

Antifungal Antibiotics

Introduction

- Antifungal antibiotics are drugs derived from microorganisms (mainly *Streptomyces* species) that inhibit or kill fungal pathogens.
- These agents are mainly used to treat superficial and systemic fungal infections caused by yeasts, molds, and dimorphic fungi.
- Unlike bacteria, fungi are eukaryotic organisms, making them more similar to human cells. Hence, antifungal agents target unique fungal components like:
 - **Ergosterol** in fungal membranes
 - **β-glucan** in fungal cell walls
 - **Fungal microtubules or DNA synthesis**

Classification

A. Polyene Antibiotics

- **Amphotericin B** – systemic use
- **Nystatin** – topical/oral (non-absorbable)
- **Natamycin** – ophthalmic use

B. Echinocandins

- Caspofungin
- Micafungin
- Anidulafungin

C. Others (Derived from natural sources)

- **Griseofulvin** – from *Penicillium* species; used in dermatophytosis

Mechanism of Action

Polyene Antibiotics (e.g., Amphotericin B, Nystatin):

- Bind to ergosterol in fungal cell membranes
- Form pores in the membrane, increasing permeability
- Leads to leakage of intracellular contents → **fungal cell death**

Echinocandins:

- Inhibit β-1,3-D-glucan synthase, an enzyme involved in fungal cell wall synthesis
- Weakens the cell wall → lysis
- Fungicidal against *Candida* spp.; fungistatic against *Aspergillus*

Griseofulvin:

- Disrupts fungal mitotic spindle by binding to microtubules
- Inhibits cell division
- Fungistatic (not fungicidal)

Pharmacokinetics (ADME)

Amphotericin B:

- **Absorption:** Not absorbed orally; given IV for systemic infections
- **Distribution:** Wide, except poor CSF penetration
- **Metabolism:** Slow; mostly unknown
- **Excretion:** Slow renal excretion
- **Half-life:** ~15 days

Nystatin:

- Not absorbed systemically
- Used topically or orally (swish and swallow) for local effect

Caspofungin (Echinocandin):

- **IV only**
- **Distribution:** Wide, but minimal CSF penetration
- **Metabolism:** Hepatic
- **Excretion:** Hepatic and renal
- **Half-life:** ~9–11 hours

Griseofulvin:

- Oral absorption enhanced with fatty food
- Deposits in keratin-rich tissues (skin, nails)
- **Metabolism:** Hepatic
- **Excretion:** Urine
- **Half-life:** ~24 hours

Pharmacodynamics

- **Amphotericin B/Nystatin:** Fungicidal; concentration-dependent
- **Echinocandins:** Fungicidal (against *Candida*), fungistatic (against *Aspergillus*)
- **Griseofulvin:** Fungistatic; time-dependent action

Therapeutic Uses

Amphotericin B:

- **Systemic mycoses:** cryptococcosis, candidiasis, histoplasmosis, aspergillosis, blastomycosis, mucormycosis
- **Fungal meningitis** (intrathecal route)
- **Leishmaniasis** (alternative to antimonials)

Nystatin:

- Oropharyngeal candidiasis (thrush)
- Cutaneous and vaginal candidiasis
- GI tract *Candida* infections

Caspofungin (and other echinocandins):

- Invasive candidiasis
- Esophageal candidiasis
- Salvage therapy in invasive aspergillosis
- Empiric therapy in febrile neutropenia

Griseofulvin:

- Dermatophytosis (tinea capitis, corporis, pedis, unguium)
- Not effective against *Candida*

Adverse Effects

Amphotericin B:

- **Infusion reactions:** fever, chills, hypotension, vomiting
- **Nephrotoxicity:** dose-limiting toxicity; tubular damage
- **Electrolyte imbalances:** hypokalemia, hypomagnesemia
- **Anemia:** decreased erythropoietin
- **Thrombophlebitis** at injection site

Nystatin:

- **Oral:** nausea, vomiting, diarrhea
- **Topical:** skin irritation, allergic reaction

Echinocandins:

- Generally well-tolerated
- Minor: fever, histamine-related reactions (rash, flushing)
- Elevated liver enzymes

Griseofulvin:

- GI upset
- Headache, confusion
- Photosensitivity
- Hepatotoxicity
- Skin rashes, Stevens-Johnson Syndrome (rare)

Contraindications

- **Amphotericin B:** Hypersensitivity, caution in renal impairment
- **Nystatin:** Hypersensitivity
- **Echinocandins:** Hypersensitivity, caution in hepatic dysfunction
- **Griseofulvin:**
 - Pregnancy
 - Porphyria
 - Severe liver disease

Drug Interactions

Amphotericin B:

- Increased nephrotoxicity with aminoglycosides, cyclosporine, NSAIDs
- Hypokalemia can enhance toxicity of digoxin and antiarrhythmics

Nystatin:

- No significant interactions (not systemically absorbed)

Echinocandins:

- Caspofungin levels ↓ by **rifampin, phenytoin**
- May ↑ cyclosporine levels (monitor liver enzymes)

Griseofulvin:

- Induces CYP450 enzymes
 - Reduces effectiveness of **warfarin, oral contraceptives**
- Alcohol may cause disulfiram-like reaction

Dose and Route of Administration

Amphotericin B:

- **IV:** 0.5–1.5 mg/kg/day (conventional)
- **Liposomal formulations:** 3–5 mg/kg/day (better safety profile)



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