Summary of Antifungal Agents

Fungi Characteristics:
- **Cell Wall**: Rigid, composed of chitin (N-acetylglucosamine)
- **Cell Membrane**: Contains ergosterol (distinct from human cholesterol)
- **Cell Structure**: Eukaryotic with a nucleus and well-defined nuclear membrane

Types of Fungal Infections:
- **Superficial Infections**: Affect skin, nails, scalp, or mucous membranes
- **Systemic Infections**: Affect deeper tissues and organs

Superficial Infections:
- **Dermatomycoses**: Infections of skin, hair, nails caused by dermatophytes (e.g., Tinea/ringworms)
- **Candidiasis**: Infections by Candida in mucous membranes (oral thrush, vaginal thrush, skin)

Systemic Infections:
- Systemic candidiasis, cryptococcal meningitis, pulmonary aspergillosis, blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis

Vulnerable Patients:
- AIDS patients
- Debilitated patients
- Organ transplant recipients on immunosuppressants
- Patients undergoing anticancer therapy

Antifungal Drug Classes and Mechanisms:
1. **Polyenes (e.g., Amphotericin B, Nystatin, Natamycin)**
   - MOA: Bind to ergosterol in fungal membranes, forming pores, increasing permeability, and causing cell death.
   - Resistance: Decreased ergosterol content, impaired binding.

1. **Azoles (e.g., Ketoconazole, Fluconazole, Itraconazole)**
   - MOA: Inhibit cytochrome P450 demethylase, disrupting membrane structure and function, inhibiting fungal growth.
   - Resistance: Mutations in demethylase gene.

1. **Allylamines (e.g., Terbinafine, Naftifine, Butenafine)**
   - MOA: Inhibit fungal squalene epoxidase, decreasing ergosterol synthesis and accumulating toxic squalene, leading to cell death.

1. **Echinocandins (e.g., Caspofungin, Micafungin, Anidulafungin)**
   - MOA: Inhibit synthesis of fungal cell wall glucan, leading to cell lysis and death.

1. **Griseofulvin**
   - MOA: Inhibits mitotic spindle formation, interfering with microtubule function and mitosis.

1. **Antimetabolites (e.g., Flucytosine)**
   - MOA: Converted to fluorodeoxyuridine monophosphate, inhibiting thymidylate synthase, disrupting DNA and RNA synthesis.

Key Drugs and Uses:
- **Amphotericin B**:
  - Drug of choice for most systemic infections.
  - Side Effects: Renal toxicity, hypokalemia, anemia, thrombocytopenia, hepatic impairment, anaphylactic shock.
  - Special Formulations: Liposomal preparations to reduce toxicity.

- **Nystatin**:
  - Treats superficial candidiasis (oral, esophageal, intestinal).
  - Not absorbed systemically.

- **Natamycin**:
  - Used for fungal keratitis.
  - Effective against Fusarium, Aspergillus, Candida, Penicillium, Cephalosporium.

- **Flucytosine**:
  - Effective against Candida and Cryptococcus.
  - Often combined with Amphotericin B.
  - Side Effects: Neutropenia, thrombocytopenia, bone marrow depression, hepatic enzyme elevation.

Clinical Use and Side Effects:
- **Polyenes**:
  - Effective in systemic and superficial fungal infections.
  - Major side effects include renal toxicity and electrolyte imbalances.

- **Azoles**:
  - Broad-spectrum antifungals used for systemic and superficial infections.
  - Major side effects include liver enzyme elevation and endocrine disturbances.

- **Allylamines**:
  - Mainly used for dermatophyte infections.
  - Side effects are generally less severe.

- **Echinocandins**:
  - Used for invasive aspergillosis and candidiasis.
  - Generally well-tolerated.

- **Griseofulvin**:
  - Used for dermatophyte infections.
  - Side effects include CNS disturbances and hepatotoxicity.

- **Flucytosine**:
  - Used in combination for severe infections.
  - Hematologic and hepatic side effects are common.

By understanding these key points, students will be well-prepared to handle antifungal treatments in clinical settings.

Ketoconazole
- **Overview**: First orally active narrow-spectrum azole for systemic mycoses.
- **Administration**: Only oral; well-absorbed in acidic environments. Bioavailability reduced by H2 blockers, PPIs, antacids, and food.
- **Pharmacokinetics**: 84% plasma protein-bound; does not enter CSF; metabolized by liver (CYP3A4) and excreted in bile.
- **Interactions**: Induced by Rifampicin (reduces concentration); inhibits CYP450 (potentiates toxicities of drugs like Cyclosporine, Phenytoin, Warfarin).
- **Uses**: Effective against many fungi (e.g., Histoplasma, Blastomyces, Candida, Coccidioides) but not Aspergillus.
- **Forms**: Available in tablets, aerosol, cream, and shampoo. Shampoo and aerosol effective for seborrheic dermatitis.
- **Side Effects**: Nausea, vomiting, liver toxicity, hair loss, endocrine disturbances (menstrual irregularities, gynecomastia, libido loss, impotence), fluid retention, hypertension. Contraindicated in pregnancy.

Triazoles
- **Examples**: Fluconazole, Itraconazole, Voriconazole, Posaconazole.
- **Mechanism**: Inhibit fungal cell membrane demethylase, damaging the membrane.
- **Advantages**: Less toxic, more effective, CNS penetration, less endocrine disturbance, resistant to degradation.

Fluconazole
- **Absorption**: Completely absorbed from GIT; bioavailability not affected by food or gastric acidity.
- **Uses**: Candidiasis, Cryptococcosis (AIDS, coccidial meningitis), prophylactic in bone marrow transplants.
- **Side Effects**: Nausea, vomiting, headache, rash, reversible alopecia, hepatic failure. Teratogenic.

Itraconazole
- **Administration**: Oral and IV; food increases absorption.
- **Pharmacokinetics**: Extensively metabolized in liver (CYP3A4); highly lipid-soluble; bound to plasma protein; does not penetrate CSF well.

- **Side Effects**: Nausea, vomiting, hypertriglyceridemia, hypokalemia, increased liver enzymes, rash.

Voriconazole
- **Potency**: More potent than Itraconazole.
- **Side Effects**: Reversible visual disturbances.

Posaconazole
- **Uses**: Prevents Candida and Aspergillus in immunocompromised patients; treats candidiasis and potentially zygomycosis.
- **Side Effects**: GI symptoms, headache.

Caspofungin
- **Class**: Echinocandin.
- **Mechanism**: Inhibits glucan synthesis in fungal cell walls.
- **Uses**: Aspergillus and Candida.
- **Administration**: IV only.
- **Side Effects**: Nausea, vomiting, flushing, liver dysfunction. Expensive.

Antifungal Drugs for Cutaneous Mycotic Infections
- **Topical Antifungals**: Amphotericin B, Nystatin, Topical Azoles, Tolnaftate, Terbinafine.
  - **Examples**: Miconazole, Clotrimazole, Butoconazole, Terconazole.
  - **Side Effects**: Contact dermatitis, vulvar irritation, edema. Miconazole can inhibit Warfarin metabolism, causing bleeding.

- **Oral Antifungals**: Fluconazole, Itraconazole, Ketoconazole.
  - **Uses**: Systemic mycosis, mucocutaneous candidiasis, other cutaneous infections.
  - **Side Effects**: Hepatitis, liver enzyme elevation, drug interactions.

Griseofulvin
- **Uses**: Dermatophytes (skin, hair, nails); replaced by Terbinafine for nail infections.
- **Administration**: Oral; absorption increased with fatty meal.
- **Side Effects**: Headache, neuritis, mental confusion, fatigue, vertigo.

Terbinafine
- **Uses**: Dermatophytes and onychomycosis (nail infections).
- **Administration**: Oral; highly protein-bound; accumulates in skin, nails, fat.
- **Side Effects**: GIT disturbances, taste/visual disturbance, severe allergic reactions, liver enzyme elevation. Not recommended for nursing mothers, renal/hepatic impairment.