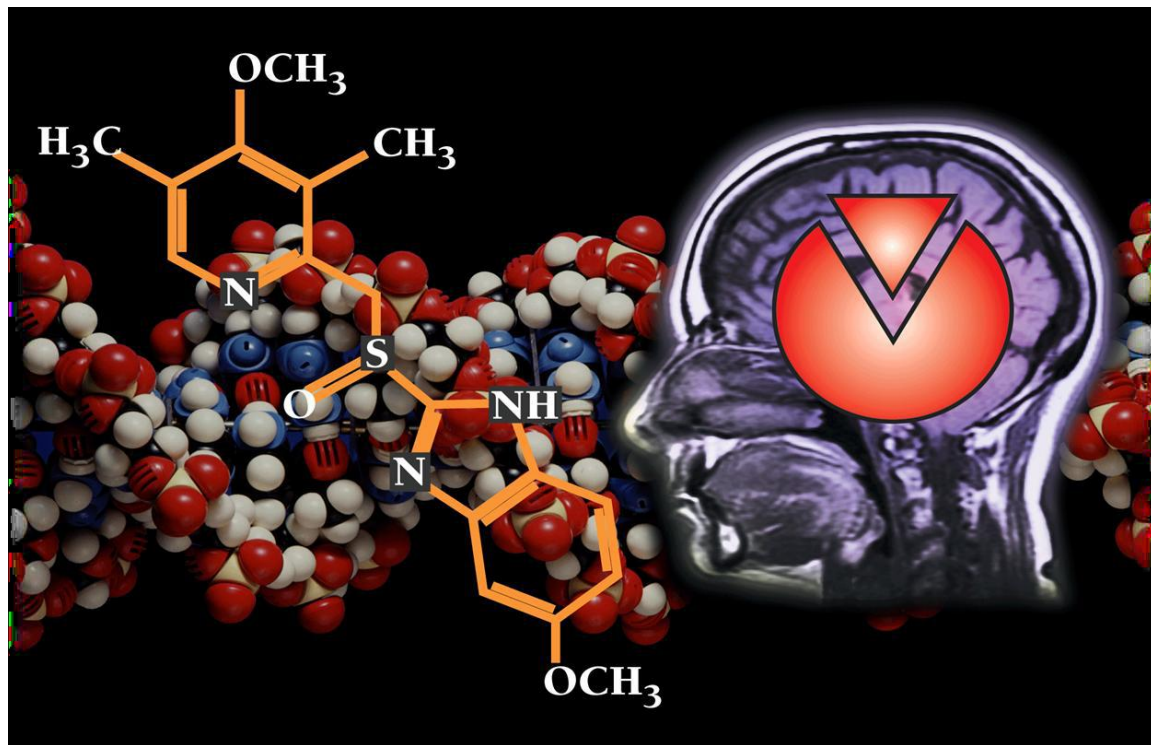


# Treatment of dysentery and Amebiasis



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# Introduction:

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

## **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):**

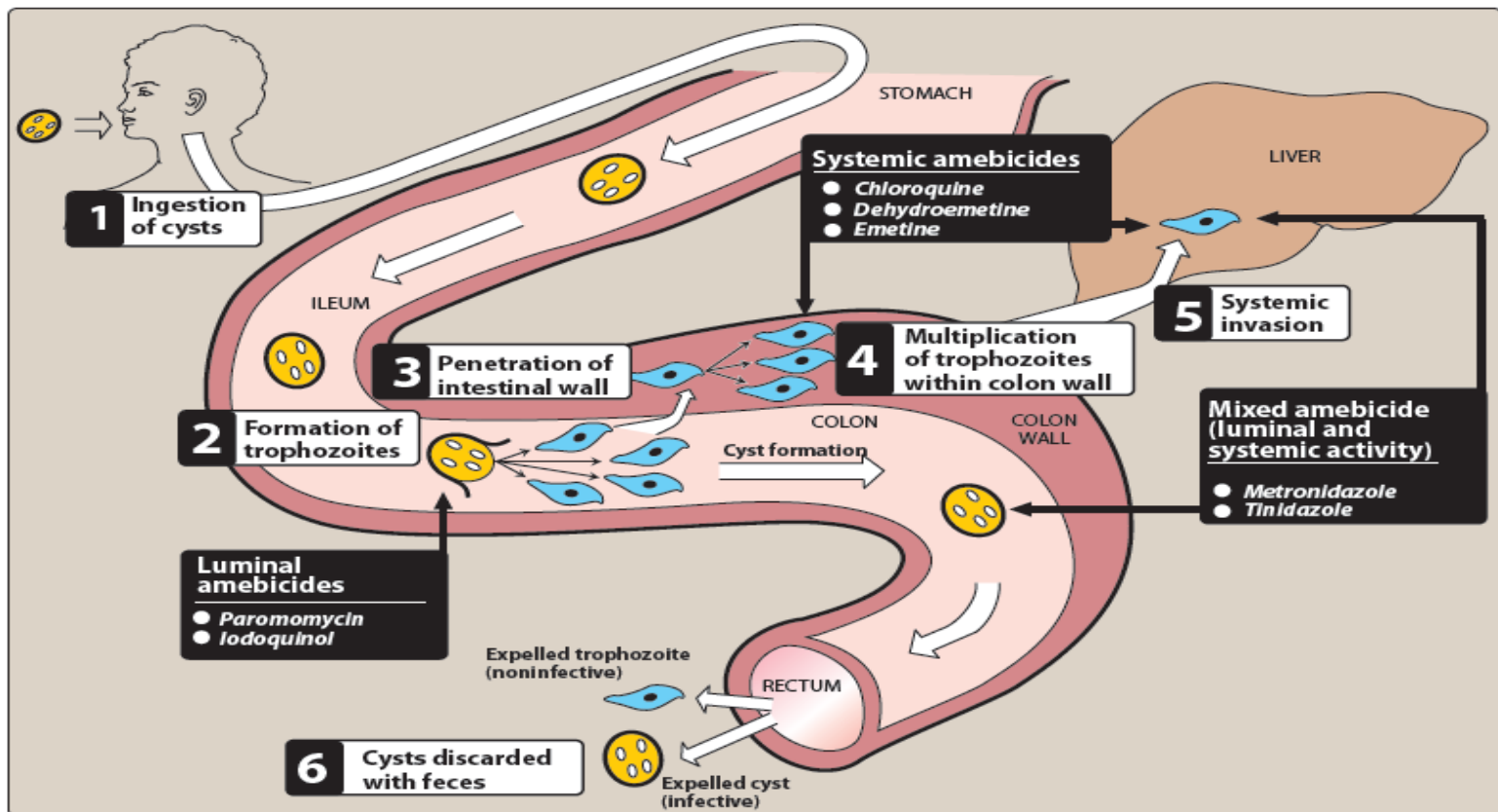
- Can survive **outside the** human body.
- When ingested, liberate **trophozoites** in the **lumen of the intestine**.

### **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**.
- In rectum, **trophozoites** transform to **cysts** and are excreted in feces.

## **The Cycle:**

1. Cysts ingestion in contaminated food or water.
2. Liberation of trophozoites in the colon.
3. Invasion & penetration of intestinal wall.
4. Multiplication of trophozoites within colon wall.
5. Systemic invasion to liver.
6. Cyst formation in rectum and excretion in feces.



## Treatment of Amebiasis

By Anti-Amebic drugs:

- A. ▪ **Luminal** Amebicides
- B. ▪ **Tissue (systemic)** amebicides
- C. ▪ **Mixed** Amebicides

### 1] Luminal Amebicides:

- Acts on the parasites in the lumen of the bowel.
- Used for treatment of **asymptomatic amebiasis** (carriers).

Drugs Include:

- A) **Diloxanide furoate**
- B) **Iodoquinol**
- C) **Antibiotics**

-Paromomycin  
-Tetracyclines  
-Erythromycin

**A) Diloxanide furoate:** Mechanism of action is unknown.

### Pharmacokinetics:

- Ester of **diloxanide + furoic acid**.
- Given **orally**. (all luminal amebicides are 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%)**.
- Direct amoebicidal action **against luminal forms**
- **Not active against trophozoites in intestinal wall or extra-intestinal tissues.**

Asymptomatic cyst carriers	<i>Iodoquinol</i> or <i>Paromycin</i> or <i>Diloxanide furoate</i>
Diarrhea/dysentery Extraintestinal	<i>Metronidazole</i> plus <i>Iodoquinol</i> or <i>Paromycin</i> or <i>Diloxanide furoate</i>
Amebic liver abscess	<i>Chloroquine</i> plus <i>Metronidazole</i> or <i>Emetine</i>

## Therapeutic Uses:

- **Drug of choice** for asymptomatic intestinal infection.
- For complete eradication of amebic infections given along with tissue amebicides.

## ADRs: (GIT as all luminal amebicides)

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

## Contraindications:

- Pregnancy.
- Children (less than 2 years).

## B) Iodoquinol:

### Pharmacokinetics:

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

## Therapeutic Uses:

- luminal amebicide for asymptomatic amebiasis

## ADRs:

- **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 <sup>131</sup>I uptake).

## Precautions:

- **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*).

## C) Antibiotics

### I. **Paromomycin Sulphate:**

### Pharmacokinetics:

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

## ADRs:

- **Gastrointestinal distress and diarrhea.**

## Contraindications:

- Severe **renal disease**
- patients with **GIT ulceration**

## II. 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**.
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## 2-Tissue (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 (intestinal wall infection or liver abscesses).

### Drugs Include:

- A. **Emetine**
- B. **Dehydroemetine**
- C. **Chloroquine (liver only)**

## A) Emetine & 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. (Not preferred)
- 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**.
- 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).

## Therapeutic 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**
- Pain at site of injection, abscesses.
- **GIT:** nausea, vomiting, diarrhea.
- **Serious toxicities:** **Cardiotoxicity, Hypotension, cardiac arrhythmias, heart failure**

## Contraindications:

- **Cardiac Disease.**
- **Renal Disease.**
- **Pregnancy.**
- **Young children.**

## B) Chloroquine:

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

## ADRs:

- **Pruritus** is common
- Nausea, vomiting, abdominal pain, anorexia.
- Blurring of vision.
- Hemolysis in G6PD deficient patients because of its oxidizing action
- Agranulocytosis.

## 3-Mixed Amebicides:

Effective against both luminal and systemic forms of the disease. Although **luminal concentration** is too low for single drug-treatment.

### Drugs Include:

- Metronidazole
- Tinidazole

## A) Metronidazole:

- Mixed amoebicide.
- Drug of choice for treating amebic infections (intestinal & Extra-intestinal).
- **Acts on trophozoites**.
- Has no effect on cysts.
- Nitro group of metronidazole is reduced by protozoan leading to cytotoxic reduced product that binds to DNA and proteins resulting into parasite death.

## Pharmacokinetics:

- Given **orally or IV**.
- Absorption is rapid and complete (Due to rapid absorption from GIT, *not reliably effective against luminal parasites*)
- **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 glucuronidation.
- Excreted in urine.
- Clearance is decreased in liver impairment

## Therapeutic 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.,
  - o Helicobacter pylori infection
  - o Pseudo-membranous colitis (*Clostridium difficile*)



## ADRs:

### GIT:

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

### CNS: Neurotoxicological effect

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

### Other:

- Dysuria, dark urine.
- Neutropenia (Abnormally low neutrophils)
- Disulfiram-like effect if taken with alcohol.

## Drug Interactions:

### Enzyme inhibitors (cimetidine, ketoconazole)

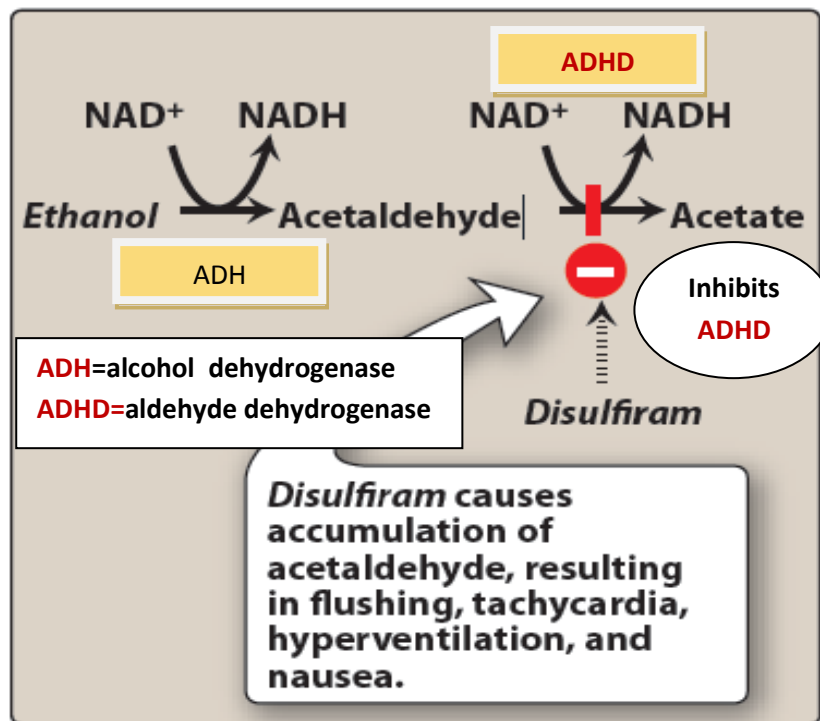
↑ increase duration of action of metronidazole

### Inducers (phenytoin and phenobarbitone).

↓ decrease duration of action of metronidazole

-Metronidazole inhibits CYP family 2C9 & 3A4 so

↑ increases anticoagulant effect of warfarin.  
↑ Increases lithium toxicity.



### Contraindications:

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

## B) Tinidazole:

- has similar activity to metronidazole BUT has longer duration of action (12-14h), a simpler dosing regimen (once a day) and a better toxicity profile than metronidazole.

# Treatment of Bacillary Dysentery

- Fluoroquinolones such as ciprofloxacin
- Cotrimoxazole (trimethoprim- sulfamethoxazole)

**Ciprofloxacin:** active against a variety of gram-positive and gram-negative bacteria. Block bacterial DNA synthesis.

### Therapeutic uses

- 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

**TOXICITY:** GIT, CNS and Tendon related (ciprofloxacin)

## Contraindicated:

- Children, pregnancy, nursing mother
- Epilepsy
- Arrhythmias.
- Should not be combined with antacids, divalent cations

## Summary

- **Maintaining fluid intake** (oral rehydration therapy or Intravenous fluid therapy) is important before treatment
- 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).
- Hepatic abscess : Metronidazole or chloroquine or emetine or dehydroemetine
- **Ciprofloxacin** is the drug of choice in bacillary dysentery.
- **Paromomycin, Tetracyclines, Erythromycin** are all antibiotics that also function as luminal amebicides.
- Both luminal amebicides **iodoquinol, and diloxanide** have unknown mechanism of action, taken orally, used in asymptomatic amebiasis, and conjugated to glucuronide
- **10% of Iodoquinol** enter circulation, and **90% of diloxanide** enters the circulation.
- **Tetracyclines** are Used in severe cases of amoebic dysentery not responding to **metronidazole combined with dehydroemetine**
- **Emetine** is an alkaloid derived from ipeca, 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**
- Given preferably **subcutaneously** but could be given by IM, **NEVER I.V.**
- Metabolized & Excreted slowly via kidney so they have a cumulative effect.
- **Dehydroemetine** is less toxic than **emetine**
- **Chloroquine**: Anti-malarial drug that is Used in combination with **metronidazole or dehydroemetine and luminal amebicide** for **amebic liver diseases**.
- **Metronidazole**: is the Drug of choice for treating amebic infections (intestinal & Extra-intestinal).
- Acts on **trophozoites**, Has no effect on cysts
- Has a **Disulfiram-like effect** if taken with alcohol.
- **Metronidazole** inhibits CYP family **2C9 & 3A4** so increases anticoagulant effect of **warfarin**, and **lithium toxicity**.
- **Tinidazole** is safer than **metronidazole**, and has a longer duration of action.
- Drugs that are contraindicated in renal disease: **Metronidazole, Emetine, Dehydroemetine, Paromomycin Sulphate**
- Drugs that are contraindicated in pregnancy: **Diloxanide furoate, Emetine & Dehydroemetine, Metronidazole**.