Protozoal infections

1. Amebiasis
2. Malaria
3. Giardiasis
4. Leshmaniasis
5. Toxoplasmosis
6. Trypanosomiasis
Protozoal infections

1. Protozoal cells (*Eukaryotes*) have metabolic processes closer to human host than prokaryotic bacterial pathogens.

2. Difficult to be treated than bacterial infections.

3. Many of antiprotozoal drugs cause toxic effects on the host.

4. Cells with high metabolic processes in the host are susceptible.

5. Examples: bone marrow stem, renal tubular, intestinal, neuronal cells.

6. Antiprotozoal are not safe during pregnancy.
Antiprotozoal Drugs

1. Chemotherapy for amebiasis
2. Chemotherapy for malaria
3. Chemotherapy for giardiasis
4. Chemotherapy for leshmaniasis
5. Chemotherapy for toxoplasmosis
6. Chemotherapy for trypanosomiasis
Fig. 46. — Amoebiasis. *E. histolytica*. Trophozoite with ingested erythrocytes to cysts. (From an original drawing by B. Jobling)
Amebiasis is an infection of the intestinal tract that occurs due to ingestion of foods or water contaminated with Entameba Histolytica cysts.
LIFE CYCLE

Entamoeba histolytica exists in two forms:

1. Cysts (infective):
   • can survive outside the human body.
   • transform to trophozoites.

2. Trophozoites (non-infective; invasive):
   • Reproduce
   • They may feed on intestinal bacteria or invade and ulcerate wall of large intestine, and may migrate to liver or other tissues.
   • transform to cysts which are excreted in feces.
Life Cycle

1. Cysts ingestion.
2. Formation of trophozoites
3. Penetration of intestinal wall
4. Multiplication of trophozoites within colon wall.
5. Systemic invasion.
6. Cyst formation in rectum and excretion in feces.
LIFE CYCLE

1. Ingestion of cysts

2. Formation of trophozoites

3. Penetration of intestinal wall

4. Multiplication of trophozoites within colon wall

5. Systemic invasion

Systemic amebicides:
- Chloroquine
- Dehydroemetine
- Emetine

Mixed amebicide (luminal and systemic activity):
- Metronidazole

Luminal amebicides:
- Diloxanide furoate
- Paromomycin
- Iodoquinol

6. Cysts discarded with feces

Expelled trophozoite (noninfective)

Expelled cyst (infective)
Clinical presentations

- Asymptomatic Intestinal infection (Carriers, passing cysts)
- Mild to moderate intestinal disease (Nondysenteric Colitis)
- Severe Intestinal infection (Dysentery)
- Hepatic abscess, ameboma (localized granulomatosus lesion of colon) and other extraintestinal disease
1. Intraluminal cysts
2. Intestinal wall trophozoites
3. Hepatic trophozoites
ANTIAMEBIC DRUGS

- Luminal Amebicides

- Tissue or systemic amebicides

- Mixed Amebicides
LUMEN AMOEBICIDES

- Acts on the parasites in the lumen of the bowl.
- used for treatment of asymptomatic amebiasis.

Include

- Diloxanide Furoate
- Iodoquinol
- Antibiotics
  - Paromomycin
  - Tetracyclines
  - Erythromycin
Tissue Amoebicides (systemic)

- acts on 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).

- Emetine
- Dehydroemetine
- Chloroquine (liver only)
Mixed amoebicides

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

- Metronidazol
- Tinidazole
METRONIDAZOLE

- Mixed amoebicide.
- Drug of choice for intestinal & extraintestinal amoebiasis.
- 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 protein binding is low (< 20%).
- Plasma half life is 8 h
Pharmacokinetics

- Metabolized in liver by mixed function oxidase followed by glucouridation.
- Excreted in urine as unchanged drug plus metabolites.
- Clearance is decreased in liver impairment.

Tinidazole has longer duration, simpler dosing regimen, better toxicity profile, than metronidazole, but is equally active.
Clinical Uses

- Extraluminal amoebiasis (combined with luminal amebicide).
- Giardiasis
- Trichomoniasis
- Broad spectrum of Anaerobic bacteria e.g.,
  - Helicobacter pylori infection
  - Pseudomembranous colitis (Clostridium difficile).
Adverse effects

1. GIT:

- Nausea
- Vomiting
- Dry mouth
- Metallic taste
- Diarrhoea
- Oral Thrush (Moniliasis, yeast infection).
Adverse effects

2. CNS: Neurotoxicological effect
   • Insomnia, dizziness
   • peripheral neuropathy, paresthesia
   • encphalopathy, convulsion (IV infusion, rare).

3. Dysuria, dark urine.

4. Neutropenia

5. Disulfiram-like effect if taken with alcohol.
disulfiram like effect

When metronidazole is given with alcohol abdominal distress, nausea, vomiting, flushing, or headache, tachycardia, hyperventilation, confusion

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<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Aldehyde</th>
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<tr>
<td>Dehydrogenase</td>
<td>Dehydrogenase</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td></td>
<td>Acetate</td>
</tr>
</tbody>
</table>
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**Drug interactions:**

- **Enzyme inhibitors (cimetidine, ketoconazole)** increases half life of metronidazole
- **Inducers (phenytoin and phenobarbitone)** increase elimination.
- inhibits CYP family 2C9 & 3A4
- Potentiate anticoagulant effect of warfarin.
- potentiates lithium toxicity.
- disulfiram (confusional & psychotic states)
CONTRAINDICATIONS / PRECAUTIONS:

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

Chemistry:

- Emetine hydrochloride is a plant alkaloid derived from ipeca.
- Dehydroemetine is a synthetic analogue

Pharmacokinetics:

- Erratic oral absorption.
- Given preferably subcutaneously but could be given by IM, NEVER I.V.
- Plasma half life is 5 days.
**EMETINE**

- Concentrated in Liver, Lungs, Spleen, Kidney, Cardiac muscle and Intestinal wall.
- Metabolized & Excreted slowly via kidney so it has 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).
Mechanism

- Act on tissue trophozoites causing irreversible block of protein synthesis.
Adverse Effects

- Dehydroemetine is less toxic than emetine
- pain at site of injection, abscesses.
- **GIT:** nausea, vomiting, diarrhoea.
- Neuromuscular weakness
- **Serious toxicities:** cardiototoxicity
  - cardiac arrhythmias,
  - Hypotension
  - heart failure
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).
Contraindications

- Heart disease
- Kidney disease
- Pregnancy
- Children
Chloroquine

- Antiamebic drug
- Antimalarial drug
- Used in combination for amebic liver diseases
- Followed by luminal amebicide.
Luminal amoebicides

- acts on the luminal parasites
- used for treatment of asymptomatic amebiasis.

Include

Diloxanide Furoate

- Iodoquinol

Antibiotics
- Tetracyclines
- Paromomycin
- Erythromycin
Diloxanide furoate

Chemistry

- Ester of diloxanide + furoic acid.

Pharmacokinetics

- Given orally.
- Split in the intestine, (90%) diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine.
- The unabsorbed diloxanide is the amoebicidal agent (10%).
Pharmacodynamics:

- Unknown mechanism of action
- Direct amoebicidal action against luminal forms.
- Not active against trophozoites in intestinal wall or extraintestinal tissues.
Therapeutic Uses

- Drug of choice for asymptomatic Intestinal infection
- For eradication of infection given along with all forms of amebiasis.
- Dose: 500 mg three times/day for 10 days.
Adverse Effects

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

Contraindications:
- Pregnancy
- Children (less than 2 years).
Paromomycin Sulphate

- Aminoglycoside, not absorbed.
- Effective against luminal forms of ameba

**Mechanism of action**

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

- Orally
- Not significantly absorbed from the GIT
- 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
**Tetracyclines**

- Very weak direct amoebicidal action.
- Mainly act *indirectly* on bacterial flora.
- Used in severe cases of amoebic dysentery not responding to metronidazole combined with dehydroemetine.
HALOGENATED HYDROXYQUINOLINES

- Iodoquinol
- Cliquinol

**Mechanism of action**

- Unknown
- Effective against organisms in GIT only Not intestinal wall or liver.

**Pharmacokinetics**

- Absorption is poor (90%), excreted in feces.
- 10% enter circulation, excreted as glucourononide in urine.
- Half life is 11-14 h
Uses

- lumen amoebicide.
- For eradication of infection given along with tissue amoebicide (metronidazole).
Adverse Effects

- Peripheral neuropathy including optic neuritis
- GIT: Nausea, vomiting, diarrhoea.
- Enlargement of the thyroid gland.
- Agranulocytosis.
- Iodine sensitivity.
- Drug interfere with thyroid function tests (increase protein-bound serum iodine thus decrease in measured $^{131}$I uptake).
Contraindications

- Optic neuropathy
- Thyroid disease
- Sensitivity to iodine
- Severe kidney disease
- **discontinued** if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever)
<table>
<thead>
<tr>
<th>Luminal amebiasis</th>
<th>Dilocanide furoate, iodoquinol paromomycin,</th>
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<tbody>
<tr>
<td>Mild-moderate intestinal infection</td>
<td>Metronidazole + luminal amebicide</td>
</tr>
<tr>
<td>Severe intestinal infection</td>
<td>Metronidazole + luminal amebicide, dehydroemetine + luminal amebicide</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>Metronidazole or dehydroemetine or chloroquine plus luminal amebicide</td>
</tr>
<tr>
<td>CLINICAL SYNDROME</td>
<td>DRUG</td>
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<td>---------------------------</td>
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<tr>
<td>Asymptomatic cyst carriers</td>
<td>Iodoquinol or Paromycine or Diloxanide furoate</td>
</tr>
<tr>
<td>Diarrhea/dysentery</td>
<td>Metronidazole plus Iodoquinol or Paromycine or Diloxanide furoate</td>
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<tr>
<td>Extraintestinal</td>
<td></td>
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<tr>
<td>Amebic liver abscess</td>
<td>Chloroquine plus Metronidazole or Emetine</td>
</tr>
<tr>
<td>Clinical Setting</td>
<td>Drugs of Choice and Adult Dosage</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 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         | 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) |
| extraintestinal disease                     |                                                                                                     |                                     |