Lecture 5: Antifungal Drugs, Part II

Flucytosine
◆ One of the oldest antifungal agents, also known as 5-fluorocytosine, 5-flucytosine, and 5-FC
◆ Its use in conjunction with AmB to treat cryptococcosis marked the beginning of combination antifungal therapy to treat variously well-defined mycoses
◆ Additional clinical indications
  ∗ Candidiasis
  ∗ Chromoblastomycosis (+/- AmB)
◆ Innately resistant/non-responsive fungi
  ∗ Candida krusei
  ∗ Scedosporium apiospermum (P. boydii)
  ∗ Dimorphs - *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Sporothrix schenckii*
◆ Mechanism of action: 5-FC taken up by a fungal-specific cytosine permease and converted to 5-fluorouracil (5-FU), which leads to two important consequences:
  ∗ Inhibition of protein synthesis - 5-FU incorporated into mRNA
  ∗ Inhibition of DNA synthesis - 5-FU converted to 5-fluorodeoxyuridine which inhibits thymidylate synthetase
◆ Resistance to 5-FC might arise from mutations in key enzymes of these pathways as well as cytosine permease
◆ Adverse affects
  ∗ Gastrointestinal complaints (most common) - likely from microflora metabolism of 5-FC
  ∗ Bone marrow damage/toxicity (dosage dependent)
  ∗ Hepatic toxicity

Azole Antifungals
◆ 1979 - first azole drug marketed: miconazole
  ∗ Toxic, but effective
  ∗ No longer commercially available
◆ First generation azole antifungals
  ∗ Ketoconazole (1981)
  ∗ Fluconazole (1990)
  ∗ Itraconazole (1992)
◆ First generation azoles
   * Excellent against *Candida* and endemic fungi (e.g., *Histoplasma*, *Coccidioides*, etc.)
   * Ineffective against most mold pathogens

◆ Second generationazole antifungals
   * Voriconazole (2002)
   * Posaconazole (not yet licensed)
   * Raviconazole (not yet licensed)

◆ Mechanism of action:
   * Inhibition of fungal cytochrome P-450 enzyme involved in ergosterol biosynthesis
   * Net result: disruption of normal structure and function of cell membrane

◆ Azoles are generally considered fungistatic agents, though in some special circumstances they are fungicidal

◆ Pharmacokinetics
   * Generally well absorbed
   * Peak serum concentrations are observed 2-3 hours after administration
   * Distributed quite well to all body tissues, including relatively high concentrations in central spinal fluids
   * Most azoles, except fluconazole, undergo hepatic metabolism by cytochrome P-450 and are eliminated as inactive metabolites

◆ Spectrum of activity
   * Dimorphic fungi: generally effective
   * Fluconazole exhibits
     * Relatively poor activity against molds
     * Moderate activity against dimorphic pathogens
     * No activity against *Candida krusei* and many strains of *Candida glabrata*
   * Fungi resistant to first generation azoles tend to be more susceptible to second generation azoles
In vitro resistance
   * Two types:
     - Primary (intrinsic) - natural resistance of fungus without previous exposure to drug
     - Secondary (acquired) - development of resistance due to exposure to the drug
   * Primary resistance
     - Generally predictable, e.g., Candida krusei
     - Problematic is the selection of intrinsically resistant strains during treatment for another fungal infection
   * Secondary resistance
     - Uncommon except in immunocompromised patients, generally those infected with HIV, receiving prolonged therapy
     - Several mechanisms of secondary resistance:
       - Alteration or over expression of cytochrome P-450
       - Exclusion of the drug from the cell via efflux pump (considered the most common mechanism)
       - Prevention of accumulation of toxic sterol intermediates

Adverse effects
   * Gastrointestinal complaints
   * Hepatic dysfunctions
   * Cutaneous symptoms
   * Endocrine disturbances
   * Drug-specific effects, e.g., blurred vision with voriconazole

Terbinafine
   * Terbinafine is a relatively new antifungal agent for oral and topical applications
   * Categorized as an allylamine
   * Generally used to treat superficial infections, particularly dermatophytes
   * Great interest in development of this drug to treat systemic fungal infections
   * Mechanism of action:
     - Inhibits squalene epoxidase, an enzyme involved in ergosterol biosynthesis
     - Accumulation of squalene disrupts the function of the cell membrane
     - Squalene is also toxic to fungi
     - Distinct from azoles in that it has a distinct preference for fungal cytochrome P-450 enzymes and not human versions
◆ Extremely broad spectrum of antifungal activity including
   ✢ Onychomycosis (nail infections)
   ✢ Tinea captitis (ringworm of the scalp)
   ✢ Dermatophyte infections
   ✢ Sporotrichosis
   ✢ Chromoblastomycosis
   ✢ Mycetoma