CHEMOTHERAPY OF AMOEBIASIS AND GIARDIASIS

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AMOEBIASIS

- Infection occurs when mature cysts are ingested and pass into the colon where they divide into trophozoites; these forms either enter the tissues or reform cysts. Amoebiasis occurs in two forms, both of which need treatment.
Bowel lumen amoebiasis is asymptomatic and trophozoites (noninfective) and cysts (infective) are passed into the faeces. Treatment is directed at eradicating cysts with a luminal amoebicide; diloxanide furoate is the drug of choice; iodoquinol or paromomycin is sometimes used.
• Tissue – invading amoebiasis gives rise to dysentery, hepatic amoebiasis and liver abscess.

• A systemically active drug (tissue amoebicide) effective against trophozoites must be used, e.g. metronidazole, tinidazole. Parenteral forms of these are available for patients too ill to take drugs by mouth. In severe cases of amoebic dysentery, tetracycline lessens the risk of opportunistic infection, perforation and peritonitis when it is given in addition to the systemic amoebicide.
• Treatment with tissue amoebicides should always be followed by a course of a luminal amoebicide to eradicate the source of the infection
CHEMICAL CLASSIFICATION

• Emetine group: eg. Emetine, dehydroemetine and its resinate
• Imidazole derivatives: Metronidazole, tinidazole, secnidazole
• Quinoline derivatives: Halogenated hydroxyquinolones: Diiiodohydroxyquinoline, iodochlorohydroxyquinoline
• 4-aminoquinolines: Chloroquine
• Antibiotics: Tetracyclines, paromomycin
• Miscellaneous: Diloxanide furoate
EMETINE

• Emetine is an alkaloid obtained from ipecac, the root of the plant Cephalis ipecacuanha
ANTIAMOEBIC ACTION

• The drug inhibits protein synthesis. Trophozoites affected by emetine show degeneration of the nucleus and reticulation of the cytoplasm. This arrests their multiplication and leads to their phagocytosis.
ABSORPTION, FATE AND EXCRETION

- Administered by deep IM injection
- **Adverse reactions**: The major drawback of emetine is its high toxicity
LOCAL REACTION

- Local pain, tenderness, stiffness and weakness of the muscles, and rarely an abscess
GI SYSTEM

• Nausea, vomiting, diarrhoea, headache, dizziness and prostration are common
CARDIOVASCULAR SYSTEM

• Tachycardia, precordial pain, hypotension, myocarditis and pericarditis. The ECG offers an early index of cardiotoxicity.
MISCELLANEOUS

• Emetine should be avoided in patients with cardiac or renal damage, in pregnant women, in old people and in young children
THERAPEUTIC USES

• Besides its use in amoebiasis, emetine may be used in paragonimus westermanii (lung fluke) and Fasciola hepatica infestations
DEHYDROEMETINE

• This semisynthetic drug, claimed to be less toxic than emetine, has similar toxicity and applications as emetine.
METRONIDAZOLE

• It is converted into an active form by reduction of its nitro group, this binds to DNA and prevent nucleic acid formation; it is bacteriostatic.

• Pharmacokinetics: metronidazole is well absorbed after oral or rectal administration and distributed to achieve sufficient concentration to eradicate infection in liver, gut wall and pelvic tissues. It is eliminated in the urine, partly unchanged and partly as metabolites. Half life is 8 H.
USES

- Metronidazole is active against a wide range of anaerobic bacteria and also protozoa. Its clinical indications are:

- Treatment of sepsis to which anaerobic organisms, eg. Bacteroides spp. and anaerobic cocci, are contributing, notably postsurgical infection, intra-abdominal infection and septicemia, but also wound and pelvic infection, osteomyelitis and abscesses of brain or lung.
• Antibiotic – associated pseudomembranous colitis (caused by Clostridium difficile)
• Trichomoniasis of the urogenital tract in both sexes
• Amoebiasis (Entamoeba histolytica), including both intestinal and extra-intestinal infection
• Giardiasis (Giardia lamblia)
• Acute ulcerative gingivitis and dental infections
• Anaerobic vaginosis
• Dose: 400mg 8-hourly; by i.v infusion 500mg 8-hourly.

• A topical gel preparation is useful for reducing the odour associated with anaerobic infection of fungating tumours.
ADVERSE EFFECTS

• Include nausea, vomiting, diarrhoea, furred tongue and an unpleasant metallic taste in the mouth; also headache, dizziness and ataxia. Rashes, urticaria and angioedema occur. Peripheral neuropathy occurs if treatment is prolonged and epileptiform seizures if the dose is high.

• A disulfiram-like effect occurs with alcohol because metronidazole inhibits alcohol and aldehyde dehydrogenase; patients should be warned appropriately.
TINIDAZOLE

• It is similar to metronidazole but has a longer t½ (13h). It is excreted mainly unchanged in the urine. The indications for use and adverse effects are essentially those of metronidazole. The longer duration of action of tinidazole may be an advantage, e.g. in giardiasis, trichomoniasis and acute ulcerative gingivitis, in which tinidazole 2 g by mouth in a single dose is as effective as a course of metronidazole.
SECNIDAZOLE

• This nitroimidazole has a longer half life
• Single dose of 2 gm
ORNIDAZOLE (Ornizen)

• Is a newer imidazole with similar properties as secnidazole
• It is available as 500 mg tablets
QUINOLINE DERIVATIVES

- They act by direct contact with the trophozoites of E. histolytica.
DIIOODOHYDROXYQUINOLINE

- Effective luminal amoebicide
- Absorption, fate and excretion: Diiodohydroxyquinoline is insignificantly absorbed from the intestinal tract and 90% of it is detected in feces.
- Adverse reactions: These are mild and uncommon.
- It is contraindicated in patients with iodine intolerance
- Preparations and dosage: Di-iodohydroxyquinoline tablet 300mg. Dose: 600mg- Thrice daily for 15 days.
IODOCHLOROHYDROXYQUINOLINE

- More useful in cyst carriers. It is not much absorbed from the GI tract and owes its antiamoebic action to a local effect. It has antibacterial, antifungal and antitrichomonal actions.

- Adverse reactions: These are usually mild (subacute Myelo-optic Neuropathy-SMON) has been reported in patients receiving this drug over prolonged periods.

- Larger doses should be avoided
THERAPEUTIC USES

• Besides its use in amoebiasis, it is also used topically in fungal infections of the skin. The major disadvantage of topical application is yellow staining of clothes and linen.

• CHLOROQUINE: Given orally, it is completely absorbed and concentrated in the liver.
**TETRACYCLINE**

- Tetracycline in large doses, probably acts in vivo by altering the intestinal bacterial flora and creating a medium unfavourable for the growth of amoebae. It may be administered in the dose of 0.25g. 6 hourly for 10-15 days, in combination with metronidazole to treat amoebic liver abscess particularly when bacterial co-infection is suspected.
- Paromomycin rarely used.
DILOXANIDE FUROATE

• This potent direct amoebicidal drug is mainly effective in chronic intestinal amoebiasis, in cyst passers and partially useful in mild acute cases.

• Given orally it is hydrolysed to diloxanide which is partly absorbed. Nonabsorbable portion acts as a luminal amoebicide. The drug is well tolerated, safe and almost non-toxic.
KURCHI

• Kurchi consists of the dried stem bark of Holarrhena antidysenterica. Kurchi has mild antiamoebic activity and is useful only in mild intestinal amoebiasis. It produces nausea and vomiting but is otherwise well tolerated.
MANAGEMENT OF AMOEBIASIS

• Amoebiasis, in general, is a difficult disease to treat because of its tendency to chronicity and the inability of various drugs to eradicate the cystic forms of the parasite completely.
ACUTE INTESTINAL AMOEBIASIS

• Metronidazole in the dose of 600 – 800mg tds for 5-7days is the treatment of choice.
• Almost 90% of patients with moderate amoebic dysentery respond clinically to oral metronidazole therapy. Severe cases may need IV metronidazole or IM emetine. The symptoms are relieved within 24hrs.
ACUTE INTESTINAL AMOEBIASIS

- Additional advantage of this drug is its effectiveness in hepatic amoebiasis which can never be entirely excluded in any case of amoebic dysentery.
- Metronidazole therapy should be followed by a course of a luminal amoebicide to ensure a cure.
• Emetine is a valuable agent for rapidly controlling the symptoms of severe infection. However its usefulness is limited by its cardiotoxicity.

• In patients presenting with fulminating amoebic colitis with toxic symptom, it is advisable to use oral tetracycline in addition.
ASYMPTOMATIC CYST PASSERS AND CHRONIC INTESTINAL AMOEBIASIS

- Diloxanide furoate 500mg 3 times daily for 10 days.
- A combination of diiodohydroxyquinoline 1.8gm daily and tetracycline 1gm daily in divided doses for 10 days.
- Chronic amoebic colitis is sometimes difficult to treat and usually more than one drug given in rotation.
HEPATIC AMOEBIASIS

- Metronidazole is the drug of choice.
- Emetine hydrochloride and chloroquine diphosphate are also effective.
- Surgical intervention may be necessary in amoebic liver abscess.
- The treatment should be followed by a course of a luminal amoebicide.
PREVENTION

• The cysts, responsible for propagation of the disease, are resistant to the agents routinely used to purify water. Chlorine, in the concentration employed to purify water, fails to kill them. It is, therefore, necessary to avoid fecal contamination of water by sanitary disposal of feces. Fly control and detection and treatment of carriers is equally important. The surest way to eliminate cysts from water is to boil it. There is no effective prophylactic therapy
GIARDIASIS

• Giardia lamblia is a flagellate protozoan parasite of the small intestine. Like E. histolytica, it has no animal host and is transmitted from man to man by fecal contamination of food and water.

• It can cause diarrhoea, anorexia, nausea, vomiting, abdominal pain and weight loss.

• Both the cysts and trophozoites may be found in the stools. Giardiasis is quite common and often exists in association with E. histolytica infection.
• Metronidazole is the drug of choice in giardiasis.
• It is given in the dose of 200mg tds for 5 days in adults and 15mg/kg/day in 3 divided doses for 5 days in children.
NITAZOXANIDE

• It is a prodrug which, after absorption, gets converted to an active metabolite, tizoxanide. It is effective against metronidazole resistant stains of G.lamblia.

• Adverse effects are mild G.I disturbances.

• Dose: Children 100-200mg bd for 3 days it also acts against E.histolytica, cryptosporidium parvum and H.pylori.

• Other drugs used are tinidazole, 2gm single dose, furazolidone (100mg qid for 7 days), mepacrine and paramomycin.
CHEMOTHERAPY OF OTHER PROTOZOAL INFECTIONS

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<tr>
<th>INFECTION</th>
<th>DRUG &amp; COMMENT</th>
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<tr>
<td>Leishmaniasis visceral</td>
<td>Sodium stibogluconate or meglumine antimoniate; resistant cases may benefit from combining antimonials with allopurinol, pentamidine, paramomycin or amphotericin (including AmBisome)</td>
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<td>Cutaneous</td>
<td>Mild lesions heal spontaneously, antimonials may be injected intralesionally.</td>
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<td>Toxoplasmosis</td>
<td>Most infections are self-limiting in the immunologically normal patient. Pyrimethamine with sulfadiazine for chorioretinitis, and active toxoplasmosis in immunodeficient patients; folinic acid is used to counteract the inevitable megaloblastic anemia.</td>
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</tbody>
</table>
Alternatives include pyrimethamine with clindamycin or clarithromycin or azithromycin spiramycin for primary toxoplasmosis in pregnant women. Expert advice is essential.

<p>| Trichomoniasis | Metronidazole or tinidazole is effective. |</p>
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<tr>
<th>Trypanosomiasis African (sleeping sickness)</th>
<th>Suramin or pentamidine is effective during the early stages but not for the later neurological manifestations for which melarsoprol should be used. Eflornithine is effective for both early and late stages. Expert advice is recommended.</th>
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<td>American (Chaga’s disease)</td>
<td>Prolonged (1-3 months) treatment with benznidazole or nifurtimox may be effective.</td>
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• Leishmaniasis is an infection with protozoan organism of the genus Leishmania. It exists in three main forms, visceral leishmaniasis or kalaazar, cutaneous leishmaniasis localized largely in South America and hence termed American leishmaniasis.
VISCERAL LEISHMANIASIS OR KALA-AZAR

• This form of the disease, produced by multiple species of Leishmania donovani and transmitted by Phlebotomus sandflies, is characterized by hepatosplenomegaly, irregular fever, anemia, leukopenia and hyperglobulinemia.

• In India, it is mostly confined to Assam, Bihar, Orissa and Bengal.
• The treatment of leishmaniasis is still disappointing. The drugs available are:

1. Pentavalent antimony compounds: Sodium stibogluconate and Meglumine antimononate

2. Diamidine derivatives: Dihydroxystibamidine isethionate and pentamidine isethionate.

• **Pentavalent antimony compounds**: their efficacy in vivo suggests their reduction into trivalent antimony compounds in the body.

• **Sodium stibogluconate**: Most preferred for the treatment of leishmaniasis. It acts by both suppressing glycolysis and fatty acid metabolism and by diminishing the net generation of ATP and GTP in the amastigotes. Leishmania can develop resistance to antimonials.
ADVERSE REACTIONS

- Metallic taste in mouth, nausea, vomiting, diarrhoea, giddiness, delirium, a considerable rise or fall in body temperature, muscular pain, jaundice. Hematuria, blood dyscrasias, cardiac toxicity and sudden death may occur.
DIAMIDINE DERIVATIVES

• These drugs are more potent but more toxic.
• Reserved for cases resistant to antimonials chemotherapy.
• They are also useful for prophylaxis against T.gambiense and in the treatment of early Gambian and Rhodesian trypanosomiasis.
PENTAMIDINE

• Two pentamidine salts are available, isethionate (Pentamidine) and mesylate.
• Administered IM
• It is concentrated in the liver and very little gets into the brain tissue.
• It interferes with amino acid transport, disrupts the mitochondria and inhibits the transformation of amastigotes to promastigotes.
ADVERSE REACTIONS

• It may cause local irritation, breathlessness, nausea, vomiting, facial flushing, pruritus, tachycardia, arrhythmia, and hypotension. The systemic toxicity includes hepatotoxicity, leukopenia, thrombocytopenia, acute renal failure, and hypocalcemia.

• About 5% of patients may develop insulin-dependent diabetes mellitus during therapy.
THERAPEUTIC USES

• Visceral leishmaniasis and mucocutaneous leishmaniasis resistant to pentavalent antimony therapy are treated with a course of pentamidine or amphotericin B.
• **Therapy of pneumocystis carinii pneumonia**: Although cotrimoxazole is highly effective in P. carinii pneumonia, its increased toxicity in patients with AIDS makes some physicians prefer pentamidine. It is also used for prophylaxis.

• **Trypanosomiasis**
MILTEFOSINE

• Originally developed as an antineoplastic agent, has recently been reported to be highly effective orally in visceral and cutaneous leishmaniasis. It is a phosphocholine derivative and probably acts by interfering with cell signaling pathways.
ORIENTAL SORE

- This condition is caused commonly by *Leishmania tropica*.
- More severe cases require local as well as systemic antimonial therapy.
AMERICAN MUCOCUTANEOUS LEISHMANIASIS

- It is caused by Leishmania brasiliensis.
- Treatment is similar to that of visceral Leishmaniasis.
- Amphotericin B is perhaps the best alternative.
TRYPANOSOMIASIS

• 1. African trypanosomiasis or sleeping sickness caused by Trypanosoma gambiense transmitted by tse-tse flies.

• 2. South American trypanosomiasis caused by Trypanosoma cruzi transmitted by blood sucking Reduviid bugs.
SURAMIN SODIUM

- Now been replaced by pentamidine
PENTAMIDINE ISETHIONATE

- This drug may serve as a substitute for suramin
MEL B (MELARSOPROLOL)

- Effective in the early and the late meningoencephalitic stages of trypanosomiasis
- Mel B is contraindicated in severely debilitated patients and in those with hepatic and/or renal damage.
MELARSONYLYL POTASSIUM (MEL W, TRIMELARSON)

• This water soluble derivative of Mel B is given as 5% solution, by IM injection.
NITROFURAZONE (FURACIN)

• The drug has been employed for trypanosomiasis in patients who have relapsed after other forms of treatment.
EFLORNITHINE HYDROCHLORIDE

• High cure rates in late stages of gambian trypanosomiasis. It is an irreversible inhibitor of synthesis of polyamines required for cell division and differentiation.
• It is teratogenic.
• Eflorinthine cream has been found useful in reducing the rate of growth of facial hair in women.
TOXOPLASMOSIS

• Pyrimethamine, a DHF reductase inhibitor, is given orally.
• The regimen recommended in affected, pregnant women is spiramycin.
TRICHOMONIASIS

• Trichomonas vaginalis is the infectious protozoan most commonly associated with vulvovaginitis during reproductive years.