Masaryk University
Faculty of Medicine

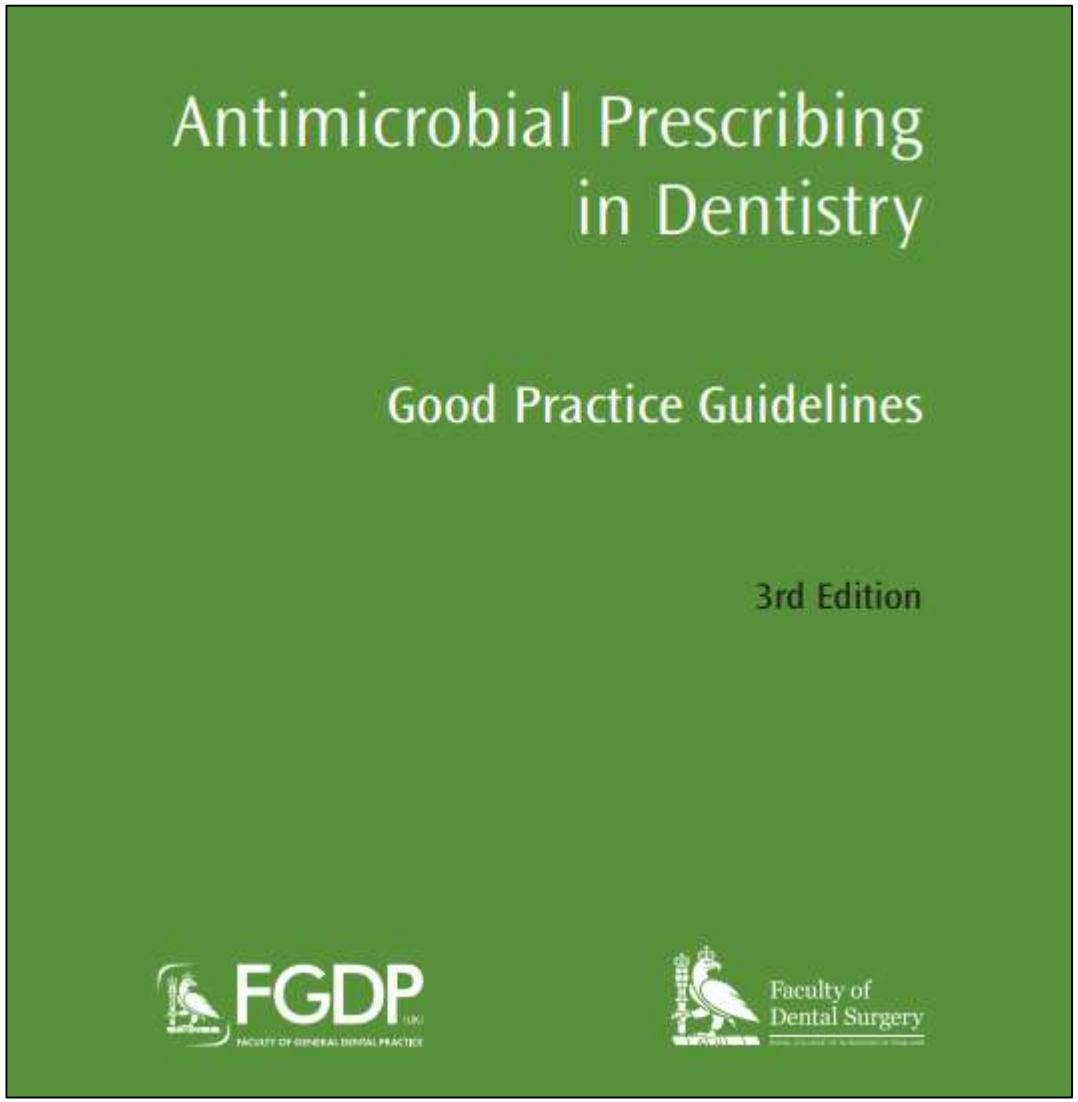
Antimycotics in Dentistry

Antimycotics for Infection Control and Prevention in Dentistry

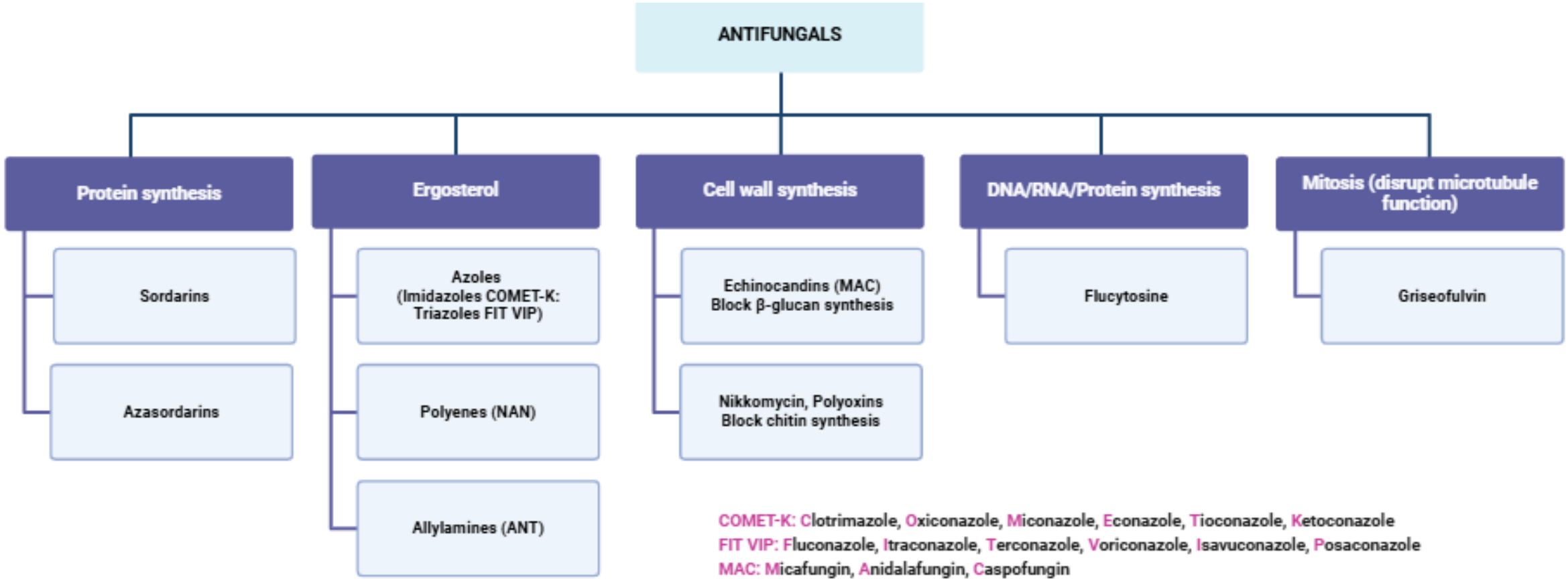
MSc. Carlos Daniel Ferreira Fonseca

29.11.2024

Before we start…



Palmer, N. (Ed). Antimicrobial Prescribing in Dentistry: Good Practice Guidelines. 3rd Edition. London, UK: Faculty of General Dental Practice (UK) and Faculty of Dental Surgery; 2020.



COMET-K: Clotrimazole, Oxiconazole, Miconazole, Econazole, Tioconazole, Ketoconazole
FIT VIP: Fluconazole, Itraconazole, Terconazole, Voriconazole, Isavuconazole, Posaconazole
MAC: Micafungin, Anidalafungin, Caspofungin
NAN: Natamycin, Amphotericin B, Nystatin
ANT: Amorolfin, Naftifin, Terbinafine

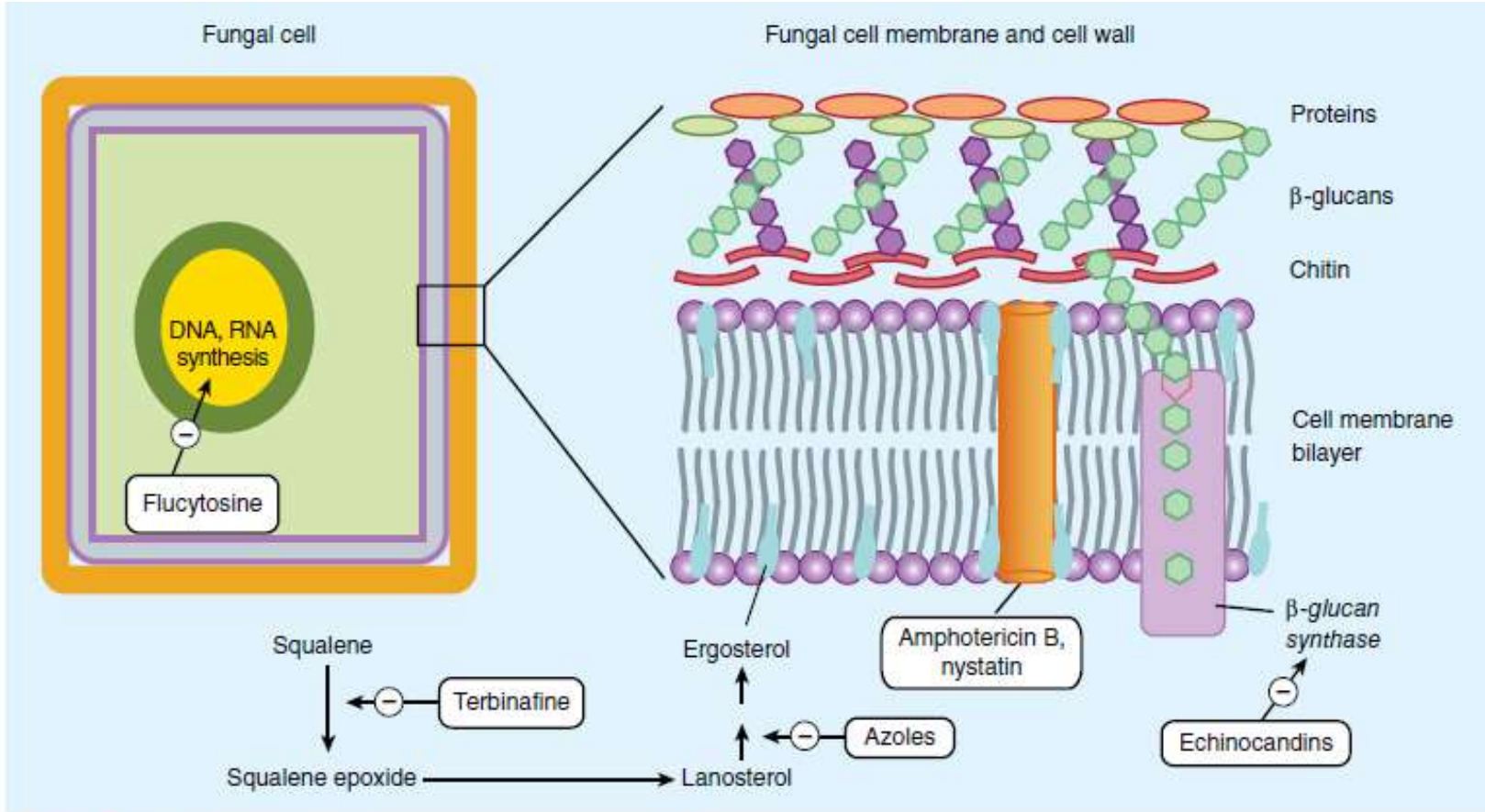
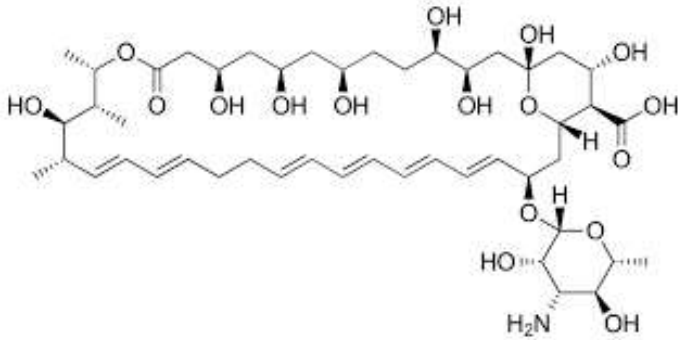


FIGURE 48–1 Targets of antifungal drugs. Except for flucytosine (and possibly griseofulvin, not shown), all currently available antifungals target the fungal cell membrane or cell wall.

Polyenes

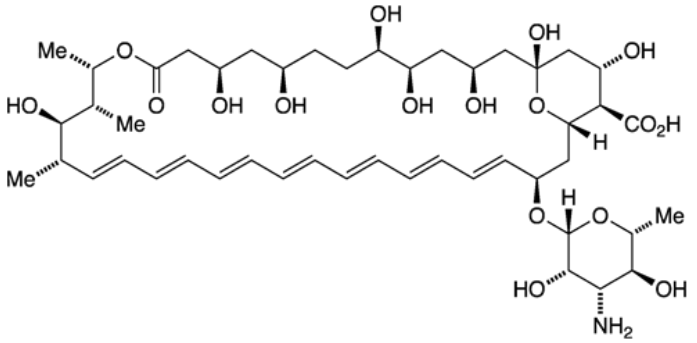


- **Local**

  nystatin
  - **Polyene** macrolide
  - Parenteral administration is very toxic
  - **Mechanism of action:** selective binding to fungi membrane → pore → altering cellular permeability - avidity for **ergosterol**
  - **Adverse effects:** nausea, vomiting and diarrhoea
  - **Modes of administration:** P.O, topical
  - Limited to topical treatment of **cutaneous and mucosal candida infections**
  - Absorption from GIT is negligible
  - Use of **nystatin oral suspension** in the mouth for several minutes four times daily before swallowing

- Other example of local administered polyene: **natamycin**

Polyenes

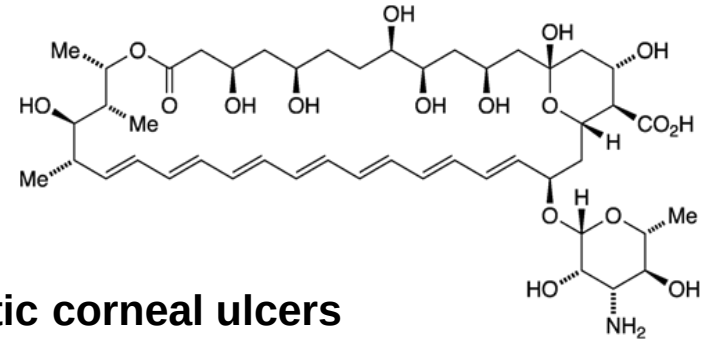


- **Systemic**

  amphotericin B

  - prepared as a colloidal suspension
  - **broadest spectrum of action** → including **mucormycosis**
  - Oral amphotericin B → effective only on fungi in the GIT
  - **Use in systemic infections** → IV administration (slow infusion)
    - Nowadays there is one azole (**posaconazole**) with less side effects and activity against mucor
  - amphipathic characteristic facilitates pore formation
  - **Mechanism of action:** selective binding to fungi membrane → pore → altering cellular permeability - avidity for **ergosterol**

Polyenes



- **Systemic**

amphotericin B

- Can be used topically for treatment of **keratitis** and **mycotic corneal ulcers**

- **Adverse effects**
  - **Infusion-Related Toxicity (**Phlebitis**):** fever, chills, muscle spasms, vomiting, headache, and hypotension
    - Ameliorated with administer normal saline infusions with the daily doses of amphotericin B
  - **Cumulative Toxicity:** Renal toxicity → renal tubular acidosis, **hypokalaemia** and **hypomagnesemia** → Torsade de points

- **Modes of administration:** P.O, IV, IT (Intrathecal), topical

- **Hepatic elimination**

Azoles

- **Local**
  - clotrimazole
  - econazole
  - miconazole
- **Systemic**
  - fluconazole
  - itraconazole
  - voriconazole
  - posaconazole

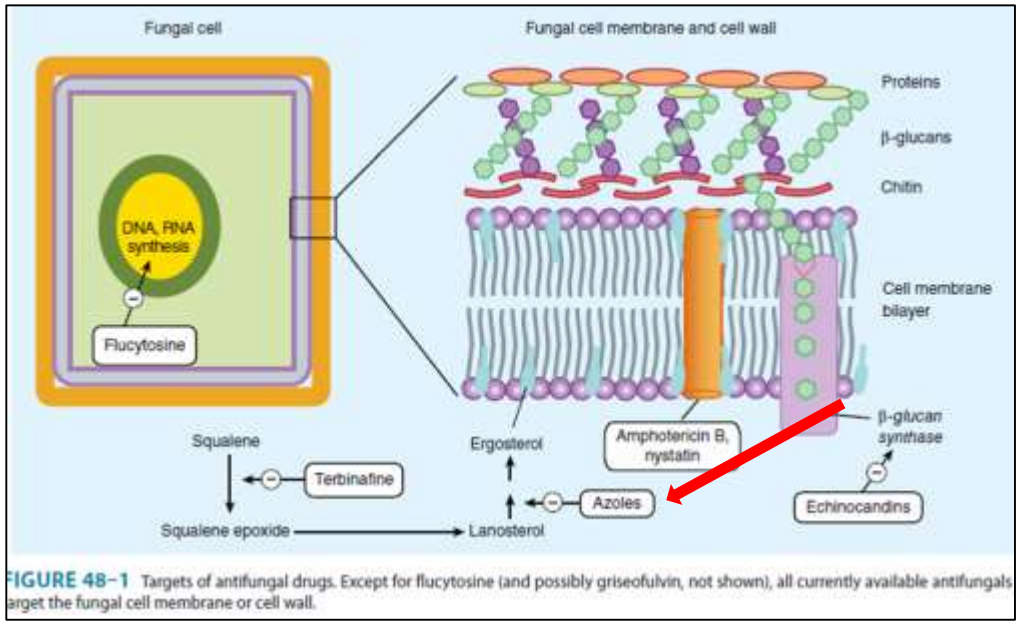


FIGURE 48–1 Targets of antifungal drugs. Except for flucytosine (and possibly griseofulvin, not shown), all currently available antifungals target the fungal cell membrane or cell wall.

Mechanism of action: inhibition of fungal cytochrome P450 enzymes (14-α-demethylase)

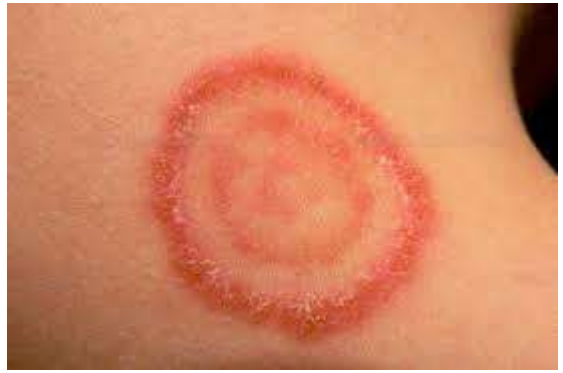
Inhibition of conversion of **lanosterol** to **ergosterol**

Interfering with fungi cell membrane

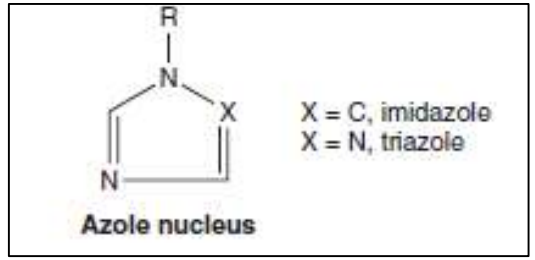
Inhibition of fungal growth

Azoles

- **Broad spectrum of action**
  - Candida
  - Cryptococcus neoformans
  - Endemic mycoses (blastomycosis, coccidioidomycosis, histoplasmosis)
  - Dermatophytes (ringworm) → Trichophyton fungus
    - Trichophyton causes athlete's foot
- **2 big families: imidazoles and triazoles**
  - Imidazole: **clotrimazole**, **miconazole**, and **ketoconazole** **(less potent)**
  - Triazole: **fluconazole**, **itraconazole** and **voriconazole** **(more potent)**
- **Inhibition of human cytochrome P450**
- **Mainly topical use**
  - **Safe use** → biggest risk is skin irritation



ringworm



Azoles

- **Peroral and IV administration → Systemic fungal infections**
- **Oral or vaginal → Candidiasis**

→ 2nd or 3rd Line after **amphotericin B**

Imidazole → ↓ selectivity and ↑ drug interactions and side effects than triazoles

- Used topically to treat skin infections
- **clotrimazole** used as a lozenge for oropharyngeal candidiasis
- **miconazole** or **clotrimazole** for vulvovaginal candidiasis
- **miconazole** or **clotrimazole** for dermatophyte infections (Tinea)

Triazoles

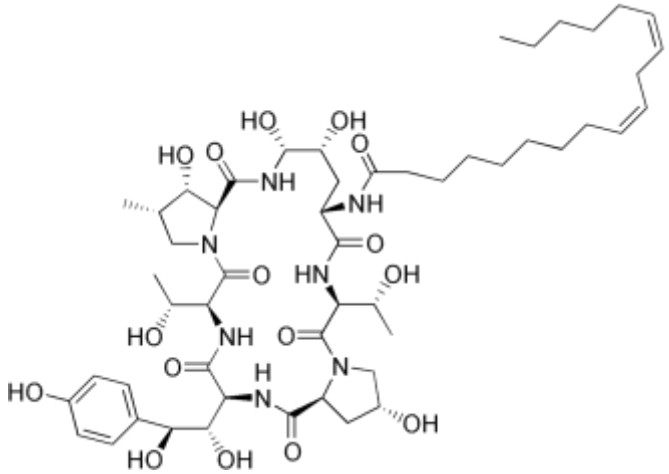
- **fluconazole** → Candidosis + ***Cryptococcus neoformans (***drug of choice for treatment and prophylaxis***)***
  - PO and IV administration
  - oral bioavailability **is high, wide therapeutic index, high CSF penetration**
  - Resistance
  - Side effects: GIT disturbances and interference with hepatic enzymes (less than with other azoles)
  - CYP2C9 (drug interaction with warfarin) and CYP3A4 inhibitor (interactions with statins, cyclosporine, tacrolimus)

Azoles

Triazoles

- **itraconazole** → Candidosis + *Cryptococcus neoformans* + ***Histoplasma* + *Coccidioides* + *Blastomyces***
- **voriconazole** → Candidosis + *Cryptococcus neoformans* + ***Histoplasma* + *Coccidioides* + *Aspergillus***
  - PO and IV administration
  - Oral bioavailability is high
  - CYP3A4 inhibitor (known interactions with statins, cyclosporine, tacrolimus)
  - **Side effects**: rash and elevated hepatic enzymes and visual disturbances (blurring and photosensitivity)

Echinocandins (-fungin)



- **Newest class of antifungal agents**
  - **caspofungin**
  - **micafungin**
  - anidulafungin

- **Spectrum of action:** *Candida* and *Aspergillus (*only with fungus that have **β(1–3)-glucan**

- **Mode of administration: IV (now well absorbed GIT)**

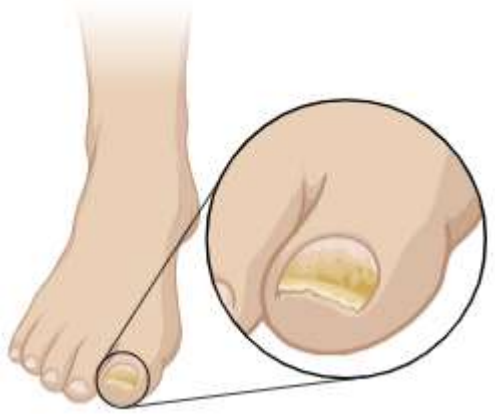
- **Treatment of disseminated and mucocutaneous candidal infections → 1st line on serious systemic infections**
  - **(1st choice over amphotericin B)**

- **Mechanism of action:** echinocandins → fungal cell wall by inhibiting the synthesis of **β(1–3)-glucan**
  - This results in disruption of the fungal cell wall and cell death

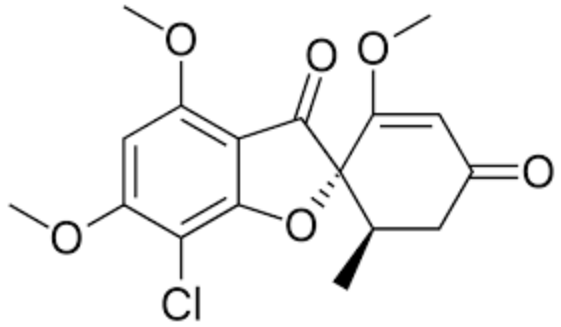
- **Side effects:** hepatoxicity (↑ liver enzymes), GIT problems, rash, facial flushing (histamine release)

Terbinafine

- **Synthetic allylamine → it is lipophilic and keratophilic → accumulates in adipose tissue and in keratin**
  - **Mode of administration:** PO, topical (1 % cream)
  - **Treatment of dermatophytosis (specially onychomycosis)**
    - 6 weeks for fingernail infections
    - 12 weeks for toenail infections
    - relapse is extremely common
  - **CYP2D6 inhibitor**
  - **Mechanism of action:** inhibiting squalene epoxidase
    - accumulation of squalene → fungicidal action
  - **Side effects:** gastrointestinal problems, headache, hepatotoxicity, dysgeusia (loss of taste)

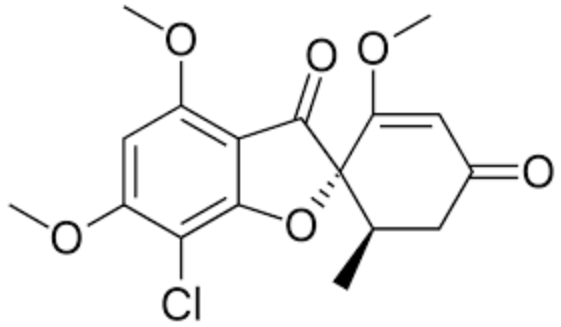


Griseofulvin



- **Derived from a species of penicillium and is also keratophilic**
  - **Mode of administration:** PO
  - **Only used in the treatment of dermatophytosis**
    - treating tinea infections of the scalp and glabrous (nonhairy) skin
  - **Mechanism of action:** interference with microtubules → interfering with mitosis
  - **Side effects:** serum sickness, serious skin reactions, a lupus-like syndrome, hepatotoxicity
  - Should not be used in pregnant women (teratogenic)
  - CYP3A4 inducer (e.g interaction with **warfarin**)
  - **Largely a 2nd or 3rd line medication after Terbinafine or Itraconazole**

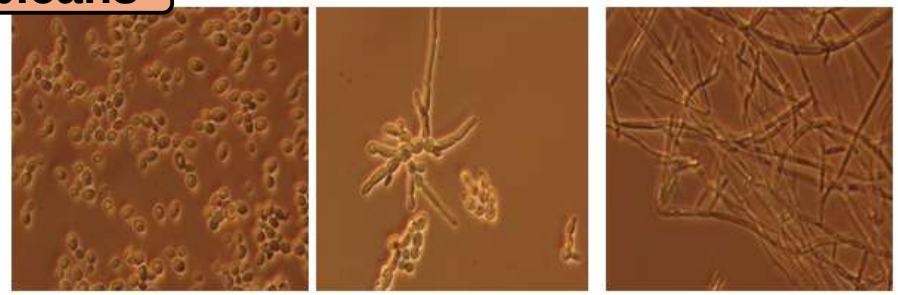
Flucytosin (or 5-FU)



- **Potent antifungal agent**
  - **Mode of administration:** PO, IV
  - **Only used in the treatment of systemic infections**
    - candidiasis, cryptococcal meningitis, and chromoblastomycosis
    - used in combination with **amphotericin-B** (increased penetration in the cell) and azoles
  - **Mechanism of action:** converted intracellularly first to 5-FU and then to 5-fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP), which **inhibit DNA and RNA synthesis**
  - **Side effects:** Bone marrow toxicity with anemia, leukopenia, and thrombocytopenia
  - Should not be used in pregnant women (teratogenic)
  - Spectrum of action is much narrower than that of **amphotericin B**

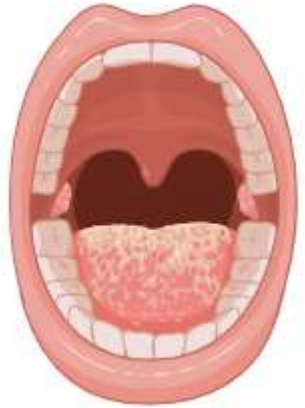
Candidosis

C. albicans



- Yeast
- **C. albicans** → most common cause of infection
- C.glabrata, C.tropicalis, C.krusei, C.auris
- **Common cause of infection in the immunocompromised (opportunistic)**
  - Antibiotic therapy, chemotherapy, diabetes, HIV
  - People with braces also have an unfavourable growth of Candida
- **Present on skin and mucous membranes**

Candidosis

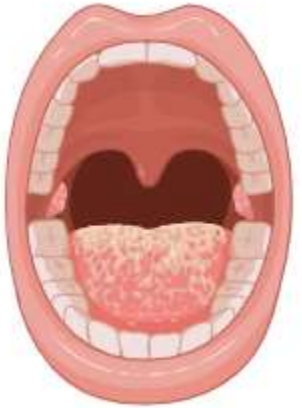


- **Present on skin and mucous membranes**
  - **Pseudomembranous candidosis** (or Thrush)
    - Stratified squamous epithelium layer → accumulation of the destroyed cells and the keratin protein
    - Common in young infants and the elderly → weak immune system
    - Raw bleeding mucosa → after scrape
  - **Erythematous candidosis**
    - Appearance of red lesions
    - Involves the same the risk factors as the previous
    - May result from loss of the pseudomembrane in pseudomembranous candidosis

Candidosis

- **Another types of lesions**
  - **Esophagus**
    - Esophagitis → individuals that suffer from HIV
    - With or without thrush
  - **Vulvovaginitis → mainly by C.albicans**
    - Discharge
    - Pain while urinating
  - **Invasive Candidosis** → Tropism towards different organs → Brain, Liver, Spleen
    - Serious
    - In immunocompromised patients
    - Can result from a formed biofilm in prosthetic devices (catheter)
    - Complications: septic shock, meningoencephalitis and pyelonephritis

Candidosis



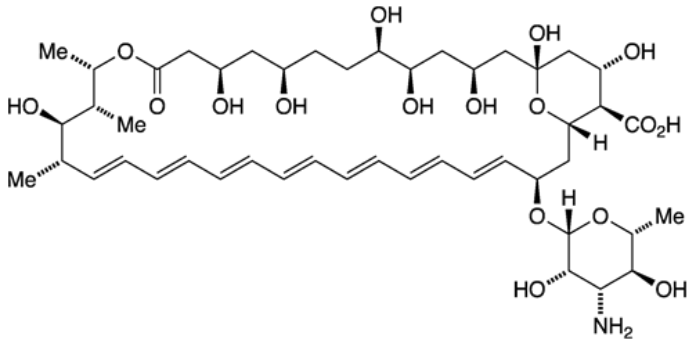
- **Pseudomembranous candidosis (and also Erythematous candidosis)**
  - **Combination of antifungal medication + local measures**
    - **nystatin**
      - Polyene macrolide
      - Parenteral administration is very toxic
      - Use of **nystatin** **oral suspension** in the mouth for several minutes four times daily before swallowing
      - **Mechanism of action:** selective binding to fungi membrane → pore → altering cellular permeability
        - avidity for ergosterol – the same for the drug **amphotericin B** (polyene)
      - **Adverse effects:** nausea, vomiting and diarrhoea
      - **Modes of administration: P.O**
      - Limited to topical treatment of cutaneous and mucosal candida infections
      - Absorption from GIT is negligible

Candidosis

- **Pseudomembranous candidosis**
  - **Combination of antifungal medication + local measures**
    - **miconazole or fluconazole**
    - Part of the azole class
      - **miconazole** as an **oral gel**
        - 2.5ml of oral gel to the affected area four times a day after food and retain near the lesion before swallowing. Use for at least seven days, after lesions have healed or symptoms have cleared
      - **fluconazole** as a **tablet** or **suspension** (children) → **Widest therapeutic index** from the azoles
        - **50 mg orally once a day for 7-14 days** (maximum 14 days unless severely immunocompromised); Increased to 100 mg a day for unusually difficult infections
      - **Mechanism of action:** inhibition of fungal cytochrome P450 enzymes (14-α-demethylase)
        - Inhibition of conversion of lanosterol to ergosterol
        - Interfering with fungi cell membrane
        - Inhibition of fungal growth

Candidosis

- **amphotericin B**



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  - Oral amphotericin B → effective only on fungi in the GIT
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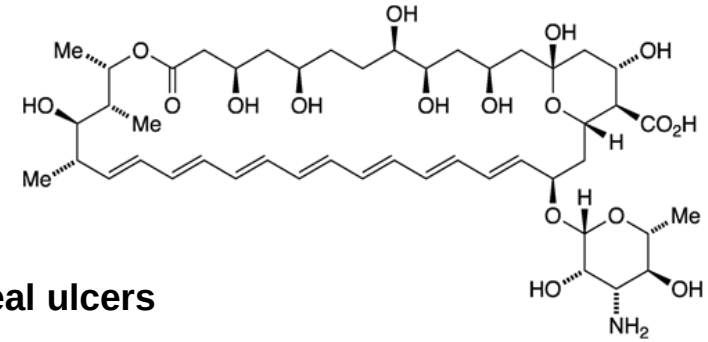
Candidosis



- **amphotericin B**

- Can be used topically for treatment of **keratitis** and **mycotic corneal ulcers**
- **Adverse effects**
  - **Infusion-Related Toxicity:** fever, chills, muscle spasms, vomiting, headache, and hypotension
    - Ameliorated with administer normal saline infusions with the daily doses of amphotericin B
  - **Cumulative Toxicity:** **Renal toxicity** → renal tubular acidosis, hypokalaemia and hypomagnesemia
- **Modes of administration:** P.O, IV, IT (Intrathecal), topical
- **Hepatic elimination**