

MUNI  
MED

# Antifungals (antimycotics)

MUDr. Alena Máchalová, Ph.D.

# Antimycotics

- Chemotherapeutics for the treatment of infections caused by pathogenic fungi:
  - ↑ incidence: immunodeficiency, DM, radiotherapy, chemotherapy, HIV, transplantations

## **Mycotic infections:**

- **superficial (local)** - skin and mucous membranes
- **systemic infections** - individuals with weakened immunity (therapy with ATB, CHT, cytostatics,...)

# Superficial mycoses

## Dermatomycoses

- trychophyton
- epidermophyton
- microsporum
- dermatophyton (tinea)



## Superficial candidiasis

Skin, nails and mucosae (oral cavity, vagina),

infections caused by Candida yeasts (most often Candida albicans).

### TINEA (synonymum pro dermatofytózu)

lokalizace	číselná dg.	synonymum
Tinea vlasů a vousů	B 35.0	tinea capitis, tinea barbae
Tinea unguium	B 35.1	dermatofytická onychomykóza
Tinea manus	B 35.2	dermatofytóza postihující dlaně nebo hřbetní část ruky
Tinea pedis	B 35.3	dermatofytóza nohy
Tinea corporis	B 35.4	dermatofytóza postihující kůži trupu, bezvousou část obličeje horní končetiny od ramen k zápěstí a dolní končetiny od třísel ke hlezňům
Tinea cruris	B 35.6	tinea inguinalis, dermatofytóza třísel

### KANDIDÓZA

Kvasinkové onemocnění sliznice ústní	B 37.0
Kvasinkové onemocnění kůže a nehtů	B 37.2

### JINÉ DERMATOMYKÓZY

Pityriasis versicolor	B 36.0
Malasezióvá folikulitida	nemá vlastní kód
Erythrasma a trichomycosis palmellina	byly přeřazeny mezi bakteriální onemocnění
Keratomycosis	dnes označení pro mykotickou keratitidu oka

## Dermatophytes

Tinea corporis (ringworm), includes tinea gladiatorum and tinea faciei

Tinea capitis (ringworm of the scalp)

Tinea cruris (jock itch)

Tinea pedis (athlete's foot)

Tinea unguium (onychomycosis)

Tinea manuum (commonly presents with "one-hand, two-feet" involvement)

Tinea barbae (beard infection in male adolescents and adults)

Tinea incognita (altered appearance of dermatophyte infection caused by topical steroids)

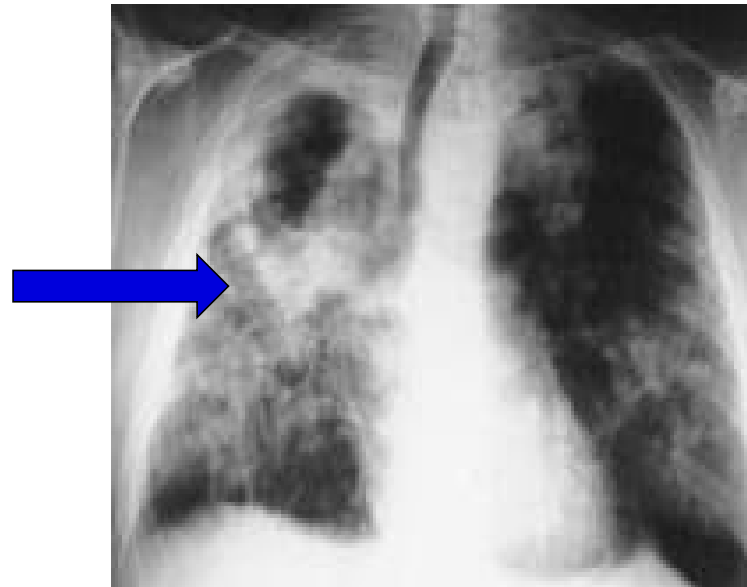
*Candida* (yeast) and mold, which may cause onychomycosis or coexist in a dystrophic nail

Pityriasis versicolor (formerly tinea versicolor) caused by *Malassezia* species

5 **Definujte zápat** Uncommon fungal skin infections that involve other organs (e.g., blastomycosis, sporotrichosis)

# Systemic mycoses

- Lung aspergillosis
- Pneumocystis pneumonia (P.carini)
- Legionella pneumonia
  
- Cryptococcal meningitis and endocarditis
- Rhinocerebral mucomyose
- Systemic candidiasis



# Risk factors for invasive candidiasis

## Iatrogenic factors

- > 3 antibiotics
- > 4 days at ICU
- > 2 days on ventilator
- central venous catheter
- parenteral nutrition
- abdominal surgery

## Factors of the patient

- chronic neutropenia
- immunosuppression
- DM
- colonization by candida
- elderly person

# The most common agents of mycotic infections

## Yeasts

Candida species

C.albicans 50-80%

C.tropicalis

C.krusei

C.glabrata

C.parapsilosis

C.lusitaniae

## Moulds

Aspergillus sp.

A.fumigatus 80-90 %

A.flavus 10-15 %

A.terreus 2-5 %

A.niger

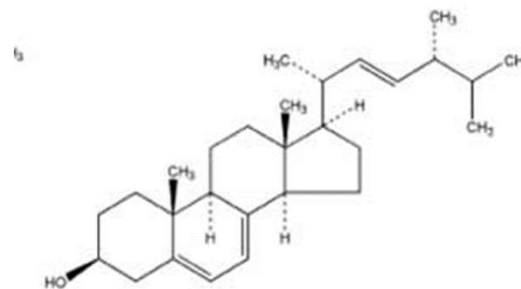


# The treatment of fungal infections

- curing deep tissue mycosis is difficult; patient may die even if given modern effective antifungals
- treatment may last up to 4-6 weeks
- surgical resection of the most affected focus may be required

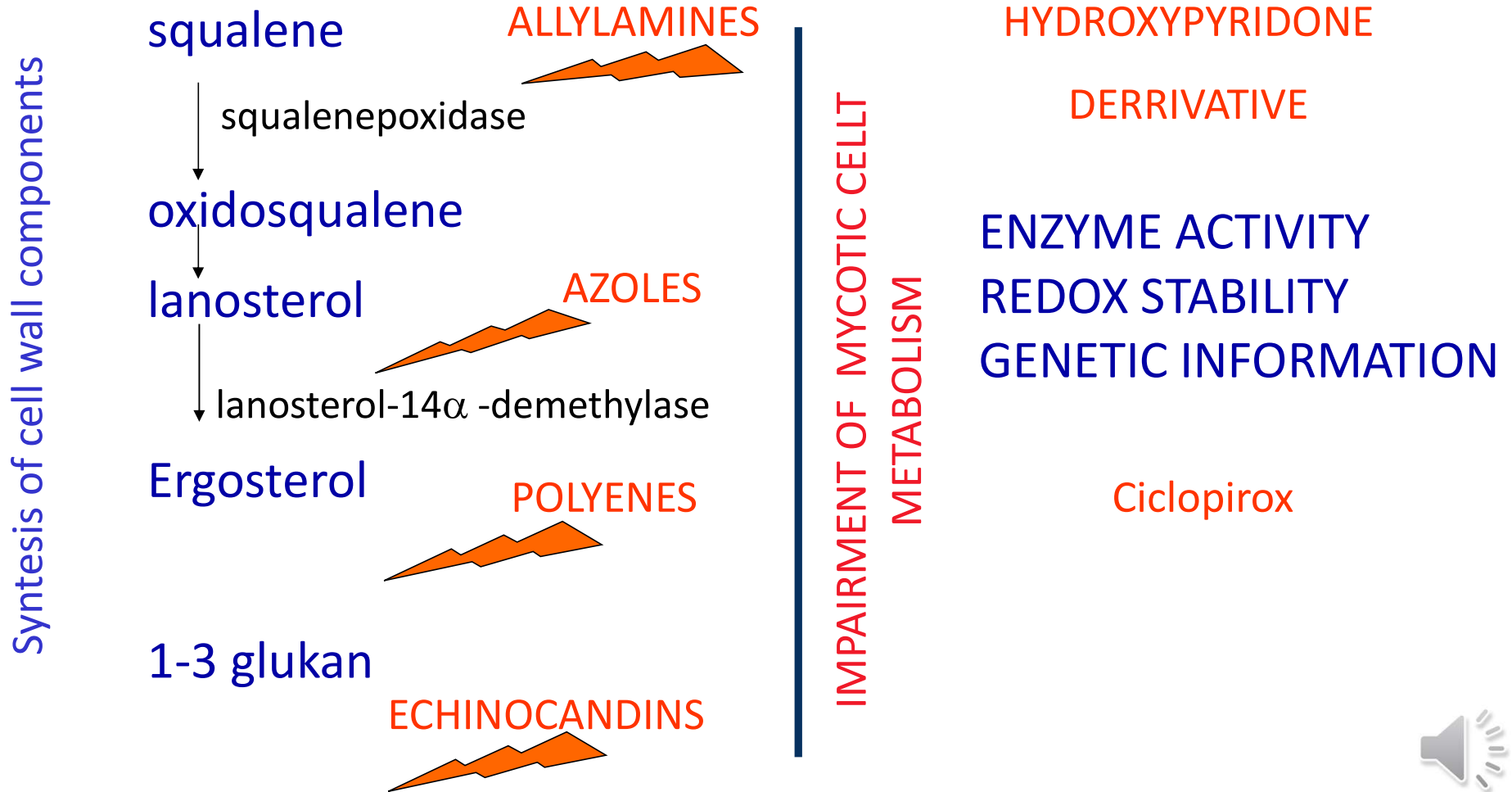
# Mechanism of action of antifungals

- Specific - interfering at a defined place of micromycet metabolism
- Nonspecific - they usually work also on bacteria and can be considered antifungal antiseptics
- Blockage of synthesis fungal lipid (ergosterol) in cell membranes

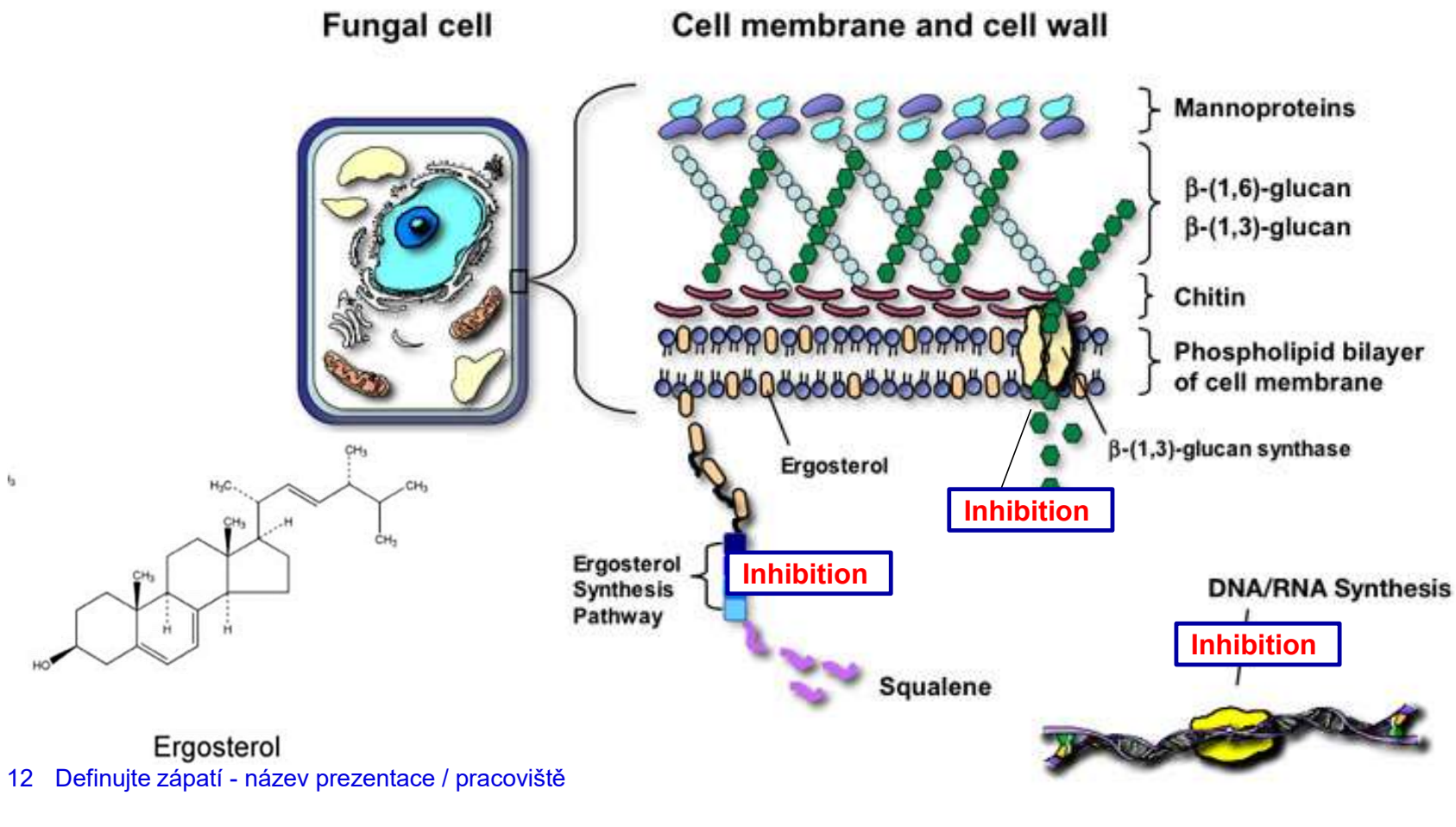


Ergosterol

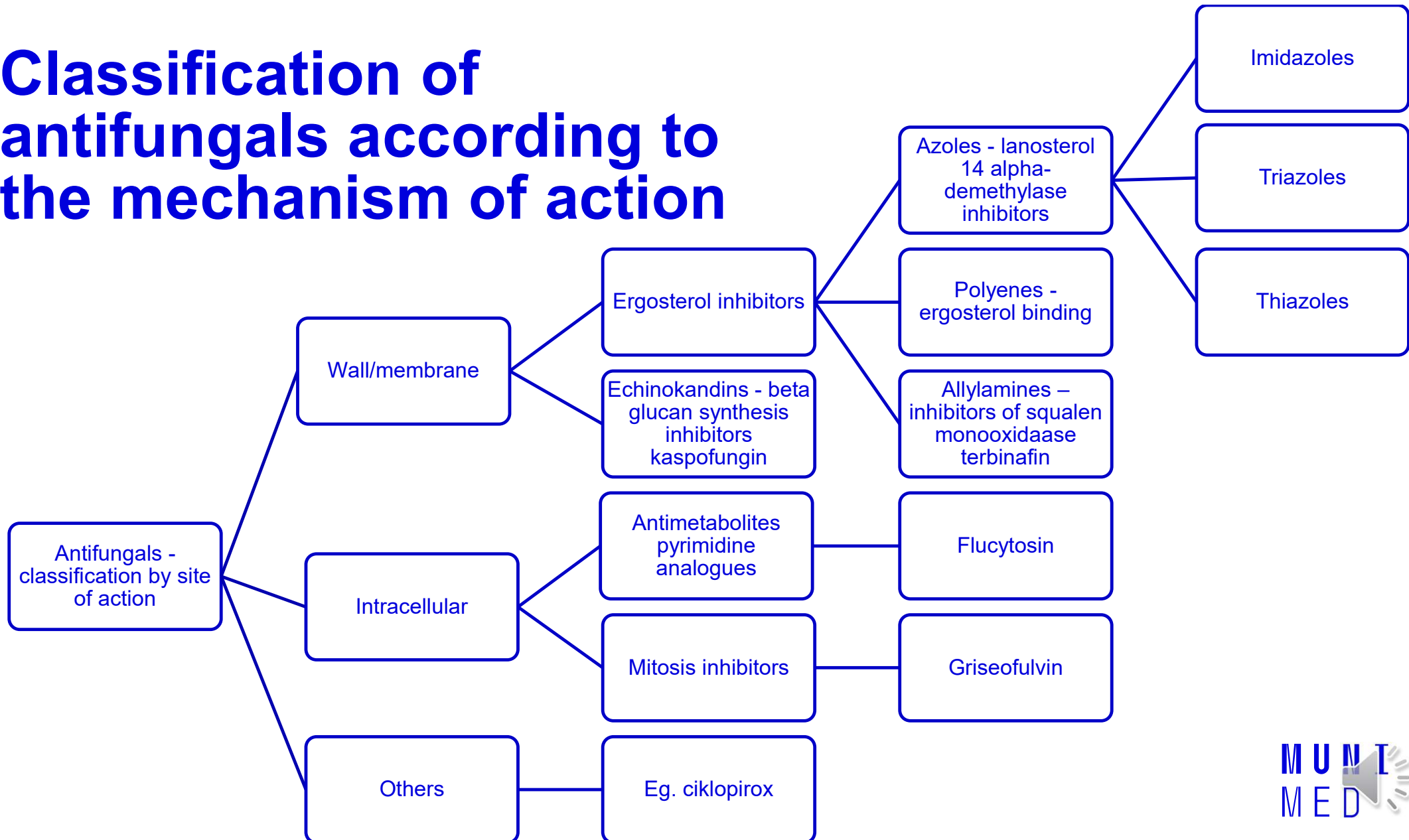
# ANTIMYCOTICS



# Mechanism of action of antifungals



# Classification of antifungals according to the mechanism of action



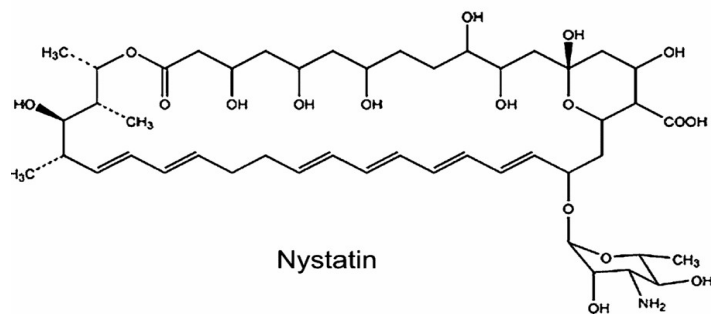
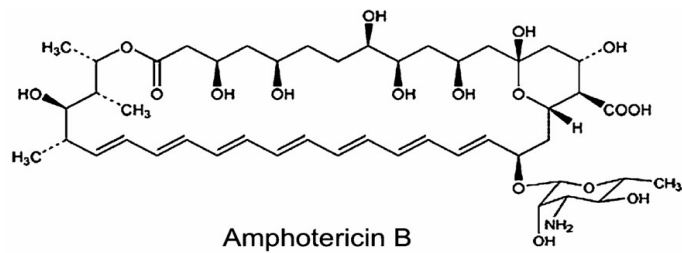
# Classification of antifungals

<b>Polyenes</b>	systemic	<i>amphotericin B</i>
	local	<i>nystatin, natamycin</i>
<b>Antimetabolites</b>	systemic	<i>flucytosine</i>
<b>Azoles</b>	systemic	<i>fluconazole, itraconazole voriconazole posaconazole</i>
	local	<i>clotrimazole, ekonazole, oxikonazole, terkonazole,...</i>
<b>Echinocandines</b>	systemic	<i>caspofungin, anidulafungin</i>
<b>others</b>	systemic	<i>Alylamines - terbinafin, griseofulvin</i>
	local	<i>ciclopiroxolamin, tolnaftate</i>

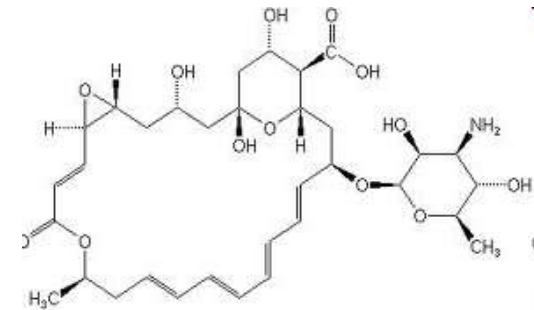


# Polyenes

## *Amphotericin B*



## *Nystatin* *Natamycin*



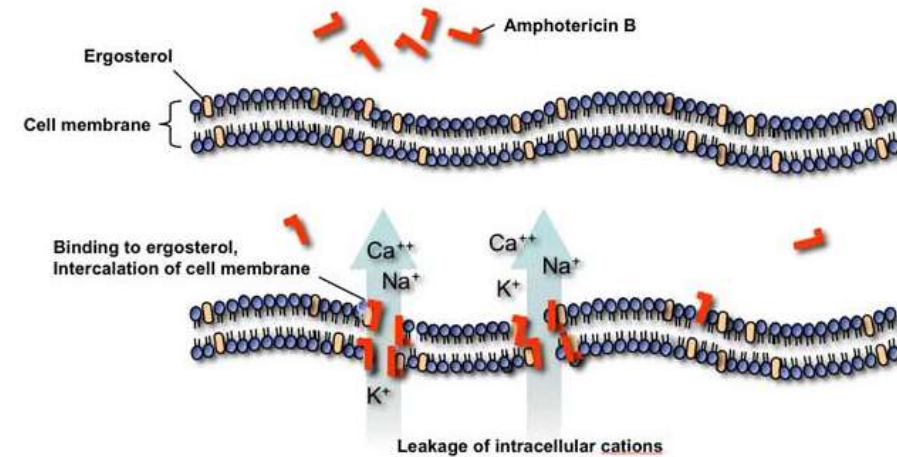
# Systemic polyenes

## – Amphotericin B

- broadest spectrum, lowest resistance
- toxic, most of patients perceive some grade of toxicity/AE
- drug of choice in aspergiloses

**MoA:** binding to ergosterol in cell wall

**I:** severe mycotic infections (life threatening), „prophylactic“ use in oncologic treatment, after trasplantations...





# Amphotericin B

## PK:

- poor GIT bioavailability, administered i.v.- lipidic complex
- difficult distribution to tissues (HEB)
- binding to proteins (95%) and cholesterol
- T1/2 15 days!

## Toxicity

- Acute or infusion related toxicity:
  - fever, chills, rigor, nausea, vomiting,
  - tachycardia, hypotension, bronchospasm
  - headache, muscle pain, joint pain,
  - allergies,
  - thrombophlebitis
- Chronic or organ toxicity:
  - **nephrotoxicity** (total dose) followed by electrolyte imbalance,
  - neuropathy
  - normocytic normochromic anemia (therapy: erythropoietin)
  - thrombocytopenia

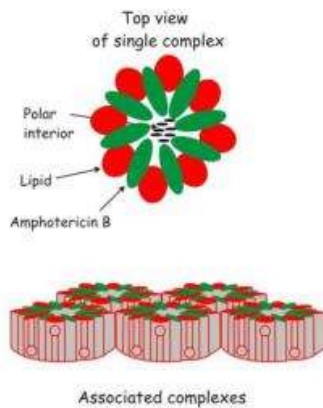


## Prevention of toxicity:

- **Liposomes** - ↓nephrotoxicity
- 3 prep:
  - *Amfotericin B lipid complex (Abelcet)*
  - *Liposomální Amfotericin B (Ambisom)*
  - *Koloid dispersion of amphotericin B (Amphocil)*
- **Premedication:**
  - Hydratation
  - Paracetamol
  - Antihistamines
  - Cortikosteroids

# Lipid Amphotericin B Formulations

## Abelcet® ABLC

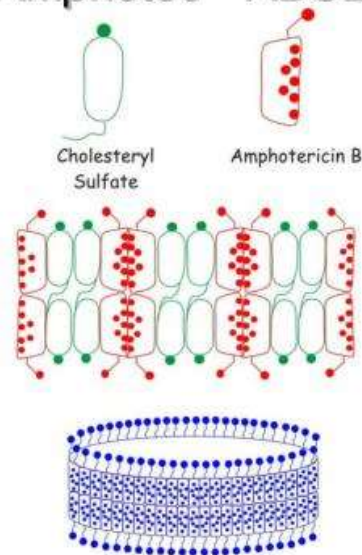


### Ribbon-like particles

Carrier lipids: DMPC, DMPG

Particle size ( $\mu\text{m}$ ): 1.6-11

## Amphotec® ABCD

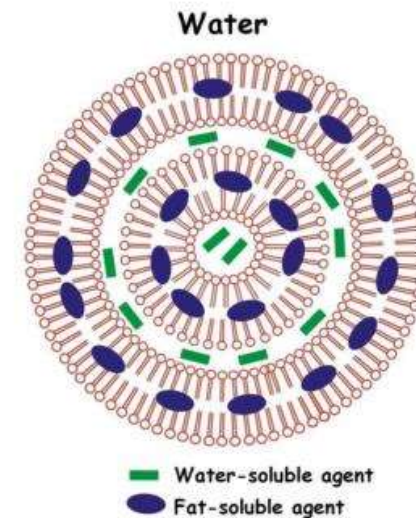


### Disk-like particles

Carrier lipids: Cholesteryl sulfate

Particle size ( $\mu\text{m}$ ): 0.12-0.14

## Ambisome® L-AMB



### Unilaminar liposome

Carrier lipids: HSPC, DSPG, cholesterol

Particle size ( $\mu\text{m}$ ): 0.08

18 Definujte zá DMPC-Dimyristoyl phosphitidylcholine HSPC-Hydrogenated soy phosphatidylcholine  
DMPG- Dimyristoyl phosphitidylglycerol DSPG-Distearoyl phosphitidylcholine

# Topical polyenes

## Nystatin (fungicidin):

I: superficial mycoses, yeasts, **the most often used antifungal drug in oral medicine**

Fungicidin, Macmiror

## Natamycine:

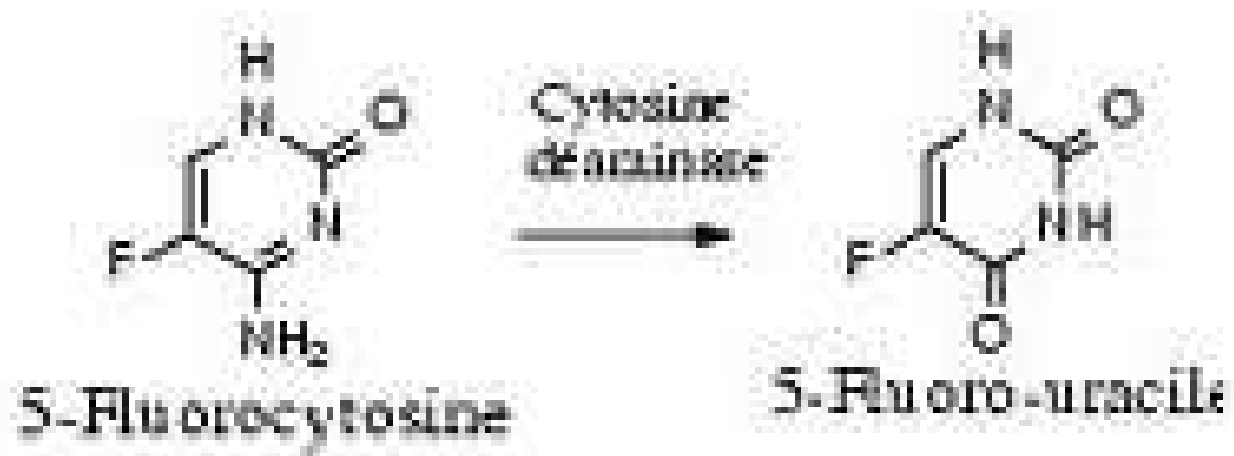
I: Candida, Trichomonas vaginalis, anguli infectiosi, vulvitis, onychomycoses

Pimafucin, Pimafucort



# Antimetabolites

## Flucytosin



# Antimetabolites

## Flucytosine (5-fluorocytosine)

- Systemic effects, narrow spectrum – candida, cryptococcus
- Good penetration into tissues (HEB, placenta, breast milk) – genotoxic, teratogenous

**MoA:** inhibition of nucleic acid synthesis

- fungistatic
- Monotherapy is rarely used - **Synergism with amphotericin B and azoles**

**AE:** granulocytopenia, GIT intolerance  
genotoxic, teratogenous



# Azoles

Systemic

Imidazoles

Ketokonazole

Mikonazole

Systemic candidoses

Triazoles

Fluconazole

Posaconazole

Itraconazole

Voriconazole

Systemic candidoses

Systemic aspergilloses

Local

Clotrimazole

Ekonazole

Oxiconazole

Fenticonazole

Tioconazole

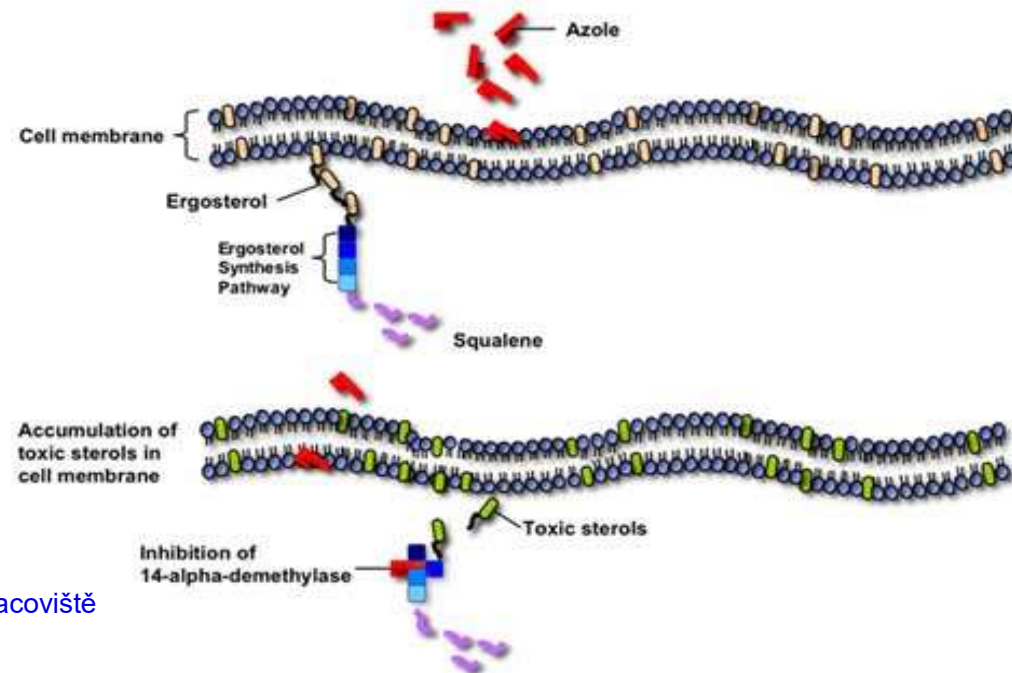
Dermacologics and gynecologics, are not absorbed

AE: irritation, contact allergies

# Azoles

## – MoA:

- inhibition of C-14- $\alpha$ -demethylase (CYP450)
- CYP and Pgp inhibition !!! - interactions + AE



# Azoles

## Ketoconazole

- accumulation in the skin (5 days after discontinuation)
- p.o., skin, hair and nail infections (dermatophytes and yeasts)
- for the treatment of endogenous Cushing's syndrome



## Flukonazol

- p.o. i.v.,
- the only hydrophilic – excretion in urine
- the highest therapeutic index, the least AE (GIT, allergies, headaches), DDI
- Great clinical experience, very often used also in children





# Azoles

## Itraconazole

p.o., variable absorption, 1st pass effect,  $\beta$ -cyclodextrin  
i.v.

high antifungal specificity incl. Aspergillus),  
does not penetrate into the CNS

AE: increased liver enzymes, skin reactions



# Azoles

## Voriconazole

- Better effect in invasive aspergillosis than amphoterecin B
- p.o. and i.v., almost complete F (95-96%)
- High fungicidal activity— candida, aspergillus
- **invasive life-threatening infections (aspergillosis, mucormycosis) candidoses rezistant to fluconazole**

## Posaconazole

- second-line drug
- prophylaxis of candidiasis in risk patients, aspergillosis resistant to AmB or itraconazole, or in intolerance of 1st line drugs



Léčivý přípravek obsahující posakonazol  
aktuálně dostupný v ČR.

# Topical (local) azoles

- **Clotrimazole** (depot in stratum corneum)
- **Econazole** (also efficient against some bacterias)
- **Oxiconazole, Fenticonazole, Tioconazole**

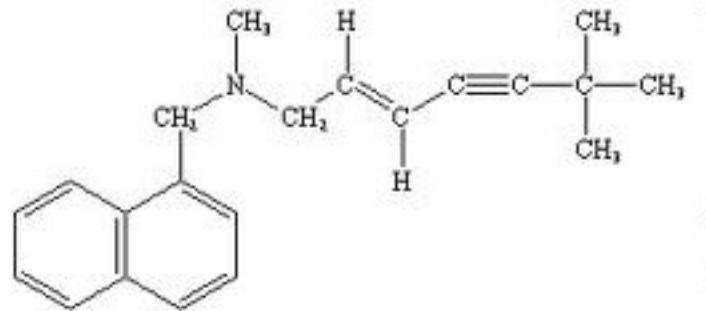
Dermacologics and gynecologics, are not absorbed

**AE:** irritation, contact allergies



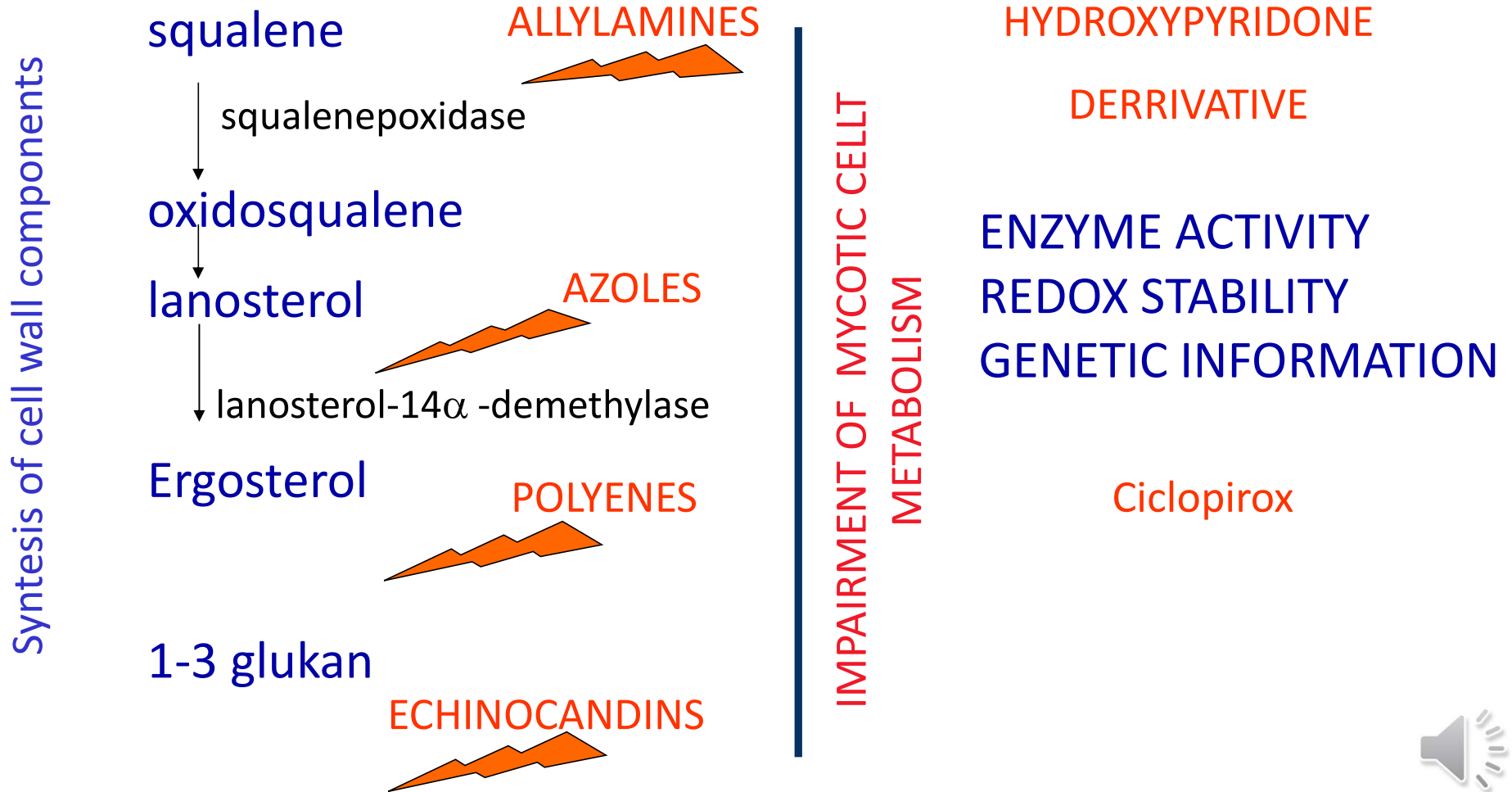
# Allylamines

## *Terbinafine*



terbinafin

# ANTIMYCOTICS



# Allylamines



## Terbinafine

**MoA:** block of squalenepoxidase

- accumulation in the adipose tissue and skin
- fungicidal activity up to 3 w after discont.

(synergistic effect with azoles)

**AE:** dyspepsia, loss of appetite

**I:** tinea, candidiasis, onychomycosis

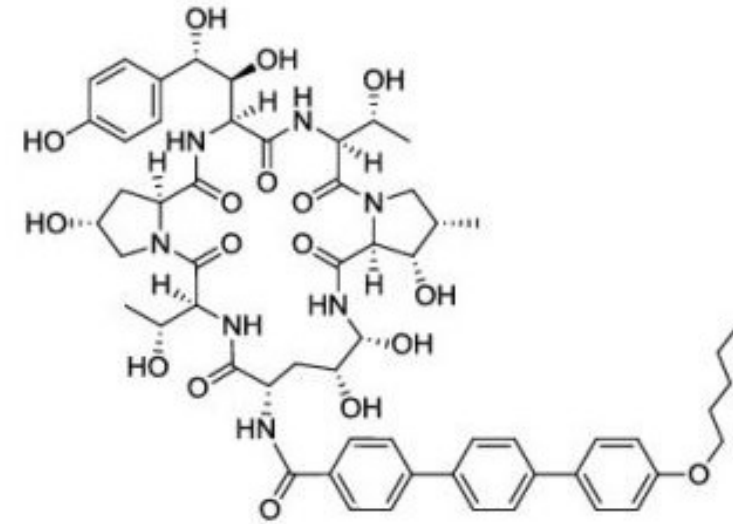
# Echinocandins

= lipopeptides

**MoA:** inhibition of glucan synthesis  
(cell wall component of many fungi and yeasts)

- parenteral administration
- synergism when combined with azoles or polyenes
- not metabolized via CYP

**AE:** **minimal toxicity**, flebitis, GIT AE, hypokalemia



# Echinocandins

= lipopeptides

- Caspofungin (*Cancidas*)
- Micafungin (*Mycamine*)
- Anidulafungin (*Ecalta*)



**I:** alternative therapies for severe invasive mycoses (aspergillosis, invasive candidiasis)

1st choice in hemodynamic instable patient with severe infection



# Other antifungal drugs

*Ciklopirox(-olamin)*

*Tolnaftate*

*(Griseofungin)*

# Ciclopirox-olamine

topical fungicidal antimycotic agent  
+ G+/G- bacteria, mycoplasmas, trichomonades

MoA: chelates  $Fe^{3+}$  (→ metalloproteins function abruption)

- i. cytochrome – blocks energy metabolism of the mycotic cell
- inh. catalase, peroxidase – block antioxidative protection

Cytoplasmatic membrane – block of transporters

- deplete essent. AA (Leu), nucleotides, ..

**antioxidant** - scavenger ROS ( $OH\bullet$ )

**inhibitor AA** → inh. synthesis a LT in human PMN cells

**antiinflammatory activity in vivo**



M U N I  
M E D

## Tolnaftate

OTC drug for the treatment of tinea pedis, tinea cruris, dermatophytosis

Fungicid

MoA similar to terbinafine

# Griseofulvin

## obsolet

Narrow spectrum, fungistatic

**MA:** interaction with microtubules – mitotic poison

- administered orally
- accumulation in stratum corneum, hair, nails
- I: dermatomycoses

AE: GIT irritation, allergy, leucopenia, hepatotoxicity, neurologic disorders

**CYP inducer**

# ANTIMYCOTICS

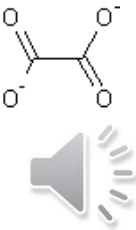
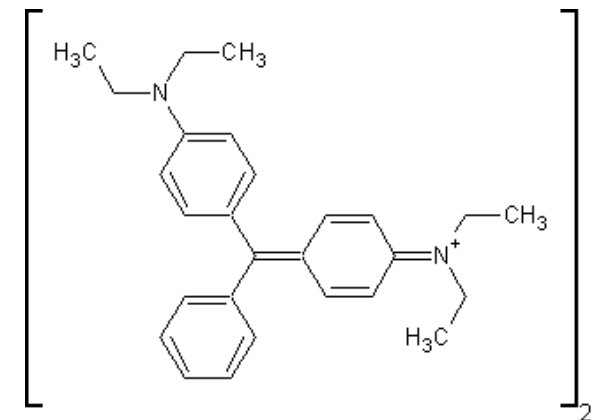
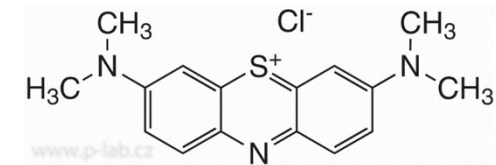
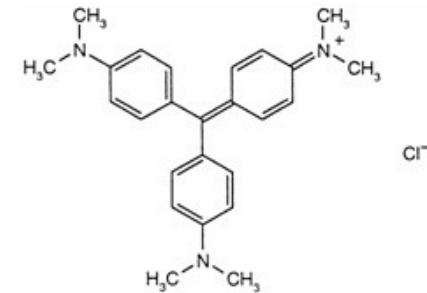
## Nonspecific antifungals

- 1) Acids and derivatives:
- Ac. salicylicum
  - Ac. boricum
  - Ac. undecylenicum
  - Ac. benzoicum

- 2) Phenols: resorcinol, hexachlorophene

3) Organic dyes:

- crystal gentian - (Methylrosanilini chloridum)
- methylene blue - (Methylthioninii chloridum)
- brilliant green - (Viride nitens)



# ANTIMYCOTICS

## Nonspecific antifungals

4) Aldehydes: formaldehyde, glutaraldehyde

5) Halogens and derivatives: iodine, iodine-povidon, iodine-glycerol  
chlorine

6) Oxidizing agents:  $\text{KMnO}_4$ ,  $\text{H}_2\text{O}_2$  (1-3%)

7) Tars: Lithanthracis pix  
Betulae pix  
Fagi pix...