ANTIFUNGAL THERAPY

General principles

1- Host defense mechanisms are often inadequate for the eradication of fungal pathogens because mammalian cells lack enzymes capable of degrading the cell wall polysaccharides of fungi.

2- Most antifungal compounds interfere with the biosynthesis of ergosterol or with its integration into the cell membrane. However, because cholesterol (found in mammalian cells but not fungi) is structurally similar to ergosterol, antifungal agents can produce serious side effects in the host.

Agents

1- Polyenes

a- **Amphotericin B** is usually the drug of choice for most systemic fungal infections. In spite of its toxicity, it continues to be used because it is more efficient than other, less toxic compounds.

(1) **Mechanism of action.** Amphotericin B has a greater affinity for ergosterol in the fungus cell membranes than for the cholesterol in the host cell membranes. When the drug binds to ergoserol, it causes **disruption of cell membrane.** The resultant increased permeability causes leakage of cytoplasmic contents and cell death. At therapeutic dosages, amphotericin B is **fungicidal**.

(2) **Administration.** Amphotericin B is usually given intravenously for extended periods (as long as 2-3 months).

(3) **Side effects** may be severe and include fever, chills, hypotension, headache, nausea, thrombophlebitis, kidney damage, and anemia secondary to bone marrow depression.

b- Nystatin

(1) **Mechanism of action.** The mechanism of action of nystatin is identical to that of amphotericin B but it is clinically effective only against *Candida albicans*.

(2) **Administration.** Nystatin is administered as a topical ointment (or orally, for treatment of candidiasis of the gastrointestinal tract). Nystatin is not absorbed when administered orally and cannot be given intravenously, so it cannot be used to treat systemic candidiasis.

2- Azoles (imidazoles and triazoles)

The clinical use of this group of antifungal agents, which includes **ketoconazole, itraconazole,** and **fluconazole,**has expanded considerably in recent years.

a- Indications. These compounds are effective for the treatment of mucocutaneous candidiasis, dermatophytosis, and some systemic fungal infections.

b- Mechanism of action. The azoles block the enzyme that converts lanosterol into 14-demethyllanosterol during the synthesis of ergosterol. At the recommended dosages, the azoles are **fungistatic**.

c- Administration. These drugs are administered as ointments and creams for topical use and orally for disseminated skin infections and systemic infections.

d- Side effects. The azole are not as toxic as amphotericin B. Nausea and other symptoms of gastrointestinal toxicity, headache, and skin rash are the most common side effects, androgen and cortisol metabolism may be affected as well.

3- **Griseofulvin** is a slow-acting drug that is used for severe skin and nail infections.

a- Mechanism of action. Griseofulvin inhibits microtubule formation and prevents the formation of the mitotic spindle, thus interfering with chromosomal separation during cell division. The drug accumulates slowly in the stratum corneum of the skin, forming a barrier that prevents fungal penetration and growth.

b- Adminsration. Griseofulvin is administered orally extended periods (up to 1 year for the treatment of nail infections).

4- **5-fluorocytosine** is a nucleotide analog that inhibits RNA and DNA synthesis. 5-fluorocytosine is mainly used in association with amphotericin B to treat cryptococcosis and is administered orally.

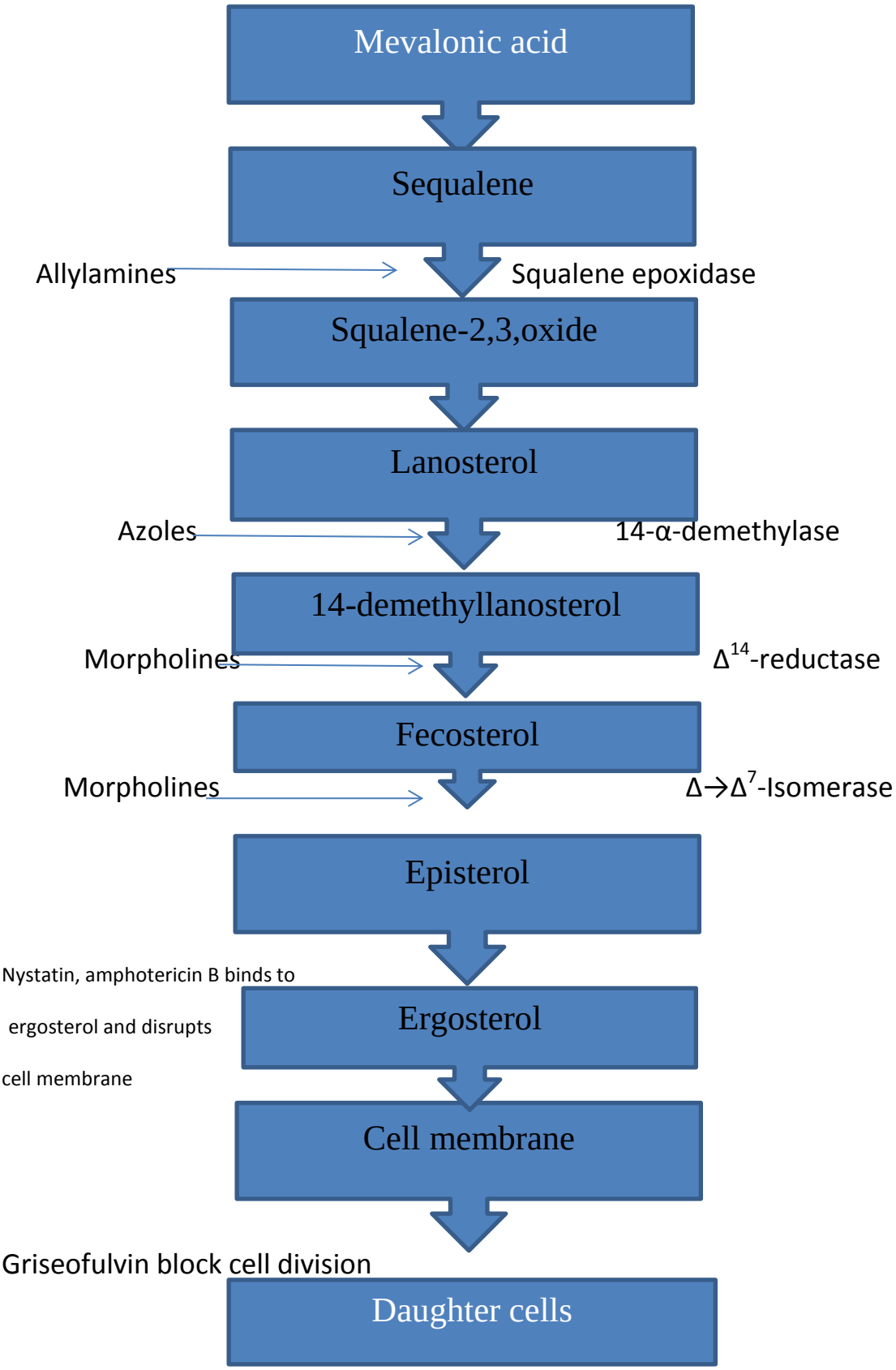
5- **Allylamines (naftifine, terbinafine)** are selective for fungi.

a- Mechanism of action. The allylamines inhibit ergosterol synthesis by preventing the oxidation of squalene.

b- Administration. These compounds can be administered topically or orally and may offer an alternative to griseofulvin for the treatment of nail infections.

c- Side effects are usually related to gastrointestinal intolerance.

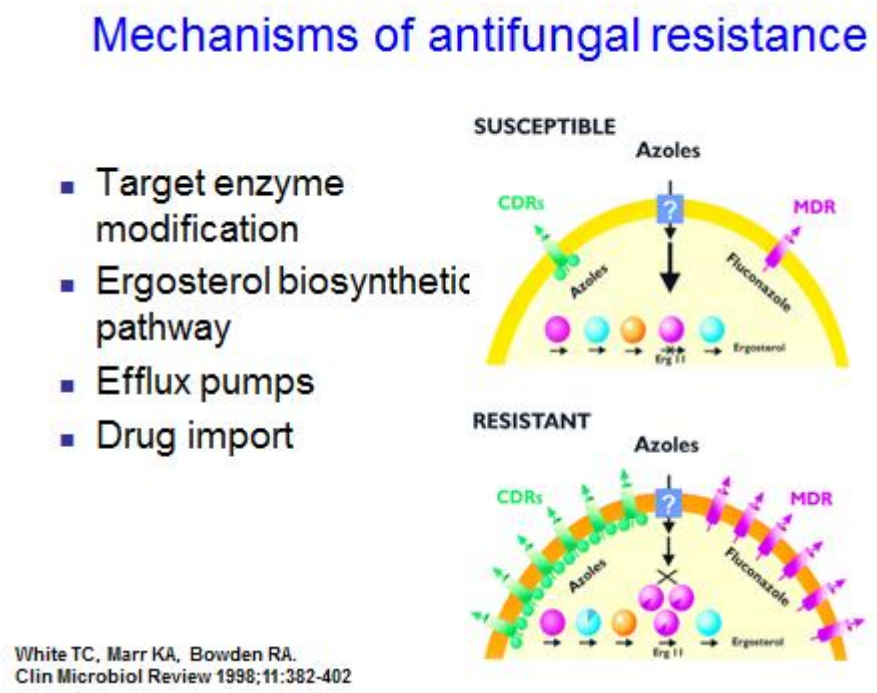
6- **Morpholines** (e.g., **amorolfine**) interfere with ergosterol synthesis by inhibiting the conversion of fecosterol into episterol. Amorofline is available in topical preparations and is used to treat dermatophytoses.

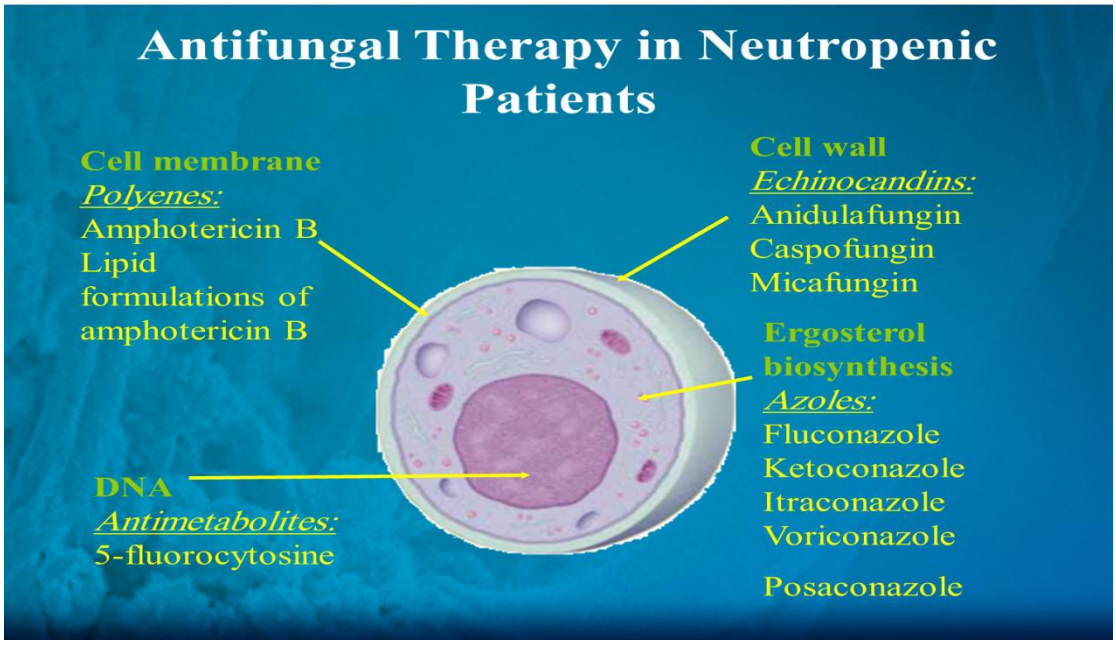


Mechanism of action of the most common antifungal agents

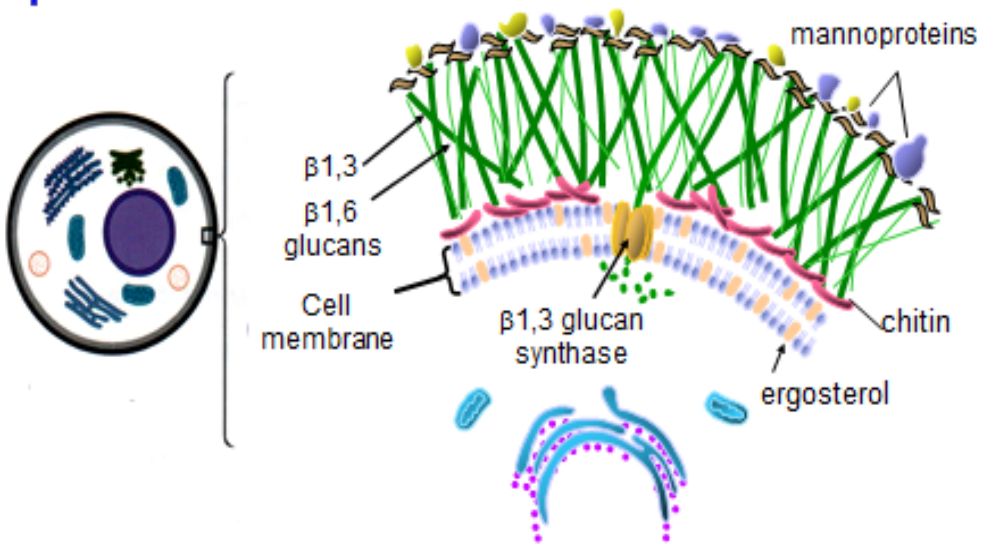
Resistance to antifungal agents.

Acquired resistance of *C. albicans* and other fungi to the azoles has been reported with increasing frequency, particularly in patients treated with these drugs for extended periods of time (e.g., patients with AIDS).



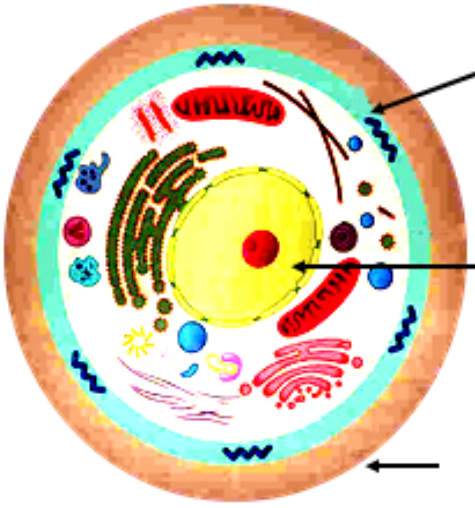


The Fungal Cell Wall



Atlas of fungal infections, Richard Diamond Ed. 1999
Introduction to Medical Mycology. Merck and Co. 2001

What are the targets for antifungal therapy?



Cell membrane
Fungi use principally ergosterol instead of cholesterol

DNA Synthesis
Some compounds may be selectively activated by fungi, arresting DNA synthesis.

Cell Wall
Unlike mammalian cells, fungi have a cell wall

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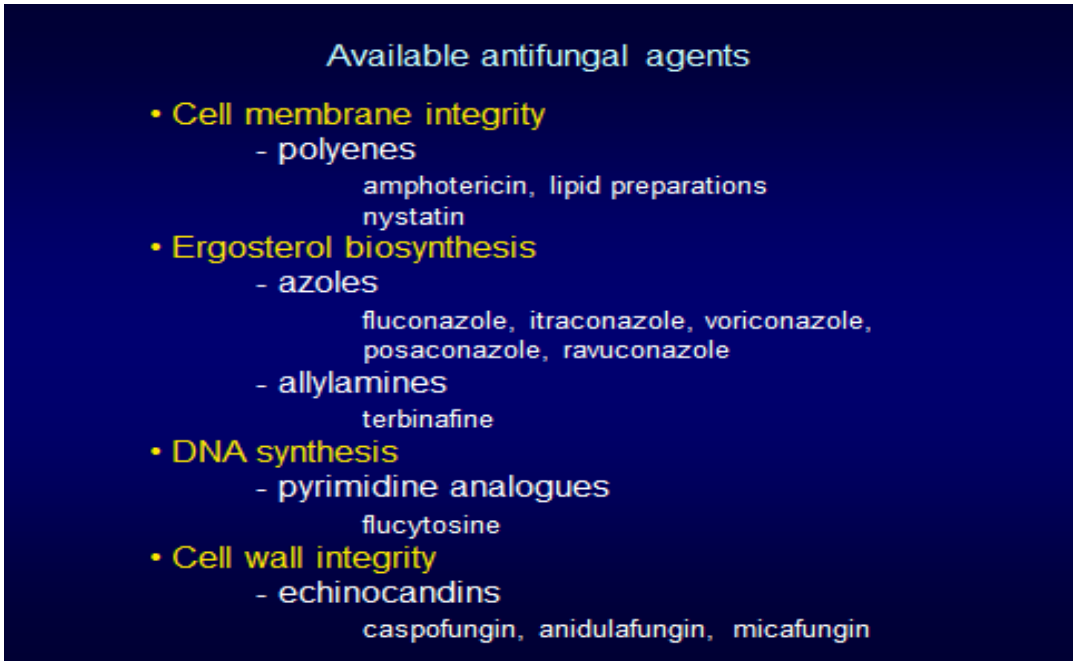
Available antifungal agents
• Cell membrane integrity
- polyenes
amphotericin, lipid preparations
nystatin
• Ergosterol biosynthesis
- azoles
fluconazole, itraconazole, voriconazole,
posaconazole, ravuconazole
- allylamines
terbinafine
• DNA synthesis
- pyrimidine analogues
flucytosine
• Cell wall integrity
- echinocandins
caspofungin, anidulafungin, micafungin