

ANTIFUNGAL AGENTS

Objectives:

1. To learn the general classes of fungal infections
2. To learn the subclassification of antifungal drugs
3. To know the mechanism of action and basic uses for antifungal drugs

Fungus is among us

Fungal infections (mycoses), though not as frequent as bacterial or viral infections, have nonetheless been increasing in incidence in the human population over the last 15 years or so, largely as a consequence of increased numbers of cancer and immunocompromised patients, who are at greater risk owing to weakened immune systems and the chronic nature of the diseases. In addition, a number of fungal infections can be difficult to treat (oft referred to as 'stubborn'), even when the offending organism is identified and appropriate therapy is applied. On the other hand, like bacteria, fungi have unique characteristics, distinct from their mammalian hosts, allowing for selective targeting of therapeutic drugs. Fungi are, however, much more complex organisms in comparison to bacteria, are in fact eukaryotic and often grow fairly slowly. Consequently, only a few drugs are aimed at interfering with cell division and have limited use. Most antifungal drugs are targeted to the cell membrane.

Major fungal infections

The number of different kinds of fungi out there is vast, and, of course, some of them are pleasant to eat. Only a small subset is capable of infecting humans. The following is a very general breakdown of types of fungal infections that occur based on site of infection:

Cutaneous = skin, hair and nails Most common
eg. 'Athlete's foot', Ringworm, and *Tinea cruris*

Mucocutaneous = moist skin and mucous membranes, Common
such as GI, perianal and vulvovaginal areas
eg. *Candida albicans*

Pulmonary/Systemic Less
frequent
eg. Invasive *Aspergillus*, cryptococcal meningitis, pulmonary histoplasmosis; also, systemic candidiasis

Systemic fungal infections are more serious as they are usually more difficult to diagnose, are chronic in nature, and, in some cases, can become life-threatening. They occur more frequently in individuals with compromised immune systems (AIDS patients; transplant patients; cancer patients). Prophylactic treatment is sometimes indicated in AIDS patients and bone marrow transplant patients, but risk of developing resistance is high. Life-threatening infections require the use of more potent but much more toxic antifungals.

Superficial fungal infections are almost always caused by dermatophytes or yeasts. In some instances, they can be rather tenacious, requiring very long treatments, sometimes with both oral and topical drugs.

Drug Classes

Note that the antifungals are classified by structure or mechanism, not by site of action, as some of them may be used, for example, either topically or systemically depending on the infection.

1. (*Macrolides*)

Amphotericin B

Mechanism of action: binds to sterols present in the plasma membrane
more selective for ergosterol = major fungal sterol
forms cytotoxic pores
broadest spectrum of any antifungal

Absorption: very poor
given slowly IV as liposome suspension, or used topically
given orally for GI fungi, but as such is really acting 'topically'

Uses:

initial **drug of choice** for **life-threatening systemic infections**

Invasive *Aspergillus* (30% survival); used with itraconazole
Cryptococcal meningitis; used with flucytosine (alternative: fluconazole)
Rapidly developing Histoplasmosis
some limited use for cutaneous (dermatophytic) infections
or mucocutaneous infections

Adverse effects: fairly toxic [some binding to mammalian membranes; effects reduced via use of liposome delivery]
- fever and chills; vomiting; muscle spasms; modest hypotension (nearly 100% but treatable; small test dose usually given to assess reactions)
- **renal impairment** (near 80%)
- hypokalemia (= reduced serum K)

Nystatin

Mechanism of action: same as for Amphotericin B

Absorption: extremely poor

Uses: much too toxic for systemic (parental) use

→ used only **topically**

local (dermal), oropharyngeal, GI and vaginal candidiasis only
[other than its nasty, bitter taste, adverse effects are uncommon]

2. (*Antimetabolite*)

Flucytosine

Mechanism of action: selectively converted by fungi to active metabolites
inhibits fungal RNA and DNA synthesis

Absorption: well absorbed; used orally (only)

Uses: **only in combination** with

→ amphotericin B for cryptococcal meningitis

→ itraconazole for blastomycoses

[high incidence of resistance as well as toxicity reduced via use in drug combinations]

Adverse effects: (narrow therapeutic window)

→ results from fluorouracil = major metabolite

- inflamed bowel (enterocolitis)

- **bone marrow toxicity**

- possible liver toxicity

3. (Cytoskeleton Agent)

Griseofulvin

Mechanism of action: proposed to inhibit microtubules

blocks fungal mitosis, therefore is **fungistatic**

also binds keratin

Absorption: poor - very insoluble

orally administered in a microcrystalline form

(improved when taken with fatty foods)

Uses:

systemic uses for dermatophytosis (eg. skin and, esp. nail infections, though for the latter terbinafine is preferred),

requiring **extended treatments** [after or sometimes with treatment with triazoles]

[also highly effective against Athlete's foot and ringworm]

Adverse effects: (low incidence)

- allergic syndrome (like serum sickness: fatigue.. - rare)

- hepatitis

- drug interaction with warfarin or phenobarbital

4. (Imidazoles)

Mechanism of action: inhibit fungal ergosterol biosynthesis

selectively inhibit fungal cytochrome P₄₅₀ enzymes

Ketoconazole

(original oral 'azole', not as selective as newer azoles, ie. significant inhibition of mammalian P450 enzymes)

Absorption: low - improved with food and low gastric pH
used orally, but has very slow onset; poor CSF and urinary tract penetration

Uses:

mucocutaneous candidiasis

coccidioidomycosis (non-meningeal)

in shampoos for seborrheic dermatitis

(largely supplanted by more expensive itraconazole or fluconazole)

Adverse effects: (narrow therapeutic window) highly dose-dependent

- nausea and vomiting

- endocrine: interferes with adrenal and gonadal steroid synthesis*

- hepatotoxicity (rare but can prove fatal)

- drug interactions

→*action on human cytochrome P₄₅₀ (eg. ↑ warfarin; ↑ cyclosporine; and vice versa)

→ decreased absorption of ketoconazole when administered with rifampin, H₂ antagonists or antacids

Miconazole and Clotrimazole

Absorption: extremely poor - both used topically: creams and, in the case of clotrimazole, oral troches (=lozenges)

Uses: wide-spread, over-the-counter use as **topical** antifungals

vulvovaginal candidiasis

dermatophytic infections (eg. *tinea corporis*)

oropharyngeal thrush (candidiasis; alternatives to nystatin)

5. (Triazoles)

Mechanism of action: inhibit fungal ergosterol biosynthesis

Itraconazole ***

Absorption: OK, low bioavailability (no CSF penetration)
- improved with food and low gastric pH

Uses: **most potent** of the azoles for systemic infections
drug of choice for **persistent dermatophytic infections**
effective against all types of Aspergillus infection
preferred agent for endemic mycoses (eg. *Histoplasma*)

Adverse effects:

- drug interactions (esp. non-sedating antihistamines)
(no effect on steroid biosynthesis; variable effect on mammalian P₄₅₀ system, less than with ketoconazole but still of potential concern)

Fluconazole

Absorption: good; used orally and IV (excellent **CSF penetration**)

Uses:

agent of choice for **cryptococcal meningitis** (unless life-threatening: use AmpB)
mucocutaneous candidiasis
prophylactically for bone marrow transplants and AIDS patients

Adverse effects: (widest therapeutic window) few and mild
concern for all azoles: newly observed emergence of resistant strains in AIDS
[resistance to azoles is otherwise fairly rare]

Voriconazole (most recently approved (2002) azole, derived from fluconazole)

Absorption: good; used orally and IV (good CSF penetration, however*)

Uses:

agent of choice for invasive *Aspergillus*
active against *Candida* (even those resistant to fluconazole), *Cryptococcus* and endemic mycoses, but ineffective against mucormycosis (soil saprophytes)

Adverse effects: sporadic visual disturbances* (~30%); hepatotoxicity (2-3%)

6. (Allylamines)

Naftifine and Terbinafine

Mechanism of action: inhibits fungal squalene metabolism
increased levels of squalene are toxic to fungi; also reduces ergosterol

Uses: effective for most cutaneous mycoses either topically (eg. tinea corporis and tinea cruris) or, in the case of terbinafine, orally for nail infections (90% cure rate, without side effects)

[not effective against *Candida*]

7. (Echinocandin)

Caspofungin (most recently approved antifungal – Jan 2001)

Mechanism of action: inhibits beta (1,3)-D-glucan synthesis, blocking cell wall synthesis

Absorption: poor; highly protein; administered IV

Uses: active against a number of fungi, but particularly effective against invasive candidiasis and aspergillosis (promising new alternative to amphotericin) via once daily IV administration; no activity against cryptococcus

Adverse effects: fever, nausea, vomiting, flushing; some irritation at inj site; elevation of liver enzymes

small

Quicklist of key drugs:

	<u>Action</u>	<u>Use</u>
Amphotericin B	Cytolytic via ergosterol binding: Forms pores in membrane	Broad spectrum: mainly for life-threatening infections; given IV via liposome suspension oral: not absorbed - topical
Nystatin	Cytolytic via ergosterol (as for Amp B)	Topical only (too toxic for systemic use); for Candida
Flucytosine	Antimetabolite (toxic to bone marrow)	in combination only for meningitis & blastomycoses
Griseofulvin	Antimitotic via microtubule Inhibition	Oral for dermatophytosis
Ketaconazole	Blocks ergosterol synthesis via P ₄₅₀ inhibition (not selective)	Oral for mucocutaneous candidiasis; coccidoidal mycoses
Miconazole Clotrimazole	Blocks ergosterol synthesis	Topical for Candida; dermatophytes oropharyngeal infection
Intraconazole	Selective block of ergosterol	Oral (no CSF penetration) for Dermatophytoses; Aspergillus; Endemic mycoses
Fluconazole	“	Oral (good CSF penetration) for Meningitis; Candida; prophylactic for marrow transplants & AIDS
Voriconazole	“	Latest triazole; oral and IV (good CSF penetration) for Aspergillus; Meningitis; Candida
Terbinafine Naftifine	inhibits squalene metabolism - squalene is toxic; also blocks Ergosterol **	Cutaneous mycoses
Caspofungin	Blocks cell <u>wall</u> synthesis via IV: inhibition of beta (1,3)-D-Glucan synthesis	invasive candidiasis & aspergillus

