

Antifungal Drugs — List of Drugs and Classification

[See online here](#)

In this article, we will study the details about various antifungal drugs, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be discussed.



Definition of Antifungal Drugs

Antifungals are the drugs that treat **fungal infections** by acting on the synthesis of the fungal cell membrane, cell wall components, membrane permeability, synthesis of nucleic acids and on the mitotic spindle function of the fungi during cell division.

Overview of Fungal Infections

Fungi are **non-motile eukaryotic** single-celled or multinucleate organisms formerly classified as plants that lack chlorophyll and cannot perform photosynthesis, hence parasitic in nature. Thousands of species have been identified, out of which some are the cause for local or **systemic fungal infection (mycoses)** in patients with **AIDS**, or humans whose immune systems are compromised by drug therapy or other means. This may cause serious, sometimes life-threatening infections.

Introduction into the host's body is mainly through wounds or inhalation into the lungs and nasal passages. Diseases caused by fungi are mainly due to the **Microsporium, Trichophyton or Epidermophyton** genera.

Various Types of Fungal Infections

Athlete's Foot

Tinea pedis (Athlete's foot): The infection is caused by *Trichophyton mentagrophytes* and *Trichophyton rubrum*. It is often located between the toes, with the space between the fourth and fifth digits most commonly afflicted; however, it can spread if not treated in time.



[Image:](#) "A severe case of athlete's foot." by James Heilman, MD. License: [CC BY-SA 3.0](#)

Ringworm Infection

Tinea corporis (ringworm): The infection is caused by *Microsporum canis*, *Trichophyton mentagrophytes* via direct skin contact with an infected individual, or by using the personal care products of the affected individual.



[Image](#): "Ringworm on the arm, or tinea corporis due to *Trichophyton mentagrophytes*." by CDC. License: [Public Domain](#)

Brazilian Blastomycosis

It is caused by ***Paracoccidioides brasiliensis*** and is a systemic infection involving mucous membranes, lymph nodes, bone and lungs and prevalent in South America. Amphotericin B, Itraconazole or ketoconazole are effective in treating the infection.

Candidiasis



[Image](#): "Human tongue infected with oral candidiasis." by James Heilman, MD. License: [CC BY-SA 3.0](#)

Candidiasis is caused by yeast ***Candida Albicans***. It is commonly present as a saprophyte in the GI tract and **genitourinary system** of human beings. However, it can infect locally or systemically and cause serious systemic infections with multi-system organ failure.

Mucormycosis

The infection is caused by the genera *Mucor*, *Rhizopus*, *Absidia*, and **Cunninghamella** with the affected areas being sinuses, eyes, blood, and brain.

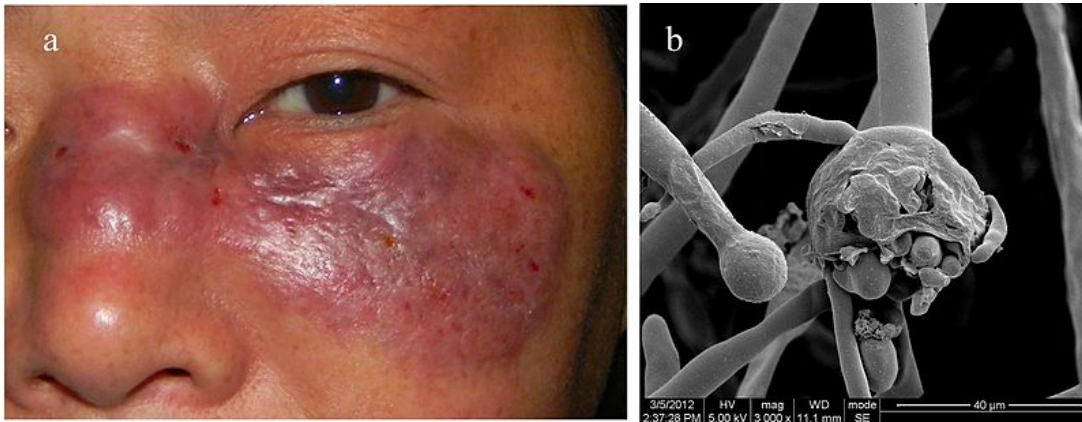


Image: "Mucormycosis" by Ran Yuping et al. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Classification of Anti Fungal Drugs

These agents are categorized as:

- Topical vs systemic (acting in the bloodstream)

Naturally occurring:

- Antifungal Antibiotics (mostly produced by Actinomycetes, classified as 'higher bacteria'). **Examples:** Amphotericin B (AMB), a polyene antimycotic, Nystatin
- Antifungals of fungal origin. **Example:** Griseofulvin, a Heterocyclic Benzofuran discovered in 1939 from a type of *Penicillium* mold

Synthetic Agents:

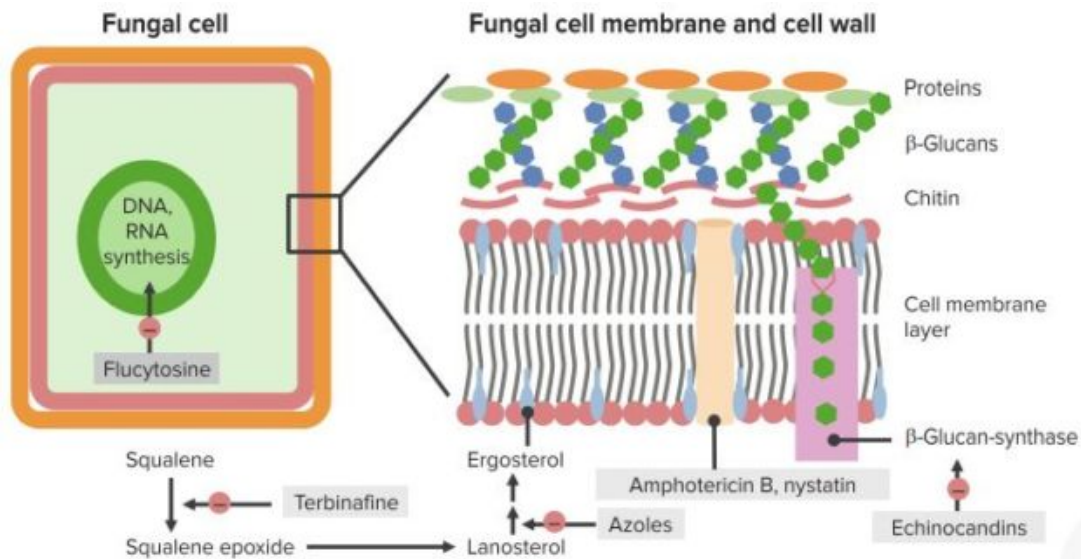
- Azoles
- Imidazoles: Clotrimazole, Econazole, Miconazole, Oxiconazole, Ketoconazole
- Triazoles: Fluconazole, Itraconazole, Voriconazole
- Anti-metabolites: Flucytosine (5-FC)
- Allylamine: Terbinafine (Lamisil)

Newest antifungals:

- Echinocandins

Membrane permeability agents	β -Glucan synthesis blockers	Microtubule function inhibitors	Nucleic acid synthesis blockers
<ul style="list-style-type: none"> • Azoles • Terbinafine • Polyenes 	Echinocandins	Griseofulvin	Flucytosine

Antifungal Drugs



"Overview Pharmacology Antifungals" Image created by Lecturio

Below you can find different kinds of antifungal drugs.

Amphotericin B (AMB)

It is derived from cultures of *Streptomyces Nodosus* and is a very large ('macrolide') molecule belonging to the polyene group of antifungal agents.

Mechanism of Action

The molecule has a high affinity for **ergosterol** present in the fungal cell membrane and combines with it in such a way to make a '**micropore**.' The basic mechanism of the drug is to disrupt the **cell membrane**. It is **fungicidal** at high and **fungistatic** at low concentrations.

Important: Amphotericin is not active against human and bacterial sterols as the predominant sterol found in bacteria and humans are cholesterol.

Indication

Amphotericin B is active against a wide range of yeasts and fungi: *Candida Albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Torulopsis*, *Rhodotorula*, *Aspergillus*, and *Sporothrix*, etc. It does not have any **anti-bacterial property**. It is the most effective drug for resistant cases of kala-azar and **mucocutaneous leishmaniasis**.

Pharmacokinetics

Amphotericin B is not absorbed orally; that is why it is administered **intravenously** and rarely **intrathecally** (for fungal meningitis). Amphotericin B has a half-life of 15 days. The excretion through urine requires a long time, although excretion occurs slowly both in the urine and bile. Penetration into the CNS is poor; about 60% of AMB is metabolized by the liver.

Side Effects

Nephrotoxicity is the most important side effect. Acute reactions may be triggered by symptoms consisting of chills, fever, aches, and pain, nausea, vomiting, and dyspnea lasting for one hour, probably due to the release of **cytokines**. To reduce the side effects

and improve the tolerability of infusion, formulations of lipid complex, colloidal dispersion, and small unilamellar vesicles have been introduced.

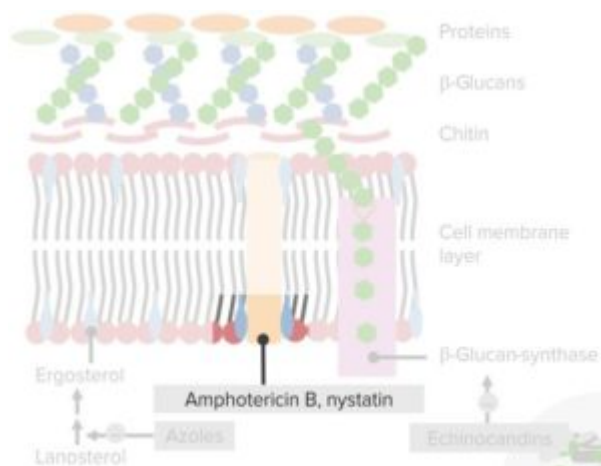
Important: Irreversible renal toxicity can result in prolonged administration (more than 4g cumulative dose).

AmBisome (liposome-based), Amphotec (a complex of amphotericin B and cholesteryl sulfate), Abelcet (consists of amphotericin B complexed with two phospholipids) are the lipidic formulations available to reduce the renal toxicity of the conventional amphotericin B; however, these are very costly.

Nystatin

It is also called **fungicidin** with a similar structure to that of Amphotericin B. It is derived from ***Streptomyces noursei*** and has high systemic toxicity, hence, it is commonly used as a topical agent.

Mechanism of Action



"Fungal cell membrane and cell wall. Nystatin" Image created by Lecturio

The molecule also has a high affinity for **ergosterol** present in fungal cell membranes and it disrupts the cell membrane.

Indication

It is used against **monilial vaginitis**, corneal, **conjunctival** and **cutaneous candidiasis** in the form of an ointment but is ineffective in **dermatophytosis**. Nystatin can be added to tetracycline to prevent monilial overgrowth caused by the destruction of **the bacterial microflora** of the intestine during tetracycline therapy.

Pharmacokinetics

It is given in the form of vaginal tablets and pastilles for local application only. Nystatin will treat **gut candidiasis** and is used in a '**swish and swallow**' routine for oral candidiasis.

Side Effects

The common side effects associated are itching, irritation and burning. Rarely, nystatin can cause diarrhea and nausea.

Griseofulvin

Griseofulvin is a narrow-spectrum antifungal agent isolated from cultures of *Penicillium griseofulvum*, and is active against dermatophytes, including Epidermophyton, Trichophyton, Microsporum, but not against fungi causing deep mycosis.

Mechanism of Action

The mechanism of action of griseofulvin is not clear. It is thought to **interfere with mitosis** during the **fungal hyphae** formation. It also causes abnormal metaphase in the division of cells by acting in a way that the daughter nuclei fail to move apart, or move only a short distance during division. It does not **inhibit polymerization of tubulin**, but binds to polymerized microtubules and disorients them.

Pharmacokinetics

The absorption of the drug is improved by taking it with a **fatty meal** and by microfining the drug particles. Griseofulvin gets deposited in **keratin** forming cells of skin, hair, and nails; concentrating in tinea infected cells because it is **fungistatic** and not cidal. The newly formed keratin is not affected by the fungus.

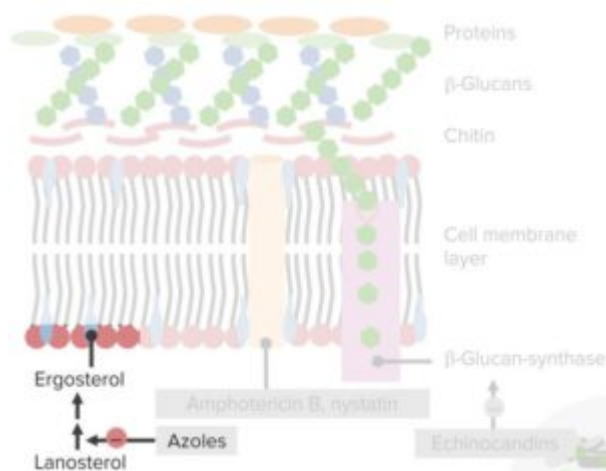
Side Effects

Effects with griseofulvin use are infrequent, but the drug causes gastrointestinal upsets, headache, and photosensitivity. **Allergic reactions** (rashes and fever) may occur. The drug is **contraindicated in pregnant** women.

Azoles and Triazole Agents

These are synthetically derived antifungal agents, both used **orally and topically**. They are used for treating a large number of infections caused by **dermatophytes, Candida**, other fungi involved in **deep mycosis, Nocardia**, some gram-positive and **anaerobic bacteria**, e.g., *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacteroides fragilis* and *Leishmania*.

Mechanism of Action



"Fungal cell membrane and cell wall. Azole antifungals." Image created by Lecturio

The azoles constitute imidazoles and triazoles subgroups and act by inhibiting **CYP P450 14 α -demethylase enzyme** in fungi which causes the conversion of **lanosterol to**

ergosterol. Other P450s in sterol biosynthesis may also be affected.

The nitrogen of the azole ring forms a bond with the heme iron of the fungal P450 preventing substrate and oxygen binding, leading to changes in shape and physical properties of the fungi membrane, leading to permeability and fluidity changes. They also inhibit the transformation of yeast cells into hyphae, the invasive and the pathogenic form of the parasite.

Ketoconazole (KTZ)

It is available in the form of a cream or in shampoos at a strength of 1 or 2 % for treating **tinea pedis, tinea corporis, tinea cruris, and cutaneous candidiasis**. It can also be administered orally.

Pharmacokinetics

The oral absorption of KTZ is improved by **gastric acidity** because it is more soluble at lower pH. **Hepatic metabolism** is extensive for the drug; metabolites are excreted through urine and feces. The half-life is short and varies from 1.5—6 hours.

Side Effects

The drug causes inhibition of **adrenocortical steroid** and **testosterone synthesis** with high doses, leading to **gynecomastia**, loss of hair and **libido** in male patients. In females, **menstrual irregularities** may occur. **Hepatotoxicity** is also a side effect but is rarely fatal.

Clotrimazole

The topical application of the drug is useful in treating **tinea pedis, ringworms, otomycosis**, and oral/cutaneous **vaginal candidiasis**. It is the preferred drug for treating **vaginitis** because of a long residual effect after a once-daily application. The drug is also combined sometimes with glucocorticoids, which are anti-inflammatory in nature.

Side Effects

The drug is well tolerated; however, causes a **local irritation with a stinging** and burning sensation occurring in some. No systemic toxicity is seen after topical use.

Fluconazole

It is marketed in the form of a tablet or suspension to treat **yeast infections** of the vagina, mouth, throat, esophagus, abdomen, and lungs.

Important: it is a drug of choice for **esophageal and invasive candidiasis** and **coccidioidomycoses**.

Pharmacokinetics

Fluconazole is 94 % absorbed; oral bioavailability is unaffected by food or gastric pH. It is primarily excreted unchanged in the urine with a $t_{1/2}$ of 25—30 hours.

Side Effects

Prominent side effects are nausea, **vomiting, abdominal pain**, rash, and headache. Elevation of **hepatic transaminase** has been noted in **AIDS** patients. As compared to

other azoles, it has the least effect on **liver microsomal enzymes**.

Voriconazole

The drug is present in the form of oral suspension, tablets or parenteral injection. It is used to treat **serious fungal infections** and may be used in patients who have not responded to other antifungal agents.

Rashes, visual disturbances, **QT prolongation** and an acute reaction on the IV injection are the significant adverse effects.

Flucytosine (5-FC)

It is an antifungal drug, which acts by blocking the **pyrimidine** and **DNA synthesis** in fungi. It is converted to its active metabolite (5-FU) by fungal cells.

The pathway of conversion is below:

Flucytosine → (5-FC) → 5-Fluorouracil (5-FU) → 5-fluorodeoxyuridine monophosphate

No toxicity in humans due to 5-FC as human cells can't convert 5-FC to 5-FU.

It is not used as a single agent for fungal infections but is used with other antifungal agents such as amphotericin B (**cryptococcal meningitis**) and itraconazole (**chromoblastomycosis**).

Side-effects are reversible bone marrow depression, liver dysfunction, and alopecia.

Terbinafine

It is fungicidal and is given in shorter course therapy and the relapse rates are low. It is particularly useful against **Dermatophytes**, especially **nail infections**, along with the treatment of **candida infection**. It is available for oral, as well as topical use.

Mechanism of Action

It acts as a non-competitive **inhibitor of 'squalene epoxidase'**, an enzyme in **ergosterol biosynthesis** by fungi. Accumulation of toxic **squalene** within fungal cells leads to the fungicidal action.

Pharmacokinetics

Approximately 75 % of oral terbinafine is absorbed. The drug is lipophilic and is widely distributed in the body, strongly plasma protein bound and concentrated in sebum, stratum corneum and nail plates. Elimination $t_{1/2}$ of 11–16 hours is prolonged to 10 days after the repeated dosing schedule.

Side Effects

The common side effects are gastric upset, rash and taste disturbance. Some cases of **hepatic dysfunction**, hematological disorder, and severe cutaneous reaction also occur.

Echinocandins

These are recently discovered antifungal drugs. Examples of drugs in this class are caspofungin and dulafungin.

They act by blocking the **synthesis of β (1–3)-glucan** in fungus.

They are active against *Candida spp.*, ***Aspergillus spp.***, ***pneumocystis carinii***; however, they are not active against ***Cryptococcus neoformans***.

They are poorly absorbed from the GI tract, thus they are only available as intravenous formulation.

They are well tolerated and have only minor gastrointestinal side-effects such as nausea and vomiting. Other side-effects are **headache** and **flushing**.

Review Questions

The right answers can be found below the references

1. Which of the following is the drug of choice for the treatment of Chromomycosis?

- A. Griseofulvin
- B. Itraconazole
- C. Amphotericin B
- D. Hamycin

2. Which of the following causes athlete's foot?

- A. Tinea capis
- B. Tinea pedis
- C. Tinea cruic
- D. Tinea unguium

3. Which of the following is the source for Amphotericin B?

- A. Streptomyces nodosus
- B. Echinococcus granulosus
- C. Streptomyces noursei
- D. Corynebacteria

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Correct Answers: 1B, 2B, 3A

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Notes