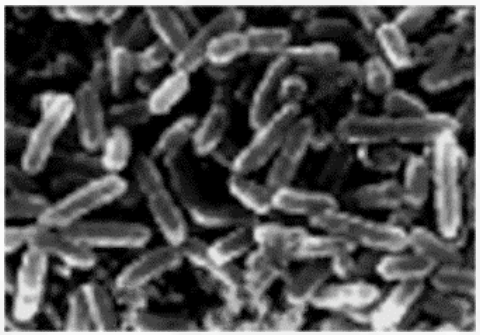
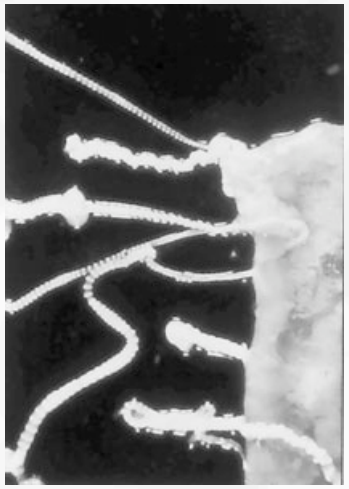
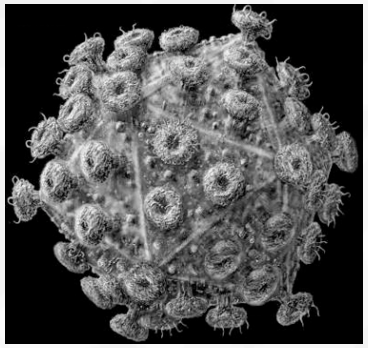
Chemotherapeutic Agents



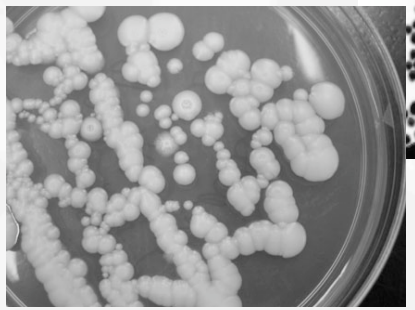


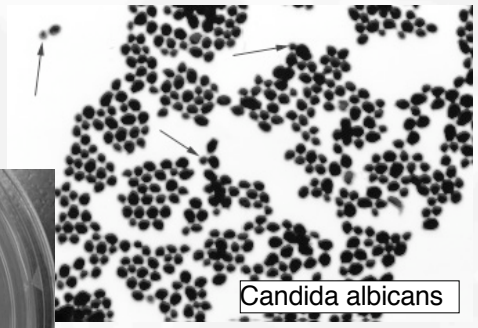


- Antibiotics
- Antifungals
- Antivirals
- Antihelmintics
- Antiprotozoal
- Anticancer drugs

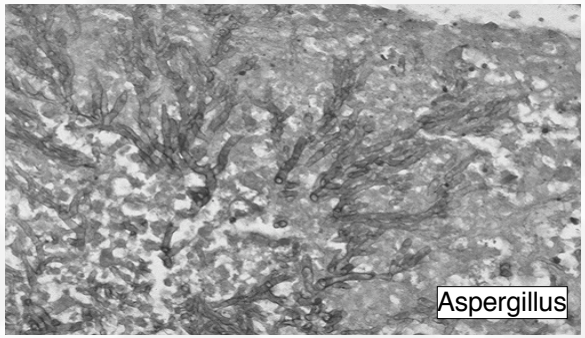
Fungal Growth Patterns

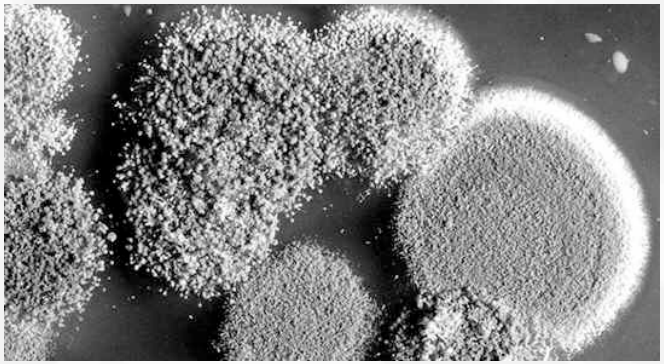
- Yeasts
  - Unicellular fungi, reproduce by budding
  - Moist mucoid or waxy colonies that resemble bacteria





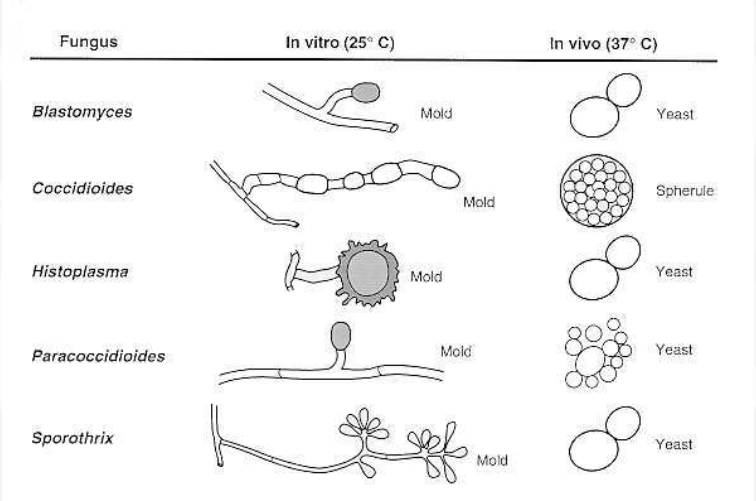
- Molds (=Filamentous Fungi)
  - Multicellular filamentous, “fluffy” colonies consisting of branching tubular structures called hyphae
  - Collection of intertwined hyphae called mycelium
  - Vegetative hyphae act like roots, penetrating the supporting medium and absorbing nutrients
  - Aerial hyphae project above the surface of the mycelium and bear the reproductive structures of the mold (often spread through the air)

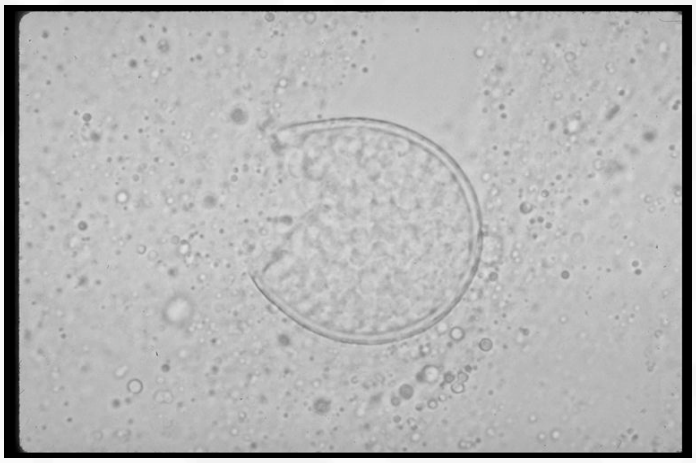




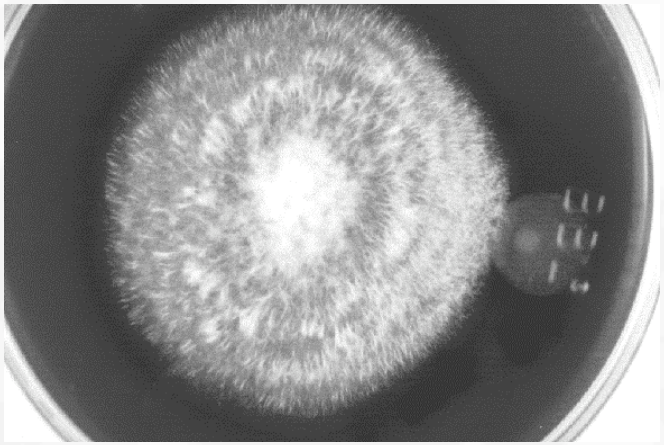
Fungal Growth Patterns

- Dimorphic Fungi
  - Grow as molds at ambient environmental temperatures (e.g. 25˚ C) where they form reproductive spore structures.
  - Spores are aerosolized and infectious
  - Inhaled spores grow as yeasts at body temperature (37˚ C) in the host





Yeast form

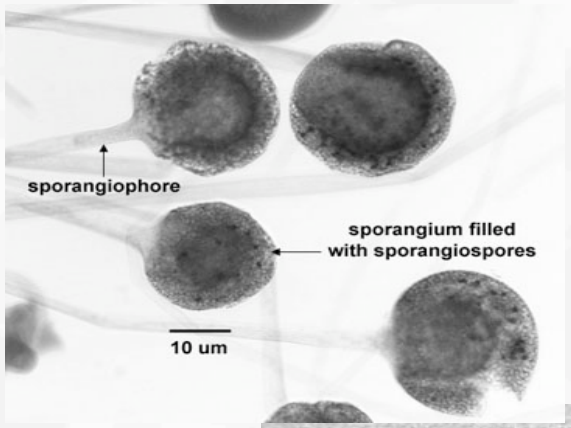


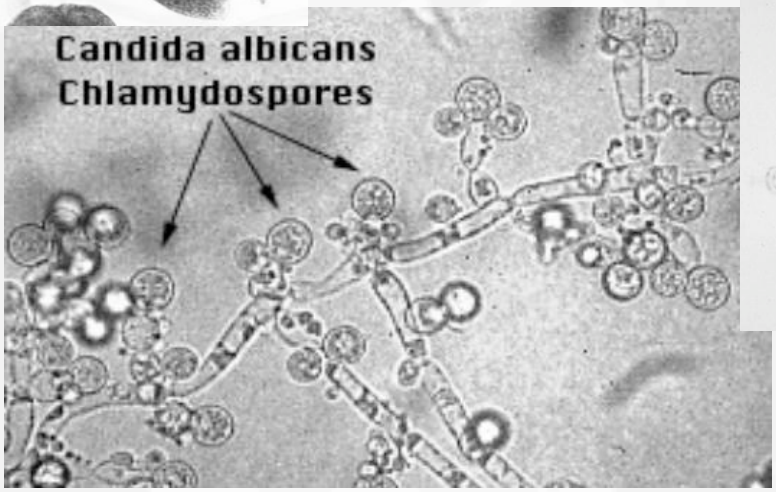
Mold form

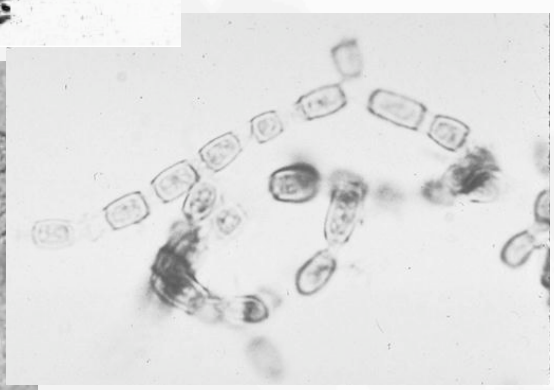
Coccidioides immitis

Fungal Habitats

- Most clinically relevant fungi reside in the soil, in bird feces, on vegetation, or on the skin and mucous membranes of mammals.
- Some have distinctive ecologic and geographical niches.



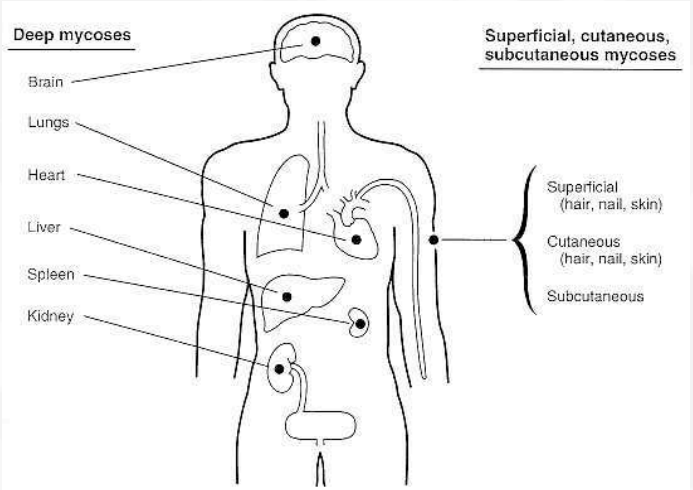




Mycosis

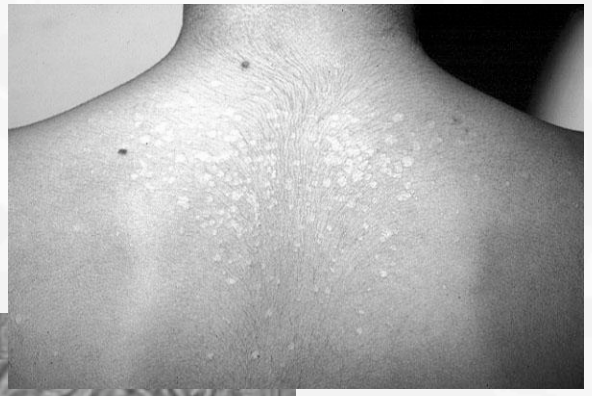
- Fungal infections (= mycosis)
  - spread generally from the environment to people (or animals) with limited person-to-person spread.
  - Skin and lungs are prominent entry site for many fungi
  - Patients with impaired cell-mediated immunity (e.g. AIDS, organ transplant) at heightened risk for severe disease.

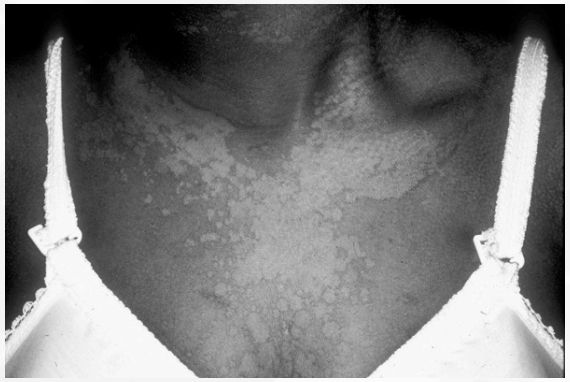
- Types of fungal infections
  - Superficial: Outer skin layer - no immune response
    caused mostly by yeasts (Dandruff)
  - Cutenous: Epidermal layers - evoke immune response
    Tinea (Ringworm, Athlete's foot, jock itch)
    caused by Dermatophytes:
  - Subcutenous: Chronic infection of subdermal tissues
    may require surgical intervention
  - Systemic: Mostly originating in the lung
    caused by virulent dimorphic fungi
  - Opportunistic: In immunocompromised conditions
    (AIDS; altered mucosal flora due to antibiotics):
    mostly Candidiasis and Aspergillosis (often cause of epidemic death in birds)

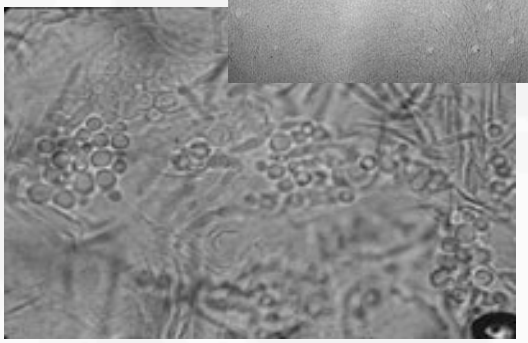


Superficial Mycoses

- Tinea versicolor (= Pityriasis versicolor)
  - Caused by a lipophilic yeast, *Malassezia furfur*
  - Normal flora of skin and scalp
  - Growth on media markedly enhanced by adding fat (Clinical mycology labs routinely stock olive oil!)







- Dandruff (= Scurf = Pityriasis capitis)
  - Caused by a lipophilic yeast, *Malassezia globosa*
  - Accellerated shedding of skin cells

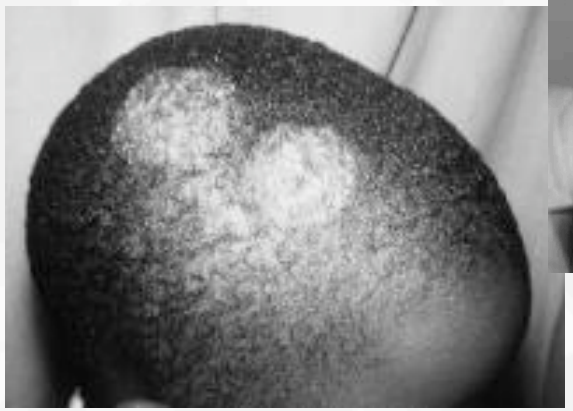
Nothing worked. And when he tried to complain they just brushed him off.

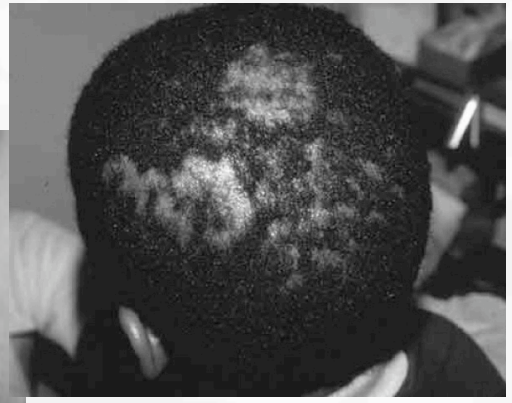
Cutaneous Mycosis

- Also known as “ringworm” and tinea (latin “worm”) because of round shape of lesions
- Infections confined to skin,hair and nails
- Caused by Dermatophyte molds (Trychophytum; Microsporum)

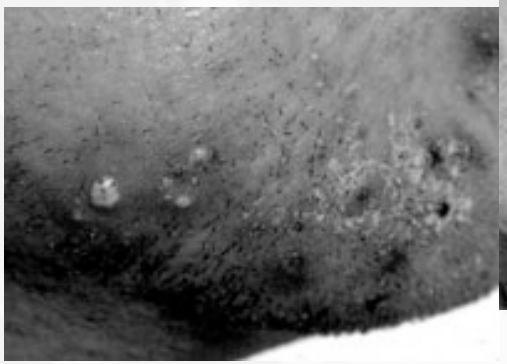
<u>Clinical classification based on location</u>:

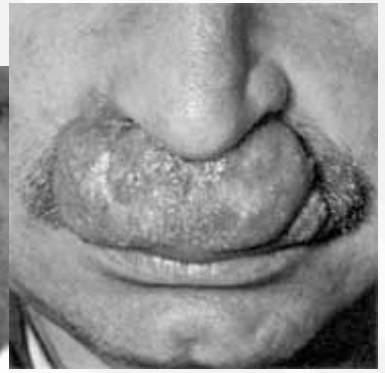
- Tinea capitis
  - Ringworm of scalp and hair





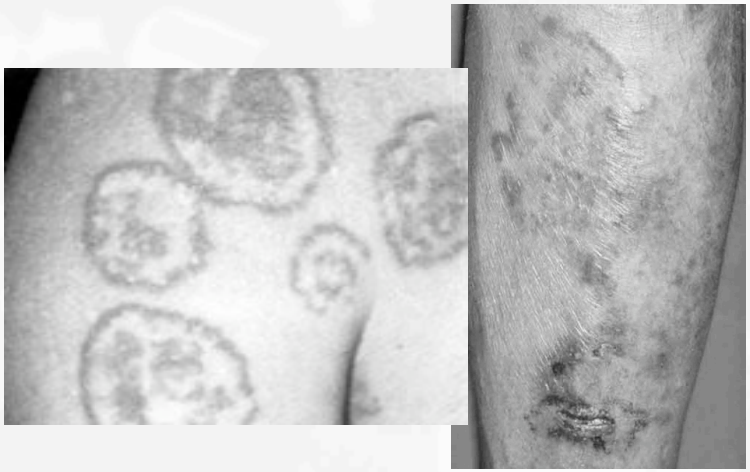
- Tinea barbae
  - Ringworm of beard region



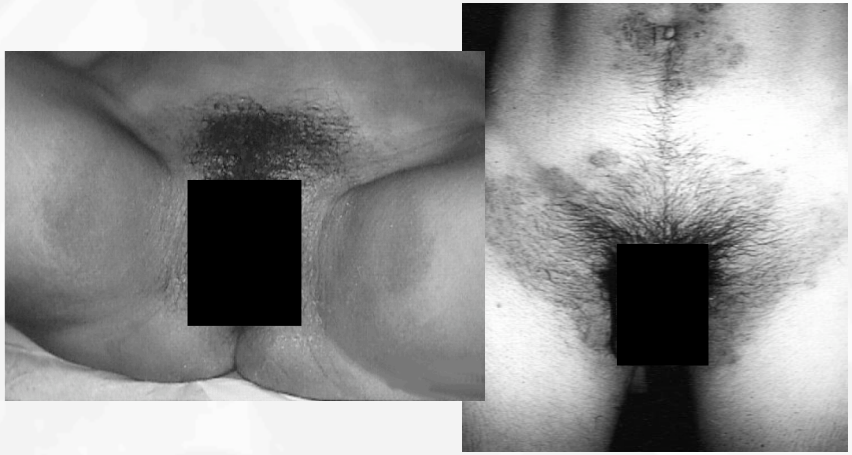


Cutaneous Mycosis

- Tinea corporis
  - Ringworm of the smooth skin of the body

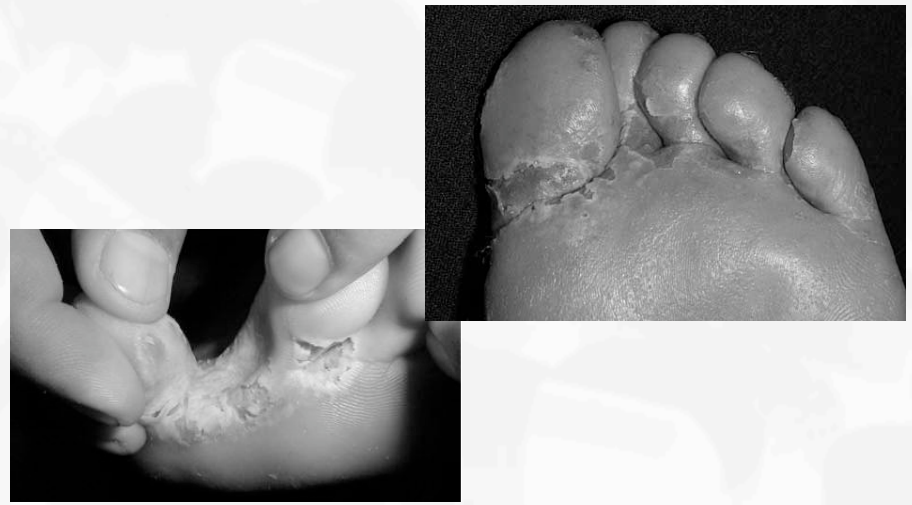


- Tinea cruris
  - Starts in groin area (“Jock itch”)
  - Causes by *Trychophytum rubrum*



Cutaneous Mycosis

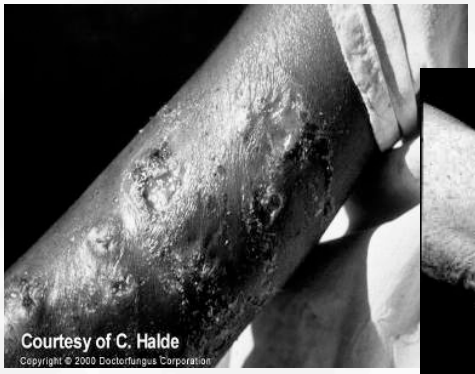
- Tinea pedis
  - Classically interdigital (”Athlete’s foot”)
  - key risk factor for invasive bacterial infections in diabetics through disruption of normal skin barriers

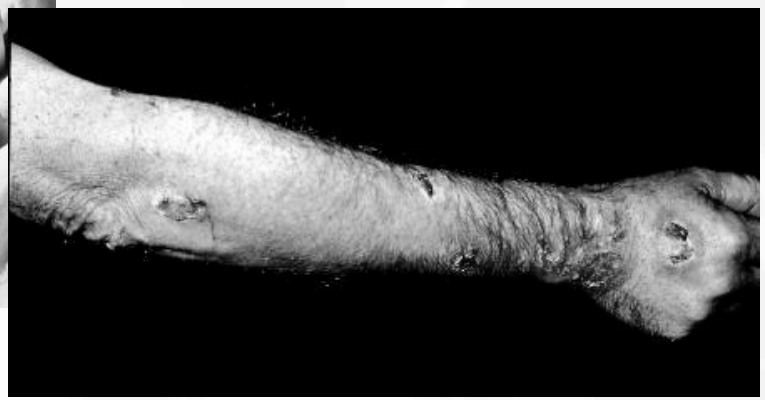


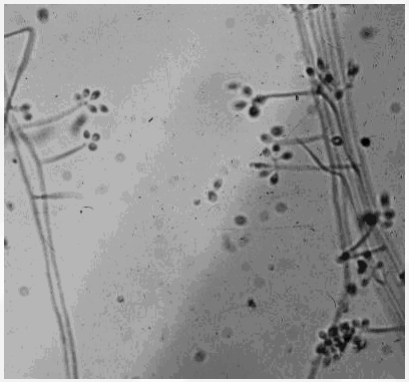
- Tinea unguium
  - Infection of finger and toe nails
  - Often associated with T. pedis

Subcutaneous Mycoses

- Sporotrichosis
  - *Sporothrix schenckii* - Dimorphic fungus
  - Found on vegetation, especially rose bushes
  - Introduced into skin by trauma (gardening!)
  - Initial ulcer develops into granulomatous nodule

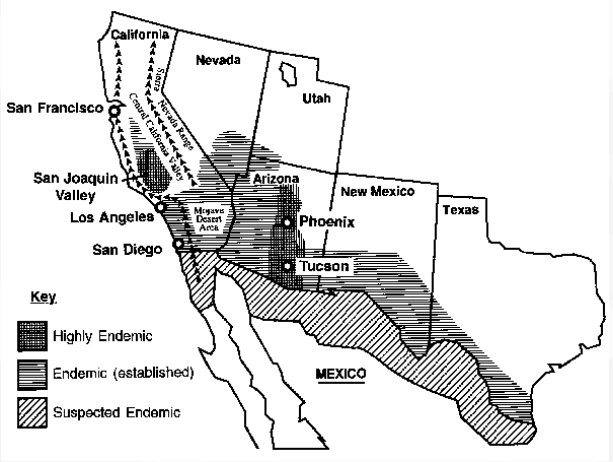






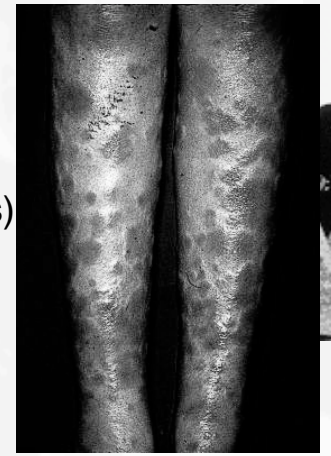
Systemic Mycosis

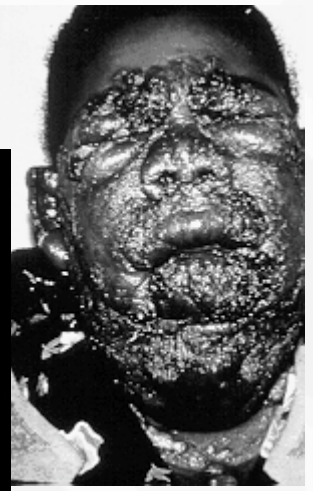
- Infections are rare (high natural immunity)
- Usually requires large inoculum
- Often endemic to specific aereas



Mostly associated with four fungi:

- *Coccidioides immitis* -> Coccidioidomycosis
  - Soil fungus (dry, dusty soil => inhalation of spores)
  - SW USA (Arizona and Central Valley of CA) and Mexico ("Valley fever")
  - Epidemic after (Northridge) earthquake or sandstorms
  - Considered most virulent fungus (select agent: BSL-3)
  - Starts with flu-like symptoms, meningitis
  - Striking racial/ethnic differences in rate of dissemination: Filipinos>African Americans>Hispanics>Asians>Caucasians (Kern County, Filipinos 0.23% of population but 22% of cases) Likely due to genetic differences in blood group/ HLA

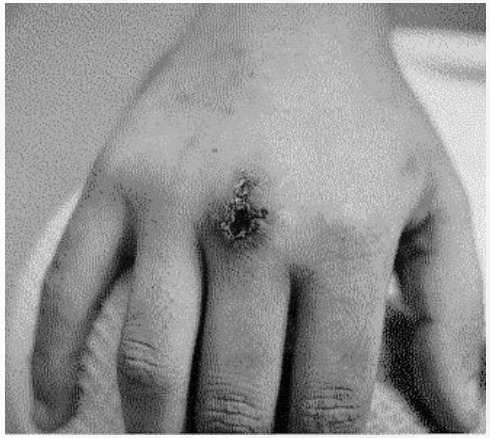


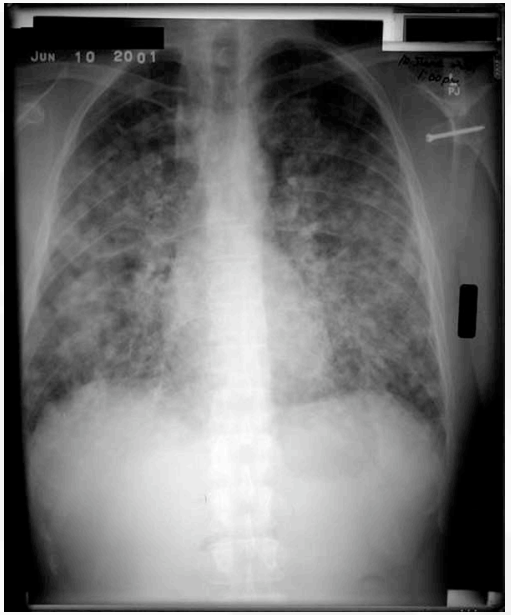


Systemic Mycosis

- *Histoplasma capsulatum* -> Histoplasmosis ("Cave disease")
  - Soil fungus (soil containing guano (bird, bat droppings)! => spores inhaled)

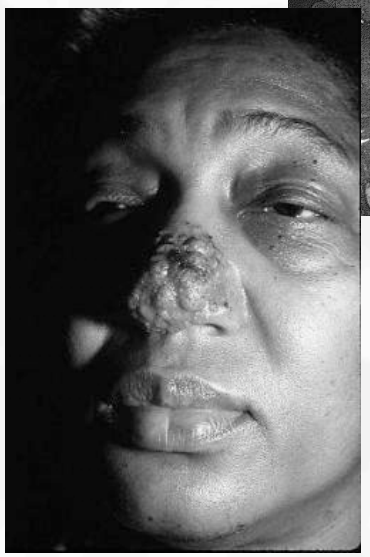
    (In 1890 European starlings were introduced into Central Park, NYC in an effort to bring all of the birds mentioned by Shakespeare to the US => Now there are 200M-1B starlings in N. America, whose droppings are a major route of transmission for histoplasma)
  - S-SE USA (Ohio and Mississippi Valley)
  - Starts with flu-like symptoms, meningitis
  - Fungus lives intracellular in macrophages => immune-evasion
  - 95% of infected individuals asymptomatic (chronic infection can lead to lung fibrosis)
  - In immunecompromised patients systemic infection develops => multiorgan failure, sepsis

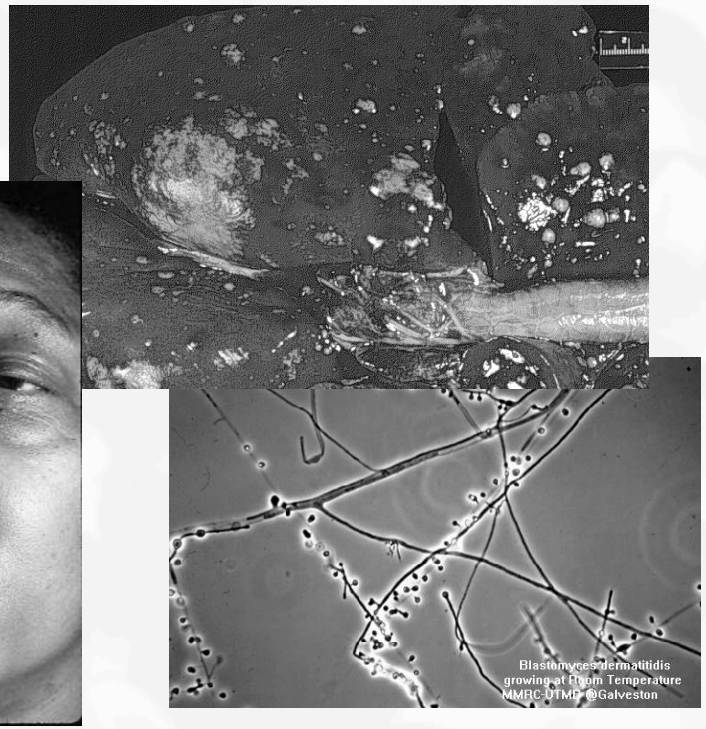




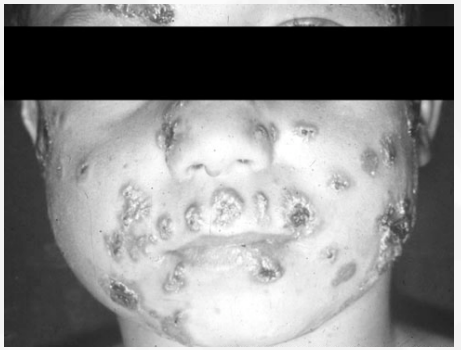
Systemic Mycosis

- *Blastomyces dermatitides* -> Blastomycosis
  - Soil fungus (=> spores inhaled)
  - S-SE USA
  - Predominantly in lung and skin





- *Paracoccidioides brasiliensis*
  - Soil fungus (=> spores inhaled)
  - Central and South America (Brazil—death rate up to 1.5/1000)

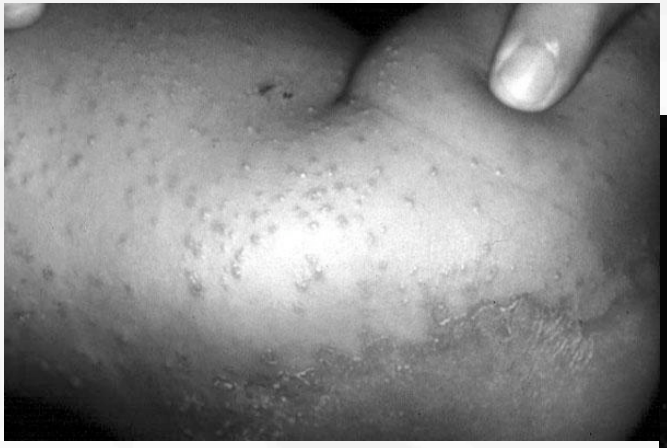


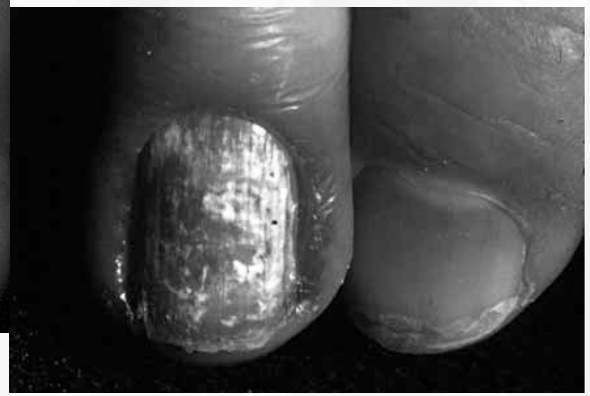
Opportunistic Mycosis

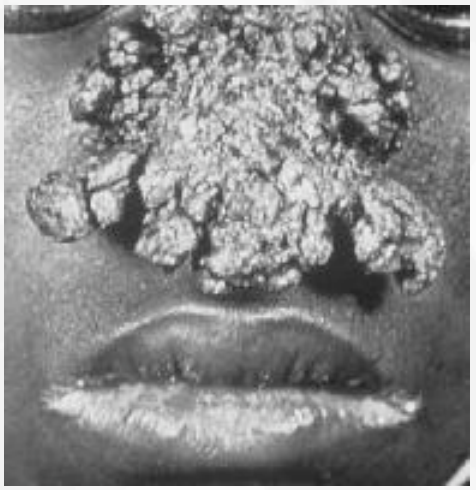
- Some fungi are commensal (mucosal flora of mouth, gut, vagina etc.)
- Usually growth balanced by microorganisms (lactobacilli)
- Only a problem in situations of compromised immune responses (AIDS, antibiotics, chemotherapy, radiation, alcoholism, etc.)

- *Candida albicans* -> Candidiasis
  - Dimorphic fungus BUT also mold at 37˚ C
  - Also other *Candida* species

  - Cutanous candidiasis: mostly in moist skin folds (obese patients):

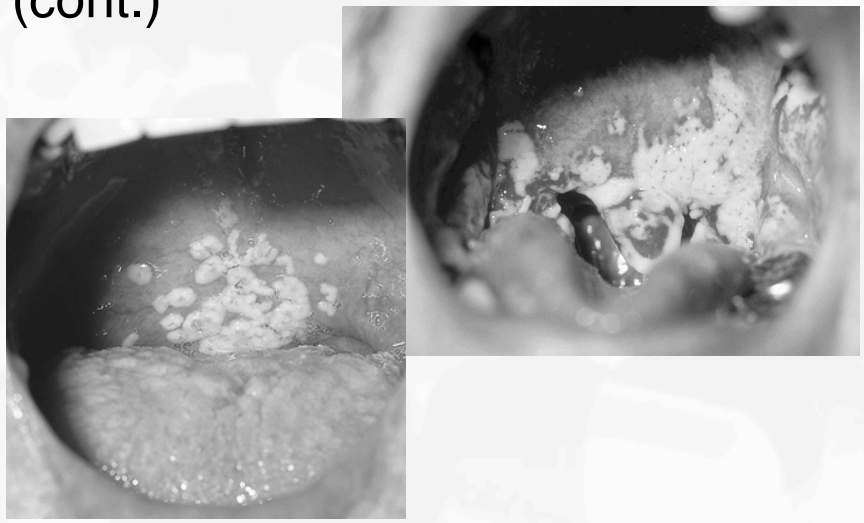




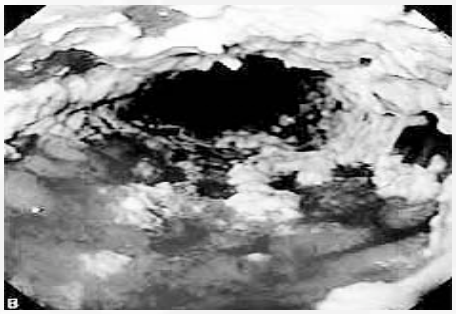


Opportunistic Mycosis

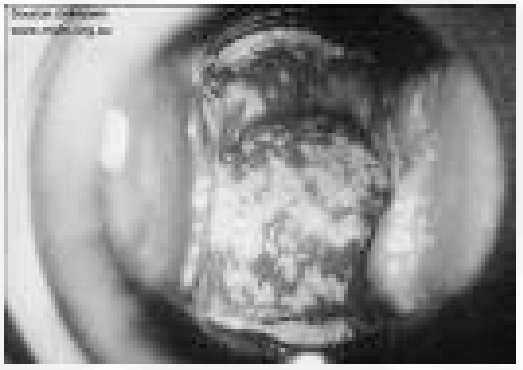
- *Candida albicans* -> Candidiasis (cont.)
  - Oral candidiasis ("Thrush")
    - Babies; denture users
    - Can progress into



Candida esophagitis

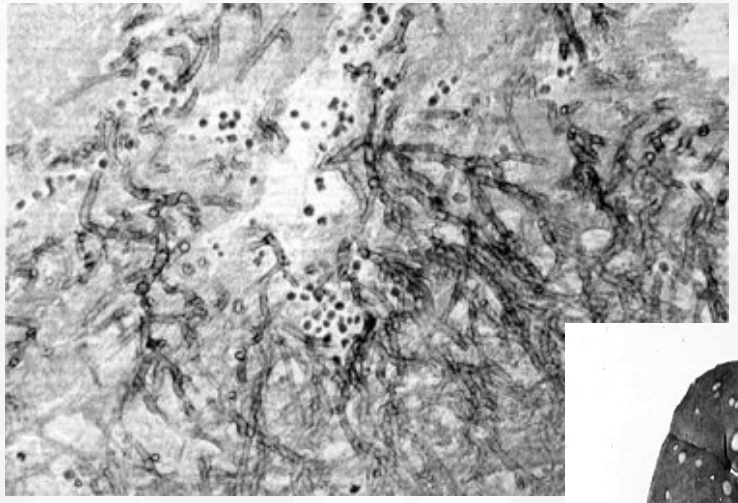


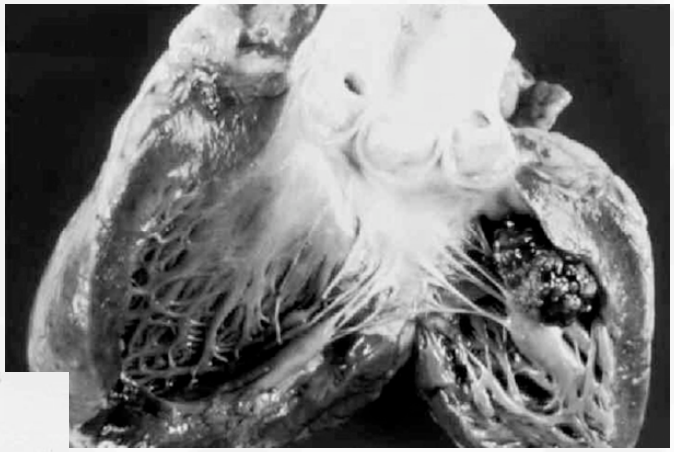
  - Vaginal candidiasis ("Yeast infection")
    - Does NOT require immune dysfunction
    - Severe itching/burning
    - Commonly associated with antibiotica use
    - Bacterial infection often falsly self-diagnosed as candidiasis (2/3 of self-diagnosed "yeast infections" actually bacterial!)

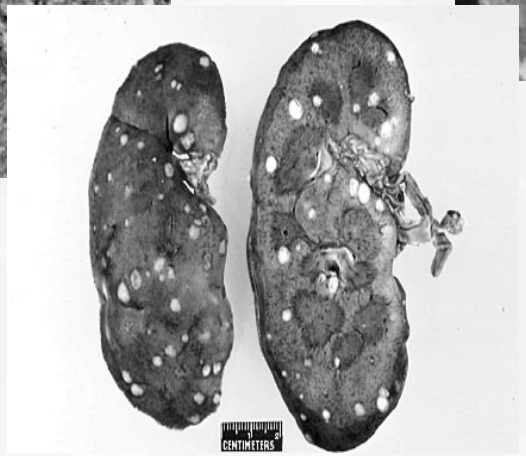


Opportunistic Mycosis

- *Candida albicans* -> Candidiasis (cont.)
  - Systemic candidiasis
    - Mucocutaneous barriers breached in patients after surgery, burns
    - Dissemination to kidneys, skin, eye, heart, bone, liver, etc.
    - Often fatal !

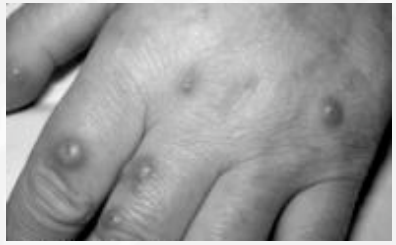


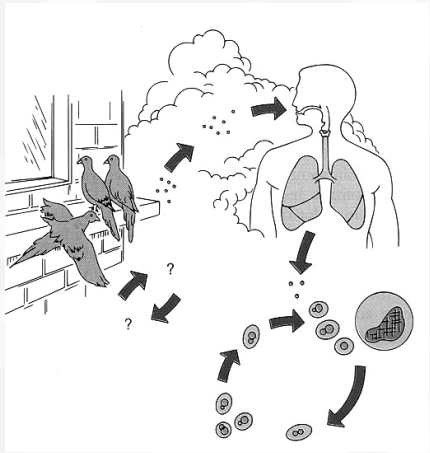




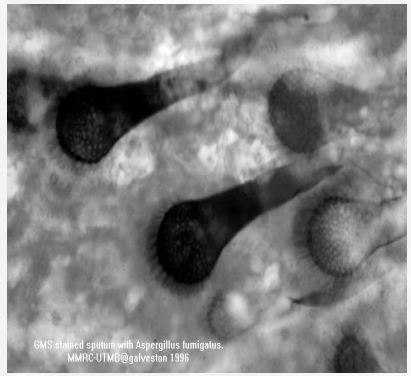
Opportunistic Mycosis

- *Cryptococcus neoformans* -> Cryptococcosis
  - Ubiquitous, but especially abundant in pigeon droppings
  - Cryptococcal meningitis most common manifestation
  - Complication in AIDS patients





- *Aspergillus sp.* -> Aspergillosis
  - Mostly pulmonary infections
  - Allergenic
    (Allergic sinusitis and allergic bronchopulmonary aspergillosis)
  - Infections common in birds



Differences between fungi and mammalian cells

	ANIMALS	**FUNGI**
Cell structure	Eukaryotic	Eukaryotic
DNA	Diploid	Haploid
Ribosomes	80S	80S
Cell wall	No	chitin, mannans, glucans
Cell membrane	Predominantly cholesterol	Predominantly ergosterol
Microtubule affinity for griseofulvin	No	Yes
Cytosine deaminase	No	Yes
Squalene epoxidase	No	Yes

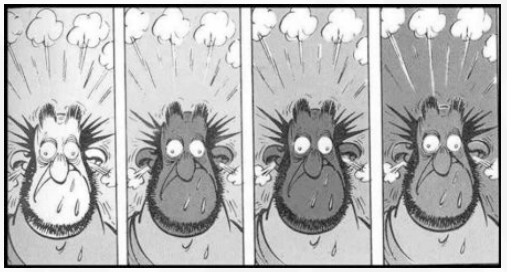
Overview of Antifungal Drugs

	MECHANISM OF ACTION
Polyenes (Amphotericin, Nystatin)	Selectively bind to ergosterol in fungal cell membrane, altering membrane fluidity and producing pores and osmotic cell death. Much less binding to cholesterol.
Azoles (Ketoconazole, Miconazole, Fluconazole, Itraconazole, Voriconazole, Posaconazole)	Selectively block ergosterol synthesis by inhibiting demethylation of lanosterol. Fungal P450 enzyme much more sensitive than mammalian counterpart.
5-Flucytosine	Converted by fungal cytosine deaminase into 5-fluorouracil; inhibits DNA synthesis. Mammalian cells lack cytosine deaminase.
Griseofulvin	Inhibit fungal growth by binding to microtubules, disrupting mitotic spindles. Mammalian microtubules less sensitive.
Echinocandins (Caspofungin, Micafungin, Anidulofungin)	Inhibit fungal Beta glucan synthesis, disrupting cell wall integrity. Mammalian cells have no cell walls.
Allylamines (Terbinafine)	Selectively blocks ergosterol synthesis by inhibiting squalene epoxidase (not found in animals)

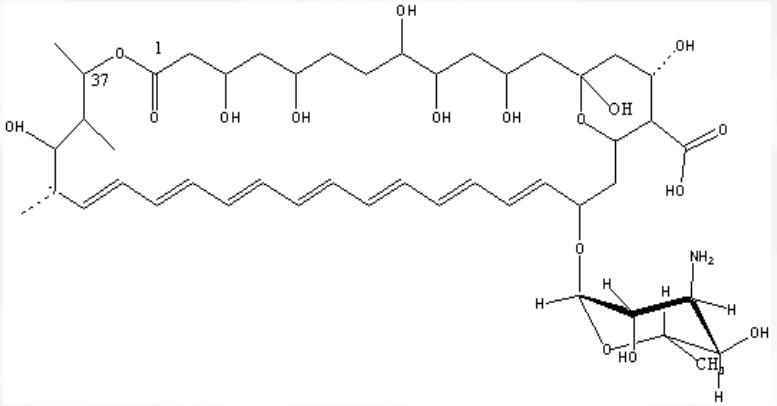
Antifungal Drugs - Polyenes

Polyenes

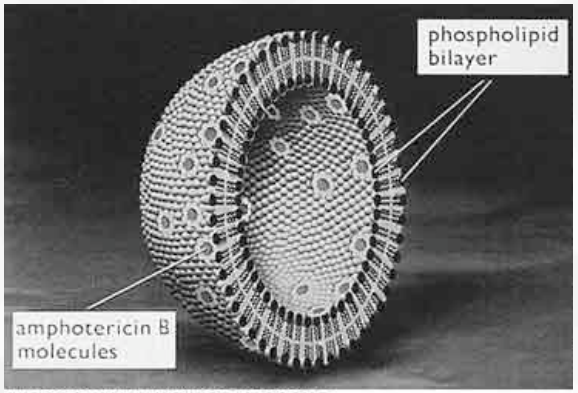
- bind to fungal membrane sterols (ergosterol)
- alter selectively permeability to K^+ (and Mg^{2+}) => Fungicidal
- Resistance due to altered sterols



- **Amphotericin B**
  - Isolated from *Streptomyces nodosus*
  - Given iv, it (poor oral absorption) and topical
  - Active against most systemic fungi
  - iv not well tolerated (chills, headaches, nausea)
  - Pronounced renal toxicity =>
    Encapsulated into liposomes
    (less drug reaches the kidneys?)



- **Nystatin**
  - Only for topical application
    (Canidida, dermatophytes)



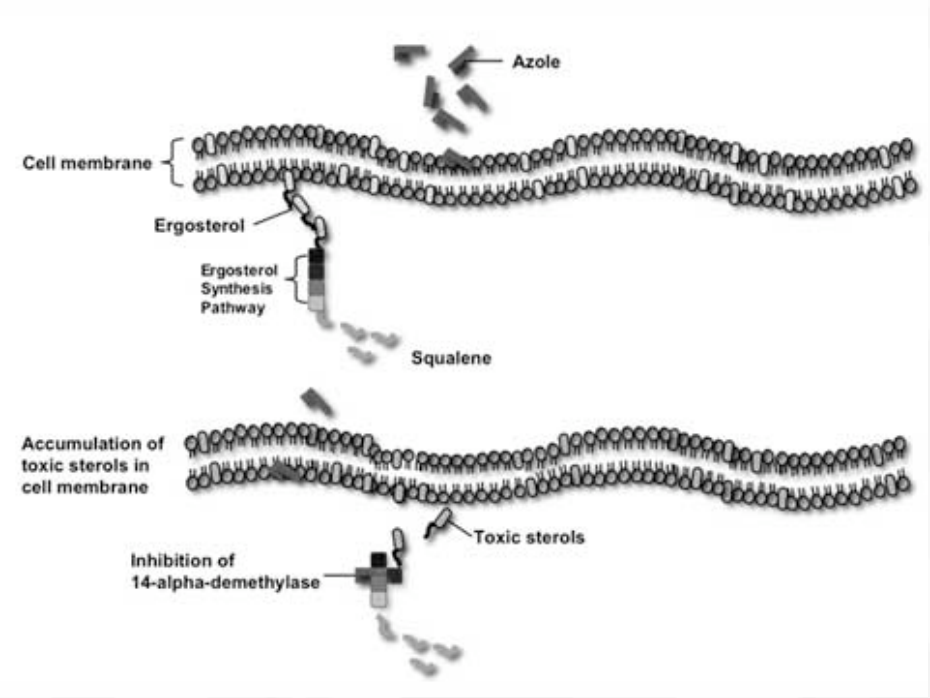
CROSS SECTION VIEW OF LIPOSOME

Antifungal Drugs - Azoles

Azoles

- inhibit the synthesis of ergosterol
  (block demethylation of lanosterol by inhibiting fungal CYP3A = 14-demethylase)
- Fungistatic
- Active against systemic fungi and dermatophytes
- Resistance due to altered 14-demethylase

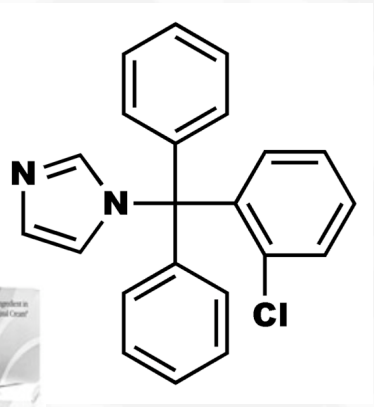
- Two groups
  - Imidazoles
  - Triazoles



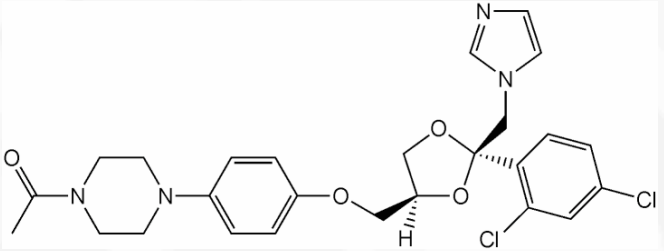
Antifungal Drugs - Azoles

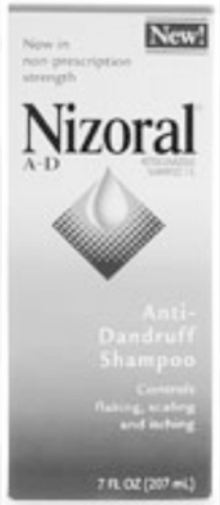
Imidazoles

- Clotrimazole
  - Only used topical
  - Candidiasis, tinea



- Ketoconazole
  - Tinea, candidiasis, blastomycosis, coccidioidomycosis
  - Also for dandruff (Nizoral®)
  - First oral -azole (mostly replaced by fluconazole and itraconazole)
  - Absorption best at low pH (antacids interfer !)
  - Does not enter CNS well

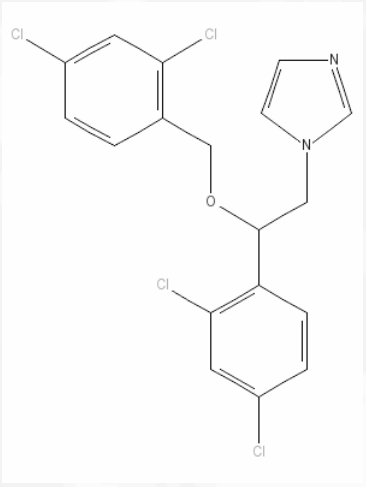




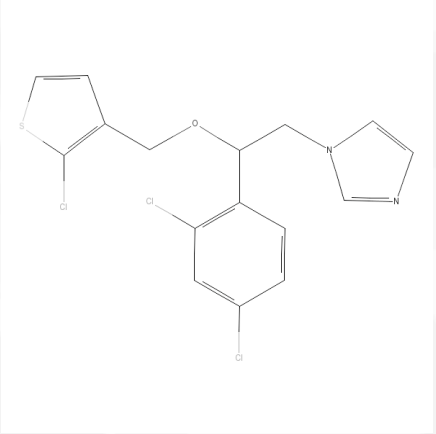
Antifungal Drugs - Azoles

Imidazoles

- Miconazole
  - Used topical and p.o. (intestinal fungal infections)
  - Also used in E6 slide film processing



- Tioconazole

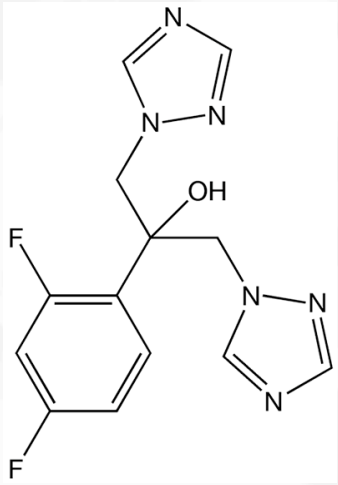


Antifungal Drugs - Azoles

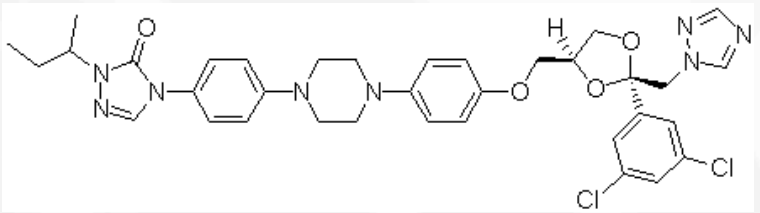
Triazoles

Newer, less toxic, more effective!

- Fluconazole (Diflucan®)
  - Used i.v. and p.o.
  - Reaches high CSF concentrations
  - 90% excreted unchanged
  - t1/2 = 25 hrs
  - Used against Candidiasis, Coccoidosis (meningitis)
  - Well tolerated



- Itraconazole (Sporanox ®)
  - Used i.v. and p.o.(p.o. poor absorption)
  - Absorption increased by acids (Orange juice, Coke!)
  - Absorption decreased by antacids
  - Does not reach CSF
  - Highly lipophilic => fatty tissue accumulation
  - Very broad spectrum

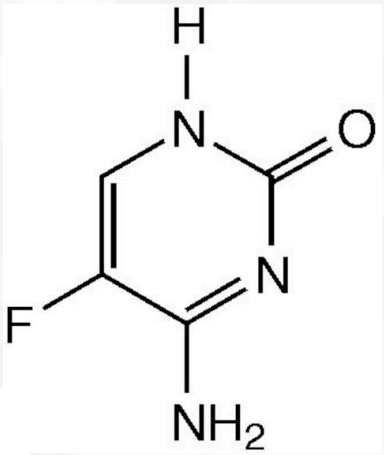


- Voriconazole (Vfend ®)
  - Used for severe systemic infections and emerging fungi (very broad spectrum)
- Posaconazole (Noxafil ®)
  - Very broad spectrum (tested against >18,000 fungi!)

Antifungal Drugs - Antimetabolites

5'-Flucytosine (Ancobon ®)

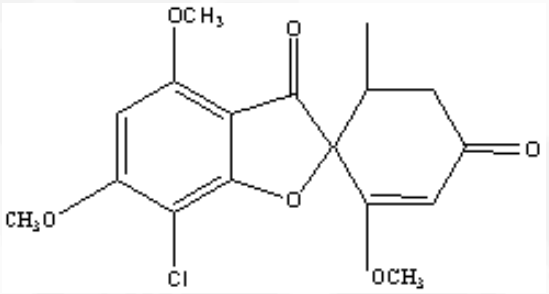
- Only available antimetabolite drug
- Activated by deamination within the fungal cells to 5-fluorouracil
- 5-fluorouracil inhibits *thymidylate synthetase*
- Also inhibits fungal protein synthesis by replacing uracil with 5-flurouracil in fungal RNA
- Resistance common (=> used in combination with other antifungals)
- Broad range (only in the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus)*
- Well orally absorbed



Antifungal Drugs - Antimetabolites

Griseofulvin (Grisactin®, Fulvicin®)

- Inhibit fungal growth by binding to microtubules => disruption of mitotic spindles => fungistatic (mammalian microtubules less sensitive)
- Mainly effective against dermatophytes (tinea) (incorporates into keratin => requires several weeks of therapy)
- Oral administration (use declining due to better drugs - e.g. Triazoles)
- Side effects: Nausea, hepato- and renal toxicity, photosensitivity,…
- Veterinary use common



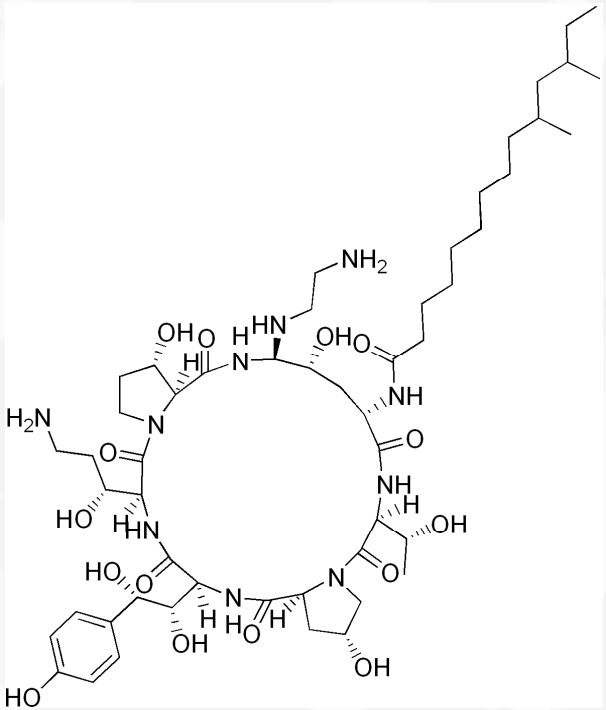
Antifungal Drugs - Echinocandins

- Inhibit synthesis of glucan in the fungal cell wall (likely block 1,3-beta glucan synthase)
- Newest antifungals
- Well tolerated

- Caspofungin
  - Used i.v.
  - Active against Candida and Aspergillus
  - Approved 2001
  - Approved 2005 for invasive Aspergillosis

- Anidulafungin
  - Used i.v.
  - Active against Candida and Aspergillus
  - Approved 2006 for invasive Aspergillosis

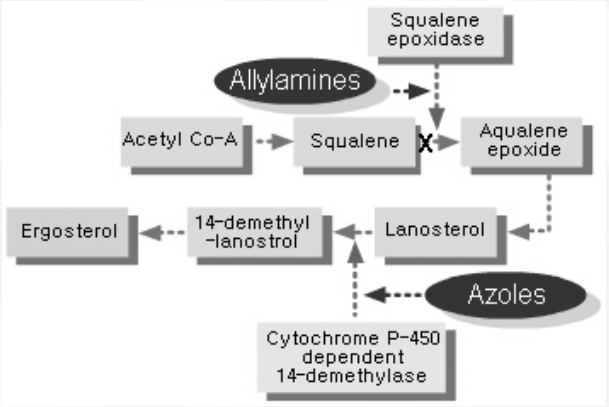
- Micafungin



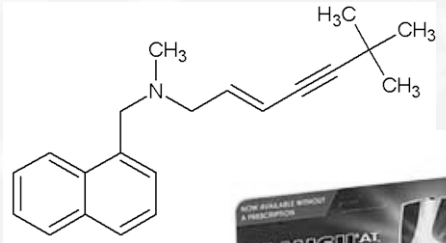
Antifungal Drugs - Allylamines

Allylamines

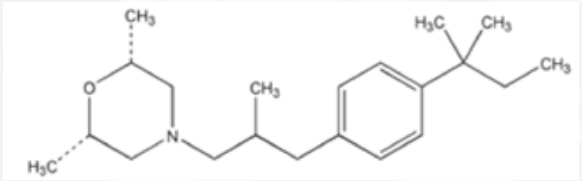
- inhibit fungal sterol synthesis (ergosterol) by inhibiting squalene epoxidase



- Terbinafine (Lamasil®)
  - Synthetic antifungal (mostly topical; p.o. for tinea unguium)
  - Lipophilic: accumulates in fat, skin and nails
  - Active against most dermatophytes (tinea, ringworm)



- Butenafine (Lotrimin® Ultra)
  - Also anti-inflammatory activity
  - Superior antifungal activity over Terbinafine



- Naftifine (Naftin®)
- Amorolfine (Loceryl®)

Antifungals - Summary