

Antihelminthic and Antifungal Drugs (Lecture 17)

Dr Chishti

Knowledge Objectives

1. Know the organisms responsible for onchocerciasis, amebiasis, and giardiasis.
2. Know the mechanisms of action of the antihelminthic drugs discussed in the lecture.
3. Know the topical and systemic antifungal agents.
4. Know the mechanism of action of antifungal agents.
5. Know the differences in absorption and adverse effects of imidazoles and triazoles.
6. Know the adverse effects of systemic antifungal agents.

Drug List

Antihelmintics

niridazole
ivermectin
mebendazole
metronidazole
thiabendazole
diloxanide fuorate
niclosamide
iodoquinol
praziquantel
pyrantel pamoate
albendazole
piperazine
diethylcarbamazepine

Antifungal Drugs

nystatin
amphotericin B
itraconazole
griseofulvin
ketoconazole
flucytosin
miconazole
clotrimazole
fluconazole

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Anthelmintic and Antifungal Drugs

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Helminths (Worms)

Pathogenic worms (Metazoa)

- Helminths require a **Primary** (Definitive) host and a **Secondary** (Intermediate) host.
- Humans are often the primary host where worms reproduce sexually producing eggs or larvae that pass out of the body and infect the secondary host.
- Clinically, two main types of worm infections occur:
(1) Alimentary canal (2) Other tissues

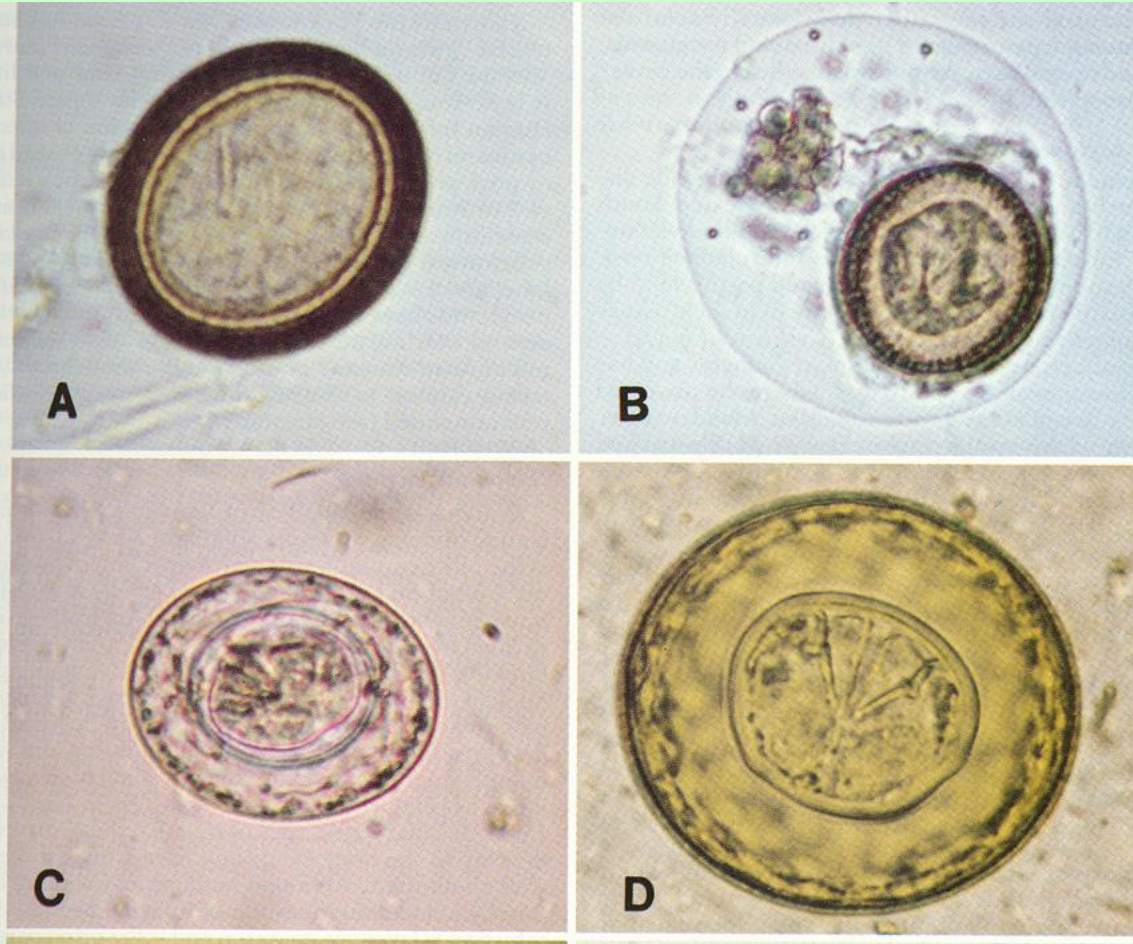
Tapeworms (Cestodes)

- Beef tapeworm (*Taenia saginata*)
- Pig tapeworm (*Taenia solium*)
- Fish tapeworm (*D. latum*)
- Dwarf tapeworm. (*H. nana*)
- **Life Cycle**
- Eggs are ingested by cows & pigs, hatch in the intestine; larvae migrate to animal muscle and become encysted. Humans eat undercooked meat, larvae excyst in the **small intestine**, mature, and lay eggs.

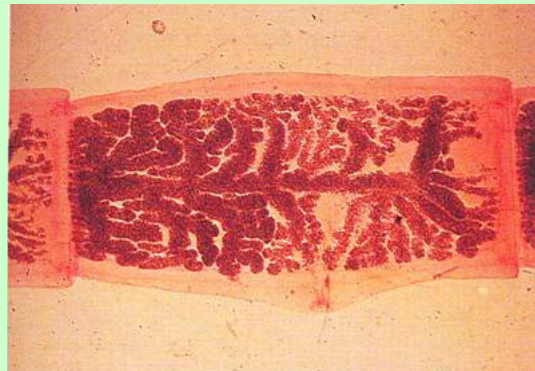
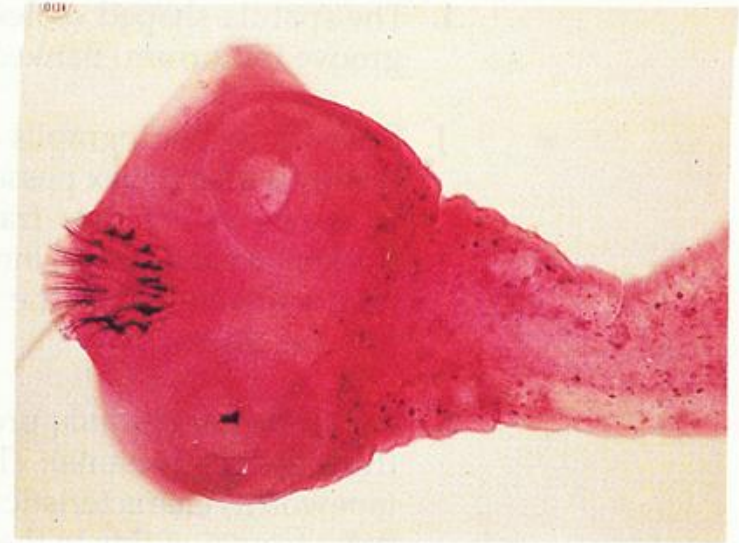
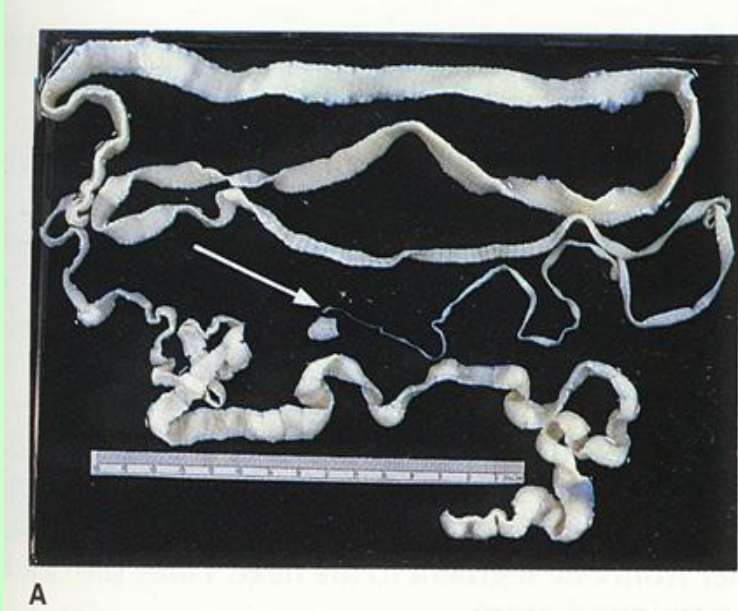
Tapeworms (Cestodes)

- Flat and ribbon-like; head (scolex)
- proglottid (individual segment), strobila (chain of proglottids), male & female organs in each mature proglottid
- **Clinical Manifestations**
- Asymptomatic, abdominal pain, chronic indigestion, **eosinophilia**.
- *T. solium*: Encysted larvae in the muscles, viscera, eye, and brain (**Cysticercosis or Neurocysticercosis**)

Tapeworms (Cestodes)

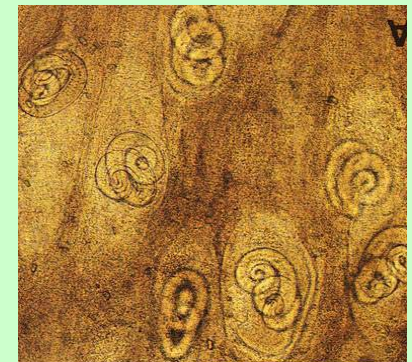
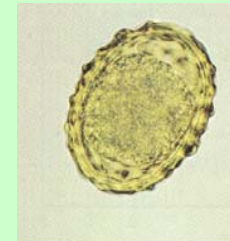


Tapeworms (Cestodes)



Intestinal roundworms (Nematodes)

- *Ascaris lumbricoides* (**common roundworm**)
- *Enterobius vermicularis* (**pinworm**)
or threadworm in UK
- *Trichuris trichiura* (**whipworm**)
- *Strongyloides stercoralis* (**threadworm**)
- *Ancylostoma duodenale* and *Necator americanus* (**hookworms**)



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Worms that live in the tissues

Flukes (Trematodes)

***Schistosoma* species (Blood fluke)**

Other flukes: intestinal, liver, lung

Schistosomiasis (**Bilharzia**) ~200 million infections

Schistosoma mansoni

Schistosoma japonicum

Schistosoma haematobium

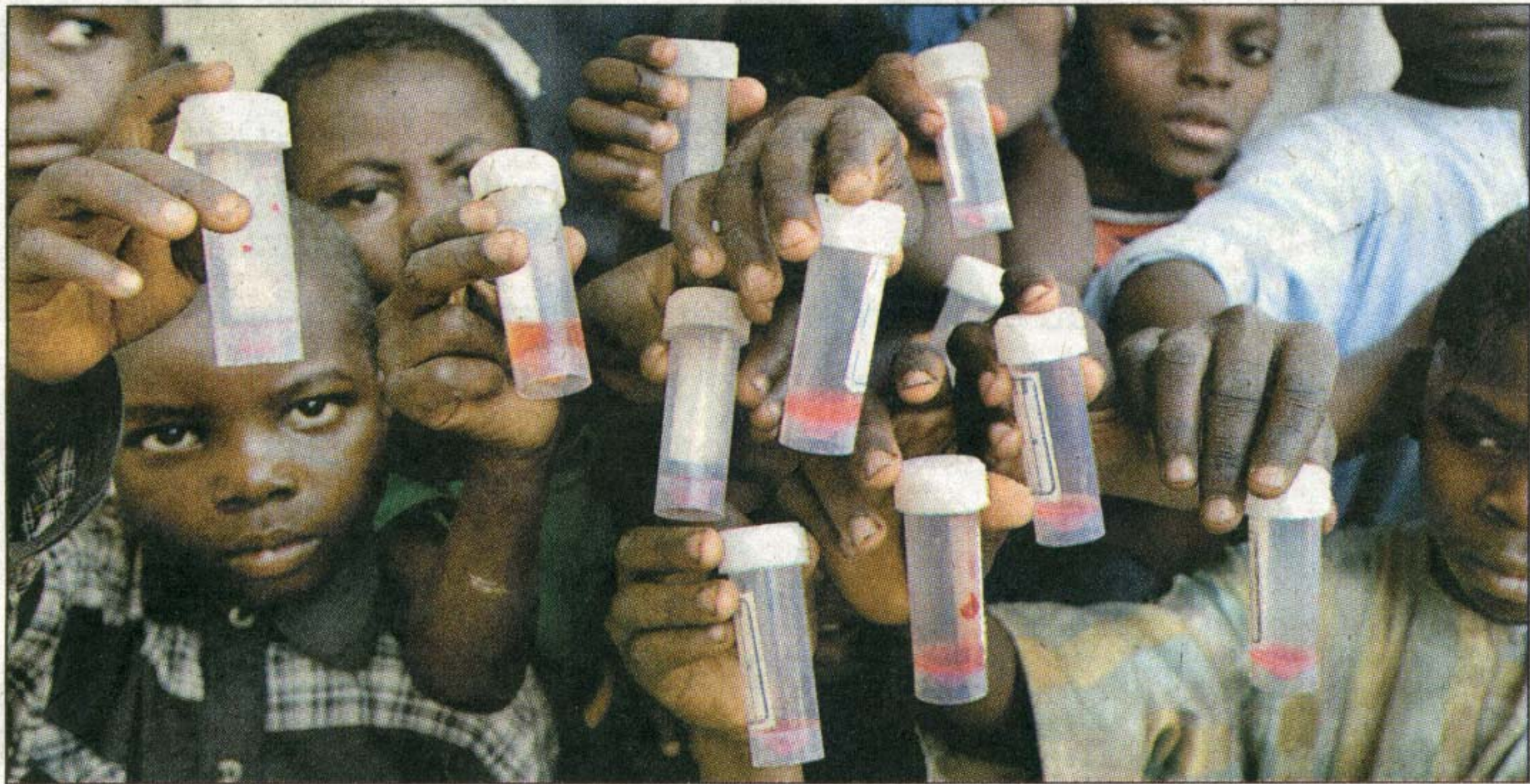
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Schistosomiasis (**Bilharzia**)

Life cycle

Adult worms of both sexes live in the veins of gut and bladder of human host. Eggs pass into the bladder and gut and produce inflammation. Blood in the urine (hematuria) and feces is common.

Eggs hatch in water and give rise to *miracidia* that enter the secondary host (**snail**). Free-swimming *cercariae* emerge that infect humans via direct skin penetration.



Tribune photo by Wes Pope

Children in Nasarawa, Nigeria, hold vials of their bloody urine, an early sign of schistosomiasis, which is spread by microscopic river parasites that burrow into skin and infect organs.

River parasite eats at children

Tissue roundworms

Trichinella spiralis: (**Trichinosis**). Pork containing encysted larvae (Trichina worm), released in small intestine, adults enter circulation, infect striated muscle fibers & encyst. In rare cases, worms can enter CNS. **Symptoms**—Headache, fever, chills, eye swelling, joint pain, muscle pain, and itching.

Dracunculus medinensis (**guinea/dragon/medina worm**)
Dracunculiasis. Larvae released from crustaceans in wells are ingested and migrate from the intestine tissues. Gravid female worms protrude out of the foot or leg ulcers. Surgical removal. Natives roll out the worm (1 meter long) on a stick.

Filariæ *Wuchereria bancrofti*, *Onchocerca volvulus*, *Brugia malayi*,
Loa loa

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Filariae

Adult filariae live in the lymphatics, connective tissue or mesentery and produce live microfilariae. Secondary host is generally mosquito.

Wuchereria and Brugia cause obstruction of lymphatic vessels producing **elephantiasis**.

Onchocerciasis is caused by the presence of microfilariae in the eye---**river blindness**

Loiasis, an inflammation of the skin and other tissues, is caused by microfilariae.

Anthelmintic Drugs

Benzimidazoles are broad-spectrum drugs.

Mebendazole (Threadworm, Hookworm, Roundworm)

Thiabendazole (Guinea-worm, Strongyloides, Hookworm)

Albendazole (Cysticercosis, Pinworms, Hookworms)

Administered on empty stomach for intra-luminal parasites and given with a fatty meal for tissue parasites.

Benzimidazoles: Mechanism of action

- Drugs bind to free β -tubulin inhibiting its polymerization. They interfere with microtubule-dependent glucose uptake by the worms. Drugs are selective for helminth microtubular function, being ~400 times more potent than the mammalian microtubules.
- Albendazole is metabolized to sulfoxide and sulfone, which may also contribute to its inhibitory function. Plasma concentration of its active metabolite is 100 times greater than mebendazole.
- Inhibitory effect takes time. Several days to expel the worms. Mebendazole is teratogenic in animals and therefore contraindicated in pregnancy.

PRAZIQUANTEL (Biltricide)

A broad-spectrum anthelmintic drug. Effective against all species of **schistosomes and **cysticercosis**. Human and animal cestodes, trematodes, and nematodes.**

Contraindications: Ocular cysticercosis and spinal Neurocystercosis. Caution in pregnancy as it increases abortion rates in rats. No driving permitted because of dizziness and drowsiness.

PRAZIQUANTEL (Biltricide)

Effective against adult schistosomes as well as immature forms and infective cercariae.

Mechanism of action

It increases the permeability of the nematode to calcium thereby causing contraction of the musculator and eventual paralysis and death of the worm. Praziquantel also causes tegumental damage so that the parasite becomes susceptible to host's immune responses.

PIPERAZINE

A cyclic secondary amine. Highly effective against *Ascaris* and *Enterobius* (Intestinal roundworm and pinworm). Flaccid paralysis and worm expulsion.

Mechanism of action

Alters membrane permeability thus blocking the response of muscle to acetylcholine.

Hyperpolarization. Inhibits neuromuscular transmission by acting as GABA, the inhibitory neurotransmitter, on GABA-gated chloride channels in nematode muscle. Paralyzed worms are expelled alive. **Contraindication:** pregnancy

PYRENTEL PAMOATE

A broad-spectrum drug against pinworms, ascaris, and hookworms.

Mechanism of action

Depolarization of the helminth neuromuscular junction causing spasm and paralysis. Some anti-cholinesterase activity.

- **Note:** Piperazine and pyrantel have opposite mechanism of action. Piperazine causes hyperpolarization (flaccid paralysis) and Pyrantel causes depolarization (spastic paralysis)

NICLOSAMIDE

Effective against adult tapeworms (cestodes) but not ova. A purgative is necessary because damaged worms may release ova. Largely replaced by Praziquantel.

Mechanism of action

Inhibits oxidative phosphorylation or stimulates ATPase activity. The scolex and proximal segment are irreversibly damaged by the drug; the worm separates from the intestinal wall and is expelled.

Contraindications: Alcohol, Pregnancy

IVERMECTIN

- Semisynthetic drug derived from natural avermectins obtained from soil actinomycete.
- Potent drug against human filariae infections. Onchocerciasis (**River Blindness**). Kills **immature microfilariae** of *Onchocerca volvulus* but not the **adult** worms.
- Could be used for *W. bancrofti* (elephantiasis). Not effective against cestodes and trematodes.
- **Contraindications:** Barbituates, Benzodiazepines, Pregnancy

IVERMECTIN

Mechanism of action

Induces tonic paralysis of the musculature. Opens glutamate-gated chloride channels (found only in invertebrates) and increases Cl⁻ conductance.

Binds to acetylcholine nicotinic receptor, increases transmission, and thus causes parasite paralysis.

OXAMNIQUINE

An alternative to **Praziquantel**. Effective against *S. mansoni* but not other trematodes. May work by intercalation in the worm DNA. **Contraindications:** Pregnancy and Driving

DIETHYLCARBAMAZINE

Effective against filarial infections of *W. bancrofti* and *L. loa*. Makes microfilariae susceptible to immune clearance. **Contraindications:** Hypertension and renal disease

- **ANTIFUNGAL DRUGS**

- Fungal infections are termed mycoses. They are either **superficial** (skin, nails, scalp, mucous membrane) or **systemic** (deeper tissues and organs)
- **Susceptibility:** Broad-spectrum antibiotics, AIDS, Immunosuppressant drugs, Cancer chemotherapy.

- **Systemic infections** (Systemic candidiasis, Cryptococcal meningitis, Pulmonary aspergillosis, Blastomycosis). Pulmonary aspergillosis is a leading cause of death in the bone marrow transplant patients. Diabetics, pregnant women, and burn victims are more susceptible to candidiasis.
- **Superficial infections** can be classified into **dermatomycoses** and **candidiasis**.
- Ringworms such as *Tinea pedis* (feet), *Tinea corporis* (body), *Tinea capitis* (scalp), *Tinea cruris* (groin). Superficial candidiasis include mucous membranes of the mouth (thrush), vagina, or skin.



**Oral candidiasis on the tongue
and soft palate.**

Antifungal Agents

Fungicidal---Capable of killing fungi

Fungistatic---Inhibits fungi growth

Two classes: Antibiotics and Synthetic agents

Antibiotics

Amphotericin-B (Fungizone)

Nystatin (Mycostatin, Nustat)

Griseofulvin (Grifulvin, Fulvicin, Grisactin)

Amphotericin and Nystatin

Mechanism of action

Fungal cells, unlike mammalian cells and bacteria, contain large amount of ergosterol in the plasma membrane. Much less affinity for cholesterol. Ergosterol helps the attachment of polyene antibiotics that act as ionophores and cause leakage of potassium ions.

Amphotericin

Fungicidal. Treatment of choice for most mycotic infections. Administered intravenously but can be topical or oral. Combination with **Flucytosine** for cryptococcal meningitis. **Renal toxicity**. Patients should be hospitalized.

Nystatin

Similar to amphotericin. Does not absorb from the mucous membranes. Used for *Candida albicans* infections, vaginitis, and stomatitis (thrush). Topical therapy. For oral candidiasis, patients hold the drug in the mouth for one minute.

Griseofulvin

Fungistatic. Administered orally. High affinity for diseased skin (binds keratin). Especially useful for ringworm and athlete's foot infections.

Griseofulvin

Mechanism of action

Acts as a fungistatic agent by binding to microtubules causing inhibition of mitosis and production of nucleated cells. Induces cytochrome 450 enzymes and causes important drug interactions.

Flucytosine

Fungistatic. Not an antibiotic. Synthetic fluorinated pyrimidine. Well absorbed after oral administration. Its concentration in the CSF is 50-90% than in plasma. Less toxic than amphotericin. Combination is treatment choice for *Cryptococcal meningitis*.

Mechanism: Flucytosine is converted to the antimetabolite 5-fluorouracil (5-FU) in fungal but not human cells. 5-FU inhibits thymidylate synthetase and DNA synthesis.

Azoles---Synthetic antifungal agents

Azoles are fungistatic and can be classified as either **Imidazoles** or **Triazoles** according to the number of nitrogen atoms in the five-membered azole ring.

Imidazoles

Ketoconazole, Miconazole, Clotrimazole

Triazoles

Fluconazole, Itraconazole, Voriconazole

Azoles

Mechanism of action

Azoles inhibit the fungal cytochrome P450 3A (CYP3A) enzyme, **lanosine 14 α -demethylase**, which converts lanosterol to ergosterol. This leads to increase in membrane fluidity and permeability and thus causes inhibition of fungal cell growth and replication.

Ketoconazole

Broad-spectrum antifungal agent, given orally, and requires acidity for dissolution. Toxic. Inhibits steroid and testosterone synthesis at high dose, resulting in gynecomastia (enlarged breasts) in some male patients.

Miconazole

Broad-spectrum agent, applied topically and intravenously. Superior drug for systemic infections.

Clotrimazole (Gyne-Lotrimin)

Broad-spectrum topical drug for vaginal and oral candidiasis. Topical applications (Athlete's foot)

Fluconazole

Does not require low gastric pH for absorption. CSF concentration is 70% that of plasma. Does not inhibit steroidogenesis. Drug of choice for fungal meningitis. Fungicidal concentrations are also achieved in vaginal tissue.

Itraconazole

Requires low pH for absorption, does not penetrate CSF. Does not inhibit steroidogenesis.

Contraindications: Histamine H1-receptor antagonists, Antacids

General treatment options of antifungal drugs

- **Amphotericin:** Topical (mycotic corneal ulcers and keratitis can be cured with topical drops). This drug is also used for treating systemic fungal disease by slow intravenous injection.
- **Nystatin:** Very similar to Amphotericin but is used only as topical drug because it is too toxic for parenteral administration. Also, it is not absorbed from skin and mucous membranes.
- **Griseofulvin:** Fungistatic drug used only in the systemic treatment of dermatophytosis.

- **Flucytosine:** Synthetic antifungal drug given orally for systemic infections.
- **Miconazole:** A topical drug generally used in creams and powders.
- **Ketoconazole:** Used both as topical agent in creams/shampoos and given orally for systemic fungal infections.
- **Clotrimazole and Tolnaftate:** Topical agents used in creams and lotions.

Thank you