

## Antifungal Agents and Antifungal Therapy

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

- 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
  - 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
- Azoles
  - Mechanism of action: all work by inhibition of the fungal cytochrome 14 $\alpha$ -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 effect
  - Types of azoles
    - Triazoles: fluconazole, voriconazole
    - Imidazoles: ketoconazole, itraconazole, posaconazole
  - 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- $\beta$ -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- $\beta$ -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 (quite 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
- 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)