

Antiamoebic Drugs

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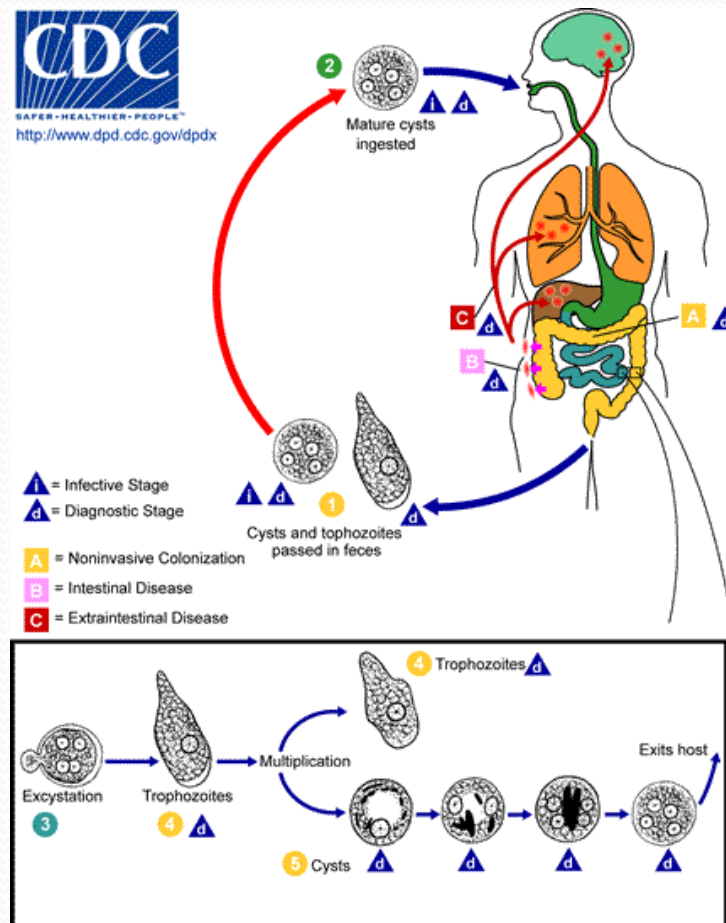
Introduction

- Protozoal infections are common among people in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate.
- However, with increased world travel, protozoal diseases, such as amebiasis, giardiasis, trichomoniasis malaria, leishmaniasis, trypanosomiasis, are no longer confined to specific geographic locales.
- Amoebiasis has a worldwide distribution (over 40 million people are infected), but it is endemic in most parts of India

Cont'd

- **Amebiasis:** (It is also called amoebic dysentery) is an infection of the intestinal tract caused by *Entameba histolytica*.
- The disease can be acute or chronic, with patients showing varying degrees of illness, from no symptoms to mild diarrhoea to fulminating dysentery.
- The diagnosis is established by isolating *E. histolytica* from fresh feces.

Life cycle of *E. histolytica*



Cont'd

- *Entameba histolytica* exists in two forms: cysts that can survive outside the body, and labile but invasive trophozoites that do not persist outside the body.
- Cysts, ingested through feces contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated.
- The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine (lumen) or simply feed on intestinal bacteria.
- The trophozoites within the intestine are slowly carried toward the rectum, where they return to the cyst form and are excreted in feces.

Cont'd

- Large numbers of trophozoites within the colon wall can also lead to systemic invasion.
- Amebiasis is infection with *Entameba histolytica*. This organism can cause;
 1. Asymptomatic intestinal infection
 2. Mild to moderate colitis
 3. Severe intestinal infection (dysentery)
 4. Ameboma
 5. Liver abscess
 6. Other intestinal infections

Antiamoebic Drugs

- **Antiamoebic Drugs –**

These are drugs useful in the treatment of infection caused by the protozoa *Entamoeba histolytica*.

Amaebiasis may manifest as:

1. Intestinal or luminal amebiasis
2. Asymptomatic cyst carrier
3. Invasive or systemic or extraintestinal amebiasis (hepatic, liver abscess, lung abscess, brain abscess))

Classification

- 1. **Tissue amoebicides**

(a) For both intestinal and extraintestinal amoebiasis:

Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, Ornidazole

Alkaloids: Emetine, Dehydroemetine

(b) For extraintestinal amoebiasis only:

Chloroquine

Classification ...Cont'd

- **2. Luminal /intestinal amoebicides**

- (a) **Amide : Diloxanide furoate, Nitazoxanide**

- (b) **8-Hydroxyquinolines: Quiniodochlor (Iodochlorohydroxyquin, Clioquinol), Diiodohydroxyquin (Iodoquinol)**

- (c) **Antibiotics: Tetracyclines**

Systemic

- Chloroquine

Luminal

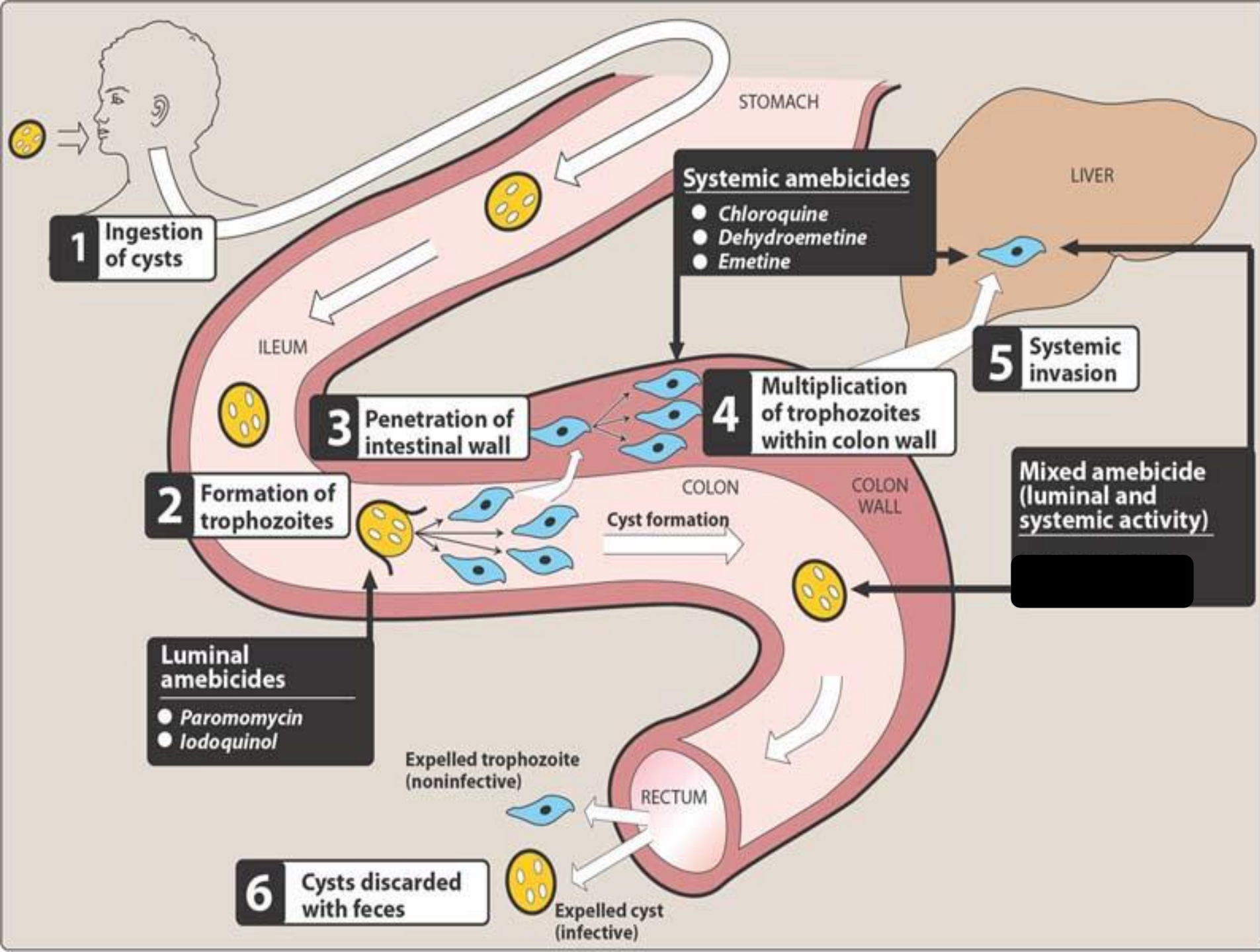
- Diloxanide furoate
- Iodoquinol
- Paromomycin
- They act on the parasites in the lumen of the bowel only

Mixed (luminal and systemic)

- Metronidazole
- Tinidazole
- Emetine
- Dehydroemetine
- They are effective against parasites in the intestinal wall and liver.

Systemic antiamebic against trophozoites

Luminal antiamebic against cyst



Metronidazole - prototype

- Metronidazole and related nitroimidazoles are active *in vitro* against a wide variety of anaerobic protozoal parasites and anaerobic bacteria.
- **The drug also has potent amebicidal activity against *E. histolytica*.**
- Metronidazole has antibacterial activity against all **anaerobic cocci** and both anaerobic gram negative bacilli, including *Bacteroides* spp., and **anaerobic spore-forming** gram-positive bacilli.
- Effective in **trichomoniasis, amebiasis, and giardiasis, and obligate anaerobic bacteria**, including *Bacteroides*, *Clostridium*, and microaerophilic bacteria such as *Helicobacter* and *Campylobacter* spp

Metronidazole

- A nitroimidazole, is the drug of choice in the treatment of extra luminal amebiasis.
- It kills trophozoites but not cysts of *E.histolytica* and effectively eradicates intestinal and extra intestinal tissue infections.

MOA

- *Metronidazole is a prodrug that is activated by reduction of the nitro group by susceptible Organisms*
 1. Some parasites (including amebas) possess (ferrodoxin-like, low-redox-potential, electron-transport proteins)
 2. these proteins remove electrons.
 3. The nitro group of metronidazole accepts the electron from reduced ferrodoxin
 4. Then metronidazole become reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.

PK of metronidazole

- Route of administration: oral and I.V.
- Oral metronidazole is almost completely absorbed from the small intestines; little unabsorbed drug reaches the colon.
- Peak plasma concentration is reached in 1- 3 hours.
- Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF).
- It is metabolized in liver primarily by oxidation and glucuronide conjugation, and excreted in urine. Plasma halflife is 8 hrs

Uses

- **Amebiasis:** Metronidazole is the drug of choice in the treatment of all tissue infections with *E. histolytica*. It is not reliably effective against luminal parasites and must be used with a luminal amebicide.
- For mild intestinal disease 400 mg TDS for 5- 7 Days. For invasive dysentery and liver abscess-800 mg TDS (children 30- 50 mg/kg/day) for 7- 10 days. In serious cases of liver abscess 1 g may be infused i.v. slowly followed by 0.5 g every 8-12 hr till oral therapy is instituted
- **Giardiasis:** It is highly effective in a dose of 400 mg TDS for 7 days. A shorter course of 3 days with 2 g/ day is equally effective.
- **Trichomonas vaginitis:** It is the drug of choice; 400 mg TDS for 7 days achieves nearly 100% cure. Additional intravaginal treatment has been given, but is not necessary except in refractory cases. The male partner should be treated concurrently in cases of recurrent infections.

Uses

- **Anaerobic bacterial infections-** They occur mostly after colorectal or pelvic surgery, appendicectomy, etc. Brain abscesses and endocarditis may be caused by anaerobic organisms. Metronidazole in combination with gentamicin or cephalosporins
- **Pseudomembranous enterocolitis** - due to *Cl. difficile* is generally associated with use of antibiotics. Oral metronidazole 800 mg TDS is more effective
- **Ulcerative gingivitis, trench mouth-** 200-400mg TDS (15-30 mg/kg/day) is quite effective because anaerobes are involved.
Helicobacter pylori gastritis/peptic ulcer -Metronidazole or tinidazole alone are relatively ineffective. However, metronidazole 400mg TDS is used along with amoxicillin/ clarithromycin and proton pump inhibitor in triple drug 2 week regimens.

Adverse effects

- Dry mouth
 - Metallic taste in the mouth and,
 - Nausea
 - Headache
- Commonly occurs
- Vomiting, Diarrhea, insomnia, weakness, dizziness, thrush, dysuria, dark urine, paraesthesias, and neutropenia are infrequently encountered.
 - Pancreatitis along with CNS symptoms eg, ataxia, encephalopathy, and seizures are rarely seen.

Cont'd

- I.V. infusion rarely causes seizures or peripheral neuropathy.
- **Precautions**
 1. The drug should be used with caution in patients with CNS diseases.
 2. Avoided in pregnancy due to the possible risk of teratogenicity just like any other azole.
 3. Dose adjustment in renal or liver impairment

DRUG INTERACTION

- Metronidazole has a disulfiram like effect when taken with alcohol.
- It potentiates the anticoagulant effect of coumarin (warfarin) type of anticoagulants.
- Phenytoin & phenobarbitone may increase the elimination of the drug, while cimetidine decreases plasma clearance by manipulating with the hepatic cytochrome enzymes.
- Lithium + metronidazole → lithium toxicity

Tinidazole

- Tinidazole, a nitroimidazole, is similar to metronidazole
- Tinidazole is as effective as metronidazole, with a shorter course of treatment, yet it is more expensive.
- Metabolism is slower; t-half is -12 hr; duration of action is longer; dosage schedules are simpler. Thus, it is more suited for single dose or once daily therapy and offers simpler dosing regimens.
- Some comparative trials in amoebiasis have reported higher cure rates.
- It appears to be better tolerated; the incidence of side effects is lower: metallic taste (2%), nausea (1 %), rash.

Pharmacokinetics:

The half life of Tinidazole is 12-14 hours

Uses

Recommended schedules are-

- **Amoebiasis:** 2 g OD for 3 days (children 30-50 mg/kg/day) or 0.6 g BD for 5-10 days.
- **Trichomoniasis and giardiasis:** 2 g single dose or 0.6g OD for 7 days.
- **Anaerobic infections:**
 - prophylactic-2 g single dose before colorectal surgery;
 - therapeutic-2 g followed by 0.5 g BD for 5days.
- **H. pylori:** 500 mg BD for 2 weeks in triple combination.

Adverse effects: toxicity profile is similar to metronidazole, but it is better tolerated.

Diloxanide furoate

- Diloxanide furoate is a dichloroacetamide derivative.
- It is a **highly effective luminal amoebicide: directly kills trophozoites responsible for production of cysts.**
- **After oral administration diloxanide furoate is split in the gut into diloxanide and furoic acid**
- 90% of the drug is rapidly absorbed then conjugated via glucuronodation to be promptly excreted in the urine.
- Diloxanide furoate exerts no antibacterial action. It is less effective in invasive amoebic dysentery, because of poor tissue amoebicidal action. However, a single course produces high (80-90%) cure rate in mild intestinal amoebiasis and in asymptomatic cyst passers.

Uses

- It is considered the drug of choice for mild intestinal/asymptomatic luminal infections
- It is used with a tissue amebicide, usually metronidazole to treat serious intestinal and extra intestinal infections.

Adverse effects: flatulence is common, nausea, abdominal cramps and rashes might also occur

- Not recommended in pregnancy

Iodoquinol

- Iodoquinol (diiodohydroxyquin) is a halogenated hydroxyquinoline.
- **MOA:** Unknown
- **Withdrawn due to risk of SMON – subacute myelo-optic neuropathy**

Emetine and Dehydroemetine

- Emetine, an alkaloid
- are effective against tissue trophozoites of *E. histolytica*, but because of major toxicity concerns they have been almost completely replaced by metronidazole.

Route of administration:

- Subcutaneous (preferred) or I.M. Never → IV

Cont'd

- Precautions:

1. The drug should not be used in patients with cardiac or renal disease,
2. Young children, or
3. In pregnancy.

Tetracyclines:

- They are active against many gram-positive and gram-negative bacteria and against some protozoa, for example, amebas.
- Mechanism of action
- Tetracyclines enter microorganisms by
 - 1- passive diffusion
 - 2- active transport.
- tetracyclines bind reversibly to the 30S subunit of the bacterial ribosomes, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA- ribosome complex.
- This prevents the addition of amino acids to the growing peptide and exerts antiamoebic activity

Chloroquine

- It is used in combination with metronidazole and diloxanide furoate to treat and prevent amoebic liver abscesses.
- It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis

- **Mechanism of action:**

Chloroquine probably acts by concentrating in parasitic food vacuoles, preventing the polymerization of the hemoglobin breakdown product, heme into hemozoin, and thus eliciting parasite toxicity due to the building up of free heme.

Adverse effects:

1. Pruritus is common,
2. **Nausea, vomiting**, abdominal pain, anorexia.
3. Headache, blurring of vision uncommon.
4. Hemolysis in G6PD deficient patients, impaired hearing, agranulocytosis, alopecia, hypotension.



Thank you

Please refer standard textbook of medical pharmacology for details(latest version)

- Goodman Gillman
- KD Tripathi
- Satoshkar and bandarkar