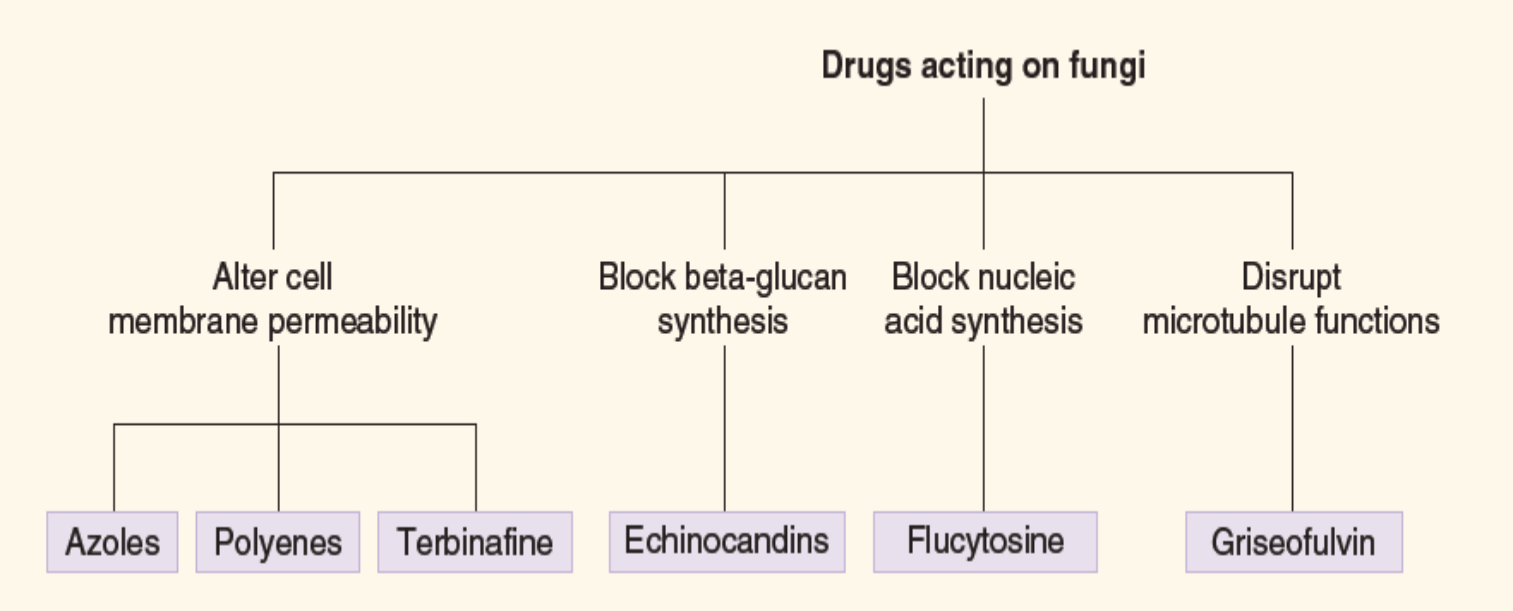
ANTIFUNGAL AGENTS

Antifungal Agents

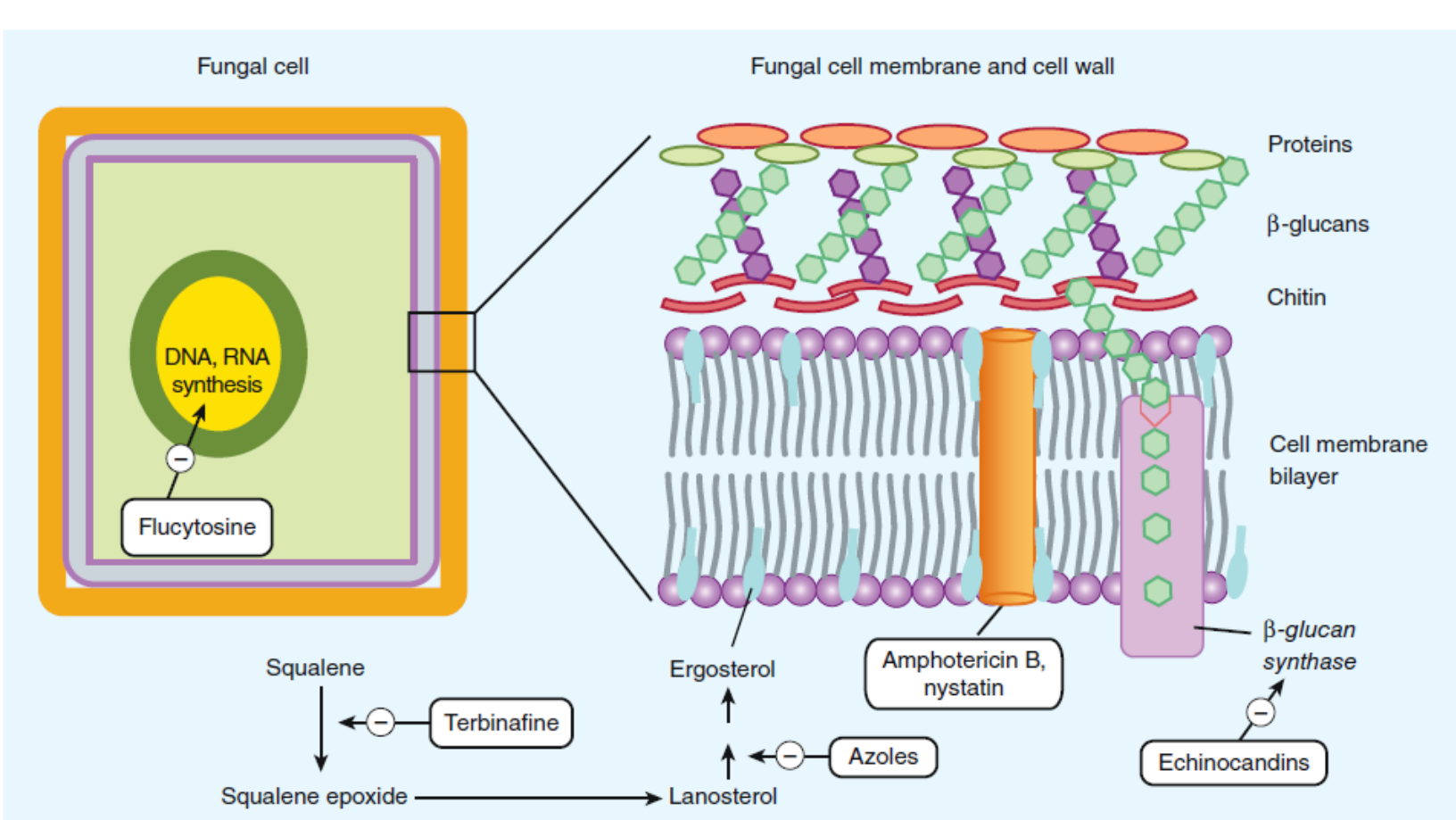
Fungal infections are *difficult to treat*, particularly in the immunocompromised or *neutropenic patient*. Most fungi are *resistant to conventional* antimicrobial agents, and relatively few drugs are available for the treatment of systemic fungal diseases.

Amphotericin B, the azoles (fluconazole, itraconazole, ketoconazole, and voriconazole), and the *echinocandins* are the primary drugs used in systemic infections. They are *selectively* toxic to fungi because they interact with or inhibit the synthesis of *ergosterol,* a sterol unique to fungal cell membranes

Antifungal Agents



Antifungal Agents



Antifungal Agents

- **Systemic:**

Polyenes (Amphotericin B), flucytosine, azoles, allylamines

- **Topical:**

Polyenes (nystatin), azoles, allylamines

Amphotericine B

MOA:

Binding to ergosterol and pore formation

- **Antifungal activity:**
- Amphotericin B remains the drug *of choice for for most systemic infections caused by Aspergillus, Blastomyces, Candida albicans, Cryptococcus, Histoplasma, and Mucor*
- Dermatophytes are resistant

Amphotericine B

- **Kinetic:**

No oral absorption, poor penetration to CSF

- **Indications:**

Slow iv infusion

Treatment of invasive, progressive, life threatening fungal diseseas, at least initially. (if clinical condition permits, after initial phase, treatment is switched to safer but slower acting oral agents eg. Azoles)

Amphotericine B

Adverse effects:

- Infusion related toxicity: chill & fever, muscle spasm, hypotension, vomiting and headache
- Renal toxicity: increase in BUN & Cr, Mg^{2+} & K^{+} wasting, Anaemia due to reduced erythropoietin production

Neurotoxicity: Intrathecal administration of amphotericin B may cause seizures and neurologic damage

Flucytosine

- **MOA:**

  Changing to 5-FU by fungus and inhibition of DNA and RNA synthesis

- **Antifungal activity:**

  C. neoformans, Candida, Synergism with Ampho B or a triazole

  Kinetics:

  It is orally and is distributed to most body tissues, including the CNS. It is eliminated in the urine

- **Toxicity**: reversible bone marrow depression, alopecia, and liver dysfunction

Azoles

Available agents:

- Imidazole: ketoconazole
- Triazoles: fluconazol, itraconazol, voriconazole

MOA:

- Inhibition of sterol 14-α demethylase(ergostrol inhibitor)
- Triazoles have more specific effect on fungal enzyme

موارد استفاده ضد قارچ های آزولی

- **کتوکونازول:**کاندیدیاز جلدی-مخاطی مزمن و درماتوفیت ها
- **فلوکونازول:**داروی انتخابی برای کاندیدیاز دهان ،حلق ، مری و انتخابی برای درمان و پیشگیری علیه مننژیت کریپتوکوکی
- **ایتراکونازول:**انتخابی برای بلاستومایسیس،اسپوروتریکس و کروموبلاستومایکوزیس زیر جلدی
- **وریکونازول:**انتخابی آسپرژیلوس مهاجم

Azoles

Kinetic:

- Acidic gastric pH is necessary for dissolution and absorption of ketoconazole and itraconazole but not fluconazole.
- Fluconazole penetrates well to CSF
- Liver metabolism is responsible for the elimination of ketoconazole, itraconazole, and voriconazole

Azoles

ADR: Ketoconazole inhibits CYP450 isozymes (interfer with warfarin, phenytoin, oral hypoglycemic drugs) , interferes with the synthesis of adrenal and gonadal steroids and may lead to gynecomastia, menstrual irregularities, and infertility. Voriconazole causes transient blurring of vision disturbances (more than 30% of patients) and is in class D drug in terms of pregnancy

Systemic Drugs for Superficial Fungal Infections

Griseofulvin

Pharmacokinetics: Oral absorption of griseofulvin depends on the physical state of the drug (ultra-micro-size formulation), high-fat foods improve absorption

MOA: Griseofulvin interferes with microtubule function in dermatophytes

Clinical uses: Griseofulvin is not active topically. The oral formulation of the drug is indicated for dermatophytoses of the skin and hair, but has been largely replaced by terbinafine and the azoles

ADR: Adverse effects include headaches, mental confusion, gastrointestinal irritation, photosensitivity, and changes in liver function. Griseofulvin decreases the bioavailability of warfarin, resulting in decreased anticoagulant effect, and it also causes disulfiram-like reactions with ethanol

Systemic Drugs for Superficial Fungal Infections

Terbinafine

MOA: Terbinafine inhibits a fungal enzyme, squalene epoxidase It causes accumulation of toxic levels of squalene, which can interfere with ergosterol synthesis. Terbinafine is fungicidal

Clinical uses: Terbinafine is available in both oral and topical forms. It is Effective against dermatophytes and canidida. Like griseofulvin, terbinafine accumulates in keratin, but it is much more effective than griseofulvin in onychomycosis

ADR:gastrointestinal upsets, rash, headache, and taste disturbances. Terbinafine does not inhibit cytochrome P450

Systemic Drugs for Superficial Fungal Infections

Azoles

The azoles other than voriconazole and posaconazole are commonly used orally for the treatment of dermatophytoses. Pulse or intermittent dosing with itraconazole is as effective in onychomycoses as continuous dosing because the drug persists in the nails for several months. Typically, treatment for 1 wk is followed by 3 wk without drug. Advantages of pulse dosing include a lower incidence of adverse effects and major cost savings. Topical forms of various azoles are also available for use in dermatophytoses.

Topical Antifungals

- Nystatin (oral drop, vaginal tablet): oropharyngeal & vaginal candidiasis
- Terbinafine (cream): tinea cruris, tinea corporis, tinea pedis
- Clotrimazol (topical cream, vaginal tablet and cream) & miconazole (topical and vaginal cream): tinea cruris, tinea corporis, tinea pedis, tinea versicolor, vaginal candidiasis
- Ketconazol (shampoo): dandruff, seborrheic dermatitis