Antifungal Agents and Antifungal Therapy

http://www.doctorfungus.org/thedrugs/

History of Antifungals
• From late 1800’s to ca. 1950, treatments for fungal infections consisted mainly of surgical interventions as well as several non-surgical treatments
  – Potassium Iodide (KI)
  – Phenol
  – Dyes
  – Noxious agents such as bromine, permanganate, and oil of turpentine with olive oil

History of Antifungals (cont.)
• First successful antifungal – supersaturated potassium iodide (SSKI)
  – Oral solution for treating cutaneous sporotrichosis
  – Limited spectrum of effectiveness
• Discovery of active and safe antifungals
  – Griseofulvin (1939 by Oxford)
  – Benzimidazole (1944 by Wooley)
  – Propamidine (1945 by Elson)
  – Nystatin (1950 by Brown and Hazen)

History of Antifungals (cont.)
• Nystatin was the first antifungal with important implications for the treatment of fungal infections
• Named new antifungal for their employer: NY (New York) – Stat (State) –in
• Brown and Hazen donated all Nystatin royalties to academic science (> $13 million)

History of Antifungals (cont.)
• Propamidine and stilbamidine (and derivatives) used to treat blastomycosis (1951)
• Amphotericin B (discovered in 1955) used to treat blastomycosis
• IV amphotericin B developed in 1960
• However, discovery of safe and effective antifungal drugs slowed over the next 30 years
History of Antifungals (cont.)

- 5-fluorocytosine (flucytosine; 5FC) – developed in 1964, was initially effective against *Candida* and *Cryptococcus*, but resistance limited its use as monotherapy
- 5FC now used in combination with amphotericin B
- The topical agents, miconazole and clotrimazole were developed in 1969

History of Antifungals (cont.)

- Additional antifungals
  - Econazole (1974)
  - Ketoconazole (1981)
  - Allylamines (1970-1980s)
  - Lipid formulations of polyenes (1970-1980s)
  - Fluconazole and Echinocandins (1990s)
- Introduction of fluconazole transformed the development of antifungals

Antifungal Targets

- Similarities of fungi and mammals have made the search for appropriate targets difficult
- Three main targets due to differences
  - Plasma membrane sterols
  - Nucleic acid biosynthesis
  - Cell wall components
Current Systemic Antifungals

- Polyenes
  - Macrolide antibiotics containing unsaturated diene bonds
  - Rapidly bind to sterols, preferentially to ergosterol
    - 'the' sterol found in fungal plasma membranes
  - Mechanism of action:
    - Disruption of the osmotic integrity of the cell membrane with subsequent leakage of intracellular ions and materials
    - Oxidative damage of membrane components

Current Systemic Antifungals (cont.)

- Two drugs currently in use:
  - Nystatin
    - First true antifungal agent discovered by Brown and Hazen (1948)
    - Secondary metabolite from the actinomycete Streptomyces noursei
    - Highly insoluble and toxic as a systemic drug
    - Used as a topical agent
Current Systemic Antifungals (cont.)

- Amphotericin B
  - Largely insoluble; often used as a deoxycholate suspension or in lipid vesicles
  - Tolerated much better than nystatin, but still toxic at high levels
  - Can cause renal failure, suppression of erythropoietin, and anemia
  - Effective against a broad spectrum of fungi; few are innately resistant
  - Resistance can be acquired

Current Systemic Antifungals (cont.)

- Mechanism of resistance (amphotericin B)
  - Reduced membrane ergosterol due to defective biosynthetic genes
  - Alterations in sterol content or structure
  - Masking of ergosterol molecules

Current Systemic Antifungals (cont.)

- Flucytosine (5-fluorocytosine)
  - Only antimetabolite of its type known to be effective against fungal infections
  - Mechanism of action: activated via deamination by fungal cells to produce 5-fluorouracil, a known inhibitor of DNA and protein synthesis (via formation of aberrant RNA)
  - Highly water soluble; used as an oral or intravenous agent
  - Fairly well tolerated but can cause bone marrow depression and gastrointestinal distress

Current Systemic Antifungals (cont.)

- Narrow spectrum agent against
  - Candidiasis
  - Cryptococcosis
  - Aspergillosis (minimally effective)
  - Chromoblastomycosis
  - Resistance is common due to mutations in
    - Plasma membrane cytosine permease, or
    - Deaminase
  - Often used in combination with amphotericin B

Current Systemic Antifungals (cont.)

- Azoles
  - Mechanism of action: all work by inhibition of the fungal cytochrome 14α-demethylase, an enzyme critical in the biosynthesis of ergosterol
  - Causes same type of damage that occurs with polyene treatment (loss of membrane integrity)
  - May take several generations to show affect
  - Types of azoles
    - Triazoles: fluconazole, voriconazole
    - Imidazoles: ketoconazole, itraconazole, posaconazole
Current Systemic Antifungals (cont.)

- Generally considered to be fungistatic, as opposed fungicidal, agents
- Fluconazole, compared to the other azoles, is highly soluble in water; other agents typically require a carrier agent (e.g., cyclodextrin) for systemic or oral use
- Mechanisms of resistance may include:
  - Alteration in demethylase
  - Overexpression of demethylase
  - Overexpression of efflux systems
  - Changes in membrane ergosterol composition

Echinocandins

- Cyclic glycopeptides that inhibit fungal 1,3-β-glucan synthesis (cell wall component)
- Best used intravenously
- Great potency against:
  - Candidiasis - fungicidal
  - Aspergillosis - fungistatic
- Cases of cryptococcosis are resistant because Cryptococcus contains 1,6-β-glucans
- Echinocandins include cilofungin, caspofungin, micafungin, and anidulafungin

Nikkomycins

- Inhibitors of chitin synthesis
- Good in vivo activity against coccidioidomycosis and blastomycosis
- Moderate activity against candidiasis, histoplasmosis, and cryptococcosis
- Exhibits synergistic activity with fluconazole and echinocandins
- Griseofulvin
  - Microtubule inhibitor (quit toxic); fungicidal
  - Treats dermatomycosis and candidiasis

Superficial Antifungal Agents

- A number of very effective drugs have been developed to treat fungal infections, but are used as topical agents due to their insolubility or toxicity
- Allylamines
  - Include butenafine, naftifine, and terbinafine
  - Mechanism of action: inhibits squalene epoxidase, an enzyme important in membrane biosynthesis (squalene accumulation is toxic)
  - Used to treat candidiasis and dermatomycosis
Superficial Antifungal Agents (cont.)

- Ciclopirox
  - Broad-spectrum antifungal and antibacterial
  - Acts by altering cell membrane integrity, active transport, and cellular respiration
  - Has anti-inflammatory activity
- Tolnaftate
  - Narrow spectrum: dermatomycosis and Malassezia infections
  - Inhibitor of squalene epoxidase

Selenium sulfide

Component of dandruff shampoos

- Heavy metal that effectively treats tinea versicolor and seborrheic dermatitis (conditions attributed to Malassezia infections)

Antifungal Therapy

- Types of therapy
  - Prophylactic
    - Prophylaxis: broad use of antifungals in a group of patients that
      - Are at risk of acquiring a fungal infection
      - Have no symptoms
    - Targeted prophylaxis: treatment for selected populations generally considered at very high risk for fungal infections due to a established condition, e.g., bone marrow transplant
  - Preemptive antifungal therapy: treatment of patients not only at very high risk for fungal infection, but also have markers indicative of early infection, e.g., colonization by Candida
    - Empiric: use of antifungal agents with findings and/or symptoms of a suspected invasive fungal disease, e.g., neutropenic patients
    - Specific: therapy directed at a specific pathogen clinically proven to be present, e.g., administration of amphotericin B and flucytosine to a patient exhibits encapsulated yeasts in spinal fluid (characteristic of cryptococcosis)