ANTIFUNGAL PHARMACOLOGY MASTER STUDY GUIDE

Comprehensive High-Yield Review & Smart Memory Anchors

Part 1: Clinical Foundations & Classifications

1. Superficial Fungal Infections

- **Dermatomycosis:** Caused by **Trichophyton, Microsporum, and Epidermophyton**. Affects the **skin, nails, and hair.**
- **The Keratin Rule:** Hair and nail fungal infections cannot be successfully cleared by standard topical treatments alone. They require systemic delivery because the active drug must have specific affinity to reach and physically incorporate into growing keratin tissue reservoirs.
- **Candidiasis Focus:** Affects the skin, mucous membranes of the mouth (thrush), vagina, urinary system, and the gastrointestinal lumen.
- **The Flora Shift Logic:** Administration of broad-spectrum antibiotics or chronic acid suppression clears out protective normal bacterial flora. This eliminates natural microflora competition and allows swallowed opportunistic fungi to reach the intestine, multiply excessively, and cause functional diarrhea and localized infection.
- **Local Action Rationale:** Most superficial infections are non-severe and treated topically. Even intestinal candidiasis is treated using oral formulations that are intentionally poorly absorbable, forcing them to remain entirely within the gut lumen to exert safe, local clinical action.

2. Systemic Fungal Infections These affect deeper tissues and visceral organs. Clinical incidence and severity have sharply risen since the 1970s due to 5 main therapeutic and demographic vectors:

- • **Antibiotics (Broad-Spectrum):** Wipe out protective bacterial normal flora, triggering opportunistic Candida overgrowth and subsequent superinfections. Clinical directive: Restrict use to multi-drug resistant cases or appropriate empirical boundaries.
- • **Immunosuppression Drivers:** Driven heavily by **AIDS**, immunosuppressant regimens, and oncology protocols. Older cytotoxic cancer chemotherapy causes direct systemic injury to rapidly replicating normal host cells (hair follicles, mucosal cells, white blood cells), causing intense immunosuppression. In contrast, newer targeted monoclonal antibodies are mechanism-directed, specifically sparing normal host immune components.
- • **Diabetes Mellitus:** Impairs general leukocyte defenses, and baseline high glucose tissue levels provide a rich, sweet metabolic growth environment for fungi.
- • **Elderly Population Growth:** Natural physiological declines in multiple baseline defensive body functions significantly increase standard susceptibility.
- • **Surgeries and Interventions:** Advanced complex procedures introduce localized hygiene, institutional contamination, and structural inoculation risks.

> **Systemic Etiology Mnemonic**
> Remember the clinical rise of systemic infections using the acronym **A.I.D.E.S.**
> • **A**ntibiotics (Broad-spectrum normal flora clearance)
> • **I**mmunosuppression (AIDS vs. Cytotoxic older chemo vs. Targeted modern antibodies)
> • **D**iabetes mellitus (High-glucose growth environment)
> • **E**lderly populations (Declining baseline organic functions)
> • **S**urgery advances (Hygiene, modern structural entry vectors)

Part 2: Polyenes (Cell Membrane Pore Formers)

1. Amphotericin B

• **Mechanism of Action:** Ergosterol is an integral structural component of fungal cell membranes, analogous to cholesterol in animals. Amphotericin B is a **highly amphipathic polyene molecule** containing a hydrophilic hydroxyl region and a hydrophobic double-bond polyene chain. **The hydrophobic region binds tightly to ergosterol within the fungal membrane/wall**. **Multiple drug molecules aggregate to assemble a transmembrane pore (ion channel) with the hydrophilic cores facing inward**. This triggers **lethal leakage of intracellular ions (K+, Mg2+) and vital macromolecules**, executing fungicidal action.

• **Antifungal Spectrum: Yeasts (Candida albicans, Cryptococcus neoformans**); **Endemic Mycoses** (Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis); **Pathogenic Molds (Aspergillus** fumigatus, and Mucor) and **the protozoan parasite Leishmania spp.**

• **Resistance Development Mechanism: Modifying the Sterol molecule** ⟶ Decreased drug binding affinity

• **Pharmacokinetics & Formulations:**

- **Oral Absorption: Poor Oral Absorption**. It is **given PO strictly to treat fungal infections of the GIT lumen.**
- **Standard Suspension: Complexed with deoxycholate (a bile acid) as an IV suspension**.
- **Liposomal Formulation: Packages the drug inside microscopic lipid delivery vehicles**. This heavily **reduces non-specific binding to human cell membranes**, **dropping the toxicity potentials and permitting larger clinical doses**.
- **Distribution & Clearance: Crosses the blood-brain barrier (BBB) poorly** under baseline conditions, but central nervous system penetration improves significantly when the meninges are actively inflamed. It remains the absolute **drug of choice for Cryptococcus neoformans meningitis when used in combination with flucytosine.** The drug has an **extremely prolonged half-life (t½ ~ 15 days),** requiring up to 2 full months (4 half-lives) to be entirely washed out from the body.

• **Serious Adverse Effects:**

- **Infusion-Related Toxicity:** Due to the rapid **release of proinflammatory cytokines** (TNF-α, IL-1, IL-2). **Triggers severe allergy-like symptoms including fever, chills, muscle spasms, vomiting, headache**. Slowing down the baseline IV infusion rate reduces these immediate effects.
- **Slower Cumulative Nephrotoxicity:** Extremely common, **occurring in over 80% of patients**, which could be either reversible or Irreversible (> 4grams cumulative dose), causing renal failure symptoms that include **impaired renal concentrating ability**, **renal tubular acidosis** and **severe potassium, sodium and magnesium wasting**, **elevation of urea and creatinine and Anemia due to reduced erythropoietin production.**
- **Intrathecal Complications:** Required for severe non-responsive meningitis; can induce **localized seizures** and severe **chemical arachnoiditis**.
- **Other Systemic Signs:** Hepatic dysfunction, acute thrombocytopenia, and systemic anaphylaxis.

2. Nystatin

Mechanistically **identical to Amphotericin B** but **with higher toxicity**. Consequently, it is restricted **only to topical administration** (formulated as creams, local ointments, and vaginal suppositories) to treat superficial fungal infections of the skin and adjacent mucous membranes.

Part 3: Pyrimidine Analogs (DNA/RNA Synthesis Inhibitors)

Flucytosine (5-FC)

• **Profile & Chemistry:** A **synthetic pyrimidine analog**.

• **Mechanism of Action:** Flucytosine is selectively **taken up by target fungal cells via** the transport enzyme **cytosine permease**. Once inside the fungal cell cytoplasm, it is **metabolized into 5-fluorouracil (5-FU)**. It is then sequentially **processed into 5-FdUMP** and **FUTP** which **Inhibit DNA and RNA Synthesis**. (Human cells do not convert the prodrug into active toxic metabolites, protecting host structures).

• **Spectrum & Use: effective against yeasts (Candida and Cryptococcus, it has Synergistic effect when combined with Amphotericin B for severe cryptococcal meningitis.** This combination is highly synergistic because membrane damage induced by Amphotericin B physically enhances flucytosine's penetration through inflamed arachnoid membranes in nervous tissues.

• **Pharmacokinetics: Well absorbed after oral administration**, has **excellent entry into the CNS**, **Excreted by the kidneys** (dose reductions essential in patients presenting with renal dysfunction)

• **Adverse Effects:**

- **Narrow therapeutic window**, with subtherapeutic levels cause rapid resistance selection, while elevated blood levels provoke rapid systemic toxicity.
- **Bone marrow depression** (causing **anemia, neutropenia**, and **most commonly thrombocytopenia**)
- **Alopecia**

Part 4: Azoles (Ergosterol Synthesis Inhibitors)

• **Profile: Synthetic, broad-spectrum, fungistatic agents**.

• **Mechanism of Action: Inhibit fungal Cytochrome P450 enzyme** (14α-demethylase) **responsible for converting lanosterol into ergosterol.** This depletion disrupts cell membrane fluidity, neutralizing membrane-associated fungal enzymes. **The net clinical effect is** the absolute **inhibition of fungal replication and growth**. Crucially, azoles **reduce the physical formation of Amphotericin B binding sites on the cell wall**.

• **Classification:**

- **Imidazoles (Ketoconazole, Miconazole, Clotrimazole):** They provoke **non-specific inhibition of human mammalian Cytochrome P450 enzymes**, therefore there **use is restricted to topical preparations**, potentially could cause **significant drug interactions** and **impaired steroidogenesis**, which may result in **impotence** and **sexual dysfunction.**

- **Triazoles (Itraconazole, Fluconazole, Voriconazole)**: Newer agents, **selectively targets fungal P450 ⟶ Can be used orally and systematically**

• **Anti-Fungal Spectrum:** Effective against many **Candida species**, **Cryptococcus neoformans**, **endemic mycoses**, and **dermatophytes**.

• **Itraconazole** and **voriconazole** expand coverage to include **Aspergillus** and **amphotericin-resistant Pseudallescheria boydii.**

• **Topical Azoles Overview:**

- **Clotrimazole, Miconazole & Econazole:**
- Formulated as **creams** to treat **dermatophytic infections**: tinea corporis (body), tinea pedis (athlete's foot between the toes), and tinea cruris (perineum and between thighs).
- Used topically for **vulvovaginal candidiasis**.
- Oral **clotrimazole** troches are used for **oral thrush**.
- **Ketoconazole: Topical cream** and **shampoo** forms are highly effective for **seborrheic dermatitis** (targeting areas dense with oil-producing sebaceous glands: scalp, face, ears, upper chest) and **pityriasis versicolor**.

Systemic Triazoles Comparison Matrix

Feature	Fluconazole	Itraconazole	Voriconazole
Kinetics & Absorption	Given PO or IV, Eliminated Renally	Given PO or IV, Eliminated Renally • Undergoes **extensive first-pass effect.** **• Requires food and low gastric pH (acidity) for optimal absorption.** **• Bioavailability is reduced by Rifamycins**	Given PO or IV, **Eliminated Hepatically**
CNS Penetration	Excellent penetration. **Achieves high, therapeutic concentrations in both CSF and ocular fluid.**	**Does not penetrate the BBB**	**Does not penetrate the BBB**
Primary Clinical Uses	**Drug of choice for fungal meningitis** (**cryptococcal, coccidioidal**) and **candidemia**. Given **long-term for prophylaxis in bone marrow transplants and AIDS** (long term use risks resistance). Useful for **Mucocutaneous candidiasis in case topical agents aren't effective.**	**Drug of choice for dimorphic fungi** (**Histoplasma, Blastomyces, Sporothrix**). Used in **extensive or resistive dermatophytosis** (When Topical Agents fail) **Nail fungal infections (onychomycosis**). Effectively **covers aspergillosis but clinically replaced by voriconazole.**	**Drug of choice for Invasive Aspergillosis** Used for **fluconazole-resistant candidiasis and cryptococcosis,** as well as **itraconazole-resistant dimorphic fungal infections.**
Distinct Key Side Effects	**Widest therapeutic index of the azole class**. **Exfoliative skin lesions (Stevens-Johnson syndrome) occur in AIDS patients** Does not severely block human steroidogenesis.	**Hypokalemia** **Allergic reactions and exfoliative dermatitis.**	Common **transient visual disturbances** (including **blurring, changes in color vision and brightness**) **affecting 30% of patients**. **Occurs immediately after a dose and resolves fully within 30 minutes.**

Part 5: Allylamines (Squalene Accumulators)

Terbinafine

• **Profile:** A synthetic, **highly lipophilic** and **keratinophilic allylamine** agent. **Highly fungicidal against dermatophytes.**

• **Mechanism of Action: Inhibits the enzyme squalene epoxidase**, **an early step in fungal cell wall ergosterol synthesis**. This causes a dual action: it **halts downstream ergosterol production** and forces a massive, **toxic accumulation of squalene** within the fungal cell cytoplasm, resulting in cell lysis and death.

• **Pharmacokinetics & Uses:** Given **PO** or **topically**. When given orally, it is **Keratinophilic ⟶ taken up intensely by the skin, nails and adipose tissues**, making it the absolute **drug of choice for fungal nail infections (onychomycosis).** Could be also used **topically for tinea cruris and tinea corporis.** When given topically, it penetrates local skin and mucous membranes into systemic circulation. Metabolized by hepatic Cytochrome P450 enzymes. Used as creams for tinea cruris and tinea corporis.

• **Adverse Effects:** GI disturbances, **skin rash and pruritus**, headache, dizziness, joint and muscle pain, and clinical **hepatitis.**

• **Note on Naftifine:** A structurally related allylamine compound that is similar but **restricted strictly to topical use for tinea cruris and tinea corporis.**

Part 6: Echinocandins (Cell Wall Glucan Blockers)

• **Profile:** The newest structural class of antifungal agents. Large cyclic peptides linked covalently to a long-chain fatty acid. Includes **Caspofungin, Micafungin, and Anidulafungin**.

• **Mechanism of Action: Inhibit the synthesis of β-(1,3)-glucan**, an essential structural **glucose polymer necessary for maintaining the physical integrity of the fungal cell wall**. **The fungus rapidly loses structural integrity, leading to osmotic lysis and cell death.**

• Pharmacokinetics:

- • **Administration: Poor absorption after oral administration** due to massive peptide size; **available exclusively via slow IV infusion.** Highly water-soluble and protein-bound.
- • **Half-Lives: Caspofungin** ~ 10 hours; **Micafungin** ~ 13 hours; **Anidulafungin** ~ 36 hours.
- • **Dosing Rules: Larger initial loading doses are required** to quickly saturate plasma proteins. Specifically required for anidulafungin, but can be needed for caspofungin and micafungin.
- • **Hepatic Guidance: Dosage adjustments are needed only in severe hepatic insufficiency**. Quick note: Unlike renal failure, mild-to-moderate hepatic dysfunction does not require dose adjustments because baseline metabolic function is relatively well-preserved.
- **Micafungin Interactions:** Increases blood levels of nifedipine, cyclosporine, and sirolimus, suggesting it acts as an inhibitor of mammalian Cytochrome P450 CYP3A4 enzymes.

• Clinical Therapeutic Uses:

- **Candidiasis:** Including **mucocutaneous infections**, **systemic septicemia** and **Esophageal candidiasis**.
- **Empiric Therapy in Febrile Neutropenia (If persistent despite administration of broad-spectrum antibiotics)**
- **Salvage Therapy:** Used as excellent salvage therapy for aggressive invasive aspergillosis refractory to or failing Amphotericin B.

• Adverse Effects Profile: (Generally well tolerated)

- **Liver Enzyme Elevation** when combined with **Cyclosporine**.
- **Anidulafungin Histamine Release:** causing systemic **flushing, rash**, and **tachycardia**.
- **Phlebitis and Thrombophlebitis at the site of administration.**