Pharmacology of antiprotozoal drugs

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Parasitic protozoa

- **Protozoa** are unicellular organisms that are widely differ in their modes of locomotion, reproduction, and habitat.
- **Parasitic protozoa**: unicellular microorganisms that **live inside other organisms (hosts)** for nutrition and shelter, causing diseases ranging from mild to sever
- Can multiply **sexually** or **asexually** within hosts, often having complex life cycles.
- **Transmission:**
- Often fecal-oral (contaminated food/water)
- vector-borne (insect bites)
- Via sexual contact.

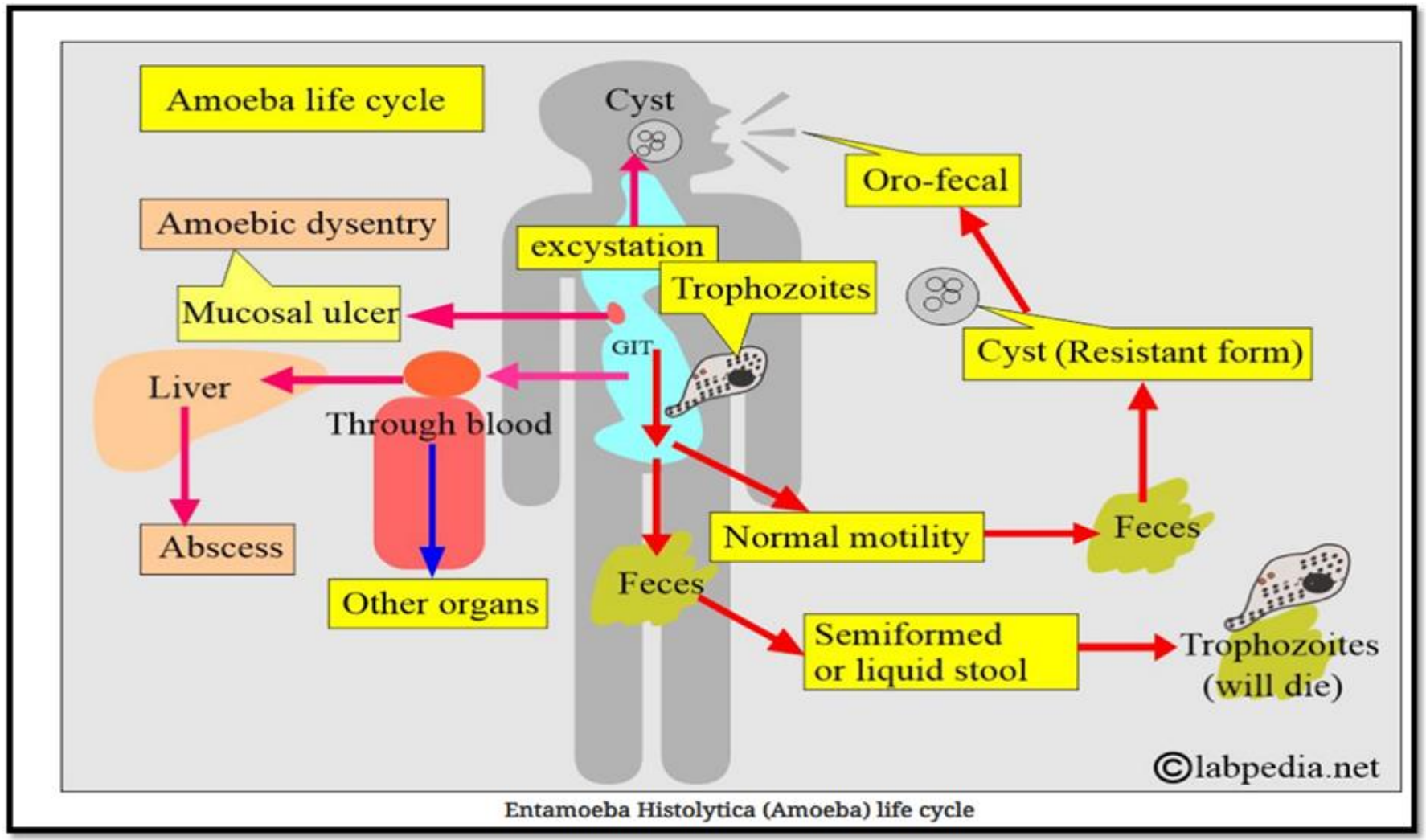
Classification of protozoa

Sarcodina
- Entamoeba

Flagellata
- Leshmania
- Giardia
- Trichomonas

Sporozoa
- Plasmodium
- Toxoplasma

Life Cycle (Entamoeba histolytica)



Entamoeba Histolytica (Amoeba) life cycle

Life cycle of entamoeba histolytica

- **Trophozoite:** active invasive stage
- **Cyst:** infective stage that (survival outside the host and transmission)

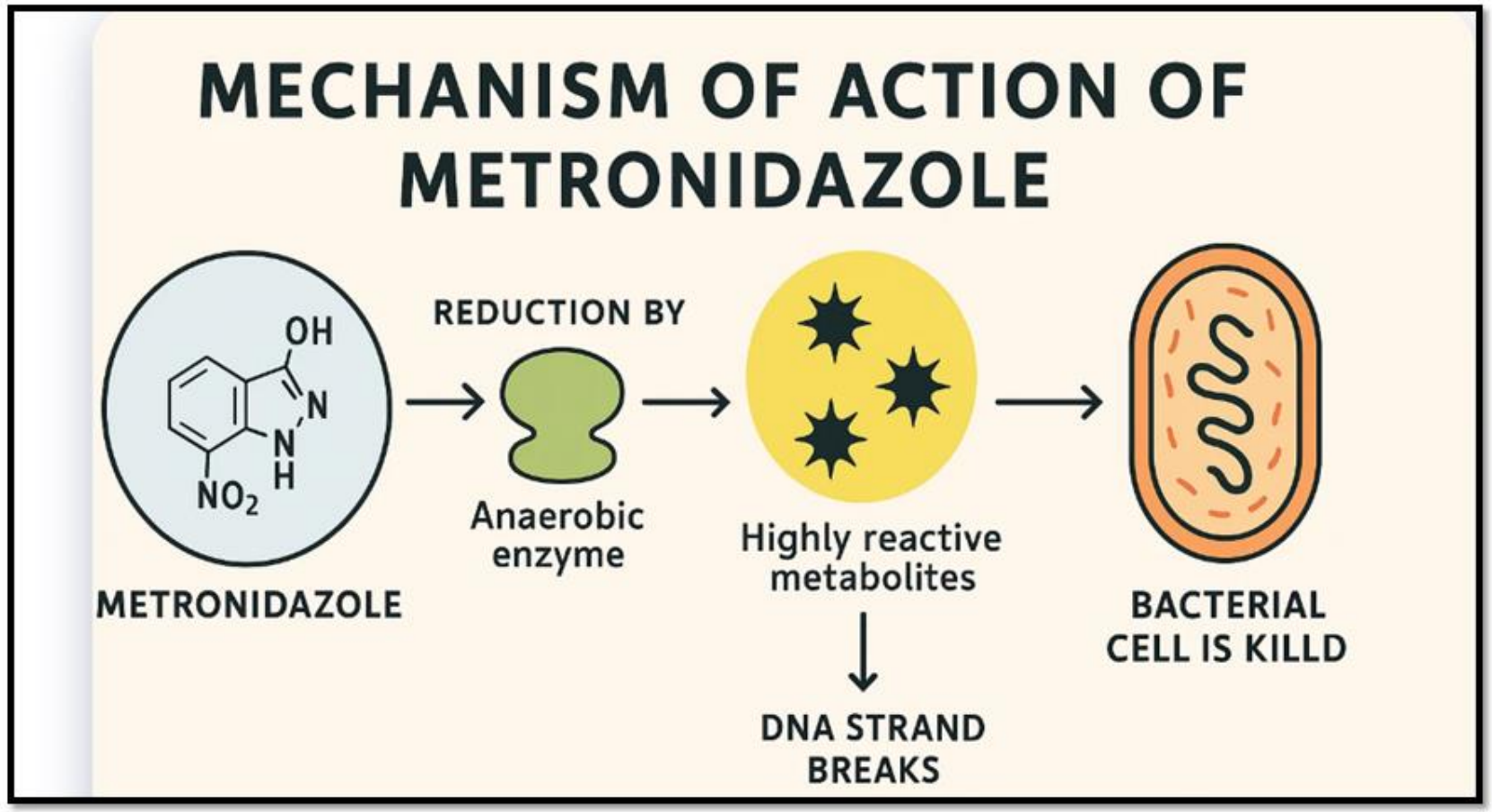
Classification of antiamebic drugs

Class	Site of action	examples
**Luminal Amebicides	Intestinal lumen (effective against cysts and trophozoites)	▪ **Diloxanide furoate** ▪ Paromomycin
Tissue Amebicides	Intestinal wall and extraintestinal tissues (e.g., liver) (**NOT cysts**)	▪ **Metronidazole** ▪ Tinidazole
Mixed Amebicides	Both intestinal lumen and tissues (**NOT cysts**)	▪ Metronidazole ▪ Tinidazole ▪ Ornidazole

Metronidazole (Flagyl)

- **First-line treatment** for **symptomatic**, **invasive amebiasis**, including amebic colitis and liver abscess.
- It kills the active E. histolytica trophozoites in the tissues and intestinal lumen but is **NOT** effective against cysts in the intestinal lumen.
- Therefore, a course of metronidazole should be followed by a **luminal amebicide (diloxanide furoate) to ensure the infection is fully eradicated and to prevent recurrence.**
- **Mechanism of action:**
- Passing into microorganisms, where its **nitro group** is **reduced by enzymes (ferredoxin)**, **creating toxic free radicals** that **damage DNA,** leading to **inhibition of nucleic acid synthesis and cell death**.
- it's a **prodrug** activated only in low-oxygen environments, making it selectively effective **against anaerobes**.

Mechanism of action of metronidazole



Indications of mertonidazole

- **Anaerobic Bacterial Infections: combined with other antibiotics for mixed infections**
- Meningitis and brain abscesses
- Dental and oral infections
- Pneumonia and lung abscess
- Peritonitis
- Prevent post-operative infections, particularly in colorectal surgery.
- Pelvic inflammatory disease.
- **Clostridium difficile (C. diff) colitis**: for mild-to-moderate cases.
- **Helicobacter pylori (H. pylori) infection** (microaerophilic): Part of a multi-drug regimen for peptic ulcers.
- **Protozoal Infections:**
- Amebiasis, including intestinal amebiasis and amebic liver abscess.
- Giardiasis.
- Trichomonas.

ADRs of metronidazole

- **Common ADRs:**
- **GIT**: Nausea, vomiting, diarrhea, and loss of appetite.
- **Taste and oral changes**: A sharp, unpleasant metallic taste OR furry or swollen tongue (hypertrophy of filiform papillae).
- Headache and dizziness.
- **Serious ADRs (Rare): require immediate medical care.**
- Peripheral neuropathy, optic neuropathy, seizures
- Stevens-Johnson syndrome (**especially if combined with mebendazole**).
- Sever allergic reaction (angioedema)
- Administered with caution in Pregnancy and breastfeeding

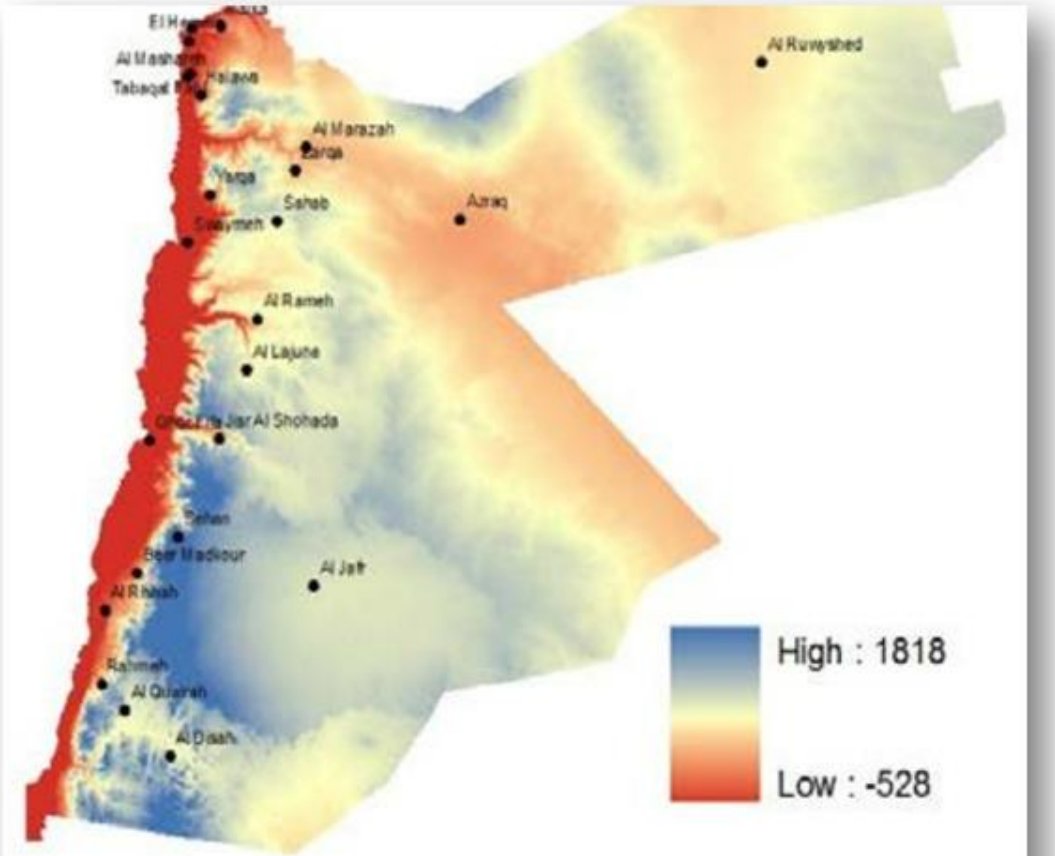
Paromomycin, Diloxanide furoate & Tinidazole

- **Paromomycin:**
- An aminoglycoside
- It is **poorly absorbed** from the gastrointestinal tract.
- **Mechanism of Action**: It kills bacteria (bactericidal) and parasites by binding to the 30S ribosomal subunit and inhibiting protein synthesis.
- **Uses:** Intestinal Amebiasis, hepatic Coma (hepatic Encephalopathy), Leishmaniasis
- **Diloxanide furoate:**
- **Mechanism of Action**: it is a **prodrug** that is hydrolyzed in the gut to its active form, diloxanide.
- Its exact mechanism is unknown, it is thought **to inhibit protein synthesis in the amoeba, thus destroying the trophozoites and preventing the formation of cysts**.
- **Tinidazole**:
- **Uses**: trichomoniasis, giardiasis, and amebiasis
- **Its mechanism of action similar to mertonidazole**

Leishmaniasis

- **Forms of Leishmaniasis:**
- **1- Cutaneous** (skin sores/ulcers) most common
- **2- Visceral** affects internal organs, most sever/fatal if untreated (kala-azar)
- **3- Muco-cutaneous** (sever sores in nose, mouth, throat, potentially disfiguring).
- **Leishmaniasis (specifically Cutaneous Leishmaniasis - CL) is endemic in Jordan**, with a significant public health concern, especially in rural areas like the Jordan Valley, southern regions, and highlands
- Leishmania major and Leishmania tropica are the common causative agents
- **Southern Jordan**: Historically recognized as an endemic region

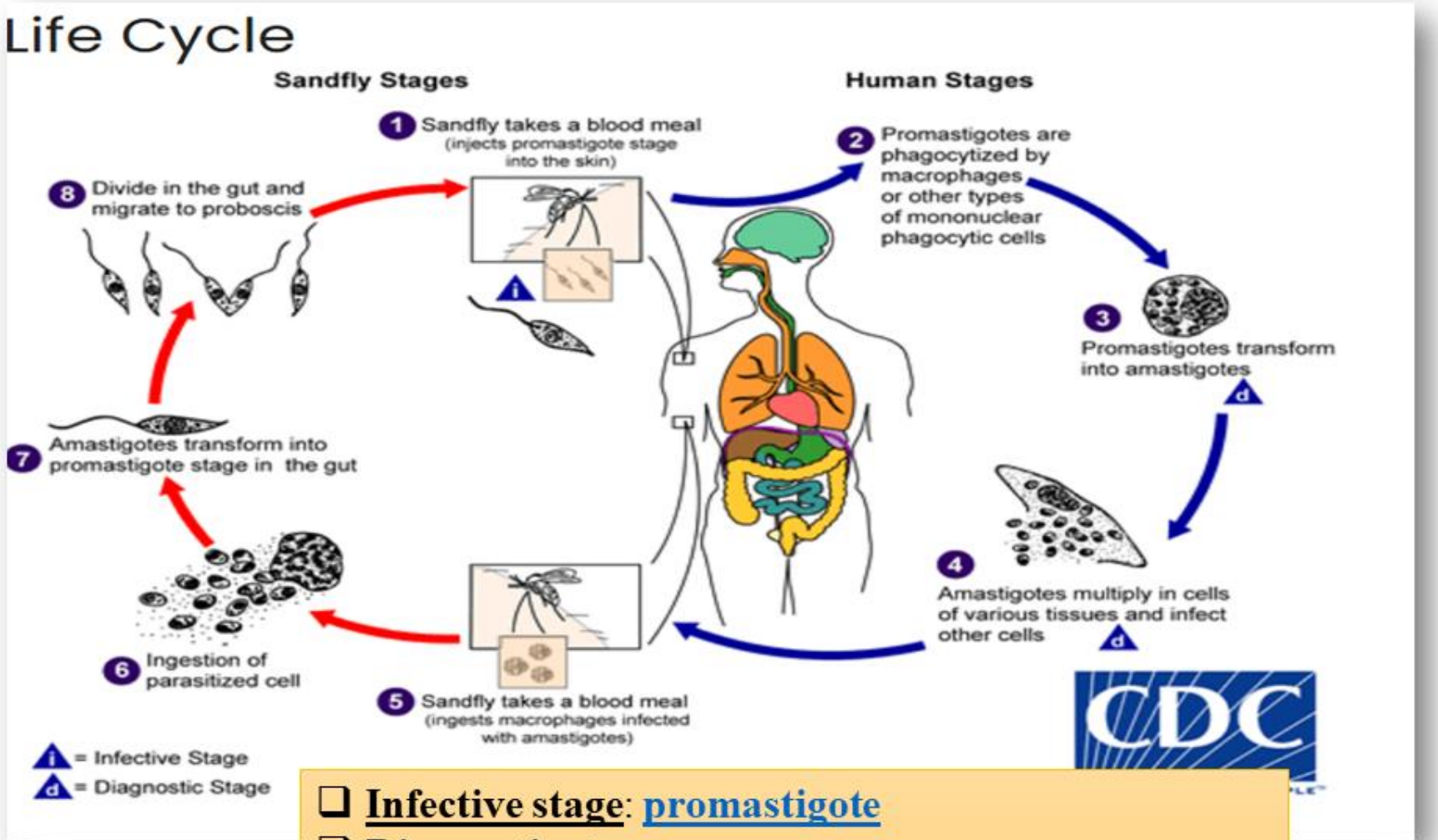
Endemic areas to leishmaniosis in Jordan



Map of Jordan showing localities from which sand flies were collected

Sand fly

Leishmania life cycle



- **Infective stage**: promastigote
- **Diagnostic stage**:

Amastigote: the form living inside human macrophages

Drug therapy of leshmaniasis

Drug	Mechanism of action	Indications	ADRs
Liposomal Amphotericin B (L-AmB)	▪ liposomal encapsulation minimizing systemic toxicity to the host ▪ AmB is released from the liposome, binds to ergosterol in the parasite's cell membrane, forms pores, causes leakage of ions (like K+, Na+), and parasite death	1- First-line (IV) for Visceral Leishmaniasis (VL) 2- Alternative for Cutaneous (CL) and Mucosal form 3- Fungal infections	▪ large size of the liposomes prevents their easy filtration through the kidneys minimizing the risk of nephrotoxicity, a major side effect of the conventional form ▪ **Infusion-Related**: fever, chills, nausea, vomiting, tachycardia ▪ **Systemic:** nephrotoxicity, hypokalemia, suppression of erythropoiesis (anemia)
***Miltefosine**	Disruption of lipid metabolism , triggers apoptosis	▪ VL ▪ CL ▪ Mucosal Leishmaniasis ▪ (oral)	▪ **Common and mild:** GIT upset **Less common and serious**: teratogenic ≠ pregnancy , lactation ▪ Disorders of fertility in males and females ▪ Impairment of liver and kidney functions
Paromomycin	inhibition of protein synthesis by binding to the parasite's ribosomes	(IM/IV) for VL and CL, often combined with Miltefosine	▪ Ototoxicity ▪ Nephrotoxicity
Pentamidine	▪ Disruption of mitochondrial function ▪ Inhibition of nucleic acid (DNA and RNA) synthesis ▪ Inhibition of protein and phospholipid synthesis.	Alternative, usually for VL	▪ Highly toxic drug used as a second-line treatment for leishmaniasis: ▪ Sever hypoglycemia, hypotension, hepatic and renal impairment

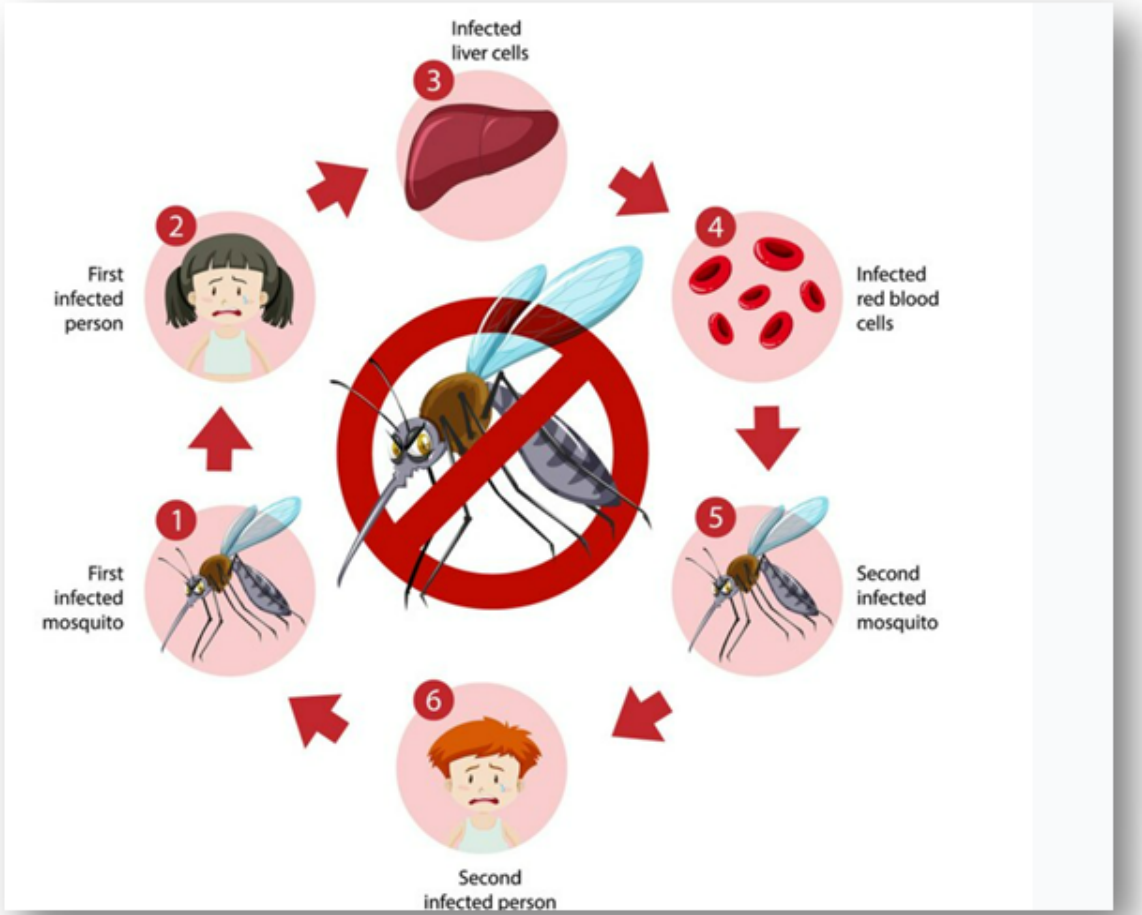
Treatment approach to leshmniasis

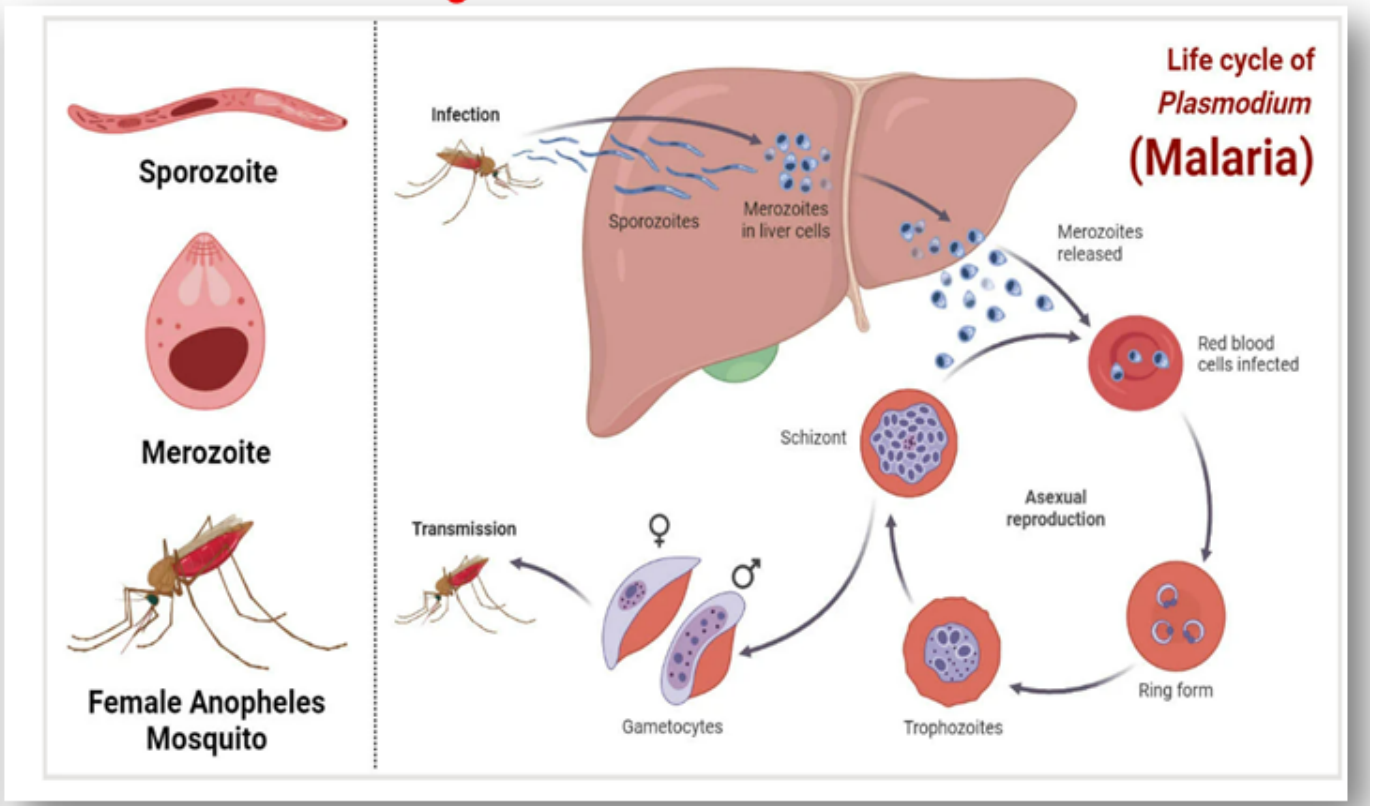
- **Pentavalent Antimonials:**
- Traditional first-line for all forms, given by injection (**sodium stibogluconate**)
- **Mechanism of action:** disruption of parasite metabolism: drug activated (**prodrug**) in parasite to trivalent form
- **Their use is limited due to** sever cardiotoxity, hepatotoxicity and nephrotoxicity and development of resistance

Visceral Leishmaniasis (VL):

- L-AmB is often first-line
- Miltefosine, Paromomycin, or Pentamidine are also used, sometimes in combinations.
- **Cutaneous Leishmaniasis (CL):**
- **Systemic drugs** (L-AmB, Antimonials, Miltefosine)
- **Topical treatments** cryotherapy or heat therapy.
- **Mucosal Leishmaniasis:**
- Miltefosine and L-AmB

Plasmodium life cycle





infective stage: sporozoite, injected into the bloodstream by an infected Anopheles mosquito during a bite, which then travels to the liver to begin the infection cycle.

Antimalarial drugs

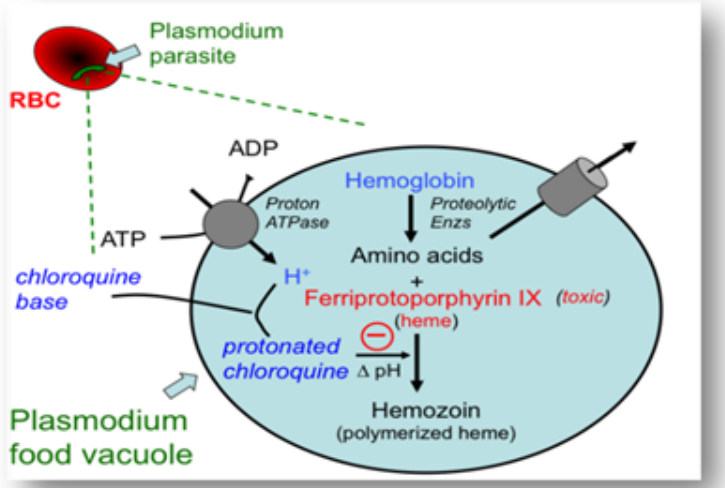
Drug class	Examples	Prophylaxis	Treatment
4-Aminoquinolines	▪ Chloroquine ▪ Hydroxychloroquine	Yes	▪ First line for P.malareae, P.vivax, P.ovale: in chloroquine-sensitive areas
Aryl aminoalchols	▪ Quinine ▪ Mefloquine	Yes: only mefloquine	▪ Sever cases ▪ Multidrug resistance cases
Antifolates	▪ Sulphadoxine-pyrimethamine (fansidar)	Yes	▪ Alternative treatment for chloroquine-resistant strains
artemisinin-based combination therapies (ACTs)	▪ artemether-lumefantrine **combine a fast-acting artemisinin derivative with a longer-acting drug**.	No	▪ First line for uncomplicated P.falciparum ▪ Chloroquine-resistant cases
8- Aminoquinolines	▪ Primaquine	Relapse prevention	▪ Radical cure (with chloroquine)
Tetracyclines	▪ Doxicycline ▪ Tetracycline	Yes (short-term travel)	▪ Sever cases (combined with chloroquine)

Chloroquine (hydroxychloroquine)

- **Mechanism of action:**
- **Being weak base**: accumulating in the **parasite's acidic food vacuole**, raising its pH and **disrupting hemoglobin digestion**; preventing detoxification of **toxic heme**: **membrane damage and parasite death**.
- **Indications**:
- **Uncomplicated Malaria**: Chloroquine is a **first-line treatment option for uncomplicated malaria** provided local **resistance is NOT present**
- **Malaria Prophylaxis (Prevention):** It is used as a preventive measure for travelers to areas of chloroquine-sensitive malaria
- Chloroquine is considered **safe for use during pregnancy and in children** at recommended doses for both treatment and prophylaxis, in sensitive areas.

Disadvantages of chloroquine

- **1- Resistance:**
- Artemisinin-based combination therapies (ACTs) are generally the current first-line treatment recommended by the **WHO** for most cases of **malaria due to global resistance**.
- 2- Chloroquine kills the asexual forms of the parasite in the red blood cells (erythrocyte stages) but is **not effective against the dormant liver stages**



Mechanism of action of chloroquine

ADRs of chloroquine

- **Common**:
- GIT upset, headache, allergy, *blurred vision
- **Serious:** with high doses, long-term use, or overdose and requires immediate medical intervention
- **1- *Ocular Toxicity**: Irreversible retinal damage (retinopathy): permanent blindness.
- **2- QT prolongation**: ventricular arrhythmias: which can be fatal.
- **3- Convulsions**
- **4- Hemolytic anemia**: in glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- **5- Hypoglycemia**

Contraindications of chloroquine

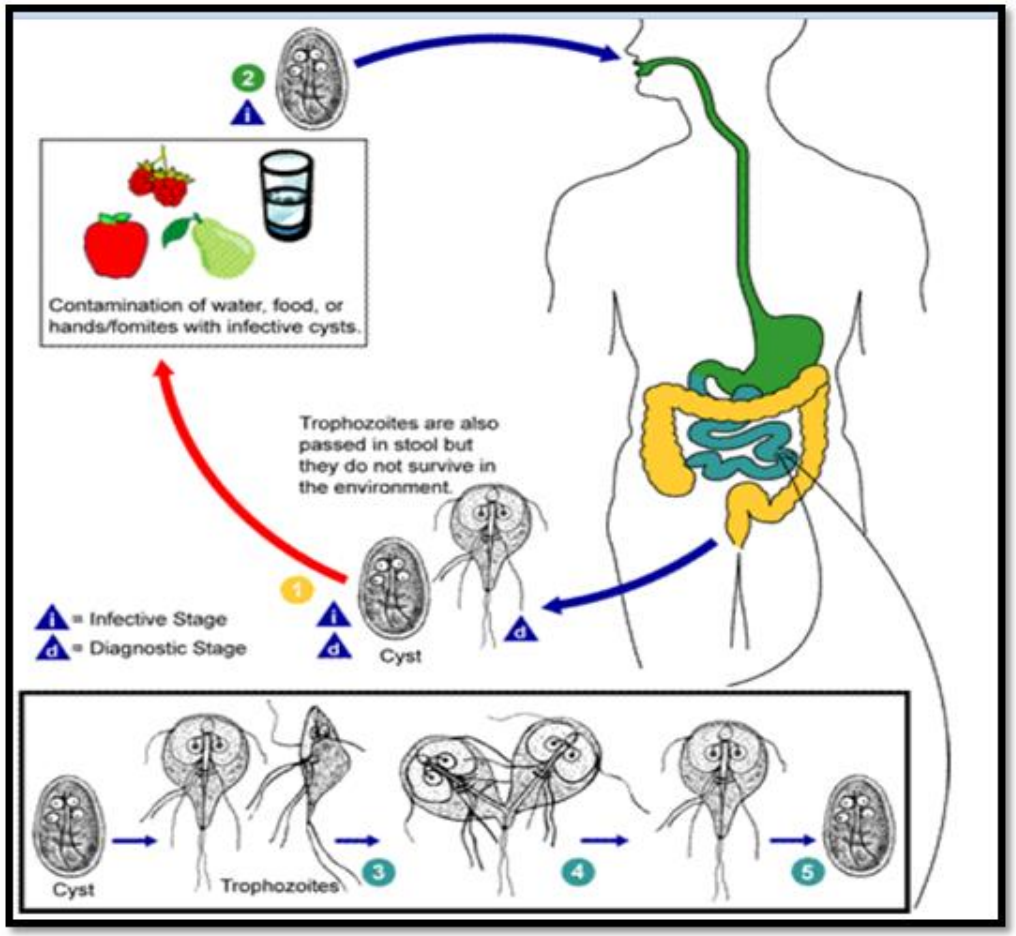
- **Pre-existing retinal or visual field changes**
- **A history of psoriasis**: it can trigger sever flare-ups (exacerbations) of the condition and may even induce new cases of psoriasis (the exact mechanism is unknown)
- **Allergy** to the drug.
- **Arrhythmia**

Differences between chloroquine and hydroxychloroquine

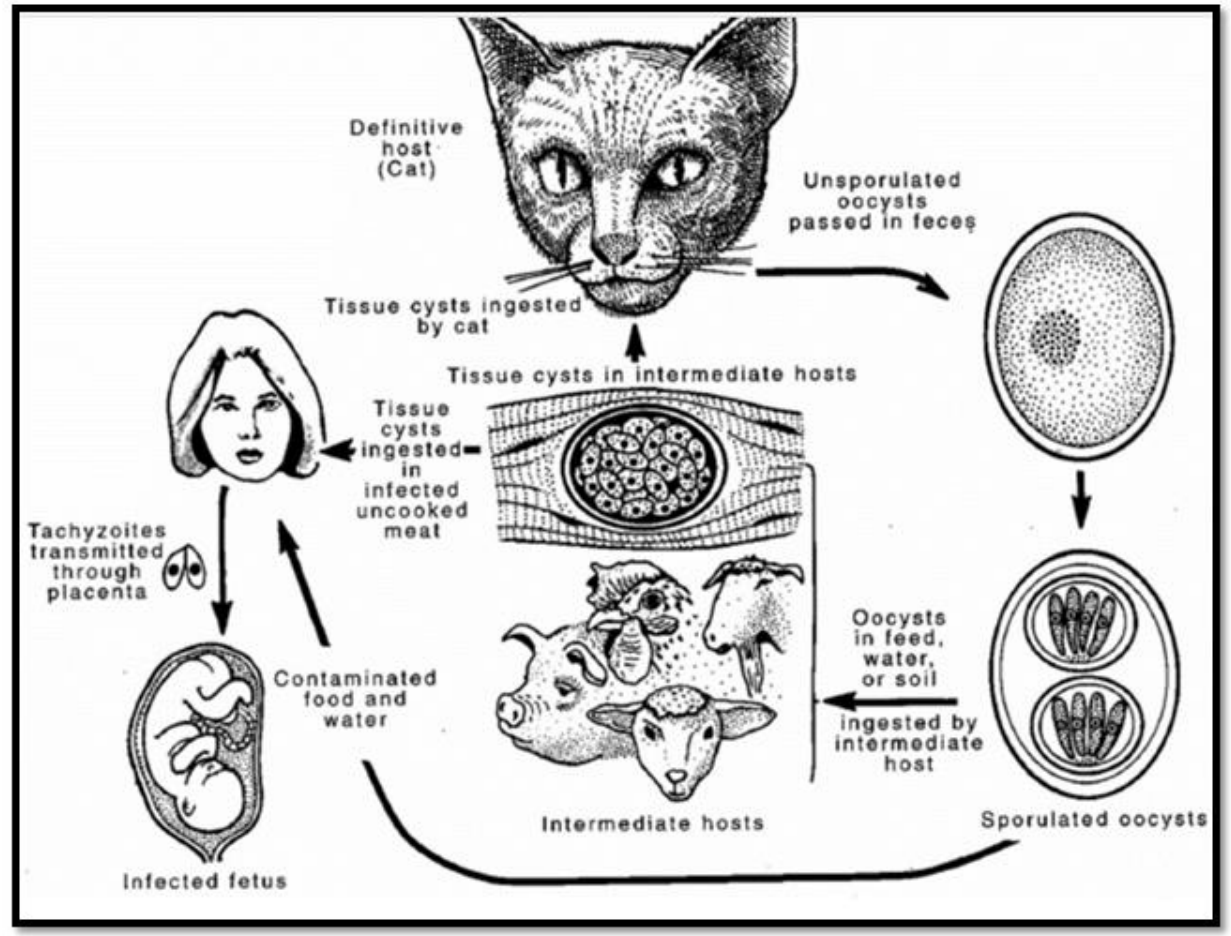
	Chloroquine	Hydroxychloroquine
Chemical Structure	4-aminoquinoline compound	**Hydroxylated** analogue of chloroquine
Toxicity	**More toxic :** Higher risk of irreversible retinopathy	Lower risk of retinopathy
Indications	Primarily for **malaria treatment** in specific regions without resistance	▪ Drug of choice for rheumatic diseases (lupus, rheumatoid arthritis) ▪ Malaria prevention

Artemisinin

- **Mechanism of action in malaria: (similar to chloroquine)**
- Concentrates in infected red blood cells, particularly within the parasite's food vacuole
- Hemoglobin breakdown releases heme iron-containing molecules
- Iron produces highly toxic free radicals.
- These radicals then attack and damage essential parasite components, leading to **rapid parasite death**



Life cycle of giardia



Life cycle of toxoplasma

	Giardia	Trichomonas	Toxoplasma
Parasite	**Giardia duodenalis**	**Trichomonas vaginalis**	**Toxoplasma gondii**
Route of infection & manifestations	▪ **fecal-oral route**, mainly by swallowing contaminated water (lakes, pools, wells) or food, or through **direct person-to-person contact**, especially in childcare settings ▪ **Gastroenteritis**	▪ **STD:** sexually-transmitted disease ▪ **Female:** frothy, yellow-green vaginal discharge with a foul odor, dysuria ▪ **Male**: burning after urination/ejaculation	▪ **Direct or indirect contact with cat feces** or by **eating undercooked meat.** ▪ Usually asymptomatic ▪ **In pregnancy with weak immunity**: pass through placenta: miscarriage, stillbirth or birth defects (blindness)
Drug therapy	▪ Metronidazolr or ▪ Tinidazole ▪ for 5-7 days	▪ Metronidazole or Tinidazol ▪ a single high dose (e.g., 2g) or a 7-day course (e.g., 500mg twice daily ▪ All sexual partners need treatment at the same time to prevent re-infection	▪ Pyrimethamine ▪ Sulphadiazine ▪ Folinic acid : with pyrimethamine to prevent bone marrow suppression and other hematologic toxicities
Alternative drugs			▪ **Clindamycin: Often used in place of sulfadiazine, typically combined with pyrimethamine and folinic acid.** ▪ **Co-trimoxazole: prophylaxis in HIV patients, CNS toxoplasmosis** ▪ **Azithromycin: for ocular toxoplasmosis.**

References

Lippincott's Illustrated Review

Pharmacology, 8th edition

Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters .*

16th edition McGraw Hill,

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

Thank you