Mycology

Mycology - the study of fungi

Fungi - includes molds and yeasts.

Molds - exhibit filamentous type of growth.

Yeasts - exhibit pasty or mucoid form of fungal growth.

- 50,000 + valid species
- Fungi stain gram positive, and require oxygen to survive.
- Fungi are eukaryotic, containing a nucleus bound by a membrane, an endoplasmic reticulum, and mitochondria. (Bacteria are prokaryotes and do not contain these)
- Fungi are heterotrophic like animals and most bacteria; requiring organic nutrients as a source of energy.

  (Plants are autotrophic)

Mycology

Immunology of the Mycoses

Antibody mediated immunity (B-cell, humoral)

- **Antibodies are often produced in response to a fungal infection, but do not confer immunity.**
- **Serological tests for identification of fungal diseases detect these antibodies.**

Cellular mediated immunity (T-cell)

- **T-cell immunity is effective in resistance to fungal infections.**

Mycology

Classifications of Fungi:

- **Geographic grouping - where they exist.**
- **Epidemiologic grouping - how organism is transmitted.**
- **Taxonomy grouping - according to morphologic and cultural characteristics.**
- **Topographic Grouping - type of mycosis produced.**

Mycology

Topographic Grouping of Fungi: (most often used)

- **Superficial - Confined to the outermost layers of the skin and hair. No host cellular or inflammatory response due to organisms being remote from living tissue. Essentially no pathology; the disease is recognized purely on cosmetic basis.**
- **Cutaneous - in the keratin of the skin, nails, and hair. These organisms prefer non-living cornified layers. The disease is called a dermatophytosis or dermatomycosis. Host response is patchy scaling or eczema eruptions. They are classified according to the area of the body that is involved.**

Mycology

Topographic Grouping of Fungi: (continued)

- **Subcutaneous - Involve the deeper layers of skin and often muscle tissue. Man is an accidental host following inoculation of fungal spores via some form of trauma. This type of infection is often identified by the presence of a characteristic tissue reaction or granule.**
- **Systemic - Attack the deep tissues and organ systems; often creating symptoms that resemble other diseases.**

Mycology

Categories of systemic disease:

- **Those caused by truly pathogenic fungi with the ability to cause disease in the normal human host when the inoculum is of sufficient size (*Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Paracoccidioides braziliensis*).**
- **Those caused by opportunistic fungi, low virulence organisms, which require the patient's defenses to be lowered before the infection is established (*Aspergillus spp. Candida albicans, Cryptococcus neoformans*).**

Mycology

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Mycology

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Mycology

Systemic mycoses:

Dissemination of any fungal agent, yeast, or bacteria-like fungus to involve any tissue or organ. Agent must be dimorphic.

- ***Histoplasma capsulatum***
- ***Coccidioides immitis***
- ***Paracoccidioides brasiliensis***
- ***Blastomyces dermatitidis***

Mycology

Systemic mycoses:

- *Histoplasma capsulatum* -
  - Histoplasmosis - an infection of the reticuloendothelial system resulting in patchy bronchopneumonia containing yeast-laden phagocytic cells within alveolar spaces.
  - Worldwide in distribution, it is endemic in the Mississippi, Missouri, St Lawrence, and Ohio river valleys.
  - Strong association with bird and bat droppings.

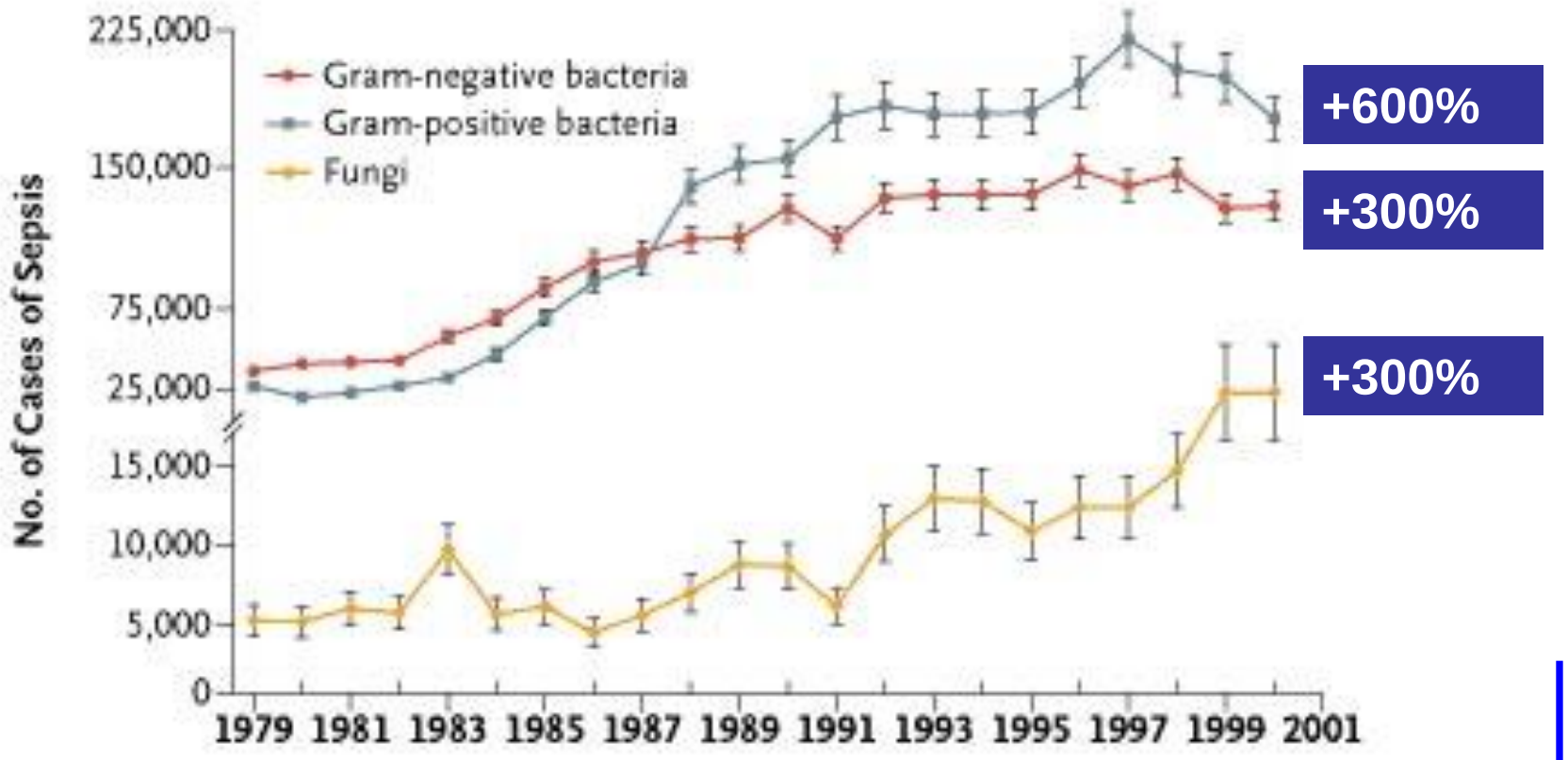
Trends in fungal diseases

- Increasing cases of invasive fungal infections
- Poor diagnostic tools
- Replacement of sensitive species by resistant ones
- Increasing use of prophylaxis and empirical therapy
- Continuing high frequency of skin infection
- Increasing awareness of the role of fungi in allergy
- Increasing drug and hospitalisation costs

Trends in fungal diseases

- Increasing cases of invasive fungal infections

Increasing rate of candidiasis in the US



Martin et al, NEJM 2003;348:1546

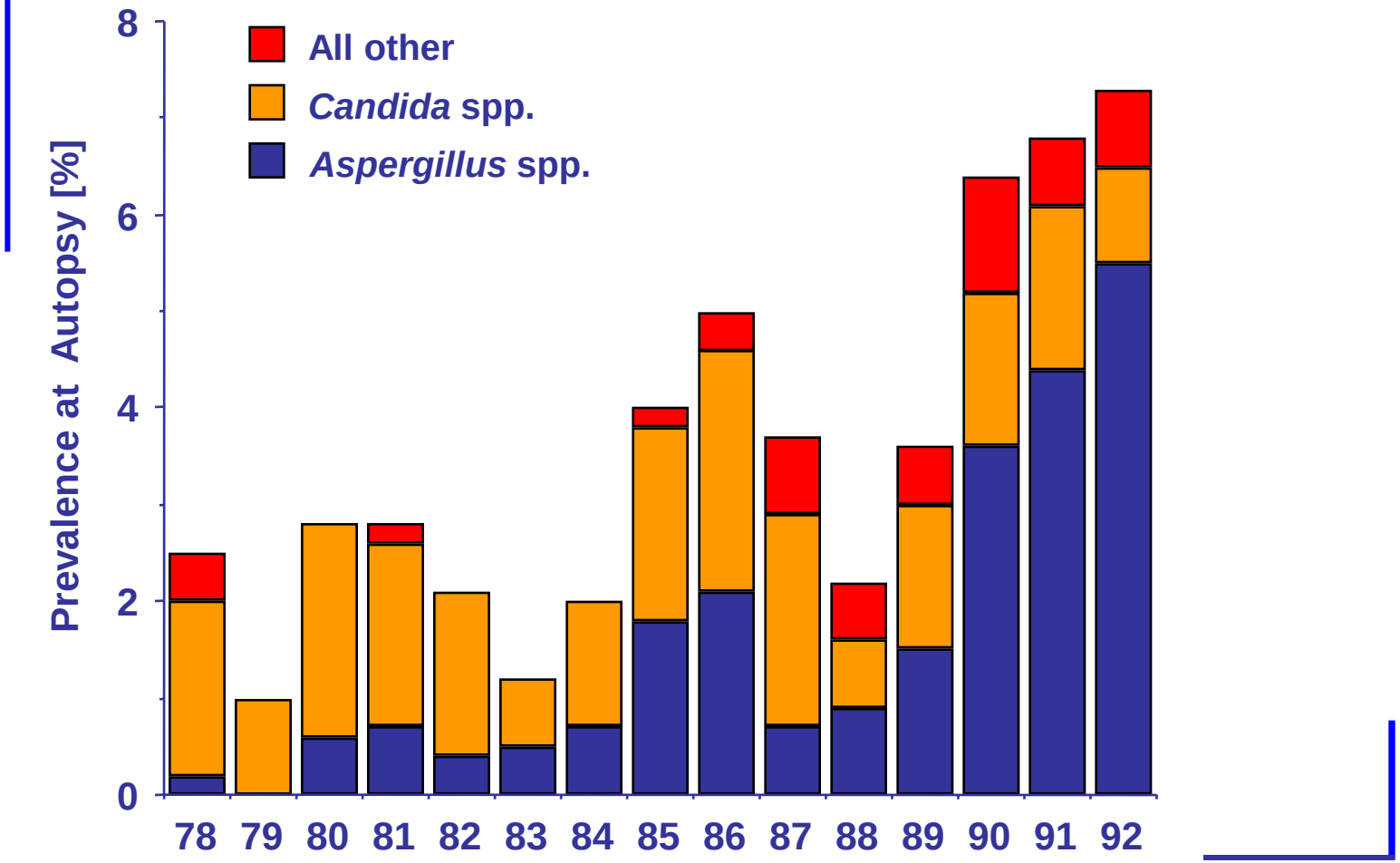
Candida bloodstream infections in the UK

2 year prospective study in 6 UK hospitals

- 18.7 candidaemias /100,000 FTE's, or 3 per 100,000 bed days
- 45% in ICU
- *C. albicans* in 65%
- Majority of isolates susceptible to fluconazole
- Outcome improved by removal of catheter

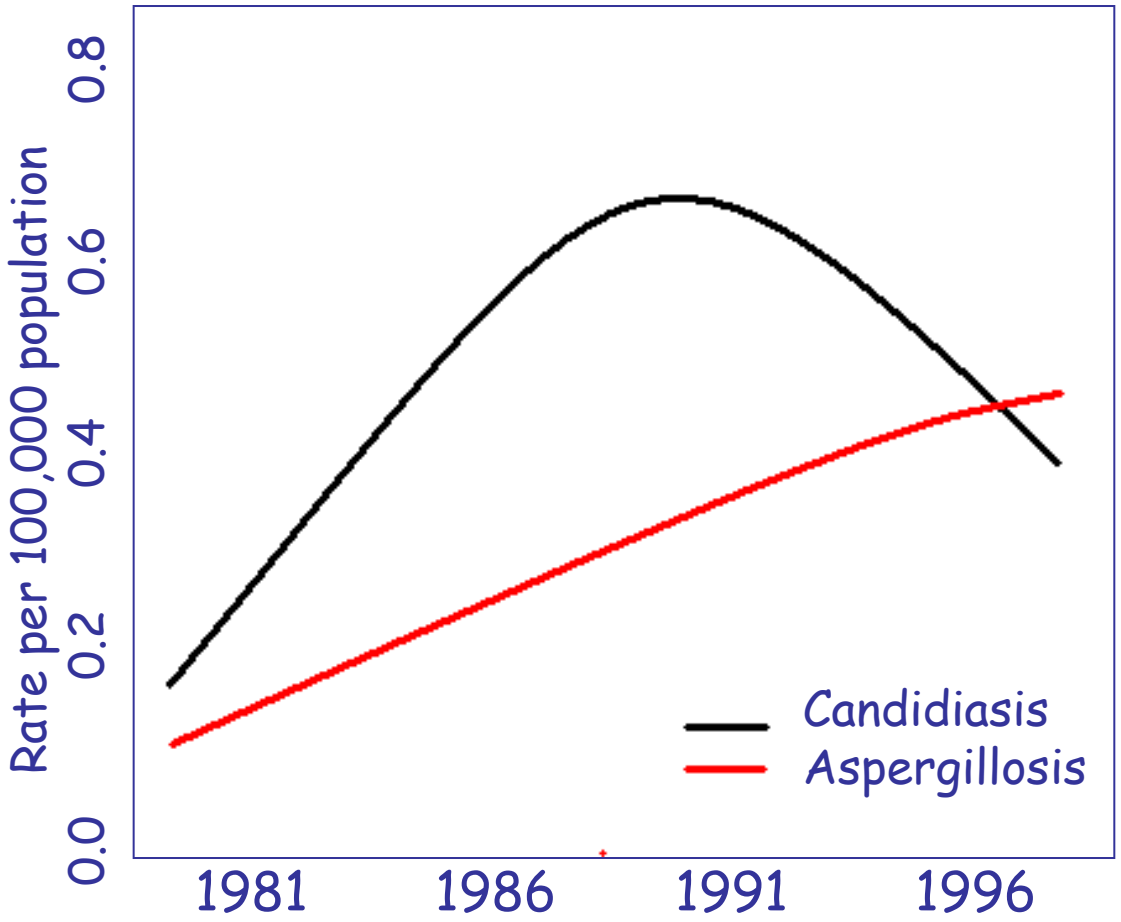
Kibbler CC et al, J Hosp Infect 2003;54:18

Prevalence of invasive aspergillosis at autopsy



Groll et al, J Infect 1996;33:23-32.

Changing incidence of fatal invasive mycoses in non-HIV patients in USA

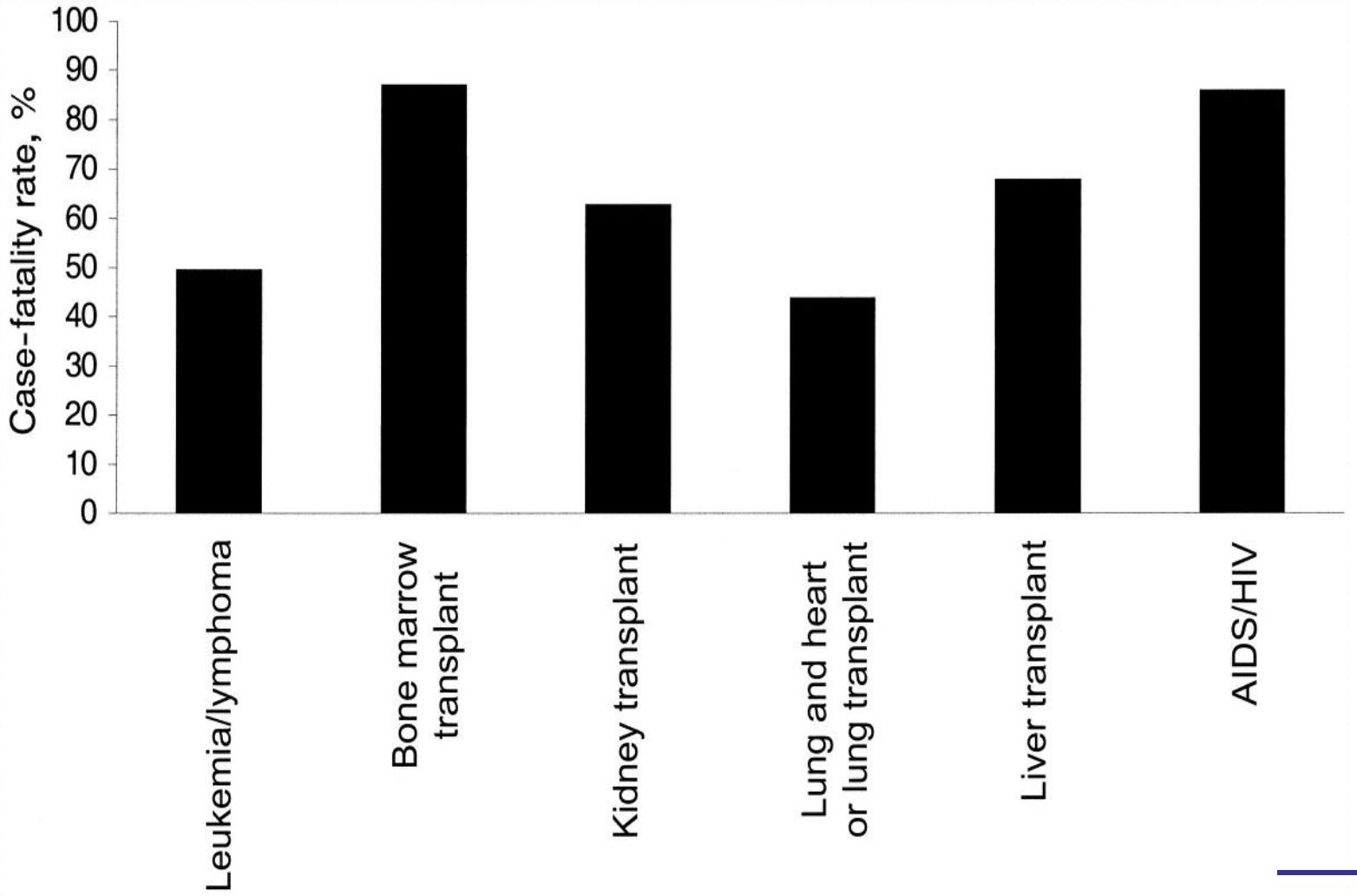


McNeil *et al*, Clin Infect Dis 2001;33:641

Invasive fungal infection – current mortality rates

	Mortality
Aspergillosis	
Pulmonary aspergillosis	50-75%
Cerebral aspergillosis	95%
Candidiasis	
Candidaemia	40%

Case fatality rate with amphotericin B



Lin et al Clin Infect Dis 2001;32:258

Trends in fungal diseases

- Increasing cases of invasive fungal infections
- Poor diagnostic tools

Trends in fungal diseases

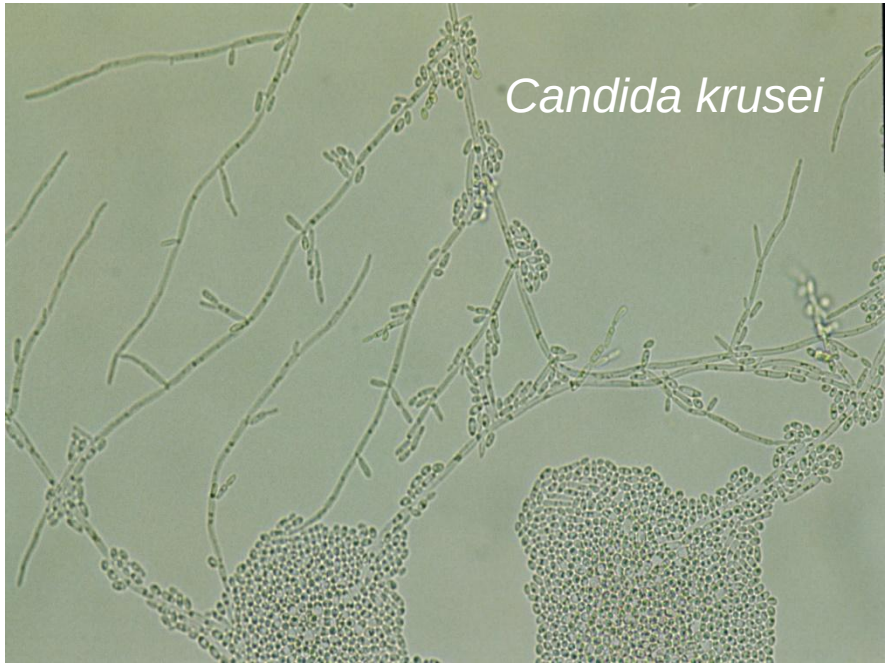
- Increasing cases of invasive fungal infections
- Poor diagnostic tools
- Replacement of sensitive species by resistant ones

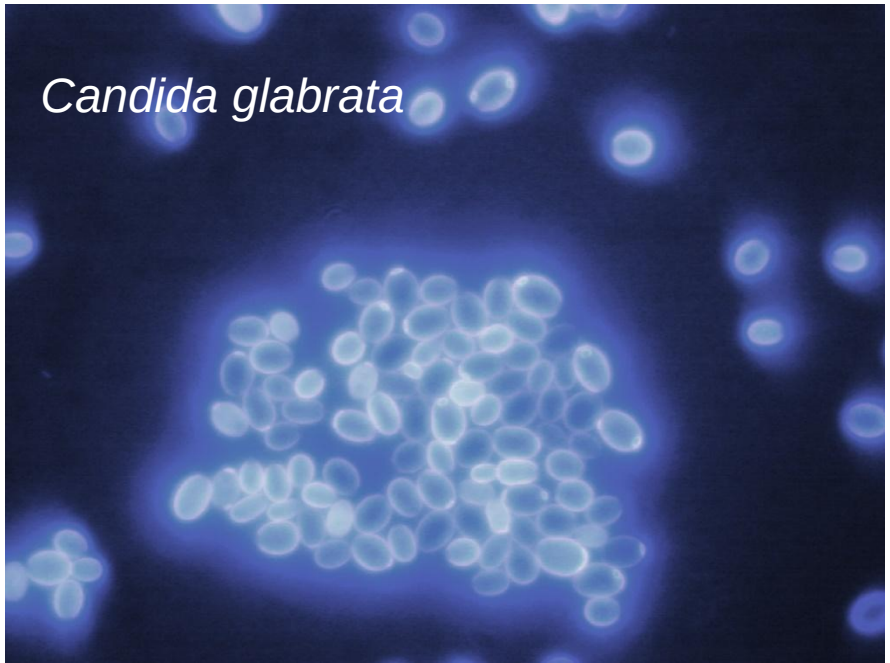
Antifungal susceptibility in *Candida* spp.

Usually susceptible	Less susceptible	Resistant
Fluconazole		
C. albicans	*C. tropicalis*	*C. glabrata*
C. parapsilosis		*C. krusei*
All others		
Amphotericin B		
C. albicans	*C. lusitaniae*	*C. krusei*
C. tropicalis		*C. glabrata*
C. parapsilosis		
Caspofungin		
C. albicans	*C. parapsilosis*	
C. tropicalis	*C. guilliermondii*	
C. glabrata	*C. lusitaniae*	
C. krusei		

Candida glabrata and *Candida krusei*

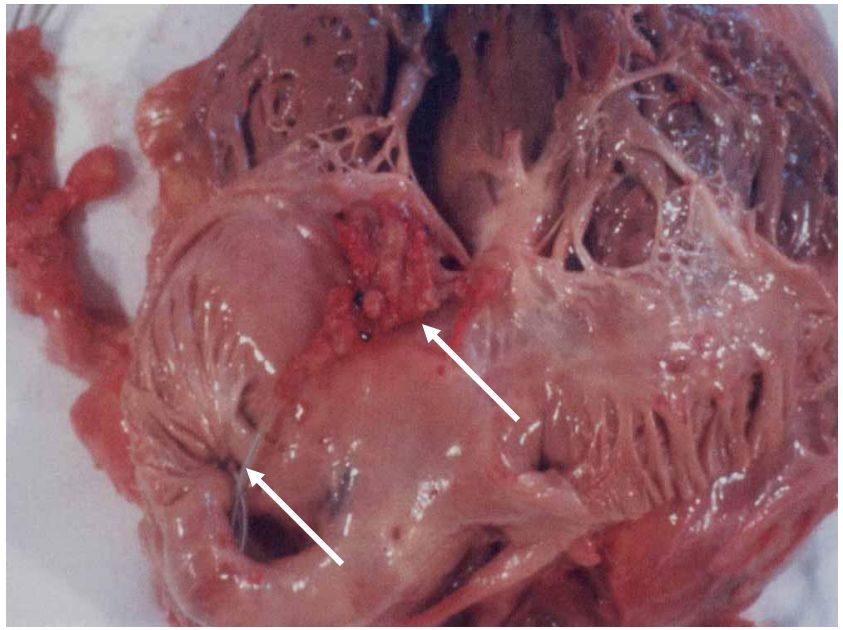
- **Fluconazole intermediate or resistant**
- **Respond poorly to amphotericin B treatment**
- **Increasingly common**





Biofilms and *Candida parapsilosis*

- 2nd most common species in blood, related to catheters and glucose solutions
- Causes biofilms which usually require removal of catheters etc, as antifungal drugs are ineffective in eradicating biofilms



Infected pacemaker and heart valve, after death

Candida bloodstream infections in European cancer patients

Prospective study of candidaemia in European cancer centres

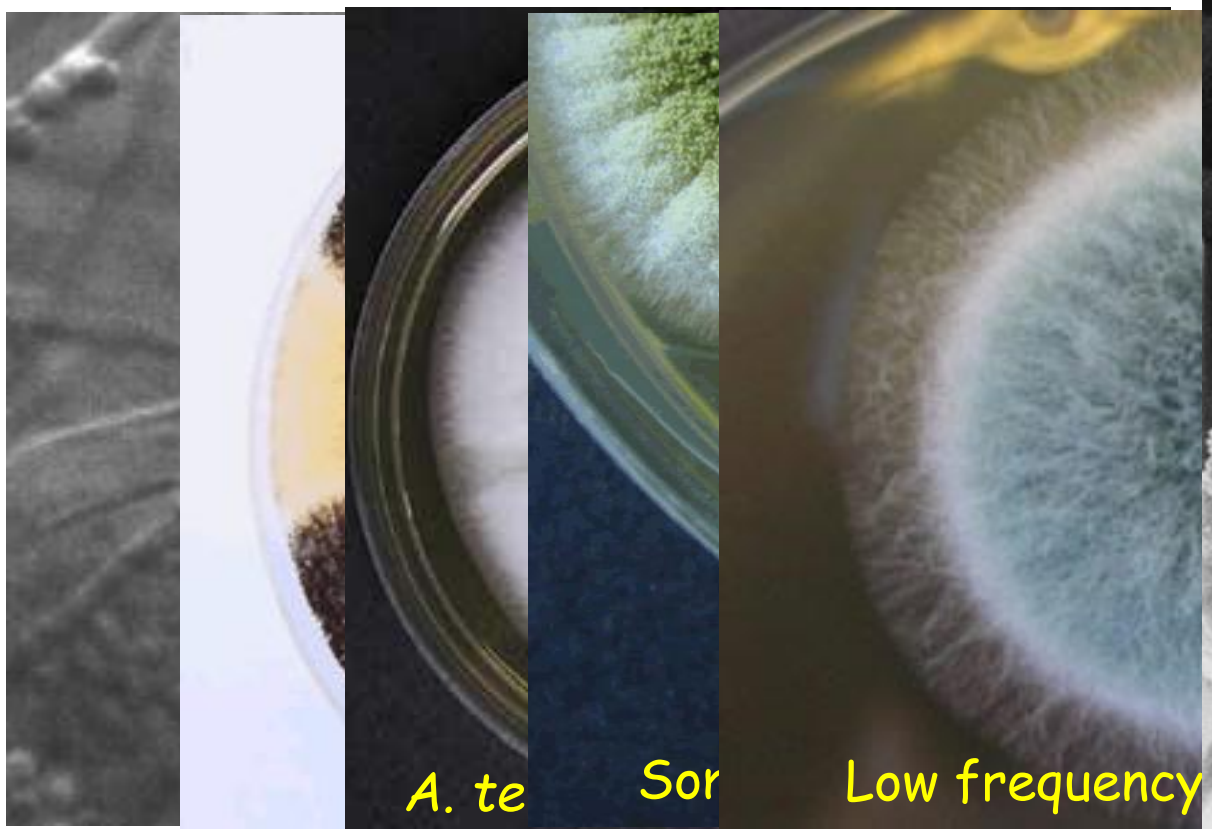
- **289 episodes**
- ***C. albicans* in 70% of cancer and 36% of leukaemia patients**
- **Other species – *C. parapsilosis* (27)**
  - ***C. tropicalis* (23)**
  - ***C. glabrata* (21)**
  - ***C. krusei* (21)**
  - ***C. guilliermondii* (11)**
  - **other *Candida* spp. (7)**

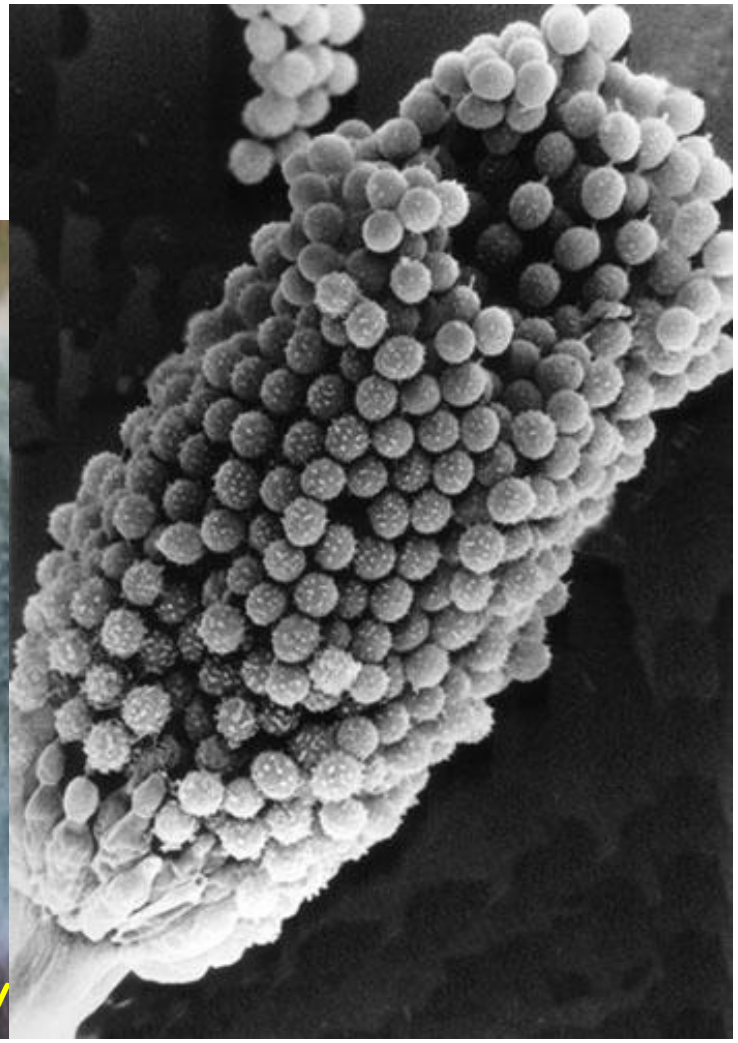
Viscoli C et al, Clin Infect Dis 1999;28:1071

Aspergillus –

38 species have caused disease

Common in the environment





www.aspergillus.man.ac.uk

Trends in fungal diseases

- Increasing cases of invasive fungal infections
- Poor diagnostic tools
- Replacement of sensitive species by resistant ones
- Increasing use of prophylaxis and empirical therapy

Prophylaxis in the surgical intensive care unit

- Fluconazole vs. placebo in *extremely* high risk surgical intensive care patients
- Placebo: 16% rate of invasive candidiasis
- Fluconazole: 8% rate

Pelz et al, Ann Surg 2001;233:542-548,

NEMIS study

Antifungal drugs protective (Relative risk 0.3)

Blumberg HM et al, Clin Infect Dis 2001:33 177-86

Trends in fungal diseases

- Increasing cases of invasive fungal infections
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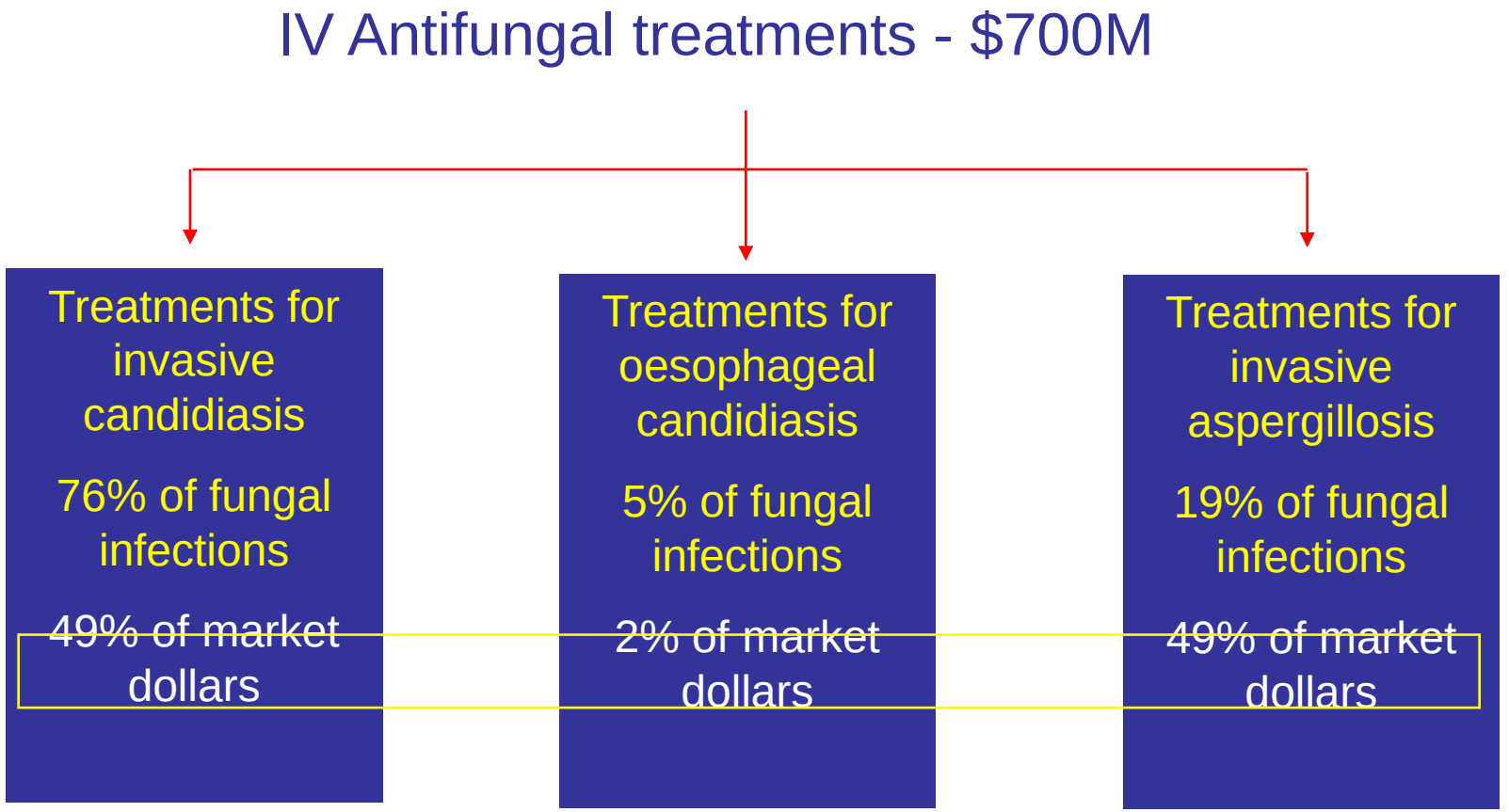
Current US antifungal market for injectables (2003)



Current drug costs in the UK

(per typical course)

Indication	IV	Oral
Candida in hospital (fluconazole)	£820	
Candida in hospital (caspofungin)	£4,676	
Aspergillus in hospital (AmBisome)	£5,538	
Aspergillus in hospital (Voriconazole)	£1,688	
Toenail infections (terbinafine)		£536
Vaginal thrush suppression (fluconazole)	£850	
Chronic pulmonary aspergillosis (voriconazole)		£20,506

Indirect costs

- Additional length of hospital stay (candidaemia)
  15-36 days

- Extra costs of each patient with aspergillosis
  $62,500 (£35,000) (1999 in US)

Trends in fungal diseases

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Table 3.5 Predominant immune defects associated with common hematologic malignancies

		Host defense impairment					
Disease		Neutropenia	Phagocyte defects	Cellular immunity	Humoral immunity	Splenic dysfunction	Anatomic disruption
AML	Disease	+++	+	−	−	−	±
	Treatment	+++		+	+	−	+++
ALL	Disease	+++	+	+	−	−	±
	Treatment	+++		++	++	−	+++
Hairy cell leukemia	Disease	++*	+	±	±	−	±
	Treatment	++		+	++	If splenectomy	±
CLL	Disease	±	+	±	+++	±	±
	Treatment	++		++	++	++	+
CML	Disease	±	+	−	−		±
	Treatment	±		±	−		±
Myeloma	Disease	±	+	±	+++		±
	Treatment	± to ++		++	++		± to +
Lymphoma	Disease	−	+	+++	±	±	±
	Treatment	± to +++		++	++	If splenectomy	± to +++
MDS	Disease	++	+	−	±		±
	Treatment	++		+	−		

++ to +++: Significant; +: known; ±: not prominent;* also monocytopenia

Table 5.1 Infections and associated complications reported during monoclonal antibody therapy for hematological malignancies

Treatment	Target	Infection complications	Overall infection rate
Rituximab	CD20	Bacterial infections, e.g., sepsis Fungal infections, e.g., *Pneumocystis* Viral infections, e.g., CMV/HBV/HCV/TB reactivation, VZV and PML	≈30%
Tositumumab	CD20	Bacterial infections, e.g., sepsis, pneumonia Viral infections, e.g., herpes zoster, herpes simplex II	13–45%
Ibritumomab tiuxetan	CD20	Bacterial infections, e.g., sepsis, pneumonia Viral infections	≈29%
Alemtuzumab	CD52	Bacterial infections Fungal infections Viral infections, e.g., CMV infection/reactivation	>50%
Gemtuzumab ozogamicin	CD33	Bacterial infections Fungal infections, e.g., pulmonary aspergillosis	28–36% (grade 3/4)
Lumiliximab	CD23	Bacterial infections, e.g., pneumonia Viral infections, e.g., parainfluenza virus	15%
Inotuzumab ozogamicin	CD22	Unknown	More data needed
Zanolimumab	CD4	Bacterial infections Fungal infections Viral infections	49%; more data needed
Muromonab-CD3	CD3	Bacterial infections	21–50%
Siplizumab	CD2	Viral infections, e.g., EBV	More data needed

Table 5.1 Infections and associated complications reported during monoclonal antibody therapy for hematological malignancies

Treatment	Target	Infection complications	Overall infection rate
Denileukin diftitox	IL-2R	Bacterial infections; more data needed	≈30%
Daclizumab	IL-2Rα	Bacterial infections	95%
		Fungal infections	
		Viral infections, e.g., CMV reactivation, respiratory viral infections, EBV	
Basiliximab	IL-2Rα	Bacterial infections	>75%
		Invasive fungal infections	
		Viral infections, e.g., CMV reactivation	
Tocilizumab	IL-6	Bacterial infections, e.g., pneumonia	More data needed
		Viral infections, e.g., herpes zoster	
Infliximab	TNFα	Bacterial infections, e.g., TB, *Listeria*	≈80%
		Invasive fungal infections, e.g., endemic mycoses, *Candida*	

CMV cytomegalovirus; *EBV* Epstein–Barr virus; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *VZV* varicella zoster virus; *PML* progressive multifocal leukoencephalopathy; *TB* tuberculous

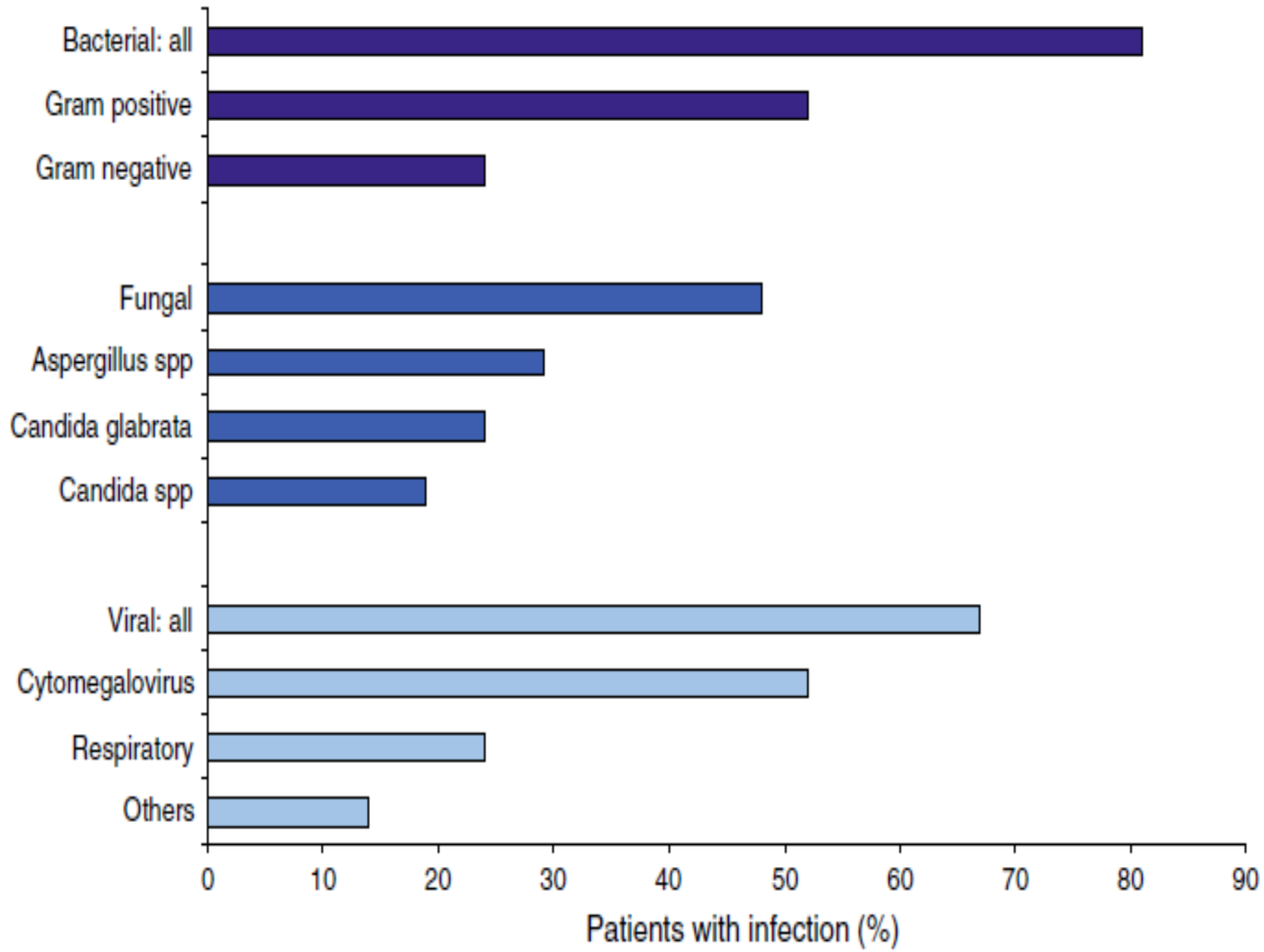


Fig. 5.4 Infections in patients treated with infliximab: retrospective analysis of 134 patients with acute GVHD [195]

Table 24.2 Patients who are at increased risk of invasive candidiasis

Congenital deficit of cellular immunity
Deficit of cellular immunity secondary to infection (HIV)
Recipients of solid organ transplant
Recipients of hematopoietic stem cell transplant
Low birth weight infants

- Invasive mold infections affecting the lungs may present with different patterns on a chest CT, including **small or large nodules**, **patchy**, **segmental**, or **wedge-shaped consolidations**, **peribronchial infiltrates** with a **tree-in-bud distribution**, and **cavitation** .
- Two CT patterns have been associated with early and late pulmonary IA: the **“halo**” and the “**crescent**” sign, respectively

- **Histopathologic** confirmation of sterile tissue invasion remains the **“gold standard**” to establish a proven diagnosis of an invasive mold infection

- The revised definitions retain the original classifications of **“proven,” “probable,” and “possible**” IMIs. For most conditions, **proven** infections require **proof of hyphal elements in diseased tissue**. To characterize a case as **probable**, a **host factor, clinical features, and a mycologic or nonculture-based surrogate marker (e.g., galactomannan, beta-glucan**, or as determined by polymerase chain reaction **[PCR**]) must be present. **Possible** invasive fungal disease is more strictly defined to include **patients with the appropriate host factors** and **sufficient clinical evidence of** invasive fungal disease, but no mycologic evidence.

Diagnostic Procedures

Afebrile patient.

- –– Daily clinical exam + body temperature at least three times daily.
- **Note**: antipyretic medication (steroids; analgesics such as metamizole)
- –– Serum C-reactive protein **(CRP)** twice weekly.
- –– *Aspergillus* antigen **(GM)** [3]twice weekly..

First fever.

- –– Update physical exam, blood cultures, clinical chemistry, CRP, interleukin-6 (IL-6), and thoracic computed tomography (CT) scan; other measures according to clinical findings

Persistent fever.

- –– Update physical exam, blood cultures, clinical chemistry, CRP, IL-6, and thoracic CT scan; consider abdominal ultrasound or magnetic resonance imaging (MRI).
- –– Check results of antigen testings.

Fever + pulmonary infiltrates.

- –– Bronchoscopy + bronchoalveolar lavage (BAL) =>microscopy + culture for bacteria;
- test for *Mycobacterium tuberculous* (MTB)
- *Pneumocystis*,
- cytomegalovirus (CMV), respiratory viruses, adenovirus,
- *Aspergillus* + other fungi; check for *Aspergillus* GM;
- ***optional***: *Aspergillus*-PCR and MTB/*Pneumocystis*-PCR.

- • ***Fever accompanied by skin lesions.***
- –– Blood cultures.
- –– Biopsy (=>histopathology and *nonfixated* =>microbiology).

Neurological symptoms ± fever.

- –– Cerebrospinal fluid (CSF) =>human herpes virus-6 (HHV-6); *Aspergillus* GM; CMV; HSV, VZV.
- –– Fundoscopy.
- –– Cranial MRI.

- ***Fever + increasing "liver function tests"*** =>viral (hepatitis B virus (HBV), varicella zoster virus (VZV); CMV, etc.), *Candida*?
- –– Liver ultrasound or CT or MRI (preferred)
- NB: *Pneumocystis jiroveci* typically accompanied by lactate dehydrogenase rise

- differential diagnosis
- including appendicitis, ischemic colitis, pseudomembranous
- colitis, or antineoplastic drug or radiation toxicity

Antifungals

Systemic & Topical

Some are fungistatic,
while others are fungicidal

Fungal Infection in Humans = Mycosis

- Major Types of Mycoses
  - superficial
  - cutaneous
  - subcutaneous
  - systemic
  - opportunistic
- Symptoms vary from cosmetic to life threatening

Antifungal Agents

- **Polyene antibiotic**
- The polyene antibiotics bind with sterols in the fungal cell membrane, principally ergosterol. This causes the cell's contents to leak out and the cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible.
  - Nystatin
  - Amphotericin B (may be administered liposomally)
  - Natamycin
  - Rimocidin
  - Filipin
  - Pimaricin

Nystatin: The first antibiotic against fungi

- Like many other antimycotics and antibiotics, nystatin is of bacterial origin. It was isolated from *Streptomyces noursei* in 1950 by Elizabeth Lee Hazen and Rachel Fuller Brown, who were doing research for the Division of Laboratories and Research of the New York State Department of Health. The soil sample where they discovered nystatin, was from the garden of Hazen's friends called Nourses, therefore the strain was called *noursei*. Hazen and Brown named nystatin after the New York State Public Health Department (now known as the Wadsworth Center) in 1954.
- The two scientists donated the royalties from their invention, over $13 million dollars, to the nonprofit Research Corporation for the advancement of academic scientific study. Elizabeth Lee Hazen and Rachel Fuller Brown were inducted into the National Inventors Hall of Fame in 1994.

Antifungal Agents

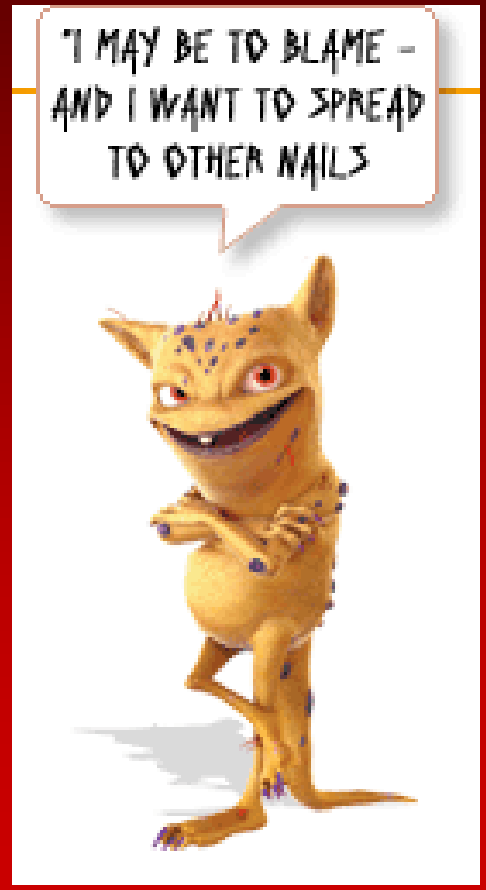
- **Imidazole and triazole**
- The imidazole and triazole groups of antifungal drugs inhibit the enzyme cytochrome P450 14α-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell membrane synthesis. These drugs also block steroid synthesis in humans.
- **Imidazoles:**
  - Miconazole
  - Ketoconazole
  - Clotrimazole
  - Mebendazole
  - Isoconazole
  - Sertaconazole
  - Thiabendazole
  - Bifonazole
  - Butoconazole
  - Econazole
  - Fenticonazole
  - Oxiconazole
  - Sulconazole
  - Tiaconazole

Antifungal Agents

- **The triazoles are newer, and are less toxic and more effective:**
  - **Fluconazole**
  - **Itraconazole**
  - **Ravuconazole**
  - **Posaconazole**
  - **Voriconazole**

Antifungal Agents

- **Allylamines**
- Allylamines inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis:
- **Terbinafine - marketed as Lamisil**
- **Amorolfine**
- **Naftifine**
- **Butenafine**



Antifungal Agents

- **Echinocandin**
- Echinocandins inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-β glucan synthase:
  - **Anidulafungin**
  - **Caspofungin**
  - **Micafungin**

Antifungal Agents

- **Antimetabolite.**

  Flucytosine is an antimetabolite.

  - Griseofulvin binds to polymerized microtubules and inhibits fungal mitosis; It is derived from the mold *Penicillium griseofulvum*.
  - Fluocinonide
  - Salicylic Acid (topical)
  - Tinactin or Tolnaftate
  - Potassium Iodide

Sources

- http://en.wikipedia.org/wiki/Antifungal
- http://www.lamisil.com/
- http://www.tinactin.com/
- http://en.wikipedia.org/wiki/Griseofulvin
- http://www.journals.uchicago.edu/CID/journal/issues/v30n4/990666/990666.text.html?erFrom=-4860378516935905751Guest
- http://www.mycology.adelaide.edu.au/downloads/antifungals.pdf#search=%22antifungal%20drugs%22
- http://en.wikipedia.org/wiki/Nystatin
- http://inventors.about.com/library/inventors/blnystatin.htm

antifungal agents

What are they?

Griseofulvin
Polyenes
Azoles
5-FC
Terbinafine
Echinocandins

antifungal agents

Mode of action

Amphotericin B binds to plasma membrane creating pores

Azoles inhibits cytochrome P450 enzymes in the fungal cell

5FC converts to 5FU, incorporated into RNA, abnormal proteins

Griseofulvin binds microtubule proteins, inhibit cell wall synthesis

Terbinafine is an ergosterol inhibitor useful for systemic mycosis

Echinocandins target their action on fungal cell wall

antifungal agents

Griseofulvin

Source *Penicillium griseofulvum*

Produced in 1939 ⟶ Not used until 1958

Spectrum

Dermatophytes

Gentles first used orally in guinea pigs prior to its use in humans

Anti-inflammatory properties

Inhibits keratolytic action

antifungal agents

VERY TOXIC

Polyenes

Polyenes are produced from *Streptomyces*

Cyclic molecules

Nystatin

Amphotericin B

Natamycin

Mepartricin

Broad spectrum

antifungal agents

Amphotericin B

Yellow powder, water insoluble

Bile salt allows solubility (weak association)

Floats free in the aqueous medium, causes toxic effects

Broad spectrum, binds to sterol in the cell membrane

Fungicidal activity @ 3 h with 1 µg/ml

Azole-amphotericin B is never synergistic

Amphotericin B and 5FC gives synergy

Candida lusitaniae is usually resistant to Amphotericin B

antifungal agents

Amphotericin B

Toxicity

- early intolerance reaction
- thrombophlebitis
- **nephrotoxicity**
- hematotoxic effects

The liposomal preparation of Amphotericin B reduces the risk of nephrotoxicity

antifungal agents

Azole Derivatives

A chemical pentacyclic structure with 2 nitrogen atoms

Water **insoluble** except fluconazole

Preferentially inhibit cytochrome P450 enzymes

Fungistatic, Modify cytochrome P450 enzyme

First generation Imidazoles:

Clotrimazole & Miconazole

Clotrimazole requires high doses – poorly tolerated

Parenteral dosages no longer available for Miconazole

antifungal agents

Cytochrome P 450 (CYP 450)

CYP is a host of enzymes that use iron to oxidize things

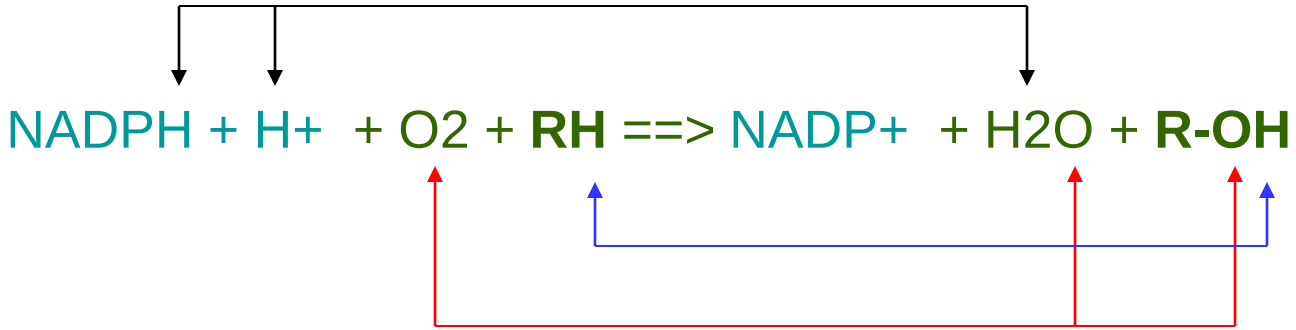
CYP disposes harmful substances by making them water-soluble

CYP is something like a hydroxyl group

P450-mediated oxidation is referred to as "*Phase I metabolism*"

CYP in man is found in the *liver, small intestine*

CYP is vital to the formation of cholesterol & steroids



antifungal agents

CYP 450 …..

Fungal plasma membranes have nonpolar sterol (ergosterol)

Amphotericin B binds to ergosterol permitting rapid leakage

Cytochrome P450 catalyzes synthesis of ergosterol

Azole antifungal agents interfere with cytochrome P450

antifungal agents

Ketoconazole

Orally well absorbed imidazole of second generation

Ketoconazole is the only imidazole for systemic use

CSF penetration is very weak

Hepatotoxicity restricts its use

Also interacts with other molecules

antifungal agents

Third generation azoles

Triazole derivatives (contain three nitrogen atoms)

Fluconazole

Itraconazole

Voriconazole

Posaconazole

Revuconazole

Satisfactory tolerability, Suitable for systemic use

antifungal agents

Fluconazole & Itraconazole

Fluconazole has been extensively used for yeast infections

Useful for systemic infections

Readily and completely absorbed by gastrointestinal tract

Distributed equally in different organs and tissue

Candida krusei Intrinsically resistant to fluconazole

Itraconazole is used to treat aspergillus infections

Entirely metabolized in the liver

Eliminated in the feces and urine

antifungal agents

Voriconazole is a modified fluconazole

A broad spectrum antifungal agent

Rapid absorption after oral administration

Distributes in tissues and body fluids

Metabolized in the liver

Eliminated in the urine in unchanged form

Azoles carry some side effects

Hepatotoxicity, gastrointestinal and endocrine toxicity

Skin rash, pruritis and other hypersensitivity

antifungal agents

Clinical Indication

Miconazole has poor tolerability given by intravenous

Ketoconazole used for endemic & superficial mycosis

Fluconazole useful for *C. albicans* and *Cryptococcus neoformans*

Voriconazole & Posaconazole have similar spectrum as other azole

Itraconazole is used to treat bronchopulmonary aspergillosis

Adverse effects: gastrointestinal, hypersensitivity & hepatotoxicity

antifungal agents

Echinocandins

Caspofungin

Caspofungin is semisynthetic, synthesized from *Glarea lozyensis*

Whitish powder, water & methanol soluble, fungicidal

Fungicidal against, Aspergilli, Candida and *P. carinii*

No cross resistance amongst strains resistant to Ampho B or azoles

No activity against *Cryptococcus neoformans, Fusarium & Rhizopus*

Effective against *Pneumocystis carinii*

Micafungin and Anidulafungin – *are under investigation*

antifungal agents

Terbinafine

Terbinafine belongs to allylamines, synthetic, highly lipophilic

Oral and topical (cream) formulations

Terbinafine inhibits ergosterol biosynthesis

Used to treat superficial mycosis

Also useful against systemic mycosis (yeast & other fungi)

Adverse reactions to terbinafine are in general transient and mild

antifungal agents

Question

Does empiric use of antifungal agents trigger resistance?

Antifungals show resistance more than they did in the past

Some fungi become resistant after exposure to antifungals

Are we going to hit MRSA like situation in mycology?

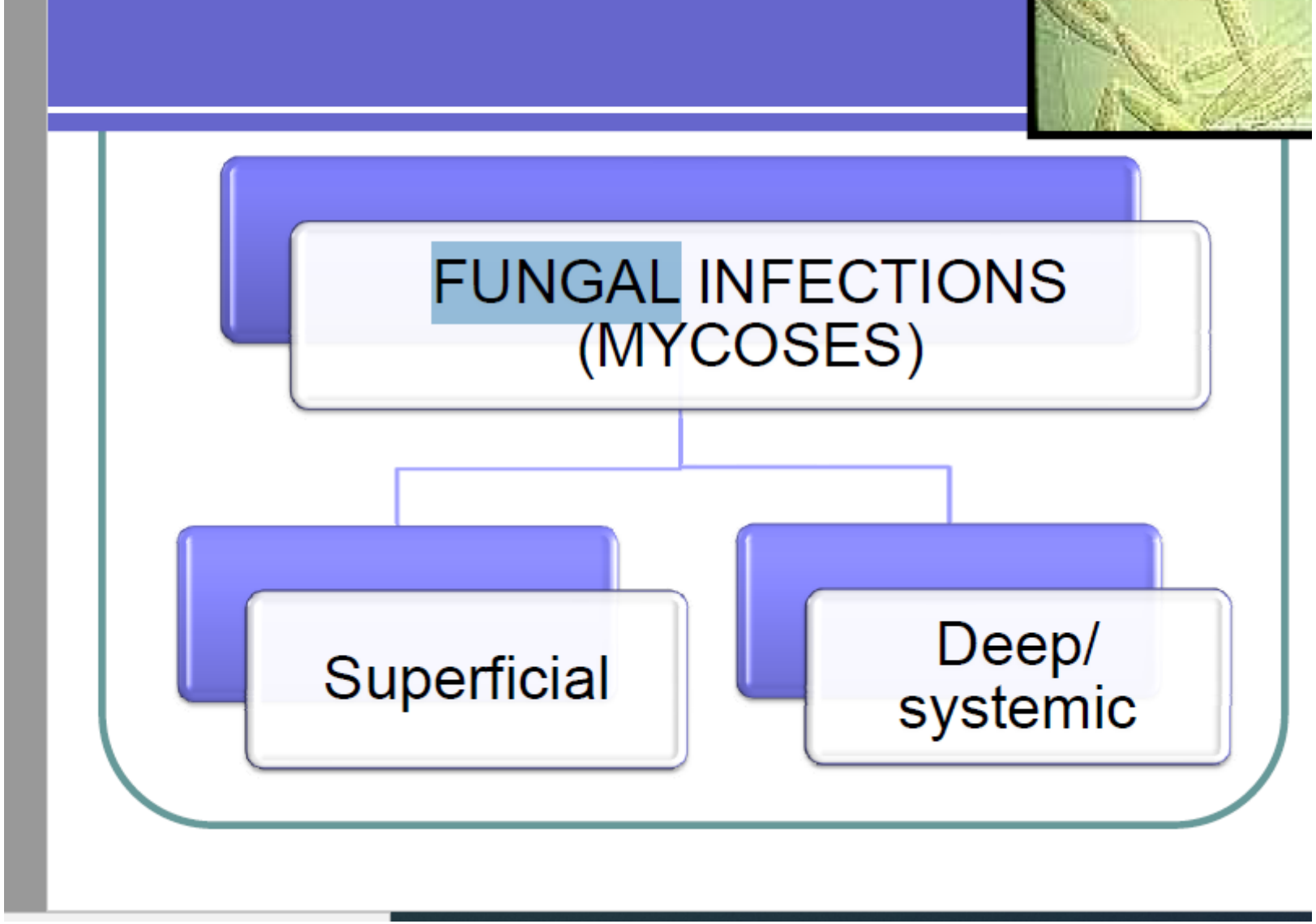
Highly unlikely

Antifungals are not over prescribed as antibiotics

Antifungal Drugs

DEEP MYCOSES

- aspergilus
- Blastomyces
- Candida
- Coccidiodes
- Cryptococcus
- Histoplasma


FUNGAL INFECTIONS (MYCOSES)
Superficial
Deep/ systemic

Antifungal drugs- Classification (5)

1. ANTIBIOTICS

Amphotericin B, (AMB), Nystatin, Hamcyin, Natamycin

Griseofulvin

2. ANTIMETABOLITES:

5-Fluorocytosine (5-FC)

inhibition of nucleic acid synthesis

Antifungal drugs- Classification

3. AZOLES

- Imidazoles: (Topical): Clotrimazole, Econazole, Miconazole, Oxiconazole
  (Systemic): Ketoconazole

Trizoles: (Systemic) Itraconazole, Fluconazole, Voriconazole

Inhibition of ergosterol synthesis

4. ALLYLAMINE: Terbinafine

Inhibition of lanosterol and ergosterol synthesis

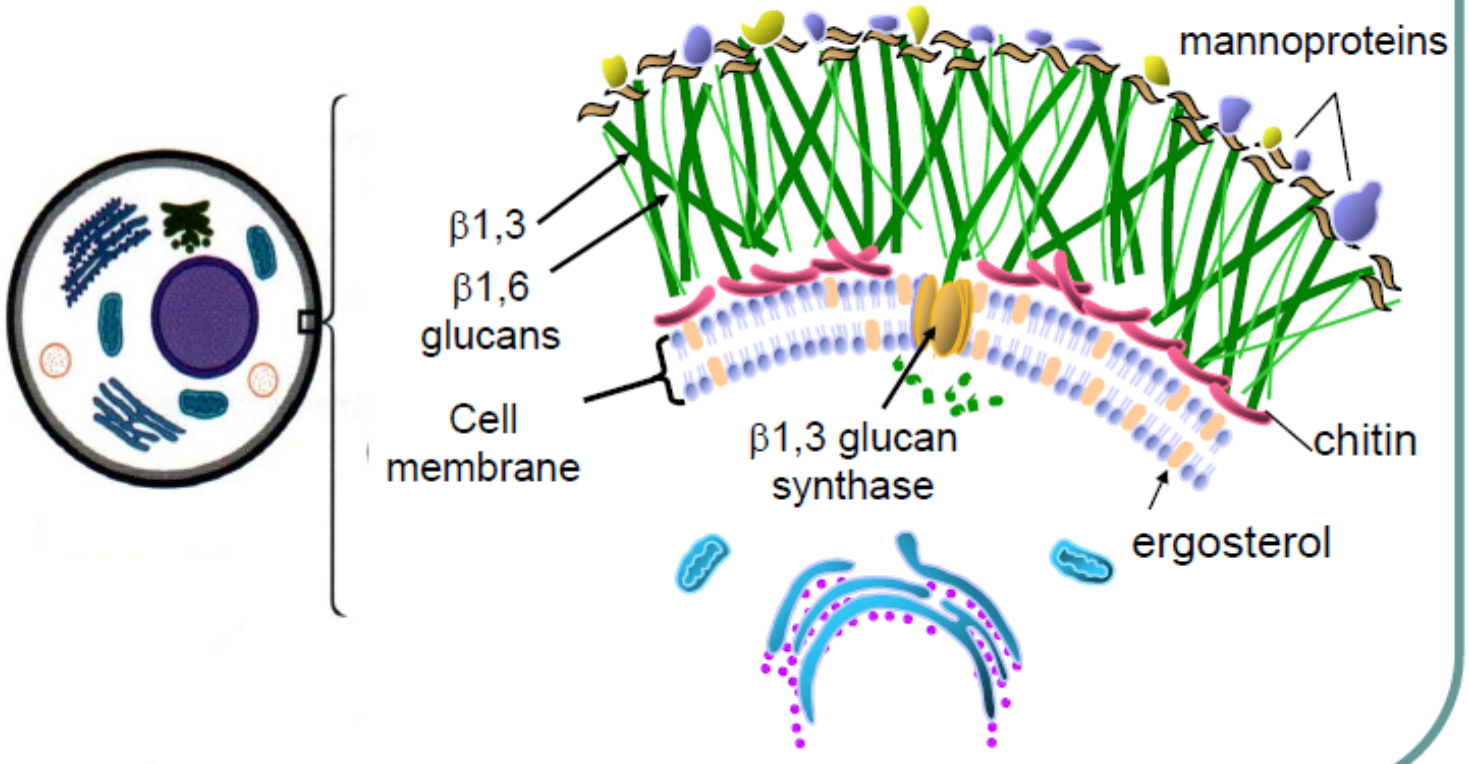
5. OTHER TOPICAL AGENTS:

Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Sod. thiosulfate.

Amphotericin B - MOA

- **In fungi:** ergosterol in membranes: higher affinity than mammalian cholesterol for AmB
- **Ergosterol:** Only present in fungal cell membrane and not in animal cell
- **Ergosterol: Polyenes** combine with it, get inserted into the membrane and several molecules together orient themselves and form a **micropore**.

The Fungal Cell Wall



Antifungal Spectrum

- Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Aspergillus, Rhodotorula.

- Resistance is rare and slow to develop
- **Pharmacokinetics**
- Poorly: crosses cell membranes, absorbed from the gut and penetration into the eye, CSF, and joint capsules

Kidney > liver > spleen > lung > heart > skeletal muscle > brain > bone > CSF > eye

- For treatment of meningitis, it must be given intrathecally

Given only via IV injection or intrathecally Selective distribution into deep tissue sites, with slow release of drug

- Classic amphotericin B deoxycholate (Fungizone™) formulation: serious toxic side effects.

  Less toxic preparations:

  1) Liposomal amphotericin B
  2) Amphotericin B colloidal dispersion
  3) Amphotericin B lipid complex

- milder acute reaction
- better tolerated
- lower nephrotoxicity
- minimal anaemia
- targeted delivery-liver & Spleen

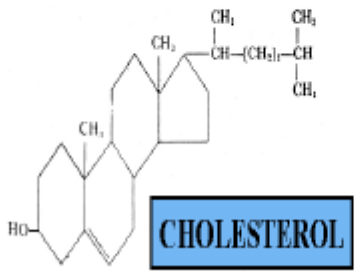
ADVERSE EFFECTS (AMB)

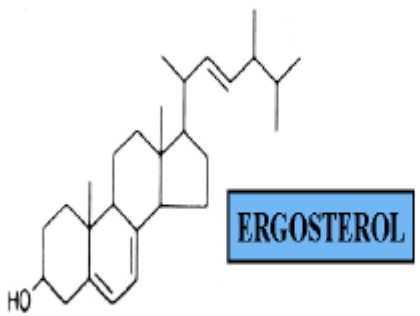
- Acute: Infusion-related
  - Chills, fever, dyspnea, nausea, vomiting, bronchospasm, hypotension, convulsions
- Chronic
  - Nephrotoxicity
- impaired concentration, impaired urinary acidification, K & Mg wasting with hypokalemia and hypomagnesemia
- Normochromic, normocytic anemia
- (↓ erythropoietin)

Drug interactions

3. AZOLES

- Better CSF penetrability
- High volume of distribution
- Dermatophytes, candida and other deep mycoses
- Triazoles are greater efficacy/lesser side effect and drug interaction





Adverse effects of fluconazole include:

- Nausea
- Vomiting
- GI upset
- Hepatotoxicity
- Exfoliative skin rash

Exfoliative Skin

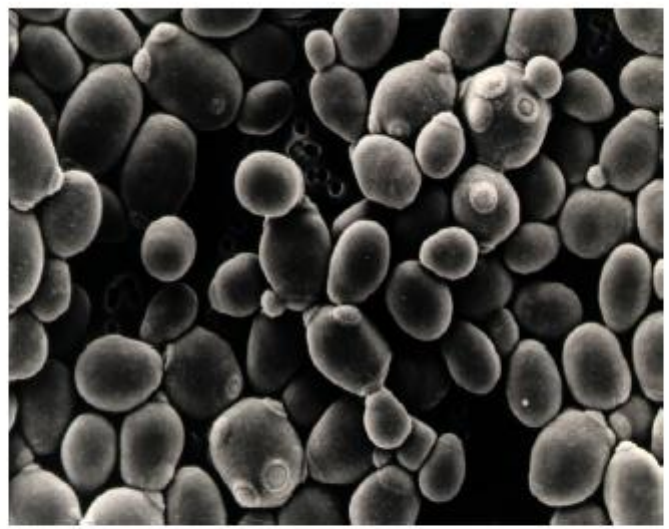
Caution:

As these are embryotoxic,
they should be avoided in pregnancy.

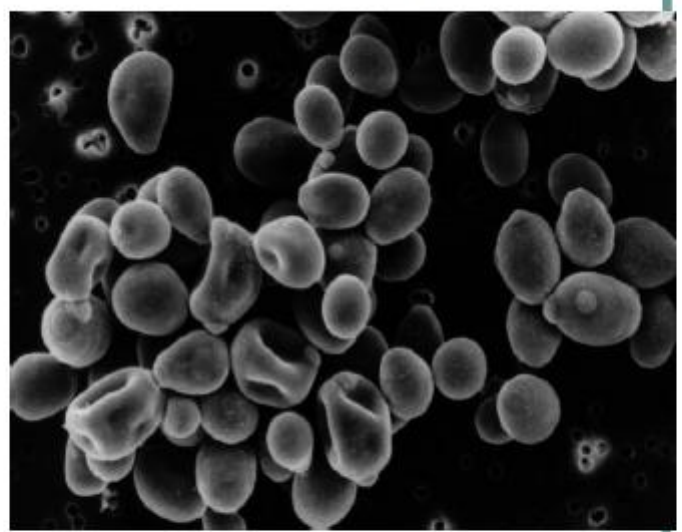
Azole Derivatives Should be Avoided in Pregnancy

Effect of azoles on *C. albicans*

Before exposure



After exposure

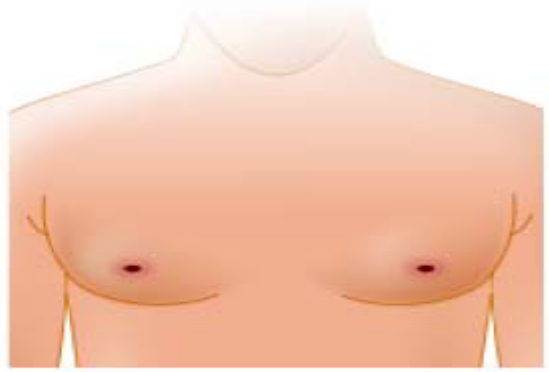


Ketoconazole

- Spectrum: yeasts and moulds - poor absorption limits its role for severe infections, generally used in mucosal infections only
- Pharmacokinetics
  - Variable oral absorption, dependent on pH (often given with cola or fruit juice)
  - $T_{1/2}$ 7-10 hours
  - Protein binding > 99%
  - Hepatic, bile and kidney elimination
  - H_2 blockers, antacids--- decrease absorption

Adverse effects of Ketoconazole include:

- Hepatotoxicity, which increases liver enzymes (rarely may develop progressive hepatotoxicity, which can be fatal).
- Gynaecomastia, loss of libido and oligozoospermia in men (the drug may inhibit androgenic hormones).
- Menstrual abnormalities, which may occur in some women.
- Salt and water retention.



Gynaecomastia

✓**Hepatoxicity (2-8%)- increase in transaminases, hepatitis**

✓**Dose related inhibition of CYP P450- responsible for testosterone synthesis**

✓**Dose-related inhibition of CYP P450 -responsible for adrenal cortisol synthesis**