Antifungal drugs

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Last update: 13.04.2011

Mycosis (fungal infections)

- **Superficial:** (affecting skin, nails, scalp or mucous membranes)
- **Systemic:** (affecting deeper tissues and organs)

- Until recently serious fungal infections were uncommon but with widespread use of broad spectrum antibiotics, which eliminate or decrease the non-pathogenic bacterial populations that normally compete with fungi, the incidence increased.

Reasons for the increase of fungal infections

- Another important factor has been the increase in the number of individuals with reduced immune responses due to AIDS, the action of immunosupressant drugs and cancer chemotherapy agents.
- This has led to an increased prevalence of ‘‘**opportunistic infections**’’ such as fungal infections, which are normally innocuous or readily overcome in immunocompetents.

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Systemic fungal diseases

Common systemic fungal diseases:

- Systemic *Candidiasis*
- *Cryptococcal* meningitis or endocarditis
- Pulmonary or cerebral *Aspergillosis*
- Rhinocerebral *Mucormycosis*
- *Blastomycosis, Histoplasmosis*
- *Coccidiomycosis* and *Paracoccidiomycosis.*

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Superficial fungal infections

Superficial fungal infections can be classified into:

- **Dermatomycosis** (infections of the skin, hair or nails caused by *Dermatophytes*)
- **Candidiasis** (yeast like organism infects the mucous membranes of the mouth, vagina or skin)

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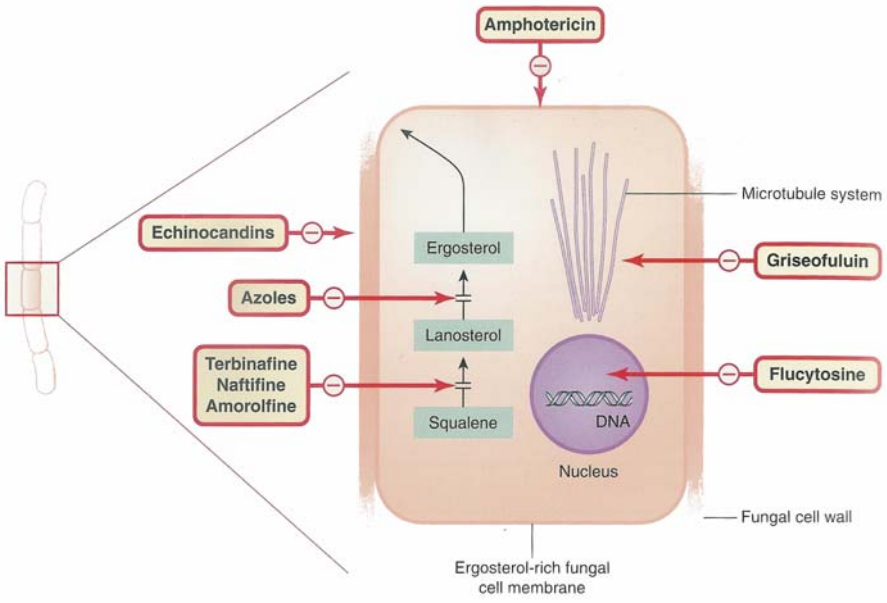

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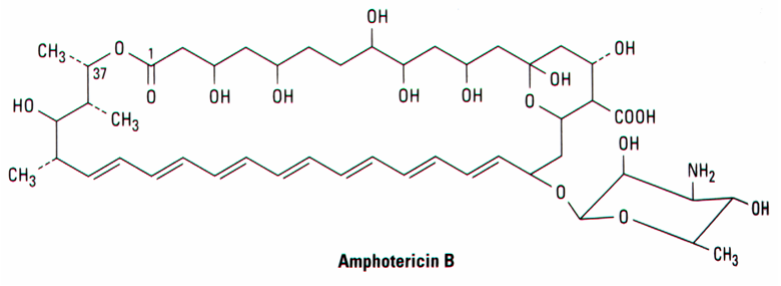
Amphotericin (B)

- It is an antibiotic of complex structure, and insoluble in water and unstable at 37°C.



Amphotericin B

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Mechanism of action

- Like other polyene antibiotics (e.g. nystatin), amphotericin binds to cell membranes and interferes with permeability and with transport functions.
- It forms a pore in the membrane, creating a transmembrane ion-channel.
- This results in a loss of intracellular K^+ ions.

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Specifity of its actions

- It has a selective action, binding avidly to the membranes of fungi and some protozoa, less avidly than mammalian cells and not at all to bacteria.
- This specificity is due to the drug's greater afinity for **ergosterol** (the fungal membrane sterol) than for cholesterol.
- It is active against most fungi and yeasts.
- Amphotericin enhances the antifungal activity of **rifampicin,** which does not otherwise has antifungal properties.

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Pharmacokinetics

- It is poorly absorbed from GIS, and is therefore only given by this route for fungal infections of GIS. For systemic infections it is given IV.
- It is highly protein bound, but found in fairly high concentrations in inflammatory exudates.
- It normally passes blood-brain barrier poorly, unless meninges are inflamed.
- It is excreted very slowly via kidneys.

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Unwanted effects

- The most common and most serious unwanted effect is renal toxicity; the incidence is up to 80%, fortunately this is generally reversed after treatment is stopped.
- Hypokalemia, and anemia can occur.
- Other unwanted effects: Impaired hepatic function, thrombocytopenia, anaphylactic reactions, chills, fever, tinnitus, headache, vomiting, local thrombophlebitis.
- Intrathecal injections can cause neurotoxicity.

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Table 48–1. Properties of conventional amphotericin B and some lipid formulations.[1]

Drug	Physical Form	Dosing (mg/kg/d)	C_{max}	Clearance	Nephro-toxicity	Infusional Toxicity	Daily Cost ($US)
Conventional formulation							
Fungizone	Micelles	1	—	—	—	—	24
Lipid formulations							
AmBisome	Spheres	3–5	↑	↓	↓	↓	1300
Amphotec	Disks	5	↓	↑	↓	↑(?)	660
Abelcet	Ribbons	5	↓	↑	↓	↓(?)	570

[1]Changes in C_{max} (peak plasma concentration), clearance, nephrotoxicity, and infusional toxicity are relative to conventional amphotericin B.

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Nystatin

- Structure and mechanism of action similar to amphotericin.
- It is virtually not absorbed from the mucous membranes and skin.
- Its use is limited to fungal infections of the skin and GIS.

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Flucytosine

- It is a synthetic antifungal agent which given orally, is active against a limited range of systemic fungal infections, being effective mainly in those caused by yeast.

Flucytosine

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Mechanism of action

- Flucytosine is converted to 5-flourouracil, which is an antimetabolite that inhibits thymidylate synthetase and thus DNA synthesis.
- The activity is specific for fungal cells because it is converted to 5-FU in mammalian cells in very small amounts.
- Some strains are naturally resistant to the drug, and among sensitive strains resistant mutants may emerge rapidly.
- Because of this, it is recommended that this drug should not be used alone.

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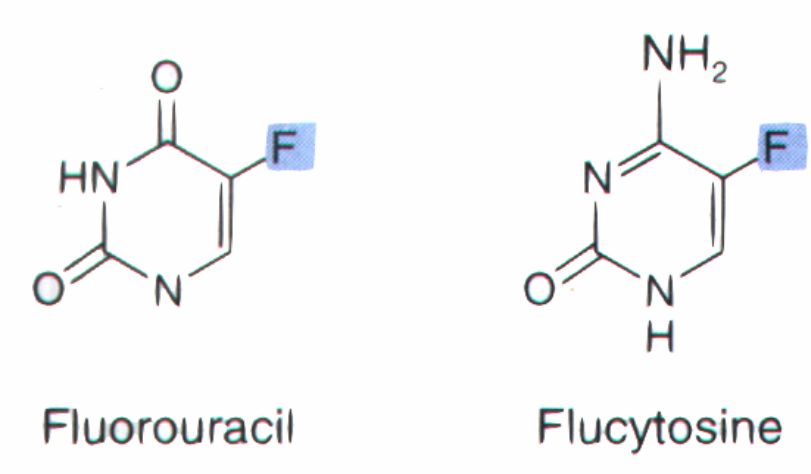

Fluorouracil Flucytosine

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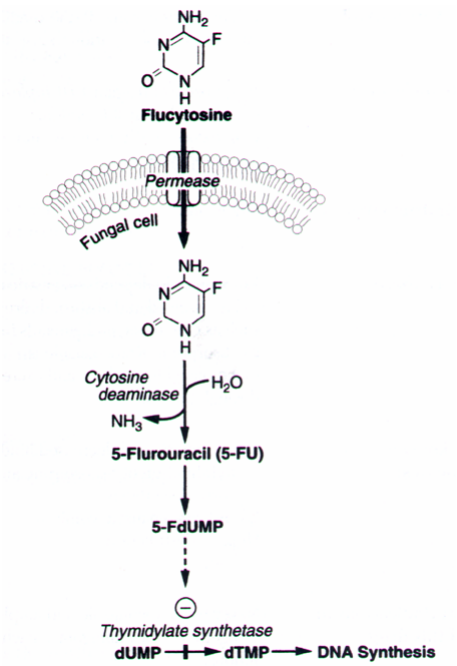

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Pharmacokinetics

- Rapidly and almost completely absorbed from GIS, and is widely distributed throughout the body fluids including the cerebrospinal fluid.
- About 85% is excreted unchanged via the kidneys.
- The drug is ≈ 20% protein bound.

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Unwanted effects

- Unwanted effects are infrequent and are due to the active metabolite 5-flourouracil.
- Gastrointestinal disturbances, anemia, neutropenia, thrombocytopenia and alopecia have occurred, but usually mild and reversible.
- Rarely hepatitis has been reported.

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Azoles

They are a group of synthetic antimycotic agents with a broad spectrum of activity. The main drugs available are:

- **Ketoconazole**
- **Fluconazole**
- **Itraconazole**
- **Voriconazole**
- **Clotrimazole**
- **Econazole**
- **Miconazole**
- **Tioconazole**
- **Sulconazole**
- **Butaconazole**
- **Oxiconazole**
- **Terconazole**

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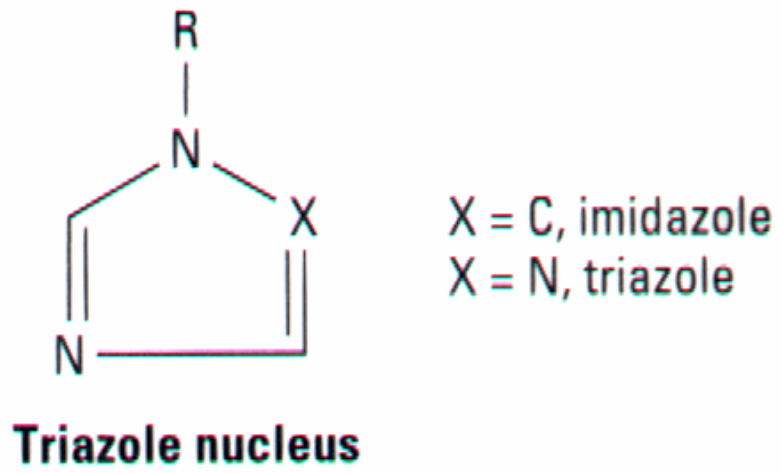
R
N
X
N
X = C, imidazole
X = N, triazole
Triazole nucleus

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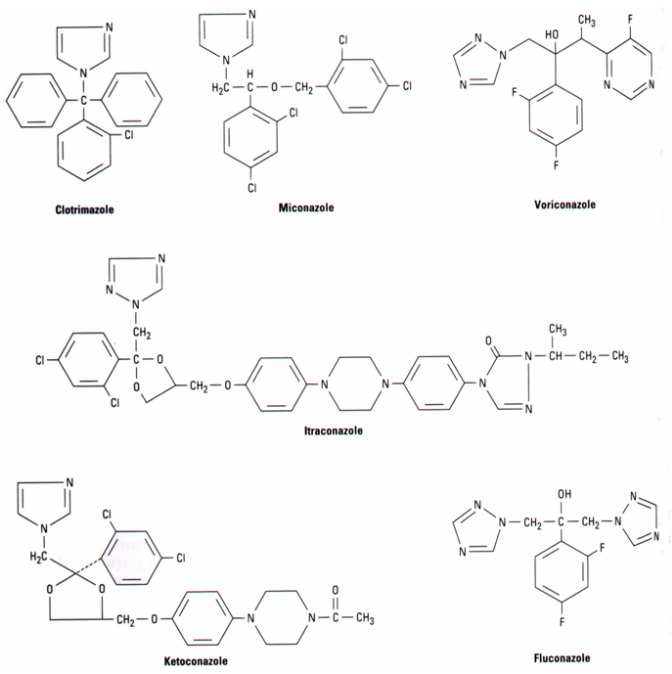
Clotrimazole
Miconazole
Voriconazole
Itraconazole
Ketoconazole
Fluconazole

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Mechanism of action of the azoles

- The azoles block the synthesis of ergosterol, the main sterol fungal cell membranes, by interacting with the enzyme necessary for the conversion of lanosterol to ergosterol.
- The overall effect is an inhibition of the transformation of candidal yeast cells into hyphe– the invasive and pathogenic from of the parasite.

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Ketoconazole

- Ketoconazole was the first azole that could be given orally to treat systemic fungal infections.
- It is effective against several different types of fungi.
- However it is toxic and relapse is common after apparently successful treatment.

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Pharmacokinetics

- It is orally active; best absorbed with low pH.
- It is widely distributed to body fluids except cerebrospinal fluid.
- It is inactivated in liver and excreted in bile and in urine.

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Adverse effects

- Liver toxicity has been reported and was fatal in few cases.
- Hepatic damage may even progress after stopping the drug.
- Other side effects include gastrointestinal disturbances and pruritus.

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Hormonal adverse effects

- In high doses it inhibits adrenocortical steroid and testosterone synthesis, the latter resulting in gynecomastia in some male patients.

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Fluconazole

- It can be given orally or IV.
- It reaches high concentrations in the cerebrospinal fluid and ocular fluids may become the drug of first choice for most types of fungal meningitis.
- Fungicidal concentrations are also achieved in vaginal tissue, saliva and nails.
- It has a half-life of ≈25 hours and excreted unchanged in the urine.

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Unwanted effects

- Generally mild, include nausea, headache and abdominal pain.
- However exfoliative skin lesions have been reported.
- Rarely hepatitis occurs.
- In the doses usually used, fluconazole does not produce the inhibition of drug metabolism and of steroidogenesis, which occurs with ketoconazole.

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Itraconazole

- It is given orally.
- Its absorption is variable and it undergoes extensive hepatic metabolism.
- Half-life ≈ 36 hours and it is excreted in the urine.
- If combined with flucytosine, it could be effective in fungal menengitis although it does not penetrate intact blood-brain barrier.

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Unwanted effects

- Unwanted effects include gastrointestinal disturbances, headache and dizziness.
- Rarely hepatitis, hypokalemia, hypertension and impotence.
- Allergic skin reactions have been reported.
- It does not inhibit steroidogenesis.

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Voriconazole

- The newest triazole in clinical trials.
- It may be given orally (bioavailibility <90%) and IV.
- Similar to itraconazole in action and antifungal spectrum.
- It undergoes hepatic metabolism however has low inhibition of P450.

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Table 48–2. Pharmacologic properties of four systemic azole drugs.

	Water Solubility	Absorption	CSF:Serum Concentration Ratio	$t_{1/2}$ (hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	...	High	...	6	Hepatic	Oral, IV

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Topical azoles

(Clotrimazole, miconazole, econazole, tioconazole, sulconazole, butaconazole, oxiconazole, terconazole)

- They are azole antifungal agents used for topical application.
- Clotrimazole interferes with amino acid transport into the organism by an action of cell membrane.
- Clotrimazole can also be given orally especially in the treatment of oropharyngeal candidiasis.

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Echinocandins I

- Echinocandins are the newest class of antifungal agent to be developed. They are large cyclic peptides linked to a long-chain fatty acid. **Caspofungin, micafungin,** and **anidulafungin** are the only licensed agents in this category of antifungals, although other drugs are under active investigation. These agents are active against both candida and aspergillus, but not *Cryptococcus neoformans*.

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Echinocandins II

Mechanism of Action

- Echinocandins act at the level of the fungal cell wall by inhibiting the synthesis of β(1-3)D-glucan. This results in disruption of the fungal cell wall and cell death.

Adverse Effects

- Echinocandin agents are extremely well tolerated, with minor gastrointestinal side effects and flushing reported infrequently. Elevated liver enzymes have been noted in several patients receiving caspofungin in combination with cyclosporine, and this combination should be avoided. Micafungin has been shown to increase levels of nifedipine, cyclosporine, and sirolimus. Anidulafungin does not seem to have significant drug interactions, but histamine release may occur during IV infusion.

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Echinocandins III

Clinical Use

- Caspofungin is currently licensed for disseminated and mucocutaneous candida infections, as well as for empiric antifungal therapy during febrile neutropenia. Note that caspofungin is licensed for use in invasive aspergillosis only as salvage therapy in patients who have failed to respond to amphotericin B, and not as primary therapy. Micafungin is licensed only for mucocutaneous candidiasis and prophylaxis of candida infections in bone marrow transplant patients. Anidulafungin is approved for use in esophageal candidiasis and invasive candidiasis, including septicemia.

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Griseofulvin

- It is a narrow-spectrum antifungal agent isolated from cultures of *Penicillium grisefulvum*.
- It is fungistatic and its mechanism of action involves an interaction with spindle formation in dividing cells and therefore with mitosis.

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Griseofulvin (continued)

- Impairment of microtubule function also interferes with the transport of material through the cytoplasm to the periphery, and this action is the basis of the inhibition of hyphal cell wall synthesis.
- In addition the drug binds to RNA inhibiting nucleic acid synthesis.
- Resistance has not been a clinical problem yet.

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Pharmacokinetics

- It is given orally, and variably absorbed from GIS.
- Then, it is taken up selectively by newly formed skin and concentrated in the keratin, there it retains much more than its plasma half-life.

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Unwanted effects

- They are infrequent.
- But the drug can cause gastrointestinal upsets, headache, photosensitivity and allergic reactions (rashes, fever).

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Topical allylamines

- Terbinafine and naftifine are allylamines available as topical creams.
- Both are effective in treatment of tinea cruris and tinea corporis.

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Terbinafine

- It is fungicidal allylamine for a wide range of skin pathogens. It selectively inhibits the enzyme squalene epoxidase which is involved in the synthesis of ergosterol from squalene in fungal cell wall.
- The accumulation of squalene is toxic to fungi. It is used to treat fungal infections of the nails.

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Unwanted effects

Usually mild and self-limiting:

- Gastrointestinal disturbances
- Rashes
- Pruritus
- Headache
- Dizziness
- Rarely hepatitis

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Table 45.1 Outline of the uses of antifungal drugs

Disease	Drug used
Systemic infections	
Systemic candidiasis	Amphotericin ± flucytosine,* fluconazole
Cryptococcosis (meningitis)	Amphotericin ± flucytosine,* fluconazole, itraconazol
Systemic aspergillosis	Itraconazole,* amphotericin
Blastomycosis	Itraconazole,* amphotericin
Histoplasmosis	Amphotericin, itraconazole, fluconazole
Coccidiomycosis	Fluconazole, itraconazole, amphotericin
Paracoccidiomycosis	Fluconazole, itraconazole, amphotericin
Mucormycosis	Amphotericin ± flucytosine*
Disseminated sporotrichosis	Amphotericin, itraconazole
Superficial infections	
Dermatomycosis	
Tinea pedis (athlete's foot)	A topical azole, or oral itraconazole
Tinea corporis (skin ringworm)	A topical azole, oral terbinafine, oral itraconazole
Tinea cruris	
Tinea capitis	Oral itraconazole
Tinea unguium (nail infection)	Oral or topical terbinafine, topical amorolfine
Candidiasis	
Skin	A topical azole, topical nystatin
Mouth (thrush)	A topical azole or nystatin, oral fluconazole
Vagina	A topical azole, oral fluconazole
Chronic mucocutaneous candidiasis	Fluconazole, ketoconazole†

*Drugs of choice
†The potential benefits of treatment should be carefully weighed against the risk of liver damage.

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Thank you...

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