

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 unguum	B 35.1	dermatofytická onychomykóza
Tinea manus	B 35.2	dermatofytóza postihující dlaň 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 inguinallis, 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
Malaseziová 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 incognito (altered appearance of dermatophyte infection caused by topical steroids)

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

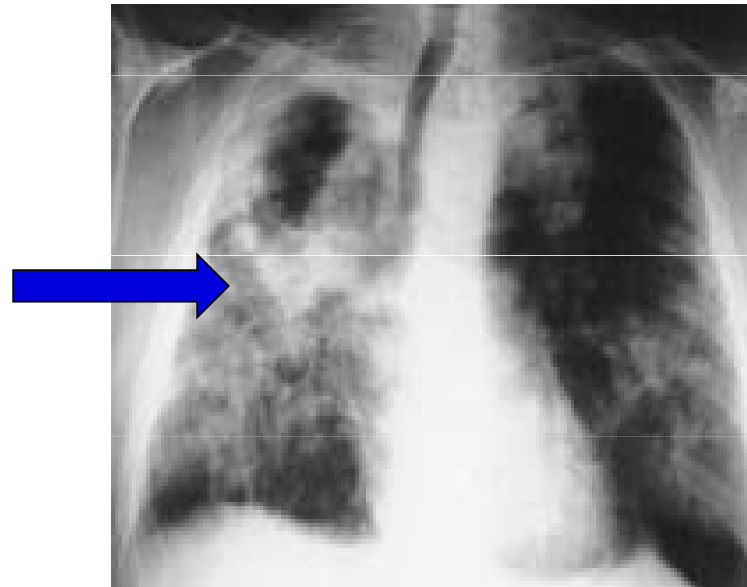
Pityriasis versicolor (formerly tinea versicolor) caused by *Malassezia* species

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 %

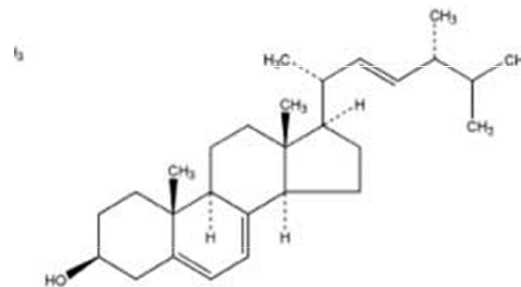
A.niger

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

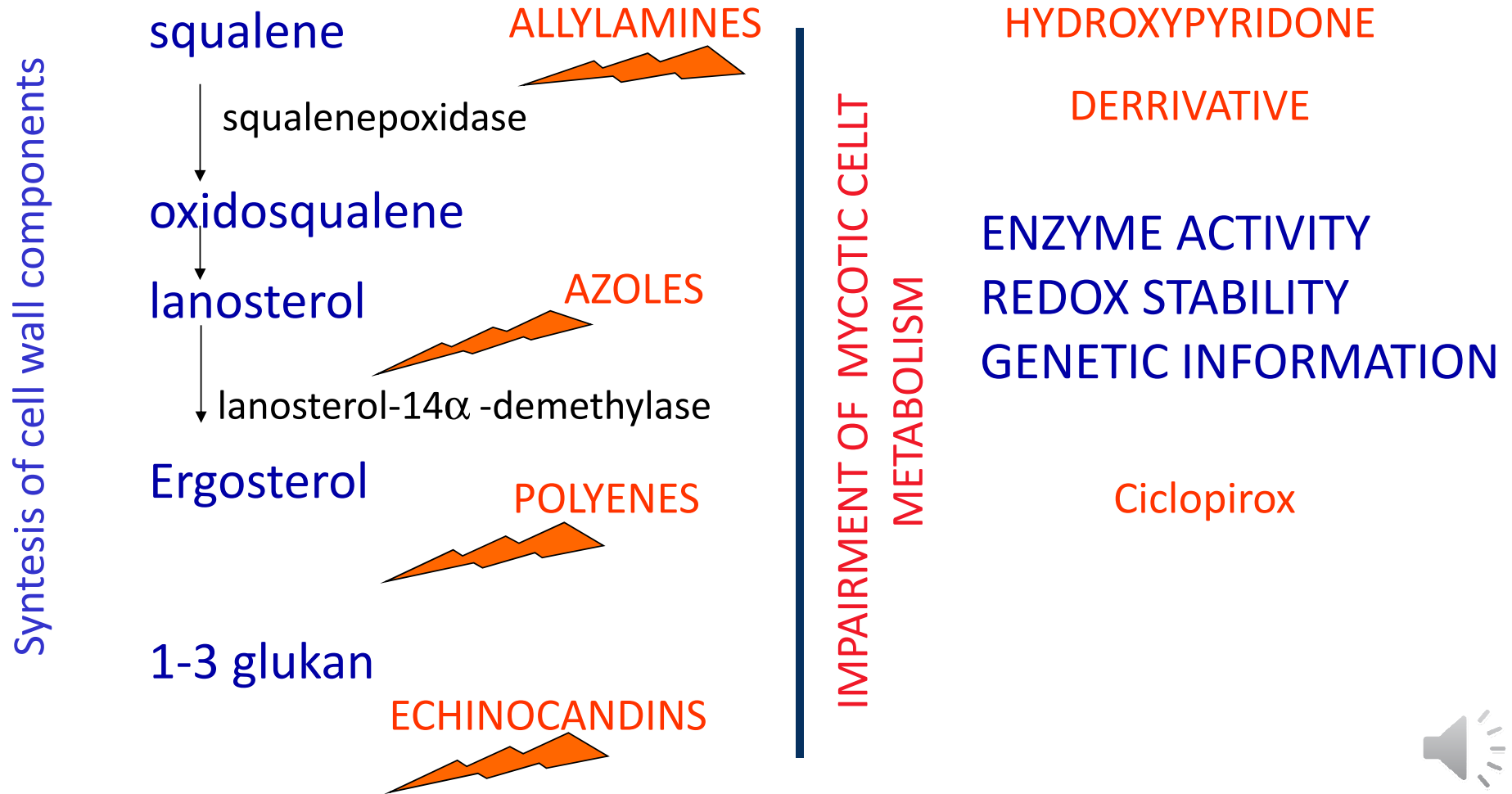
Mechanism of action of antifungals

- 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

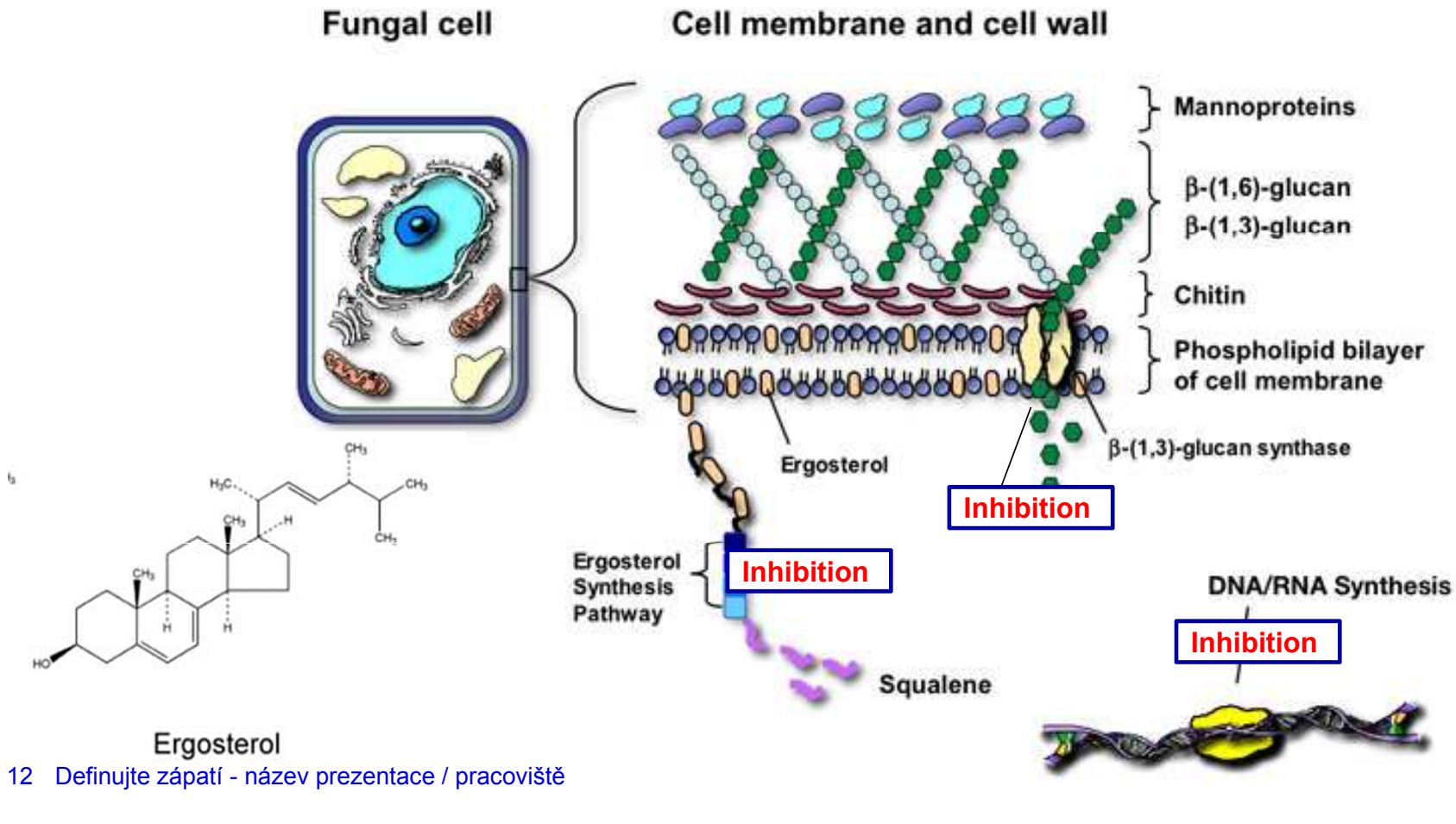


Ergosterol

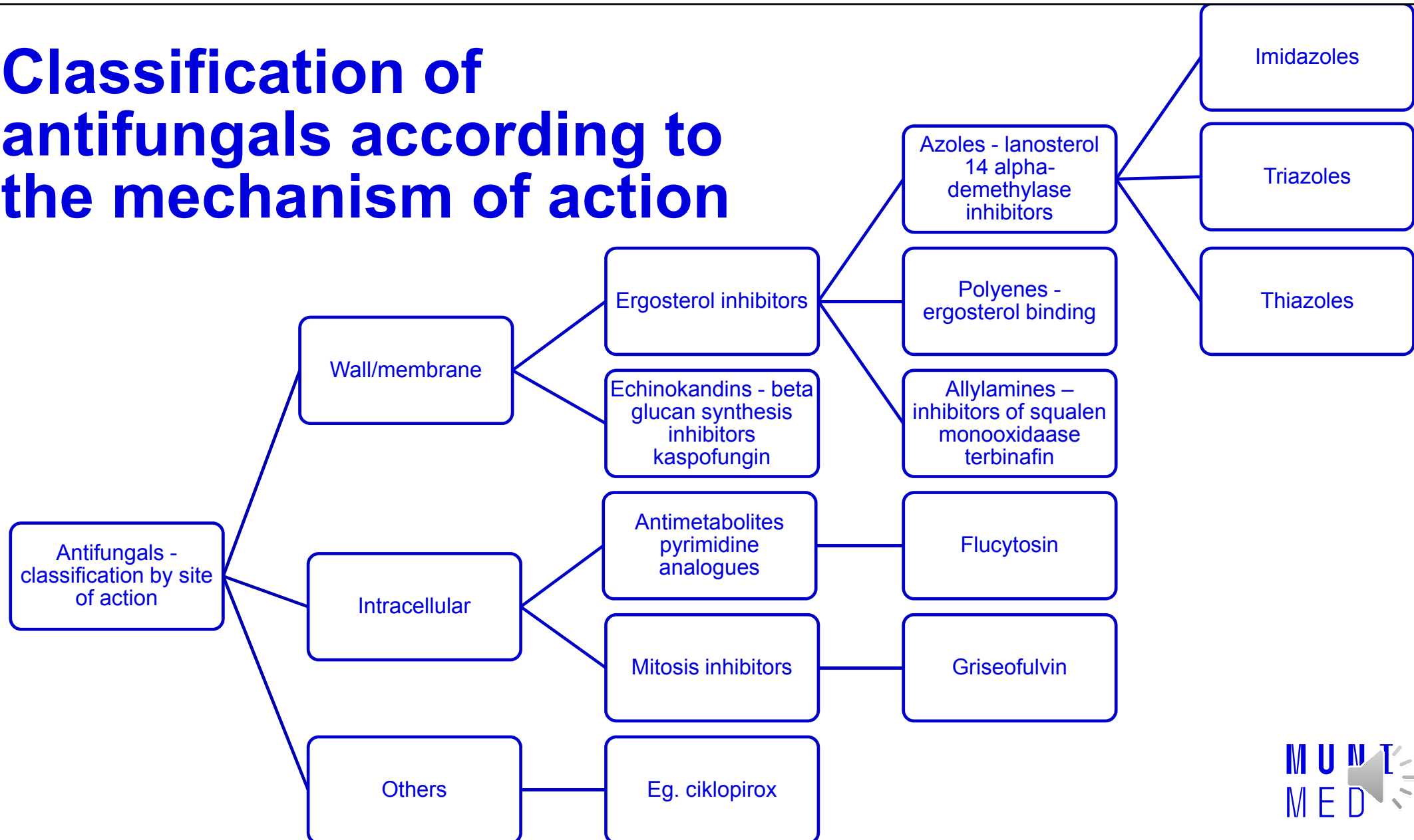
ANTIMYCOTICS



Mechanism of action of antifungals



Classification of antifungals according to the mechanism of action



Classification of antifungals

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



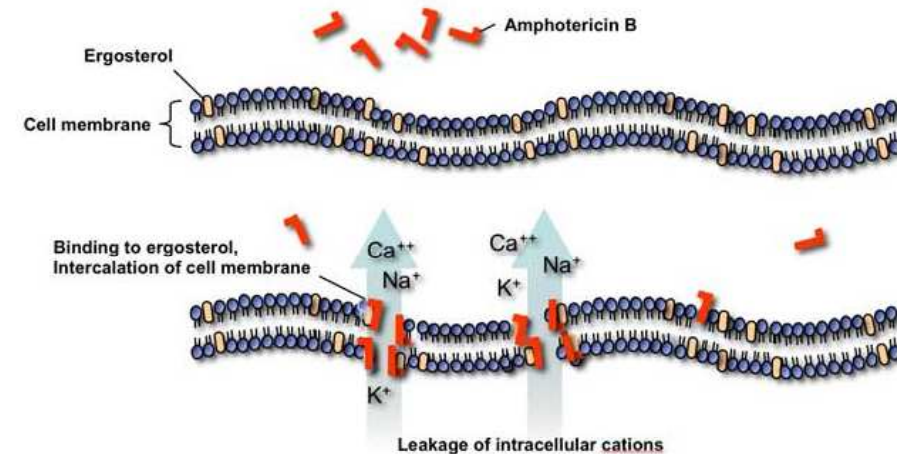
Systemic polyenes

– 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 manifestations:

- fever, chills, rigor, nausea, vomiting,
- tachycardia, hypotension, bronchospasm
- headache, muscle pain, joint pain,
- allergies,
- thrombophlebitis

▪ Chronic manifestations:

- **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

Topical polyenes

Nystatin (fungicidin):

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

Fungicidin, Macmiror

Natamycine:

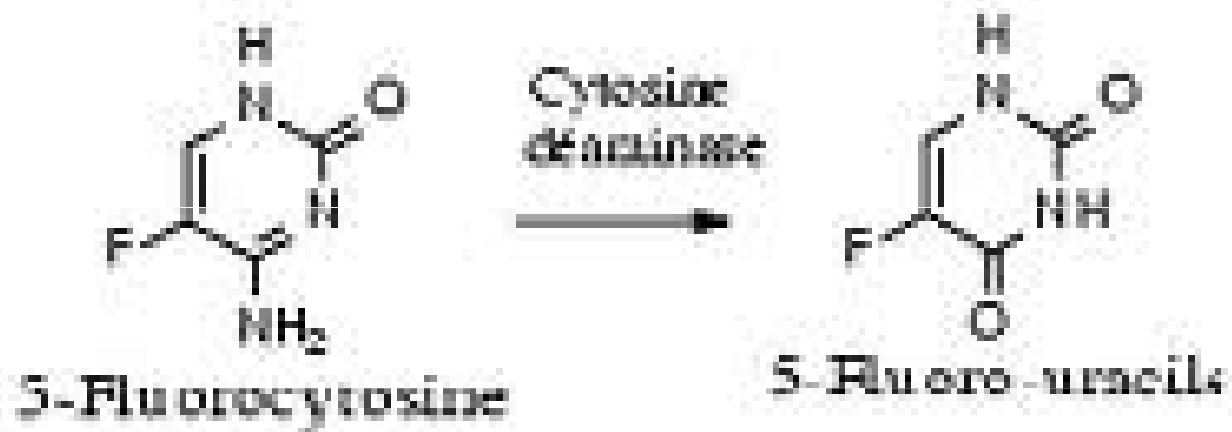
I: Candida, Trichomonas vaginalis, anguli infectiosi, vulvitis, onychomycoses

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

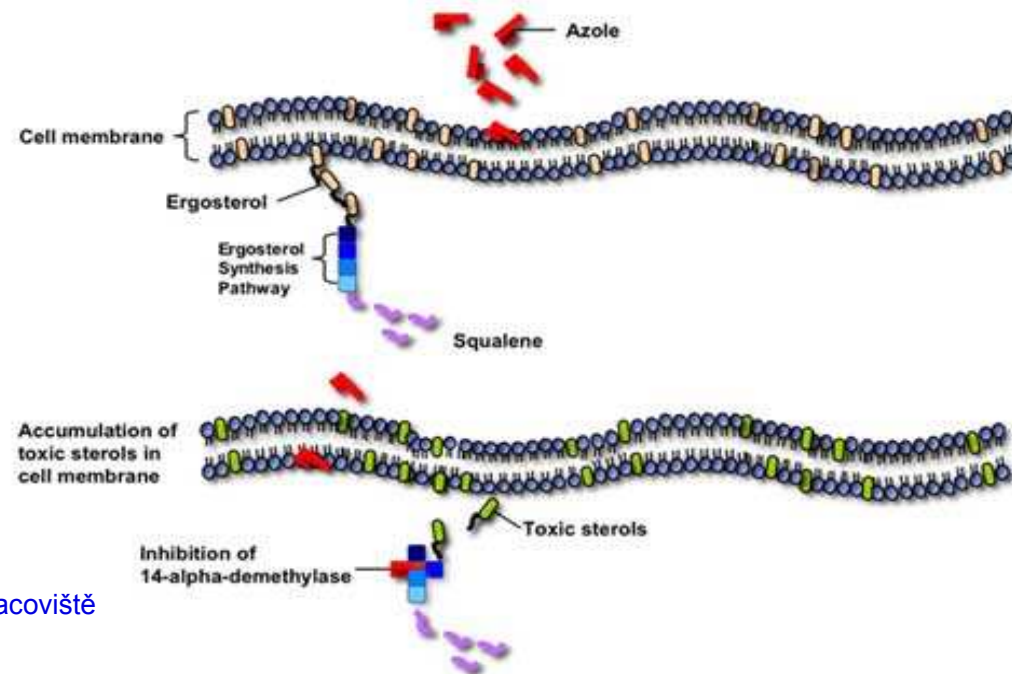
Tioconazole

Dermacologics and
gynecologics, are not
absorbed

AE: irritation,
contact allergies

Azoles

- **MoA:**
- inhibition of C-14- α -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, β -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**

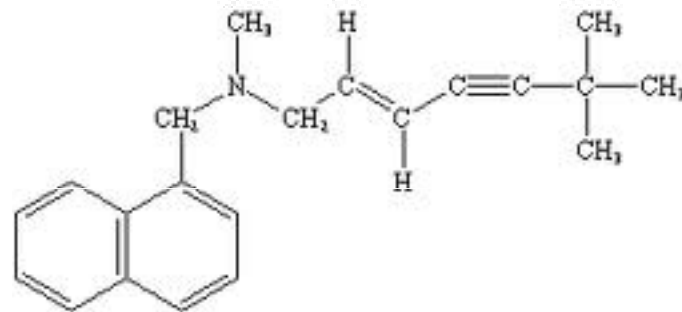
Dermacologics and gynecologics, are not absorbed

AE: irritation, contact allergies



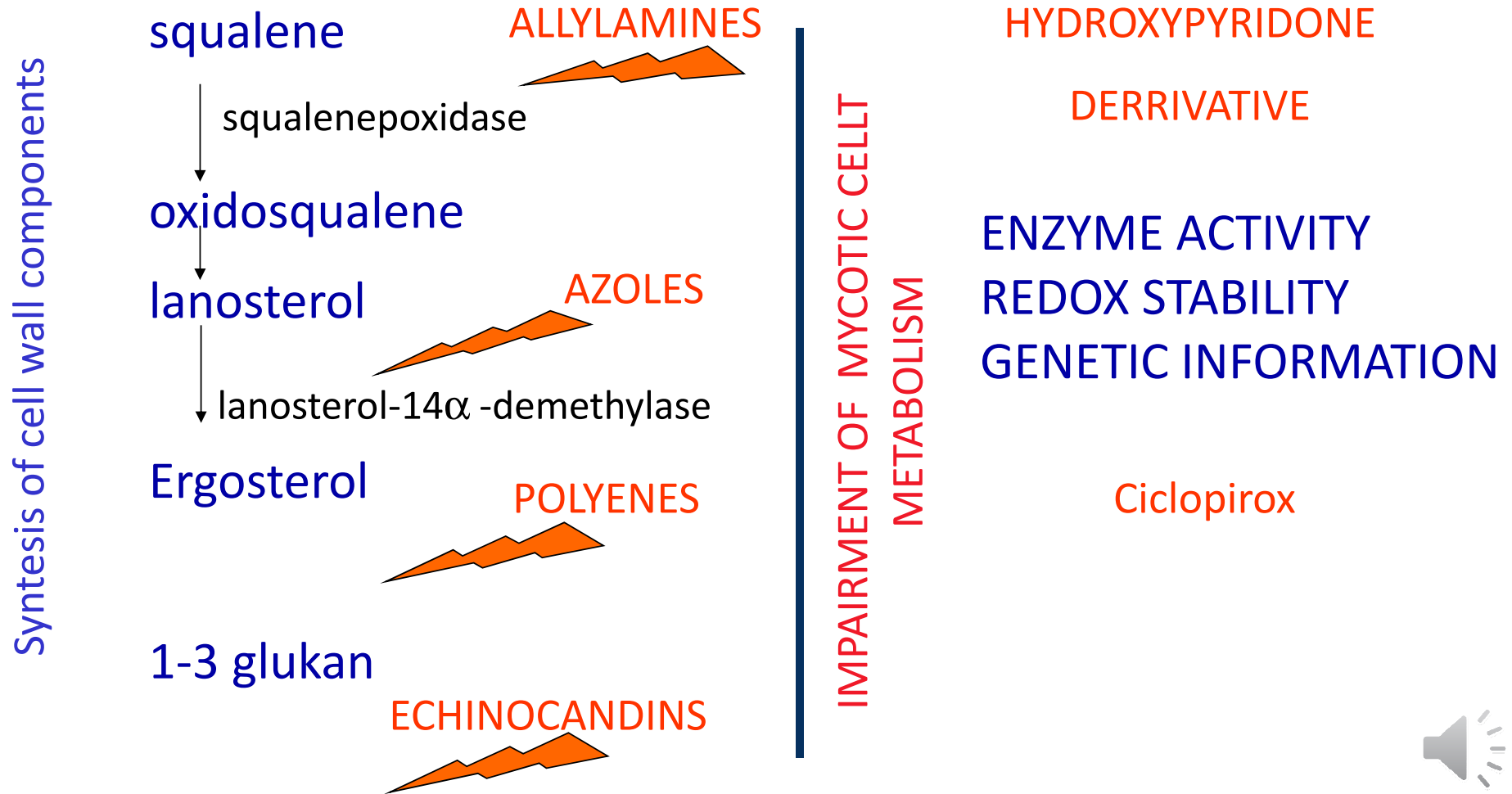
Allylamines

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 ketoconazole

AE: dyspepsia, loss of appetite

I: tinea, candidiasis, onychomycosis

Echinocandins

= lipopeptides

- Caspofungin (*Cancidas*)
 - Invazivní kandidóza, aspergilóza
- Micafungin (*Mycamine*)
 - Invazivní kandidóza
- Anidulafungin (*Ecalta*)
 - Invazivní kandidóza



Echinocandins

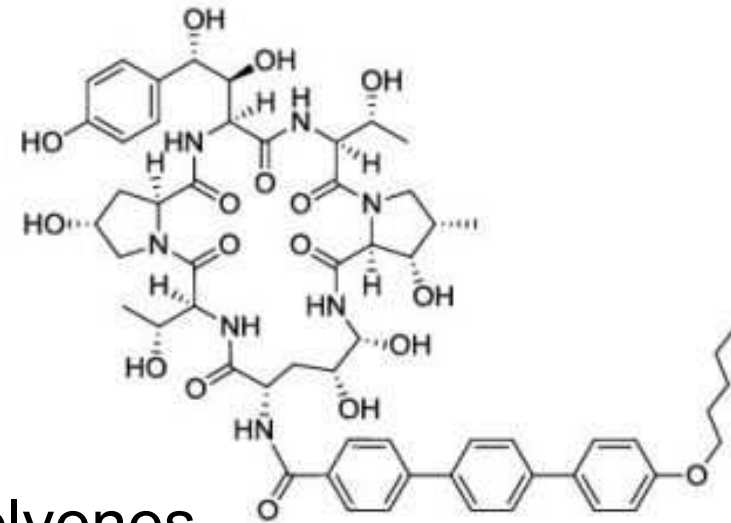
MoA: inhibition of glucan synthesis
(cell wall component of many fungi and yeasts)

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

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

1st choice in hemodynamic instable patient with severe infection

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



Other antifungal drugs

Ciklopirox(-olamin)
Tolnaftate
(Griseofungin)

Ciclopirox-olamine

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

MoA: chelates Fe^{3+} (➡ metaloproteins 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•)

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

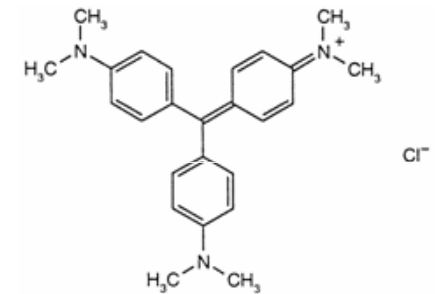
AE: GIT irritation, allergy, leucopenia, hepatotoxicity, neurologic disorders

CYP inducer

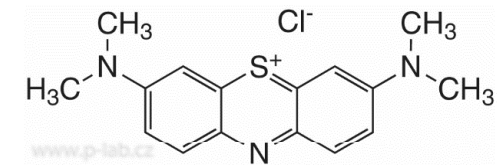
ANTIMYCOTICS

Nonspecific antifungals

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

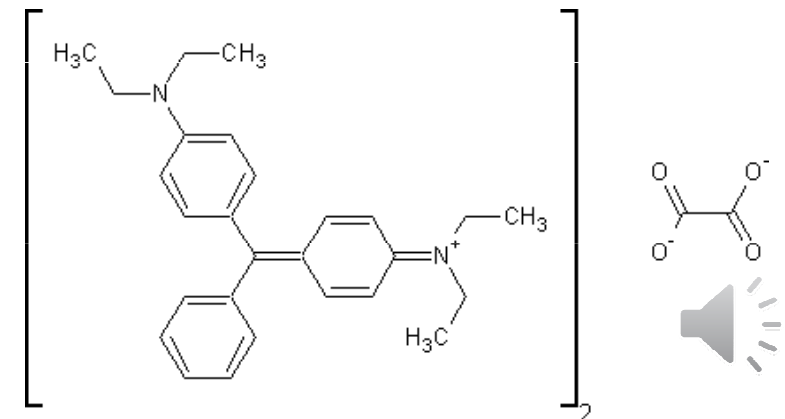


- 2) Phenols: resorcinol, hexachlorophene



- 3) Organic dyes:

- crystal gentian - (Methylrosanilini chloridum)
- methylene blue - (Methylthionini 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: KMnO_4 , H_2O_2 (1-3%)

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