Antifungal agents

- A history of pharmaceutical neglect:
  - Rare
  - Difficult to devise
  - Difficult to test in vitro
  - Not renumerative
- Escalating pace of research but
- Old gold standard

Available classes

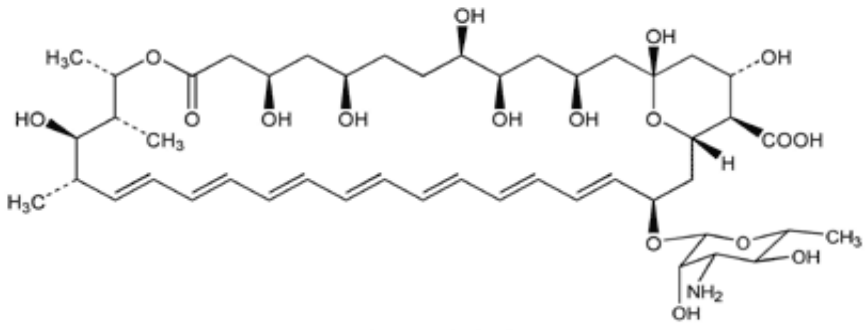
- **Polyenes** (cell membrane synthesis
- **Azoles** (cell membrane synthesis)
- **Echinocandins** (cell wall synthesis)
- Miscellaneous (nucleic acid, cell membrane synthesis)

1. Polyenes

- First antifungal antibiotics
- Isolated from Streptomyces spp.
- General structure:
  - Polyenes (multiple conjugated double bonds)
  - Macrolides (large rings with lactone linkage)

Polyene structure

Lipophilic, hydrophobic, hydrophilic, amphipathic, amphoteric

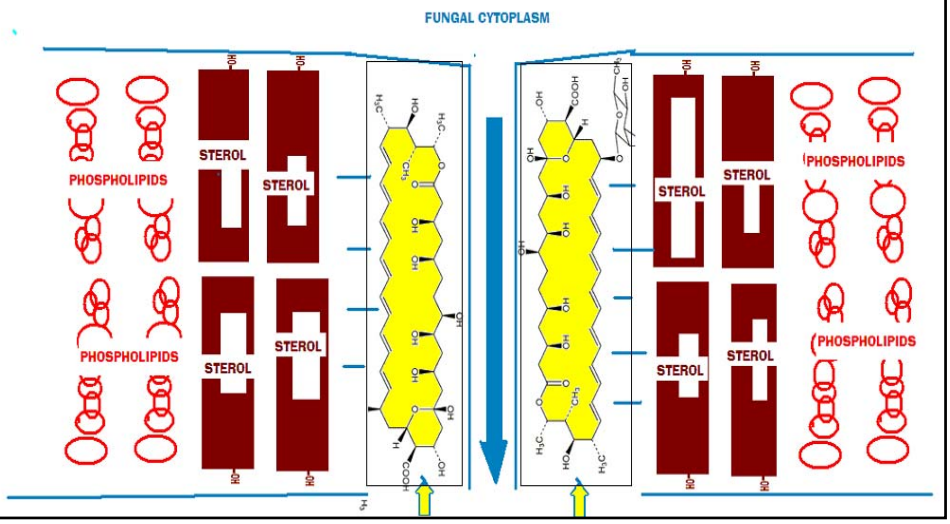


amphotericin B

Polyene mechanism of action

- Macrolide ring inserts into membrane parallel to phospholipid chains, binding to sterols
- Cylindrical channels form
- Cations, then macromolecules leak out
- Cell dies

Polyene action



Polyene resistance

- Most clinically important fungi sensitive
- Dermatophytes resistant
- Inducible resistance rare (old drugs still work)
- Inherent resistance due to deminished membrane ergosterol with less affinity for drug

Polyenes: Nystatin

- 1950 in NYState
- Topical administration only
- Too toxic for systemic administration
- Uses:
  - Skin and mucosal candida infection especially oral thrush. No effect on dermatophtyes

Amphotericin B

- 1954 from Venezuela
- Not soluble in water at physiologic pH
- Not orally absorbed
- Occasional oral use of suspension for "topical" treatment of oral or esophageal candidiasis
- IV use: gold standard of antifungals

Amphotericin B

- Colloidal dispersion in deoxycholate (bile salt)
- Protein bound. Urine and CSF concentrations low. Tissue stores slowly released
- Significant toxicity:
  - Infusion-related
  - Cumulative

Infusion-related AmB toxicity

- Dramatic infusion-related **fever, chills, nausea, vomiting, diarrhea, dyspnea**
- ?cytokine/prostaglandin related
- Treatment: symptomatic premedication
  - Acetaminophen
  - Benadryl
  - Cortisone
  - Demerol
  - ?Duration of infusion

Cumulative AmB toxicity

- **Renal**: characteristic cation-wasting nephropathy days-weeks into treatment. Low K+, Mg++, elevated creatinine. Treatment-limiting. (vasoconstriction, tubular cell lysis)
- **Hematologic**: characteristic normocytic anemia (direct marrow toxicity /renal)

Amphotericin B uses

- Systemic fungal diseases caused by
  - **Yeasts** (candidiasis, cryptococcosis)
  - **Molds** (aspergillosis, mucormycosis)
  - **Dimorphs** (histo, blasto, cocci)
- Toxicity has shaped usage patterns

Amphotericin B modifications

- Drug encased in liposomes or otherwise highly lipid associated has less toxicity and equivalent efficacy
- Mechanism unclear (?direct delivery by macrophages)

- **Liposomal**
- **Lipid complex**
- **Colloidal dispersion**

- Used in confirmed disease
- **$$$**

2. Azoles

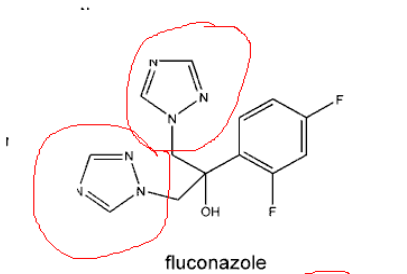
- 1970s to present
- From topical to powerful oral and IV drugs

- Imidazoles: 2N in 5-membered ring
- Triazoles: 3N in 5-membered ring

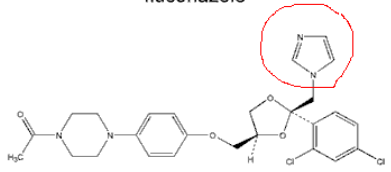
Azole structures

- Fluconazole: bis-triazole

- Ketoconazole: imidazole



fluconazole



ketoconazole

Azole mechanism of action (and toxicity)

- Inhibit fungal cytochrome P450 enzymes which demethylate lanosterol to ergosterol
  - Block formation of ergosterol
  - Cause accumulation of toxic alpha-14 methyl esters in fungal cell
  - Sabotage membrane integrity
- "Fungistatic"

Toxicity of Azoles

- inhibit cholesterol-dependent steroid hormone synthesis (testosterone; cortisol)
- Lead to ccumulation of metabolites with aldosterone-like effects
- Interfere with metabolism of other cytochrome P450 metabolized drugs

Resistance to Azoles

- Intrinsic, esp. nonalbicans Candida
- Inducible rare, but increasing with increasing use
  - Alteration in P450 enzymes
  - Membrane lipid changes with decreased permeability

Older Azoles

- **Clotrimazole** (Mycelex, Desenex, Lotrimin, Gyne-lotrimin)
- **Miconazole** (Monistat)
- **Terconazole** (Terazol)

- Topical only
- Minimal toxicity
- Used for dermatophyte and mucosal candidal infections

Newer azoles: Ketoconazole

- 1983
- Soluble in water at acid pH
- Highly protein/tissue bound
- Dose-related adrenal and testosterone suppression

Clinical uses:

- Mucosal candidiasis (largely supplanted)
- Sporotrichosis
- Cocci
- Pityriasis and dermatophytes (Nizoral shampoo)

Newer azoles: Fluconazole

- 1990
- Soluble in water at neutral pH.
- Good oral absorption, urine and CSF penetration
- IV form available
- Toxicity primarily hepatic

Clincal uses:

- Cryptococcal meningitis
- Mucosal and esophageal candidiasis
- Systemic candidiasis (efficacy rivals AmB in some settings)
- Cocci

Newer azoles: Itraconazole

- 1992
- Poorly water-soluble
- Protein and tissue-bound.
- Very high adipose and keratinized tissue levels

Clinical uses:

- Sporotrichosis
- Histoplasmosis
- Blastomycosis
- Cocci
- Nail dermatophytes
- Some activity against aspergillosis, sometimes.

Newest azole: Voriconazole

- Synthetic derivative of fluconazole with oral and IV dosing
- Unique visual toxicity

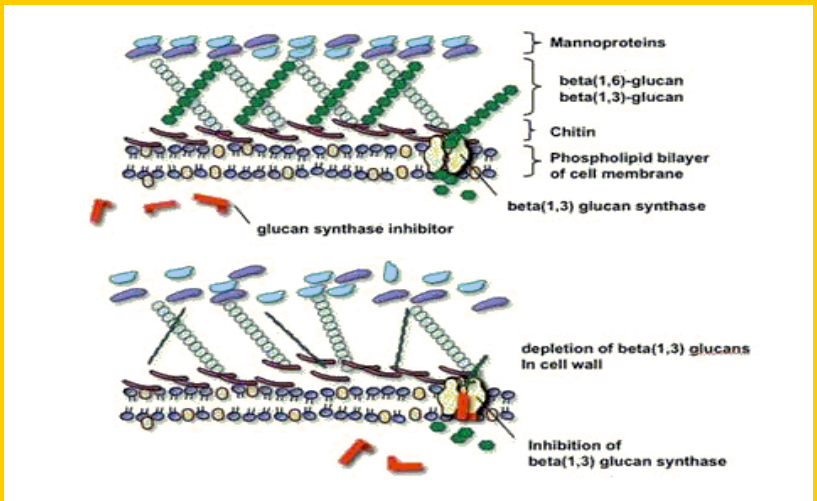
Clinical uses:

- Enhanced in vitro activity against Aspergillus, resistant Candida
- Promising in vivo results

3. Echinocandins

- Inhibit fungal cell wall synthesis
- Irreversible inhibitors of 1,3 beta glucan synthase
- "Fungicidal" against wide range
- Little direct human toxicity

Echinocandin action



Echinocandins

Caspofungin: January 2001

- Slow IV infusion with infusion-related events, but generally well tolerated
- Approved for invasive aspergillosis failing other therapy

Others: **Micafungin** for esophageal candidiasis

Other agents

Griseofulvin (1939)

- Disrupts microtubules
- Active only against **dermatophytes**, and not very.
- Relatively nontoxic
- Heading out

Allylamines and thiocarbamates

- Inhibit squalene epoxidase (ergosterol synthesis)
- **Dermatophytes** only
- Lamisil (terbinafine)

Fluorocytosine (5-FC, Flucytosine)

- Deaminated to 5-FU by bacterial and fungal cells
- Inhibits DNA synthesis in range of pathogens
- Rapid evolution of resistance precludes solo use
- Synergy in cryptococcisis , ?others
- Toxicity: **bone marrow suppression**, gastritis

Clinical options: mucosal candidiasis

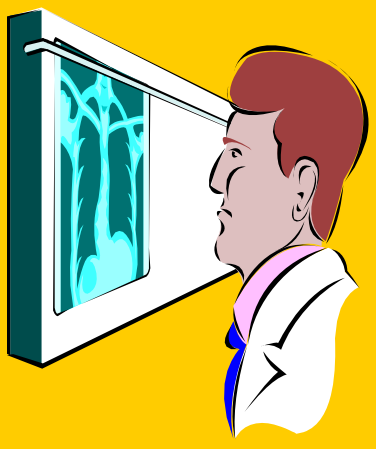
- Topical polyene
- Topical azole
- Oral azole
- IV azole
- IV Amphotericin B
- Echinocandin?
- Remove breach in defense!

Clinical options: dermatophytes

- Topical azole
- Systemic azole (especially nails)
- Allylamine
- (griseofulvin)

Clinical options: Histo, Blasto, Cocci

- Amphotericin B
- Lipid-associated amphotericin B
- Newer azoles, oral or IV



Clinical options: cryptococcal meningitis

- Amphotercin B
- Fluconazole
- Itraconazole
- Synergy with 5-FC

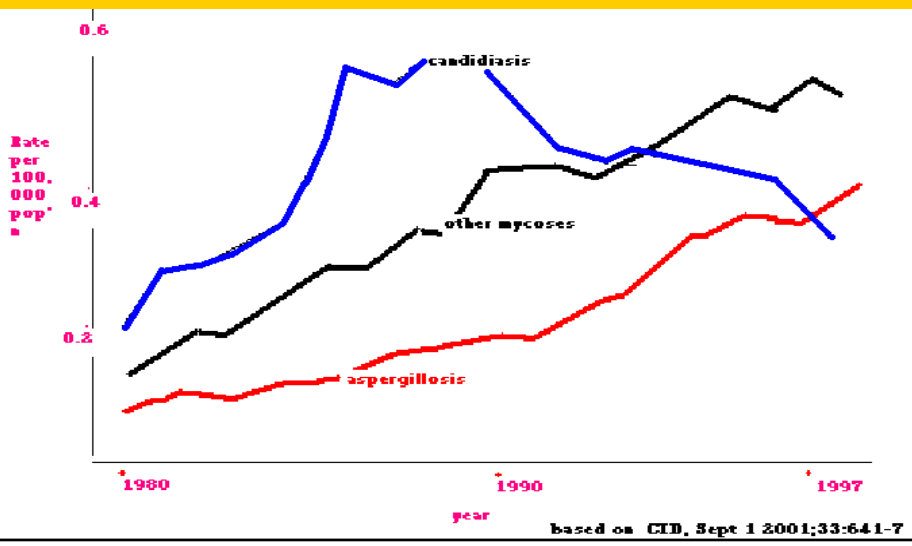
Clinical options: systemic candidiasis

- Amphotericin B
- Lipid-associated amphotericin B
- Fluconazole
- Voriconazole
- Caspofungin

Clinical options: aspergillosis

- Amphotericin B
- Lipid-associated amphotericin B
- Voriconazole
- Caspofungin

Mortality due to mycoses, 1980-97

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