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Antiprotozoal Drugs



CHEMOTHERAPEUTIC AGENTS

CHLOROQUINE, PYRIMETHAMINE, METRONIDAZOLE

OVERVIEW

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.

Because they are unicellular eukaryotes, the protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens.

Most antiprotozoal agents have not proven to be safe for pregnant patients.

AMEBIASIS

Chloroquine ARALEN

Dehydroemetine DEHYDROEMETINE

Iodoquinol YODOXIN

Metronidazole FLAGYL

Paromomycin HUMATIN

Tinidazole TINDAMAX

MALARIA

Artemether/lumefantrine COARTEM

Atovaquone-proguanil MALARONE

Chloroquine ARALEN

Mefloquine LARIAM

Primaquine

Pyrimethamine DARAPRIM

Quinine/Quinidine QUALAQUIN,
QUINIDINE GLUCONATE

TRYPANOSOMIASIS

Benznidazole RADANIL

Eflornithine

Melarsoprol

Nifurtimox

Pentamidine NEBUPENT

Suramin GERMANIN

LEISHMANIASIS

Miltefosine IMPAVIDO

Sodium stibogluconate

TOXOPLASMOSIS

Pyrimethamine DARAPRIM

GIARDIASIS

Metronidazole FLAGYL

Nitazoxanide ALINIA

Tinidazole TINDAMAX

Summary of antiprotozoal agents

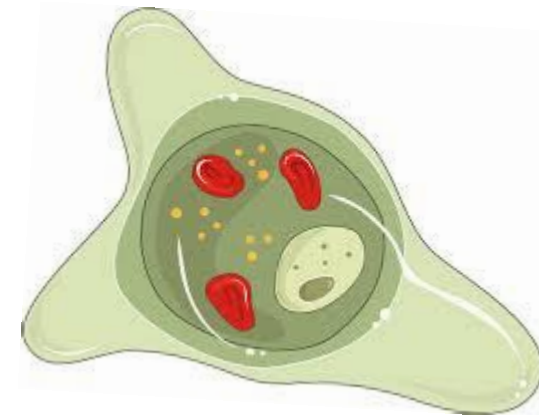
II. CHEMOTHERAPY FOR AMEBIASIS

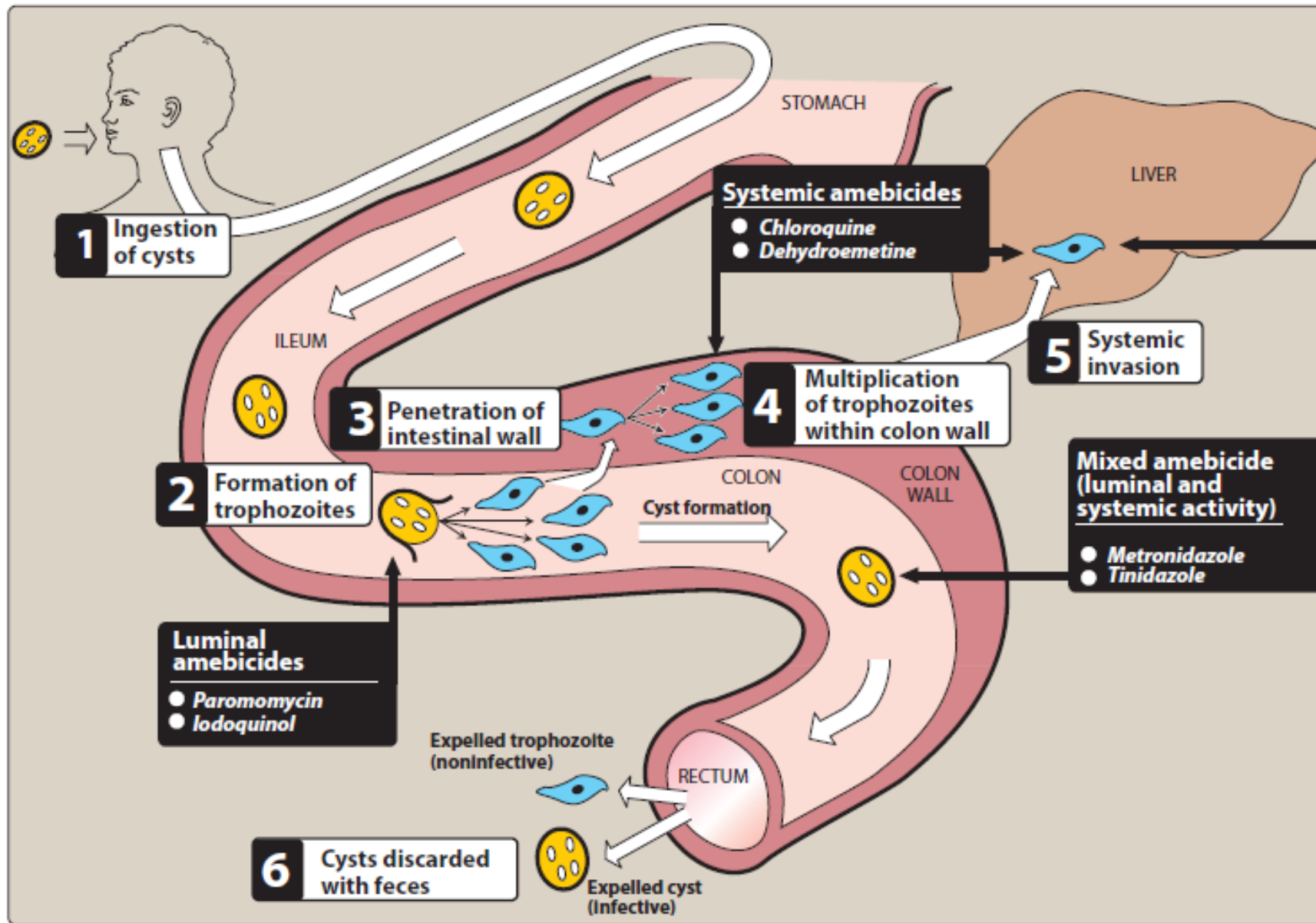
Amebiasis (also called **amebic dysentery**) is an infection of the intestinal tract caused by Entamoeba histolytica.

The disease can be acute or chronic, with varying degrees of illness, from no symptoms to mild **diarrhea** to fulminating **dysentery**.

The **diagnosis** is established by isolating *E. histolytica* from feces.

Therapeutic agents for amebiasis are classified as **luminal, systemic, or mixed** amebicides according to the site of action.





Life cycle of *E. histolytica*

II. CHEMOTHERAPY FOR AMEBIASIS/ A. Mixed amebicides

1. Metronidazole:

Metronidazole, a nitroimidazole, is the **mixed** amebicide of choice for treating amebic infections.

Metronidazole is also used in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, **anaerobic** cocci, and **anaerobic** gram-negative bacilli (for example, Bacteroides species) and is the drug of choice for the treatment of pseudomembranous colitis caused by the **anaerobic**, gram-positive bacillus Clostridium difficile.

II. CHEMOTHERAPY FOR AMEBIASIS/ A. Mixed amebicides

1. Metronidazole: a. Mechanism of action:

The **nitro group** of metronidazole is able to serve as an electron acceptor, forming reduced **cytotoxic compounds** that bind to proteins and DNA, resulting in death of the E. histolytica trophozoites.



II. CHEMOTHERAPY FOR AMEBIASIS/ A. Mixed amebicides



1. Metronidazole: b. Pharmacokinetics:

Metronidazole is completely and rapidly absorbed after **oral** administration.

For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as iodoquinol or paromomycin. This combination provides cure rates of greater than 90%.

Metronidazole distributes well throughout body tissues and fluids. Therapeutic levels can be found in **vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF)**.

Metabolism of the drug depends on hepatic oxidation of the metronidazole side chain by mixed-function oxidase, followed by glucuronidation.

II. CHEMOTHERAPY FOR AMEBIASIS/ A. Mixed amebicides

1. Metronidazole: c. Adverse effects:

The most common adverse effects are nausea, vomiting, epigastric distress, and abdominal cramps.

An unpleasant, **metallic taste** is commonly experienced.

If taken with alcohol, a **disulfiram-like reaction** may occur.

d. Resistance: Resistance to metronidazole is not a therapeutic problem for amebiasis, although strains of trichomonads resistant to the drug have been reported.

II. CHEMOTHERAPY FOR AMEBIASIS/ A. Mixed amebicides

2. Tinidazole:

Tinidazole is a **second-generation** nitroimidazole that is **similar to metronidazole** in spectrum of activity, absorption, adverse effects, and drug interactions.

It is used for treatment of amebiasis, amebic liver abscess, giardiasis, and trichomoniasis.

Tinidazole is as effective as metronidazole, with a shorter course of treatment, but it is **more expensive**.

Alcohol consumption should be avoided during therapy.

II. CHEMOTHERAPY FOR AMEBIASIS/ B. Luminal amebicides

1. **Iodoquinol**: Iodoquinol, a halogenated 8-hydroxyquinolone, is amebicidal against **E. histolytica** and is effective against the luminal **trophozoite and cyst** forms.
2. **Paromomycin**: Paromomycin, an **aminoglycoside antibiotic**, is only effective against the intestinal (luminal) forms of E. histolytica, because it is **not absorbed** from the gastrointestinal tract.

Paromomycin is directly amebicidal and also an alternative agent for cryptosporidiosis and giardiasis. **Gastrointestinal** distress and diarrhea are the principal adverse effects.

II. CHEMOTHERAPY FOR AMEBIASIS/ C. Systemic amebicides

1. **Chloroquine:** Chloroquine is used in combination with metronidazole to treat amebic **liver** abscesses.

It eliminates trophozoites in liver abscesses, but it **is not useful in treating luminal** amebiasis. Therapy should be followed with a luminal amebicide. Chloroquine is also effective in the treatment of **malaria**.

2. **Dehydroemetine:** Dehydroemetine is an alternative agent for the treatment of amebiasis. The drug inhibits protein synthesis by **blocking chain elongation**.

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	<i>Iodoquinol</i> or <i>paromomycin</i>
Diarrhea/dysentery Extraintestinal	<i>Metronidazole</i> plus <i>iodoquinol</i> or <i>paromomycin</i>
Amebic liver abscess	<i>Metronidazole</i> (or <i>tinidazole</i>) plus <i>iodoquinol</i> or <i>paromomycin</i>

Some commonly used therapeutic options for the treatment of amebiasis.

III. CHEMOTHERAPY FOR MALARIA

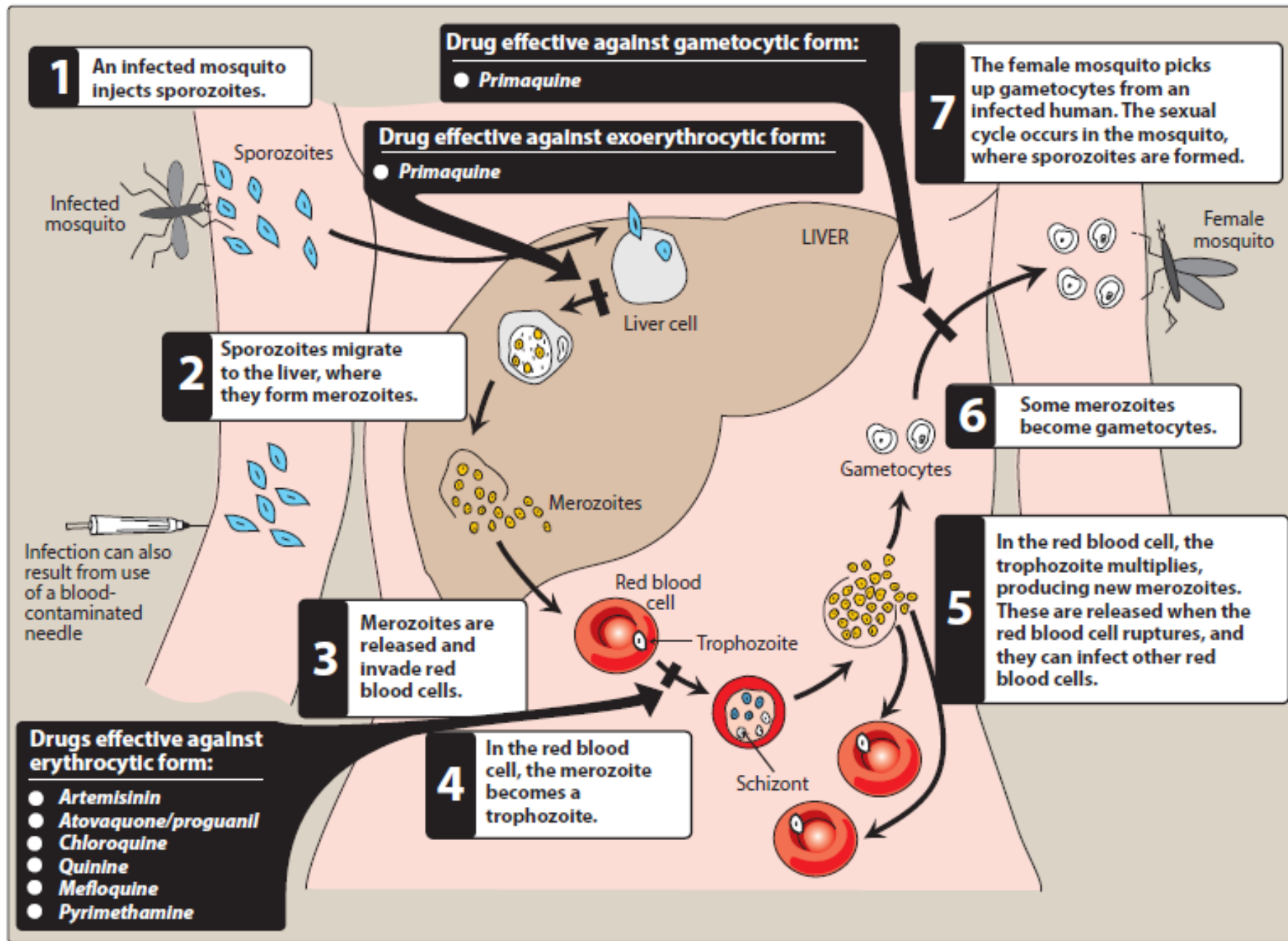


Malaria is an acute infectious disease caused by four species of the protozoal genus **Plasmodium**. It is transmitted to humans through the bite of a female **Anopheles mosquito**.

Plasmodium falciparum is the most dangerous species, causing an acute, rapidly fulminating disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs).

P. falciparum infection can lead to **capillary obstruction and death** without prompt treatment.

Plasmodium vivax causes a milder form of the disease. Plasmodium malariae is common to many tropical regions, but Plasmodium ovale is rarely encountered.



A summary of the life cycle of the parasite and the sites of action of the antimalarial drugs

III. CHEMOTHERAPY FOR MALARIA/ A. Primaquine

Primaquine, an 8-aminoquinoline, is an oral antimalarial drug that eradicates primary **exoerythrocytic (tissue)** forms of plasmodia.

The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease.

Primaquine is **not effective against the erythrocytic** stage of malaria and, therefore, is used in conjunction with agents to treat the erythrocytic form (for example, chloroquine and mefloquine).

III. CHEMOTHERAPY FOR MALARIA/ A. Primaquine



Mechanism of action: metabolites of primaquine are **oxidants** that are responsible for the schizonticidal action.

Adverse effects: Primaquine is associated with **drug-induced hemolytic anemia** in patients with **glucose-6-phosphate dehydrogenase deficiency**. Large doses of the drug may cause abdominal discomfort and occasional methemoglobinemia.

Primaquine should not be used during **pregnancy**. All Plasmodium species may develop **resistance** to primaquine.

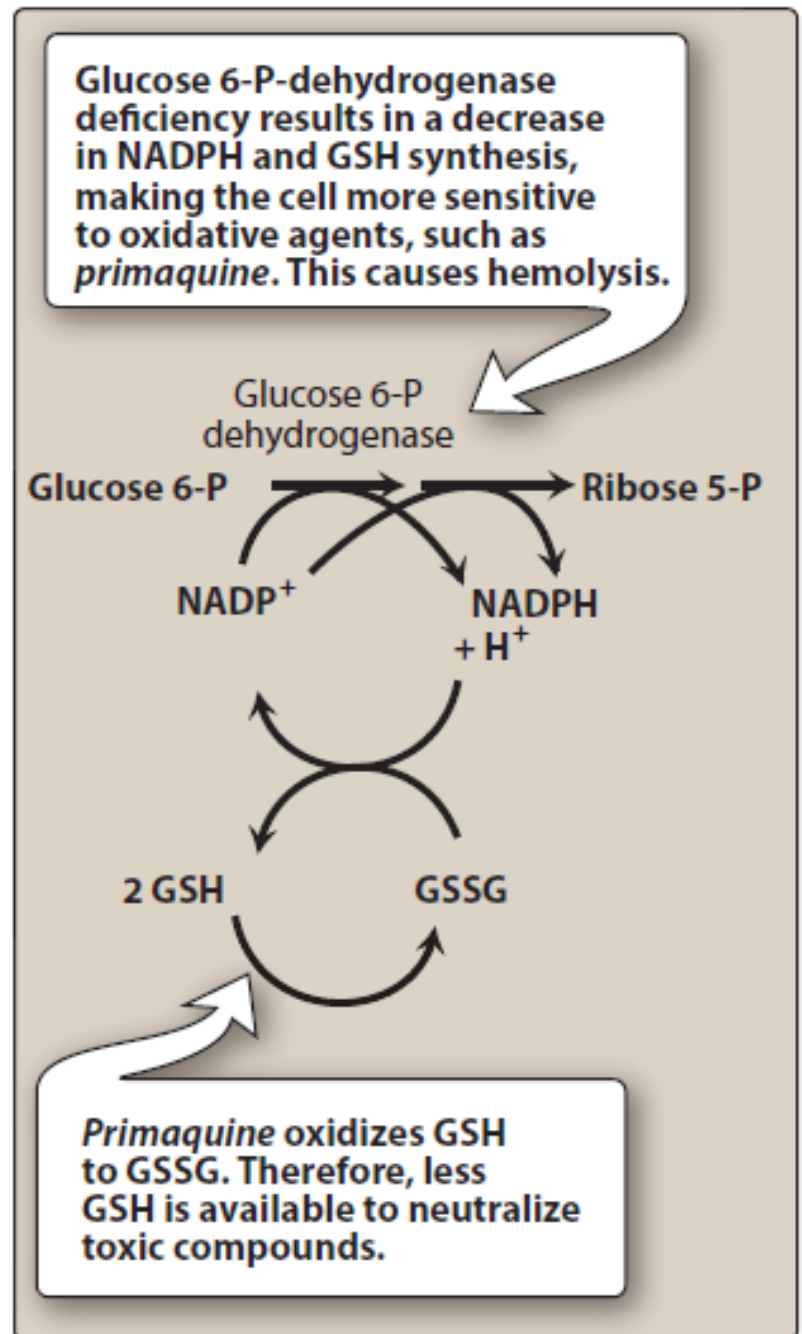
Mechanism of primaquine-induced hemolytic anemia.

GSH = reduced glutathione;

GSSG = oxidized glutathione;

NADP⁺ = nicotinamide adenine dinucleotide phosphate;

NADPH = reduced nicotinamide adenine dinucleotide phosphate



III. CHEMOTHERAPY FOR MALARIA/ **B. Chloroquine**



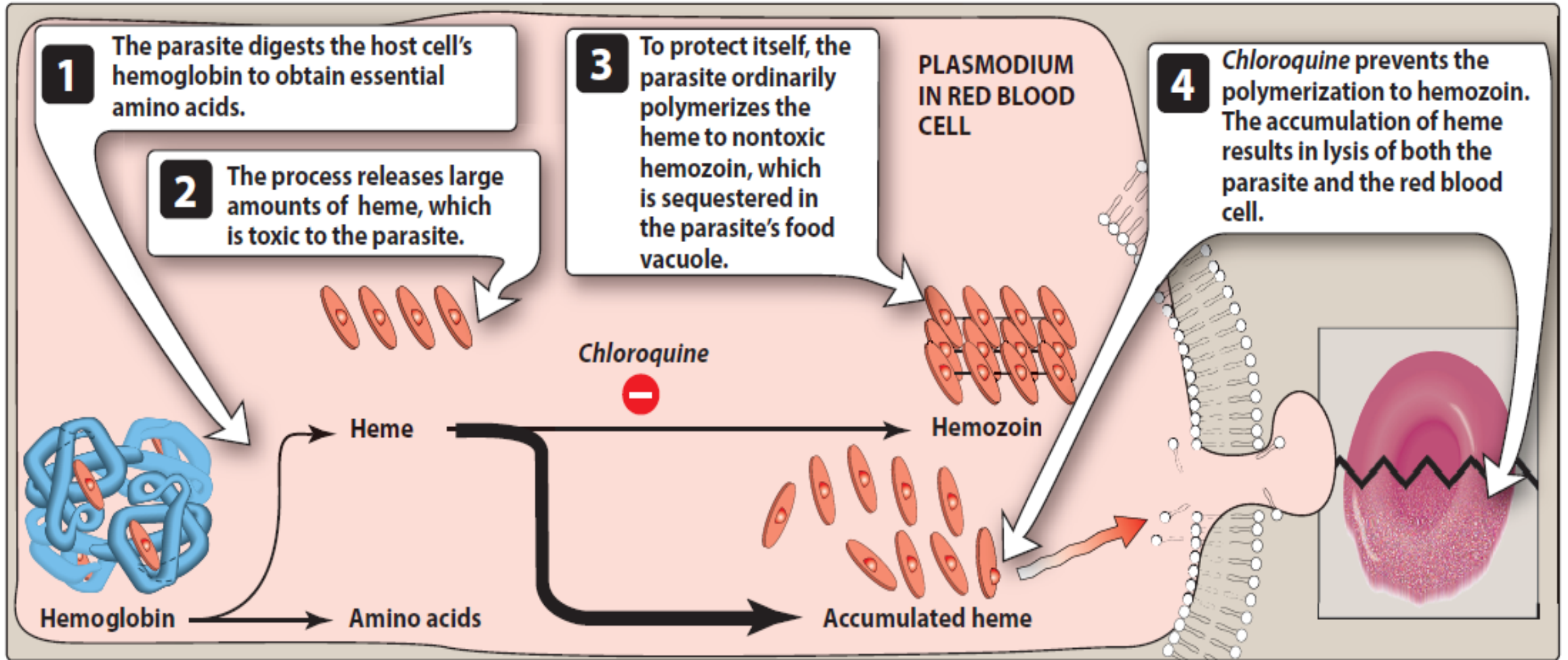
Chloroquine is the drug of choice in the treatment of **erythrocytic P. falciparum** malaria.

It is highly specific for the **asexual form** of plasmodia.

Chloroquine is used in the **prophylaxis** of malaria for travel to areas with known chloroquine-sensitive malaria.

It is also effective in the treatment of **extraintestinal amebiasis**.

Hydroxychloroquine is an alternative to chloroquine for the prophylaxis and treatment of chloroquine-sensitive malaria.



Action of chloroquine on the formation of hemzoin by Plasmodium species

III. CHEMOTHERAPY FOR MALARIA/ **B. Chloroquine**



Mechanism of action: After traversing the erythrocytic and plasmodial membranes, chloroquine (weak base) is concentrated in the acidic food vacuole of the malarial parasite, primarily by ion trapping.

In the food vacuole, the parasite **digests the host cell's hemoglobin** to obtain essential amino acids.

However, this process also releases large amounts of **soluble heme**, which is toxic to the parasite. To protect itself, the parasite polymerizes **the heme to hemozoin** (a pigment), which is sequestered in the food vacuole.

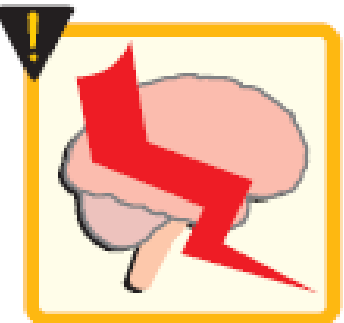
Chloroquine specifically **binds to heme**, preventing its **polymerization** to hemozoin. The increased pH and the accumulation of heme result in **oxidative damage** to the phospholipid membranes, leading to lysis of both the parasite and the red blood cell.

III. CHEMOTHERAPY FOR MALARIA/ **B. Chloroquine**

Adverse effects: Side effects are minimal at low prophylactic doses. At higher doses, gastrointestinal upset, pruritus, headaches, and **blurred vision** may occur.

Discoloration of the nail beds and mucous membranes may be seen on chronic administration.

Chloroquine can prolong the **QT interval**, and use of other drugs that also cause QT prolongation should be avoided if possible.



III. CHEMOTHERAPY FOR MALARIA/ C. Atovaquone–proguanil

The combination of atovaquone–proguanil is effective for chloroquine-resistant strains of P. falciparum, and it is used in the prevention and treatment of malaria.

Atovaquone inhibits mitochondrial processes such as electron transport, as well as ATP and pyrimidine biosynthesis.

Cycloguanil, the active metabolite of **proguanil**, **inhibits plasmodial dihydrofolate reductase**, thereby preventing DNA synthesis.

The combination should be taken with food or milk to enhance absorption.

III. CHEMOTHERAPY FOR MALARIA/ **D. Mefloquine**

Mefloquine is an effective single agent for prophylaxis and treatment of infections caused by **multidrug-resistant forms of P. falciparum**.

Mefloquine is well absorbed after oral administration and is widely distributed to tissues. It has a long half-life (**20 days**) because of enterohepatic circulation and its concentration in various tissues.

Because of the potential for neuropsychiatric reactions, mefloquine is usually reserved for treatment of malaria when other agents cannot be used.

ECG abnormalities and cardiac arrest are possible if mefloquine is taken concurrently with quinine or quinidine.

All Plasmodium species except chloroquine-resistant <u>P. falciparum</u>
<i>Chloroquine</i>
Chloroquine-resistant <u>P. falciparum</u>
<i>Atovaquone-proguanil, Artemether/lumefantrine</i> <i>Alternate: Mefloquine, Quinine plus: Doxycycline or clindamycin</i>
Prevention of relapses: <u>P. vivax</u> and <u>P. ovale</u> only
<i>Primaquine</i>
Prevention of malaria
Chloroquine-sensitive geographic areas
<i>Chloroquine</i>
Chloroquine-resistant geographic areas
<i>Atovaquone-proguanil, Doxycycline, Mefloquine</i>
In pregnancy
<i>Chloroquine or mefloquine</i>

Therapeutic options in the treatment of malaria

III. CHEMOTHERAPY FOR MALARIA/ E. Quinine

Quinine, originally isolated from the bark of the **cinchona tree**, interferes with heme **polymerization**, resulting in death of the erythrocytic form of the plasmodial parasite.

It is reserved for severe infestations and for **chloroquine-resistant** malarial strains. Quinine is usually administered in combination with doxycycline, tetracycline, or clindamycin.

The major adverse effect of quinine is **cinchonism**, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not reasons for suspending therapy.

Drug interactions include potentiation of **neuromuscular-blocking agents** and elevation of **digoxin** levels if taken concurrently. Quinine absorption is reduced by **aluminum-containing** antacids

III. CHEMOTHERAPY FOR MALARIA/ **F. Artemisinin**

Artemisinin and its derivatives are recommended first-line agents for the treatment of **multidrug-resistant P. falciparum** malaria.

To prevent the development of resistance, these agents should not be used alone. For instance, artemether is coformulated with lumefantrine and used for the treatment of uncomplicated malaria.

[Note: Lumefantrine is an antimalarial drug similar in action to quinine or mefloquine.]

The antimalarial action involves the **production of free radicals** resulting from cleavage of the drug's endoperoxide bridge by heme iron in the parasite food vacuole. These agents may also covalently bind to and damage specific malarial proteins.

III. CHEMOTHERAPY FOR MALARIA/ **G. Pyrimethamine**



Pyrimethamine inhibits plasmodial **dihydrofolate reductase** required for the synthesis of **tetrahydrofolate** (a cofactor needed for synthesis of nucleic acids).

Resistance to this combination has developed, so it is usually administered with other agents, such as artemisinin derivatives.

Pyrimethamine in combination with sulfadiazine is also used against **Toxoplasma gondii**.

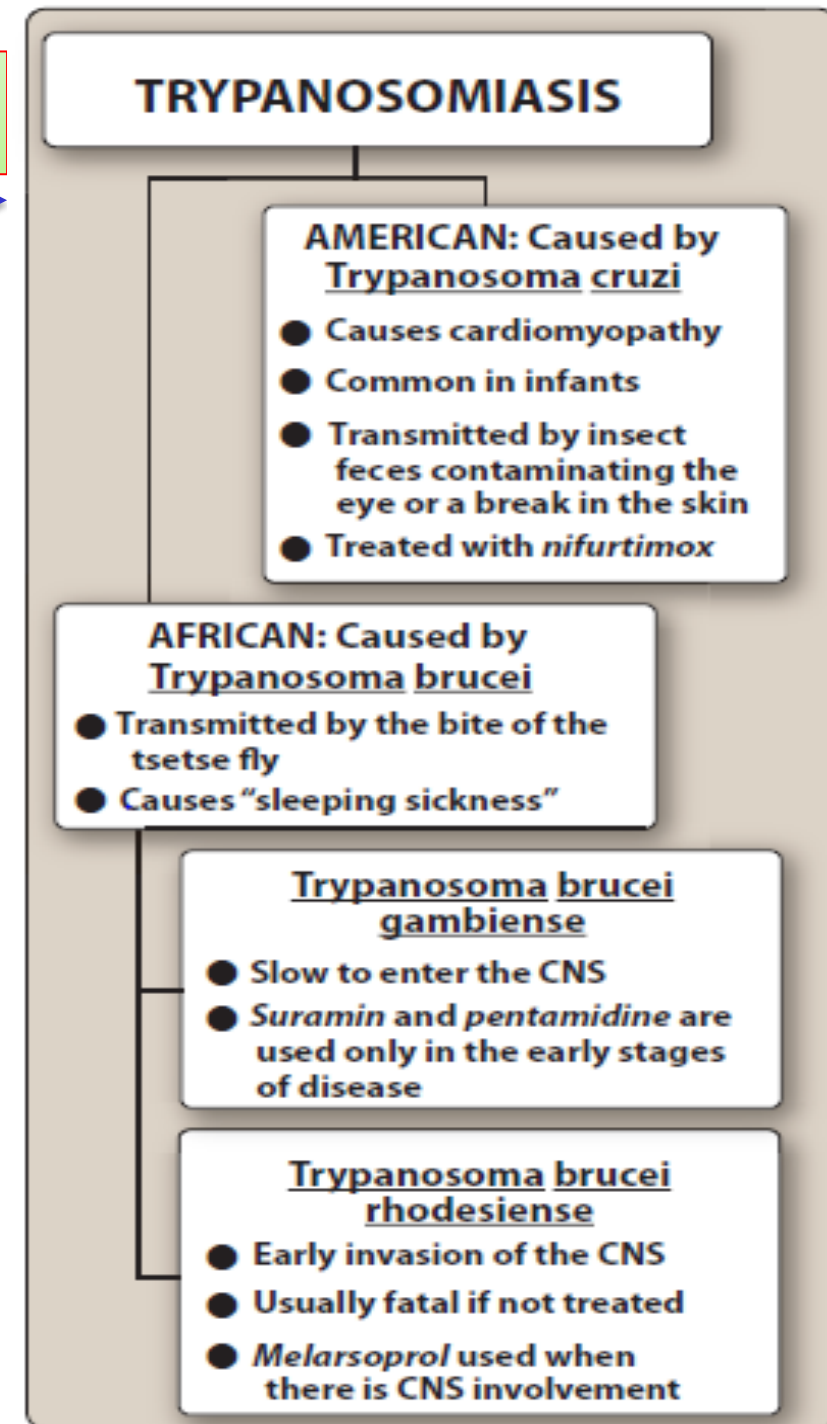
If megaloblastic anemia occurs with pyrimethamine treatment, it may be reversed with **leucovorin**.

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS

African trypanosomiasis (sleeping sickness) and **American trypanosomiasis (also known as Chagas disease)** are two chronic and, eventually, fatal diseases caused by species of **Trypanosoma**.

In African sleeping sickness, *T. brucei gambiense* and *T. brucei rhodesiense* Initially live and grow in the blood.

The parasite later invades the CNS, causing inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep.



IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **A. Pentamidine**

Pentamidine is active against a variety of protozoal infections, including African trypanosomiasis due to T. brucei gambiense, for which it is used to treat the first stage (hemolympathic stage without CNS involvement).

Pentamidine is also an alternative for prophylaxis or treatment of infections caused by Pneumocystis jirovecii.

[Note: P. jirovecii is an atypical fungus that causes pneumonia in immunocompromised patients, such as those with HIV infection.]

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **A. Pentamidine**

Mechanism of action: The drug interferes with parasite synthesis of **RNA, DNA, phospholipids, and proteins.**

Adverse effects: Serious renal dysfunction may occur, which is reversible on discontinuation. Other adverse reactions include hyperkalemia, hypotension, pancreatitis, hypoglycemia, hyperglycemia, and diabetes.

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **B. Suramin**

Suramin is used primarily in the first stage (without CNS involvement) of African trypanosomiasis due to T. brucei rhodesiense.

It is very reactive and inhibits many enzymes, especially those involved in **energy metabolism**, which appears to be the mechanism correlated with trypanocidal activity.

Suramin must be injected intravenously. It binds to plasma proteins and does not penetrate the blood–brain barrier well.

It has a long elimination half-life (more than 40 days) and is mainly excreted unchanged in the urine.

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **C. Melarsoprol**

Melarsoprol, a trivalent arsenical compound, is used for the treatment of African trypanosomal infections in the second stage (CNS involvement). It is the only drug available for **second stage trypanosomiasis due to T. brucei rhodesiense**.

The drug reacts with **sulfhydryl groups** of various substances, including enzymes in both the organism and host.

Adequate trypanocidal concentrations appear in the CSF, making melarsoprol the agent of choice in the treatment of T. brucei rhodesiense, which rapidly invades the CNS.

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **D. Eflornithine**

Eflornithine is an irreversible **inhibitor of ornithine decarboxylase**. Inhibition of this enzyme halts the production of polyamines in the parasite, thereby leading to cessation of **cell division**.

The IV formulation of eflornithine is a first-line treatment for second-stage African trypanosomiasis caused by T. brucei gambiense.

[Note: Topical eflornithine is used as a treatment for unwanted **facial hair in women**.]

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **E. Nifurtimox**

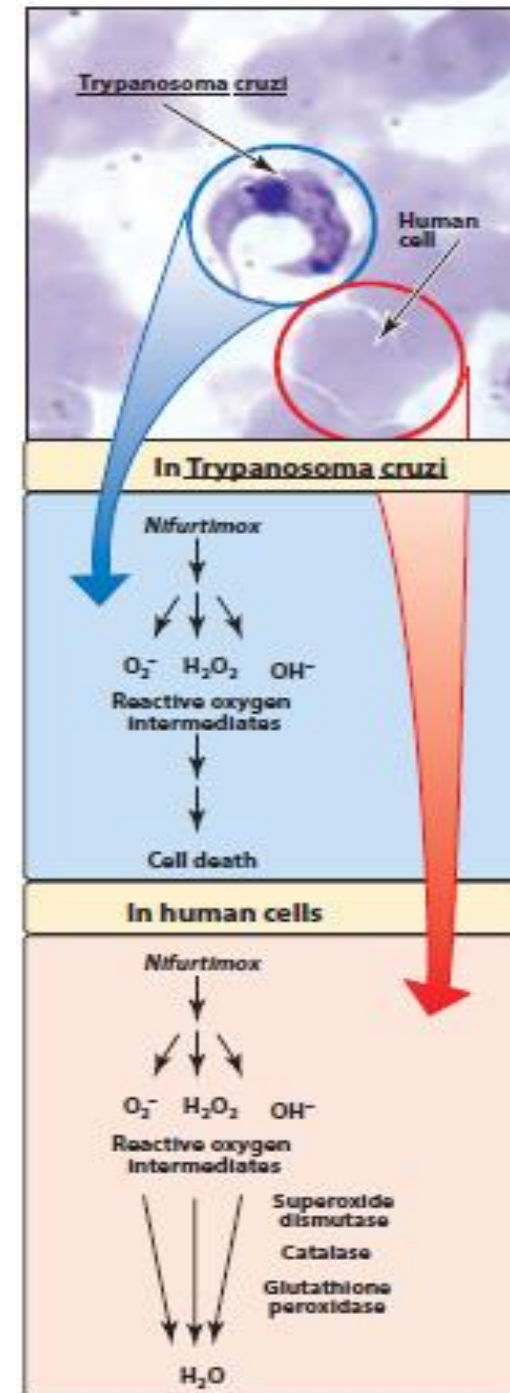
Nifurtimox is used in the treatment of T. cruzi infections (Chagas disease).

It may also be useful for the treatment of second-stage T. brucei gambiense.

Nifurtimox generates intracellular **oxygen radicals**, such as superoxide radicals and hydrogen peroxide. These highly reactive radicals are toxic to T. cruzi.

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS/ **F. Benznidazole**

Benznidazole mechanism of action **similar to nifurtimox**. It tends to be **better tolerated** than nifurtimox and is an alternative for the treatment of Chagas disease.



V. CHEMOTHERAPY FOR LEISHMANIASIS



There are three types of leishmaniasis: cutaneous, mucocutaneous, and visceral (liver and spleen).

Leishmaniasis is transmitted from animals to humans (and between humans) by the bite of infected **sandflies**.

For visceral leishmaniasis, parenteral treatments may include amphotericin B and pentavalent antimonials, such as sodium stibogluconate, with pentamidine and paromomycin as alternative agents.

V. CHEMOTHERAPY FOR LEISHMANIASIS/ A. Sodium stibogluconate

The exact mechanism of **action has not been determined**.

Because it is not absorbed after oral administration, sodium stibogluconate must be administered **parenterally**, and it is distributed in the extravascular compartment.

V. CHEMOTHERAPY FOR LEISHMANIASIS/ B. Miltefosine

Miltefosine is the first orally active drug for **visceral** leishmaniasis. It may also have some activity against cutaneous and **mucocutaneous** forms of the disease.

Miltefosine appears to interfere with **phospholipids in the parasitic cell membrane** to induce apoptosis.

The drug is teratogenic and should be avoided in pregnancy.

VI. CHEMOTHERAPY FOR TOXOPLASMOSIS

One of the most common infections in humans is caused by the protozoan T. gondii, which is transmitted to humans when they consume raw or inadequately cooked **infected meat**.

An infected pregnant woman can transmit the organism to her fetus. Cats are the only animals that shed oocysts, which can infect other animals as well as humans.

The treatment of choice for this condition is a combination of **sulfadiazine** and **pyrimethamine**. **Leucovorin** is commonly administered to protect against folate deficiency.

Pyrimethamine with clindamycin, or the combination of trimethoprim and sulfamethoxazole, are **alternative treatments**. Trimethoprim/sulfamethoxazole is used for prophylaxis against toxoplasmosis (as well as P. jirovecii) in **immunocompromised patients**.

VII. CHEMOTHERAPY FOR GIARDIASIS

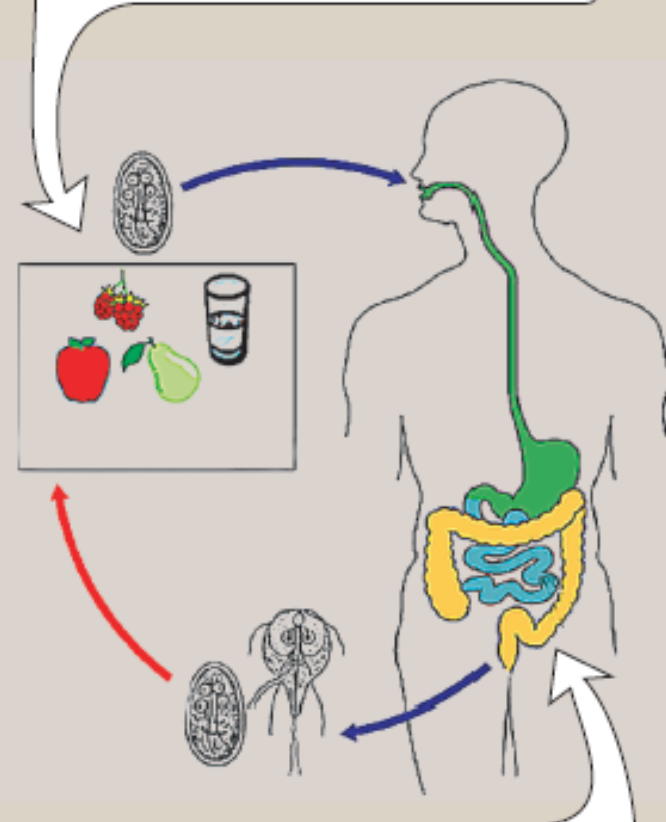
Giardia lamblia has two life cycle stages: the **binucleate trophozoite** with four flagella and the drug-resistant, **four-nucleate cyst**.

Ingestion, usually from **contaminated** drinking water, leads to infection.

The trophozoites exist in the small intestine and divide by binary fission.

Occasionally, cysts are formed that pass out in stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immunocompromised patients.

Both cysts and trophozoites can be found in feces. Infection occurs by the ingestion of cysts in contaminated water or food, or by the fecal-oral route (via hands or fomites).



In the small intestine, excystation releases trophozoites. Trophozoites multiply in the lumen of the proximal small bowel, where they can be free or attached to the mucosa by a sucking disk. Encystation occurs as the parasites move toward the colon.

VII. CHEMOTHERAPY FOR GIARDIASIS

The treatment of choice is oral **metronidazole** for 5 days. An alternative is **tinidazole**, which is as effective as metronidazole in the treatment of giardiasis. This agent is administered orally as a single dose.

Nitazoxanide, a nitrothiazole derivative, is also approved for the treatment of giardiasis.

The anthelmintic drug **albendazole** may also be efficacious for giardiasis,

Paromomycin is sometimes used for treatment of giardiasis in pregnant patients.