★ Does not eradicate **cysts** from intestine due to good oral absorption.
P.K	• Given orally or IV • Absorption is rapid and complete • Wide distribution to all tissues and body fluids (CSF, saliva, milk). • Short Plasma half life is (8 h). • Metabolized in liver (by CYP-450) by mixed function oxidase followed by glucuronidation **(consider drug interactions).** • Clearance is decreased in liver impairment. • Excreted in urine.
Uses	★ **Drug of choice** for treating invasive amebic infections (intestinal & extraintestinal amebiasis) ○ **Should be followed by luminal amebicides** • Giardiasis • Trichomoniasis • Anaerobic bacterial infections ○ Peptic ulcer (Helicobacter pylori)[1]. ○ Pseudomembranous colitis (Clostridium difficile)[2].
ADRs	**GIT:** • Dry mouth, metallic taste. • Nausea, vomiting, diarrhea. • Oral Thrush (Moniliasis, yeast infection). **CNS: Neurotoxic effects** • Insomnia, dizziness • Peripheral neuropathy, paresthesia. • Encephalopathy, convulsion (IV infusion, rare). **Other ADRs:** • **Dysuria**, dark urine, **neutropenia**. • **Disulfiram-like effect** if taken with alcohol[3].
C.I	• CNS diseases.(If I.V) • Alcohol intake ★ Pregnancy and breastfeeding women ★ Severe renal disease ★ Severe hepatic disease
Drug Inter-action	**Enzyme inhibitors** E.g. cimetidine, ketoconazole → **increase** duration of action of Metronidazole **Enzyme inducers** E.g phenytoin, phenobarbitone[4] → **decreased** duration of action of Metronidazole **Metronidazole inhibits CYP-450 (2C9 & 3A4) so:** • increases anticoagulant effect of **warfarin** • Increases **lithium** toxicity
Alcohol inter-action	• Combining metronidazole and alcohol **causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia,hyperventilation.** Ethanol —(Alcohol dehydrogenase)→ Acetaldehyde —(Aldehyde dehydrogenase, ✕)→ Acetate

1: as part of the triple therapy (PPI + Clarithromycin + metronidazole
2: Vancomycin can also be used.
3: not only alcohol, other substances such as some antivirals could also cause disulfiram-like effect if given with metronidazole.
4: & rifampicin.

A) Tissue or Systemic Amebicides cont...

Drug	Tinidazole
M.O.A	• Has similar activity to metronidazole but better potency
P.K	• **Advantages of tinidazole :** ○ has **longer** duration of action (12-14h) ○ a **simpler** dosing regimen[1] ○ **a better** toxicity profile than metronidazole[2]

Drug	• Emetine • Dehydroemetine
M.O.A	• Both are **effective against tissue trophozoites** of *E. histolytica* causing irreversible block of protein synthesis.
P.K	• Emetine is an alkaloid derived from ipeca[3] while dehydroemetine is a synthetic analog. • Have erratic oral absorption (not given orally). • Given preferably subcutaneously but could be given IM, **Never given as I.V**[4] • **Has long plasma half life** about 5 days • Should not be used for more than 10 days (usually 3-5 days) • Metabolized & excreted slowly via kidney so they have a cumulative effect[5]. ★ Because of **major toxicity concerns** they have been almost **completely replaced by metronidazole**[6]**.**
Uses	• Amoebic liver abscess • Intestinal wall infections ★ Severe forms of amebiasis **acute amoebic dysentery, dehydroemetine** is preferable due to less toxicity (3-5 days)
ADRs	• Dehydroemetine is less toxic than Emetine (safer) ★ **Serious toxicity: cardiotoxicity** (Hypotension, cardiac arrhythmias, heart failure) • GIT: nausea, vomiting, diarrhea
C.I	• Patients with cardiac or renal disease • Young children • Pregnancy

Drug	Chloroquine
M.O.A	• Anti-malarial drug.
Uses	• Used in combination[7] with metronidazole or dehydroemetine **for amebic liver diseases.**
ADRS	• Pruritus is common ★ Blurring of vision[8] ★ Hemolysis in G6PD deficient patients[9] • Nausea, vomiting, abdominal pain, anorexia

1: means less frequency of administration.
2: has the same side effects but to a lesser extent.
3: عرق الدهب
4: Due to high CVS toxicity.
5: May cause the patient to reach to level of toxicity .
6: usually only used in countries where metronidazole & tinidazole are unavailable.
7: or alone
8: (ALERT: CNS flashbacks) due to retinal deposition (retinopathy).
9: oxidizing drugs should be avoided in patients with G6PD deficiencies (which include: Sulfa drugs, trimethoprim and chloroquine).

B) Luminal Amebicides

Drug	Diloxanide furoate
M.O.A	• M.O.A is unknown • **Direct**[1] amoebicidal action against luminal forms (**Cyst**) • Not effective against trophozoites in intestinal wall or extra-intestinal tissues.
P.K	• Ester of diloxanide +Furoic acid • Given orally • It **split** in the intestine liberating diloxanide ★ The little **unabsorbed diloxanide** **is the amoebicidal agent** • The absorbed portion is excreted in urine
Uses	★ **Drug of choice** for asymptomatic intestinal infection(cyst passers) • To eradicate cysts of E.histolytica after treatment of invasive disease with systemic amebicides
ADRs	• Flatulence • Nausea, vomiting, abdominal cramps.
C.I	• Pregnancy • Children (less than 2 years).

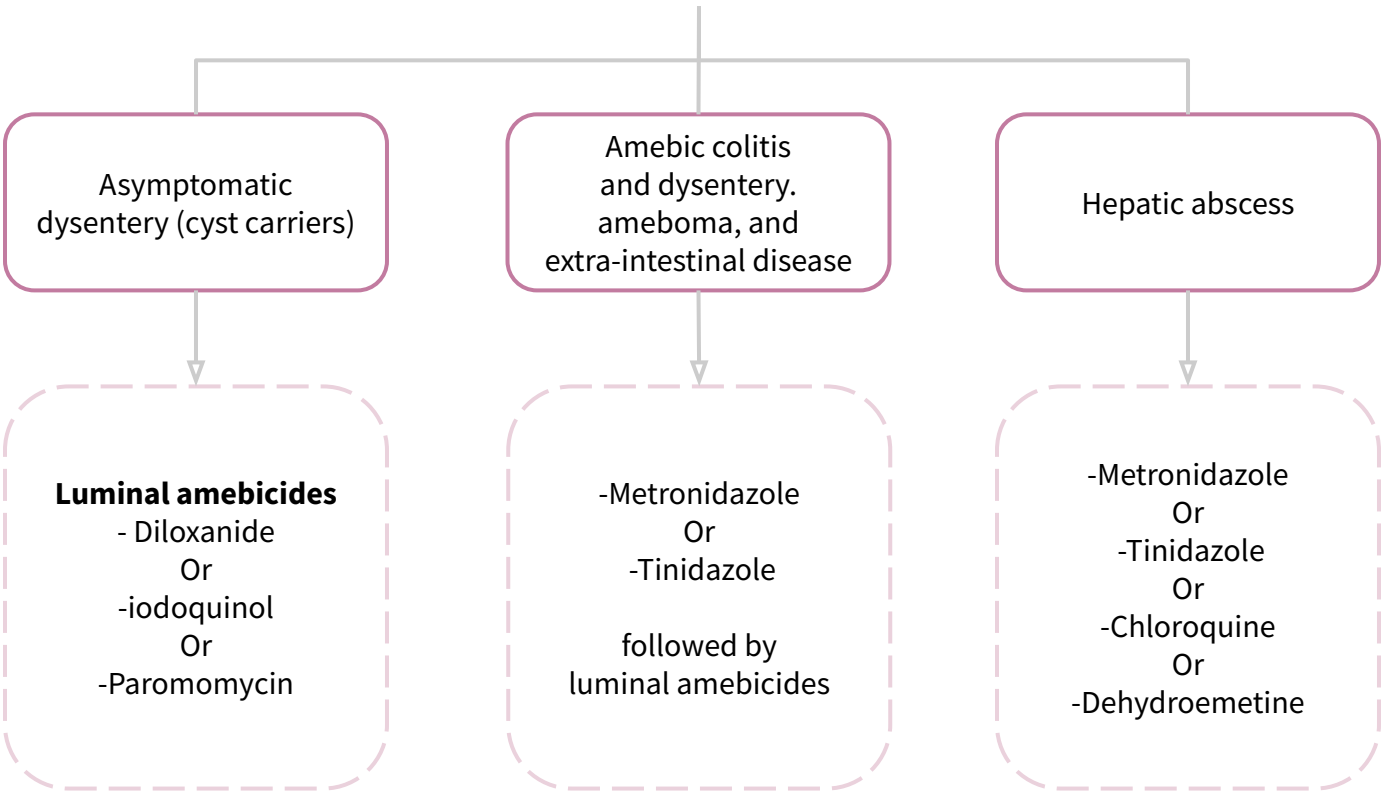
Drug	Iodoquinol
M.O.A	• M.O.A is unknown • Effective against the **luminal forms** of amebiasis
P.K	• Is given orally • Poorly absorbed, excreted in feces.
Uses	• Luminal amoebicide for asymptomatic amebiasis
ADRs	• **GIT:** Nausea,vomiting, diarrhea. ★ Peripheral neuropathy including optic neuritis[2] ★ Enlargement of the thyroid gland[2] • Iodine sensitivity[3] • interference with thyroid function tests ○ increase protein-bound serum iodine, decrease in measured (I^{131} uptake).
C.I	★ should be used with caution in patients with optic neuropathy, or thyroid disease • discontinued if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus,fever)

1: should come in contact with the infected tissue to be effective (which is the lumen of intestines).
2: Even though it is poorly absorbed, the small traces of iodine that is absorbed is enough to cause all of these ADRs.
3: drug should be DISCONTINUED if patient shows any sign of iodine toxicity such as urticaria or eczema.

B) Luminal Amebicides cont...

Drug	Paromomycin sulphate
M.O.A	• Aminoglycoside[1] antibiotic • **Direct amebicidal action:** causes leakage by its action on cell membrane of parasite • **Indirect effect:** killing of bacterial flora[2] essential for proliferation of pathogenic amoebae
P.K	• Effective only against luminal forms of ameba • Given orally • Not significantly absorbed from GIT • Small amount[3] absorbed is excreted unchanged in urine (may accumulate with renal insufficiency)
Uses	★ Use in **chronic amebiasis** to eliminate cysts (in cysts passers)
ADRs	• Gastrointestinal distress and diarrhea
C.I	• Severe renal disease • Patients with GIT ulceration

Summary For Treatment of Amebiasis



1: In general, aminoglycosides are usually only given parenterally due to their poor oral absorption, but because paromomycin sulphate is used to treat a parasite in the intestines, it is given orally so it could come in contact with the lumen (the poor oral absorption is used as an advantage).
2: That the amoeba normally feeds on.
3: sometimes enough to cause aminoglycosides usual ADR (phototoxicity and nephrotoxicity)

Bacillary dysentery treated by:

Beta-lactams

-Ampicillin, Amoxicillin
-3rd gen[1] cephalosporins (Cefixime, ceftriaxone)

Macrolides

Azithromycin

Fluoroquinolones

Such as :
Ciprofloxacin, ofloxacin

Cotrimoxazole

Trimethoprim-sulfamethoxazole[2] (TMP-SMX) commonly used in traveler's diarrhea.

- Resistance to ampicillin, amoxicillin and sulfonamides has been reported worldwide, and these agents **are not recommended as empirical therapy**
- Antimicrobial therapy is typically administered for 5 days.

Drug	Ciprofloxacin
M.O.A	• Active against a variety of gram-positive and gram-negative bacteria • Block bacterial DNA synthesis[3] and growth (DNA gyrase and topoisomerase)
Uses	★ Fluoroquinolones are **first-line** treatment for shigellosis ★ Bacterial diarrhea caused by shigella, salmonella and E coli • Drug of choice for bacillary dysentery • Urinary tract infections • Respiratory tract infections • Soft tissues, bones, and joint infections
ADRs	• Arthropathy (damage of growing cartilage) • Phototoxicity • Liver toxicity • GIT disorder (nausea, vomiting, diarrhea) • CNS disorders (headache, dizziness) ★ CVS disorders (prolong QT interval) Most Serious
C.I	• Children, pregnancy, nursing mother. • Epilepsy • Should not be combined with antacids, divalent cations • Arrhythmias

Drug	Cephalosporins (Cefixime , Ceftriaxone)
M.O.A	• Act by inhibiting cell wall synthesis interfering with synthesis of peptidoglycan (major structural component of bacterial cell wall)
P.K	• Oral cefixime or parenteral ceftriaxone are **safe and effective**
Uses	• 3rd generation cephalosporins are **Second line** therapy • In case of children or patient **allergic** to sulfonamides, cephalosporins or azithromycin may be used. • Drug of choice in case of pregnancy or children (cotrimoxazole and ampicillin are also safe, used depending on sensitivity)

1: more effective against gram negatives
2: used together to provide synergic effect (each one of them alone is bacteriostatic, together they are bactericidal).
3: = bactericidal

Quiz

MCQ

Q1- A 24-year-old sexually active woman presents with vaginal itching and a greenish, frothy vaginal discharge. Her boyfriend is asymptomatic. She is prescribed with metronidazole for Trichomonas infection. Which of the following is involved in metronidazole's action?

(A) Blocking folic acid synthesis
(B) Inhibition of DNA synthesis
(C) Inhibition of PBPs
(D) Inhibition of ribosomes

Q2-A 25-year-old sexually active woman presents to her primary care physician with vaginal itching and a greenish, frothy vaginal discharge. Her boyfriend is asymptomatic. She is prescribed metronidazole for Trichomonas vaginalis. Which of the following should be told to avoid while taking metronidazole?

(A) Alcohol
(B) Aspirin
(C) Caffeine
(D) Grapefruit juice

Q3- A 20- year- old patient presents to the clinic with acute severe dysentery diarrhea , the doctor said it was caused by amoeba. what Antiamebic drug should be given?

(A)Chloroquine
(B)Diloxanide furoate
(C)Dehydroemetine
(D)Tetracycline

Q4-Which of the following drugs interferes with thyroid function tests?

(A)Diloxanide furoate
(B) Iodoquinol
(C) Metronidazole
(D) Diloxanide furoate

Q5- A patient came with dysentery diarrhea and fever after investigation an organism gram -ve, non-lactose fermenter was found. A diagnosis of shigellosis was made. What is the most suitable drug?

(A)TMP-SMX
(B)Azithromycin
(C)Diloxanide furoate
(D)Ciprofloxacin

SAQ

- **A patient was given a antiamebic drug later he experienced metallic taste.**

Q1- Mention the drug and its MOA :
Q2- Enumerate 3 ADRs :
Q3- mention 3 C.Is:

- **A 36 year-old patient with bacterial diarrhea and fever caused by salmonella.he was given an antibiotic, later presents with prolonged interval Q-T.**

Q1- Mention the drug and its M.O.A:
Q2- mention other drug that can be used :

Answers:

MCQ

Q1	B
Q2	A
Q3	C
Q4	B
Q5	D

SAQ

Q1	Metronidazole ,Tissue amoebicide that acts on trophozoites by:Inhibiting DNA replication
Q2	Dry mouth, peripheral neuropathy, dysuria
Q3	Severe renal disease, Severe hepatic disease, pregnancy
Q4	Ciprofloxacin, Block bacterial DNA synthesis and growth (DNA gyrase and topoisomerase)
Q5	Ceftriaxone

Share with us your ideas !

Good Luck , Future Doctors!

Team Leaders:

May Babaeer **Zyad Aldosari**

This Amazing Work Was Done By:

May Babaeer **Raghad AlKhashan**

Told you I'll drop a reference