Antifungal Agents and Antifungal Therapy

Current Systemic Antifungals

• Polynenes
  – 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 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
  – 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 (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)