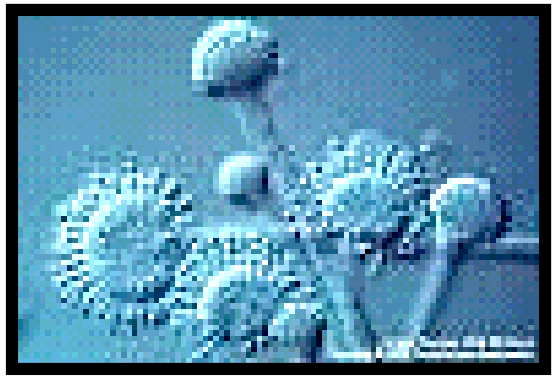
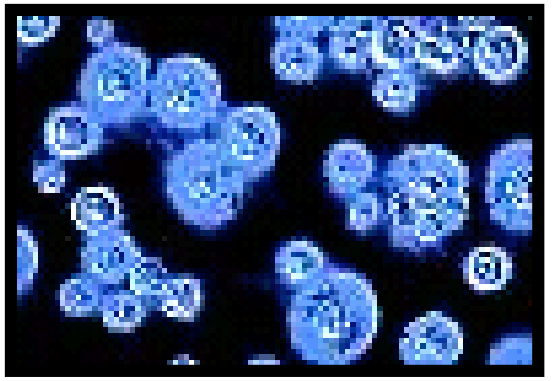
Antifungal Pharmacology

Deborah Fox, Ph.D.
Children's Hospital
3219 RIC
504-896-2766
dfox@chnola-research.org



Special thanks to:
John Perfect, MD
Andy Alspaugh, MD
Sevtap Arikan, MD
John Rex, MD
www.doctorfungus.org



Objectives

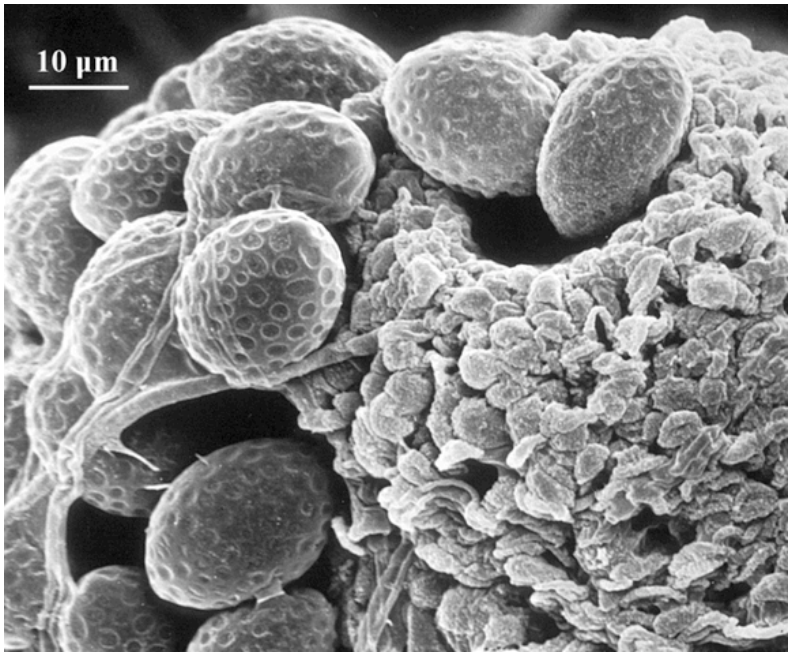
- To recognize the clinical significance of fungal infections
- To identify the antifungal agents and their mechanisms of action
- To evaluate potential antifungal drug interactions and toxicities
- To differentiate the mechanisms of antifungal drug resistance

Lecture outline

- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary

Mycology Resources

- http://www.doctorfungus.org
- http://mycology.adelaide.edu.au/mycoses
- http://mycology.cornell.edu/
- http://www.mycology.net/



Lecture outline

- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary

Medical Problems Caused by Fungi

1) Allergic disease

2) “Mushroom” poisoning

3) Mycotoxins

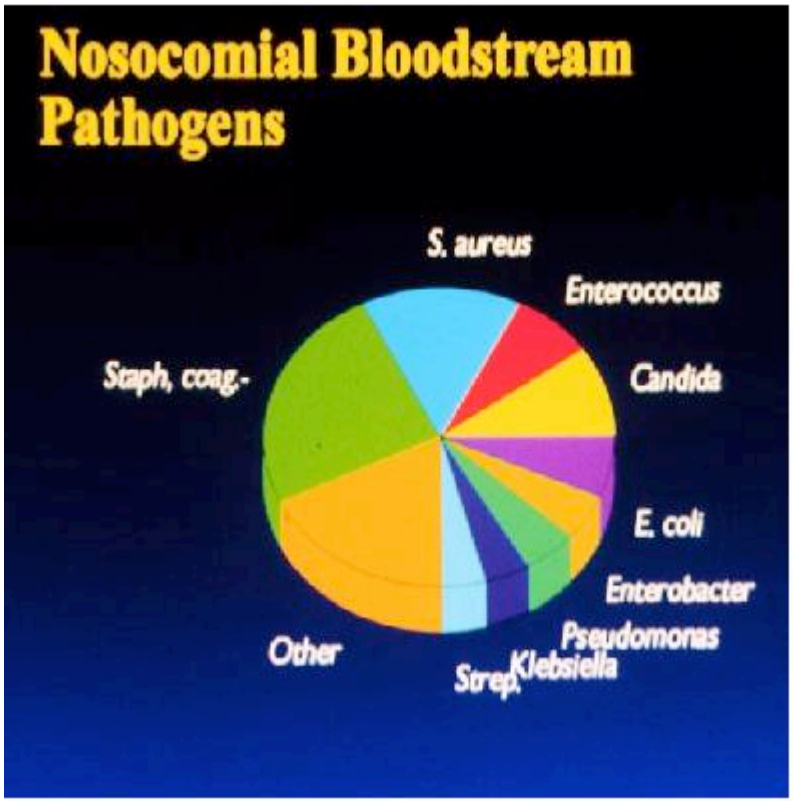
Secondary metabolites

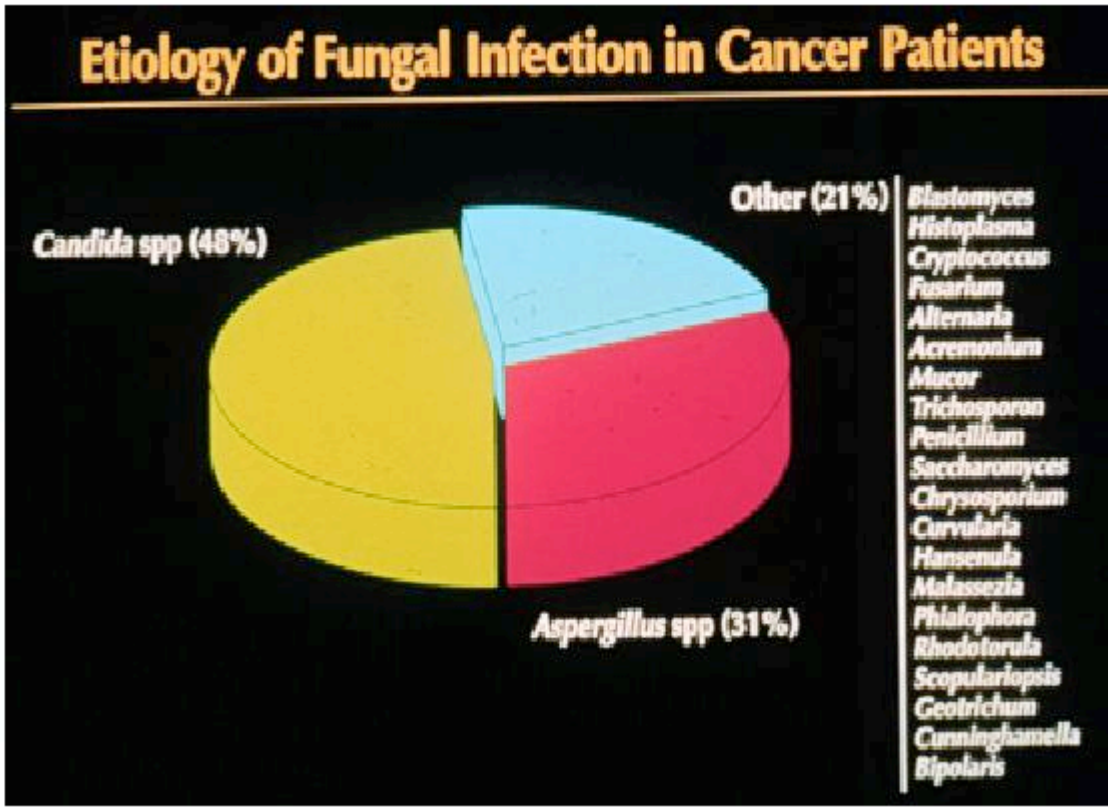
--many have industrial uses

--Fusarium mycotoxin -- USSR after WWII

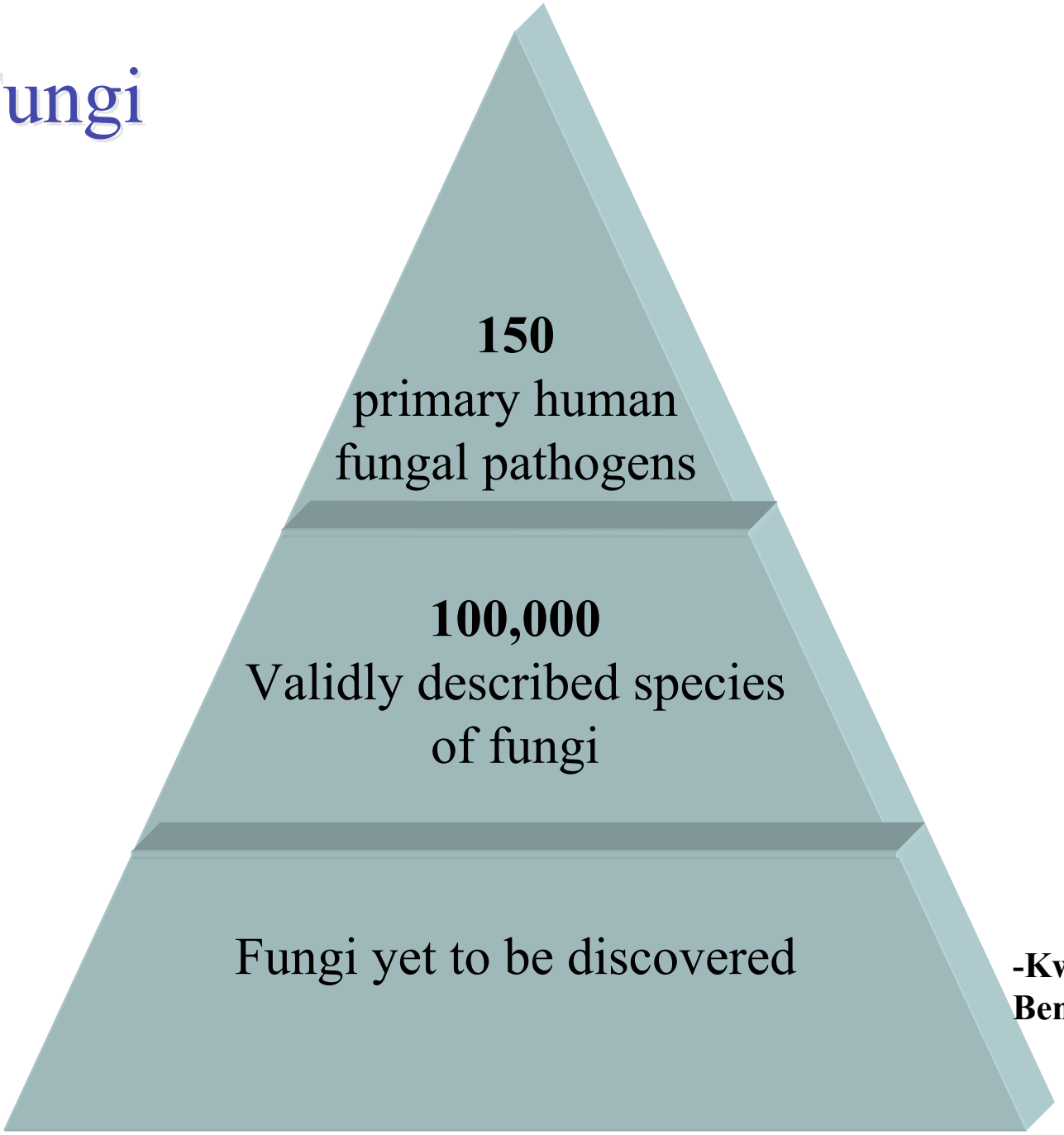
--*A. flavus* “aflatoxin”

4) **Mycoses -- infection and resulting disease cause by fungi**


Nosocomial Bloodstream Pathogens
S. aureus
Enterococcus
Staph, coag.-
Candida
E. coli
Enterobacter
Pseudomonas
Other
Strep
Klebsiella

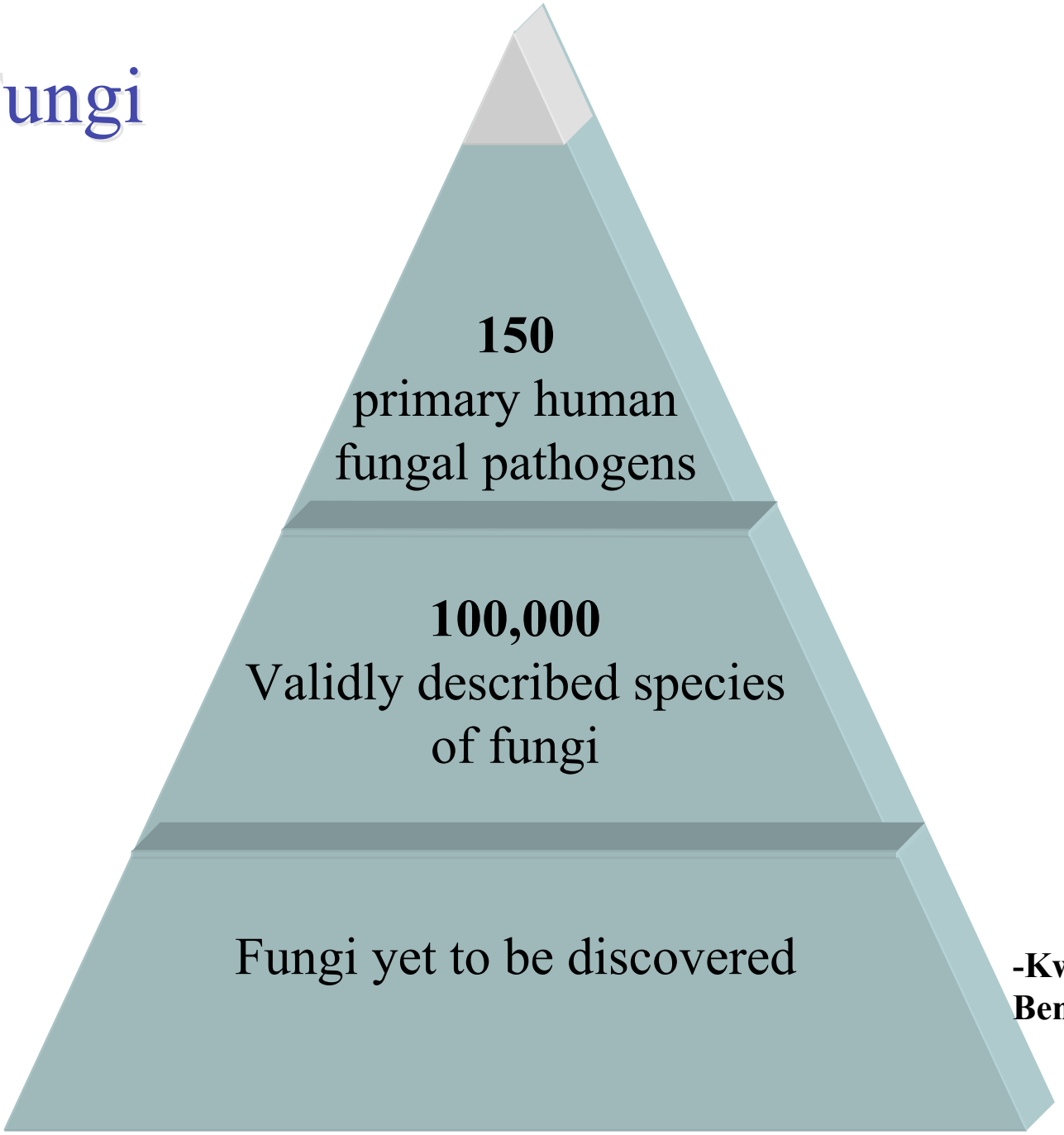

Etiology of Fungal Infection in Cancer Patients
Other (21%)
Candida spp (48%)
Aspergillus spp (31%)
Blastomyces
Histoplasma
Cryptococcus
Fusarium
Alternaria
Acremonium
Mucor
Trichosporon
Penicillium
Saccharomyces
Chrysosporium
Curvularia
Hansenula
Malassezia
Phialophora
Rhodotorula
Scopulariopsis
Geotrichum
Cunninghamella
Bipolaris

The Fungi



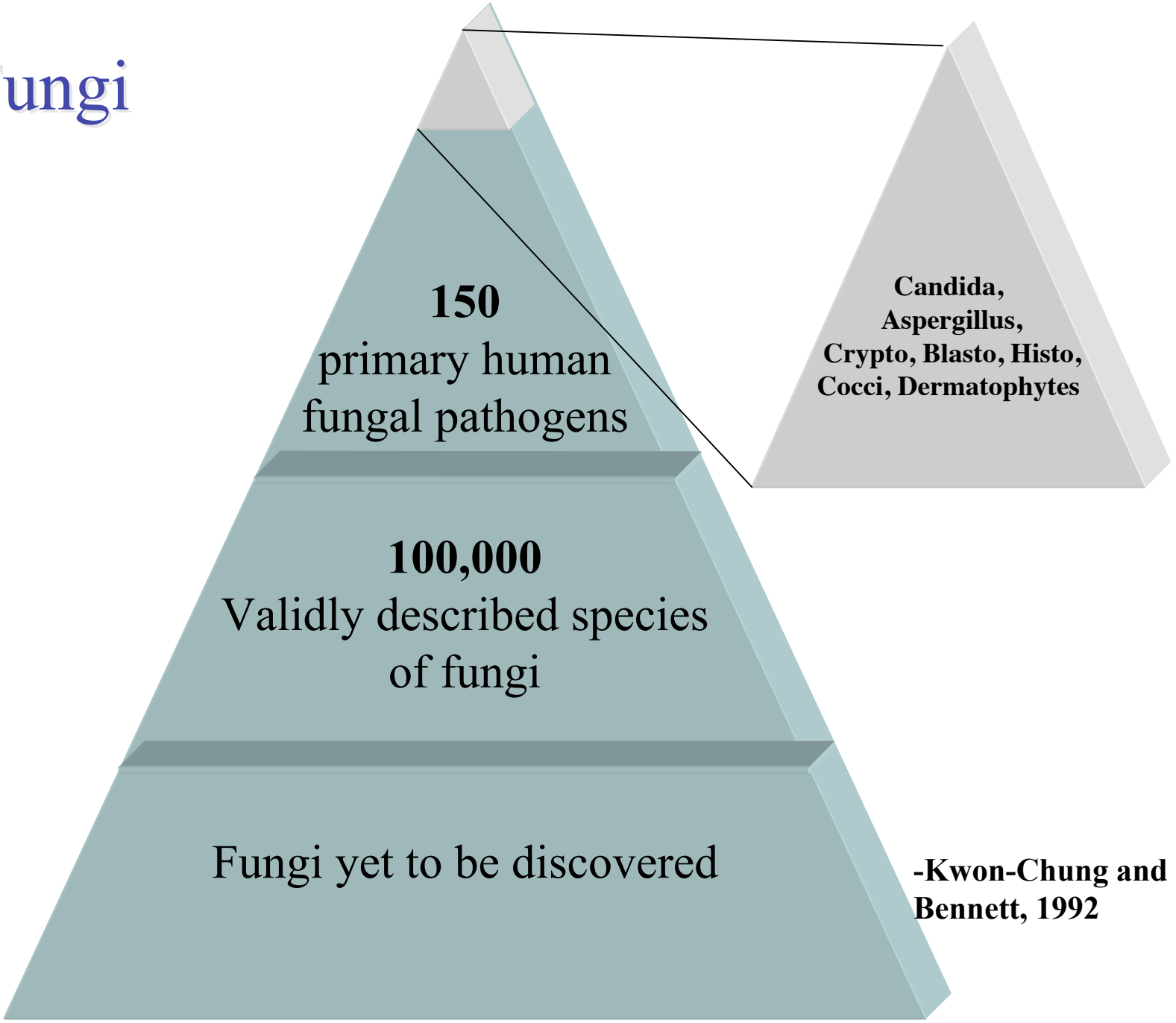
-Kwon-Chung and Bennett, 1992

The Fungi



-Kwon-Chung and Bennett, 1992

The Fungi



-Kwon-Chung and Bennett, 1992

Recent events in fungal diseases

Problems of today:

a. Growing population of immunocompromised

i. Modern medical practices: transplantations, indwelling catheters, surgeries, anti-cancer therapies, broad-spectrum antibacterials, immunosuppressants; mycoses: especially candidiasis and aspergillosis

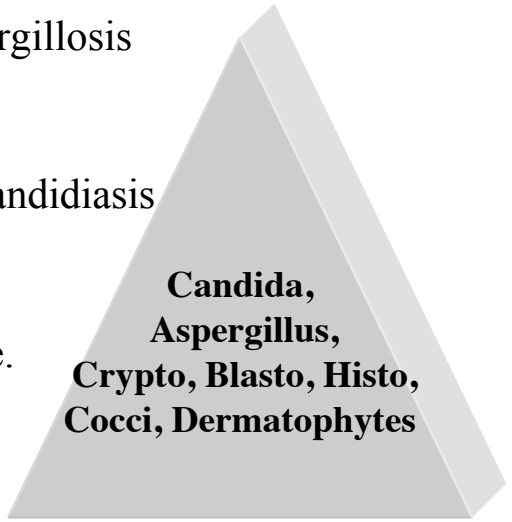
ii. Natural diseases: AIDS; mycoses: especially candidiasis and cryptococcosis

iii. Mean age of population is increasing; mycoses: especially candidiasis

b. Special problems associated with immunocompromised.

i. Mycoses often are more severe, difficult to treat and diagnose.

ii. Number of disease-causing fungi has increased.



c. Mobile population.

i. People commonly travel through areas of endemic mycoses, which presents diagnostic challenges.

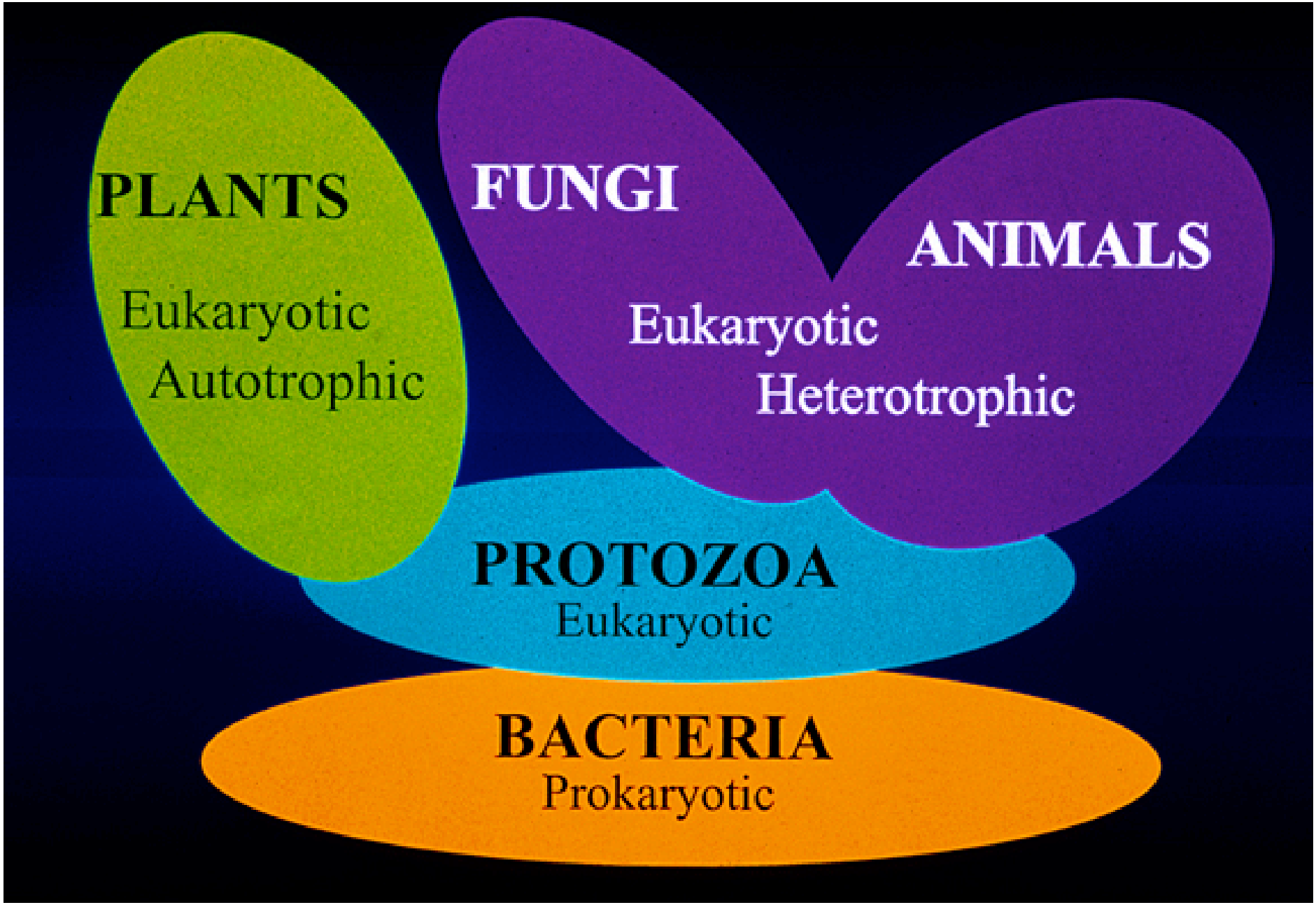
Advances in research:

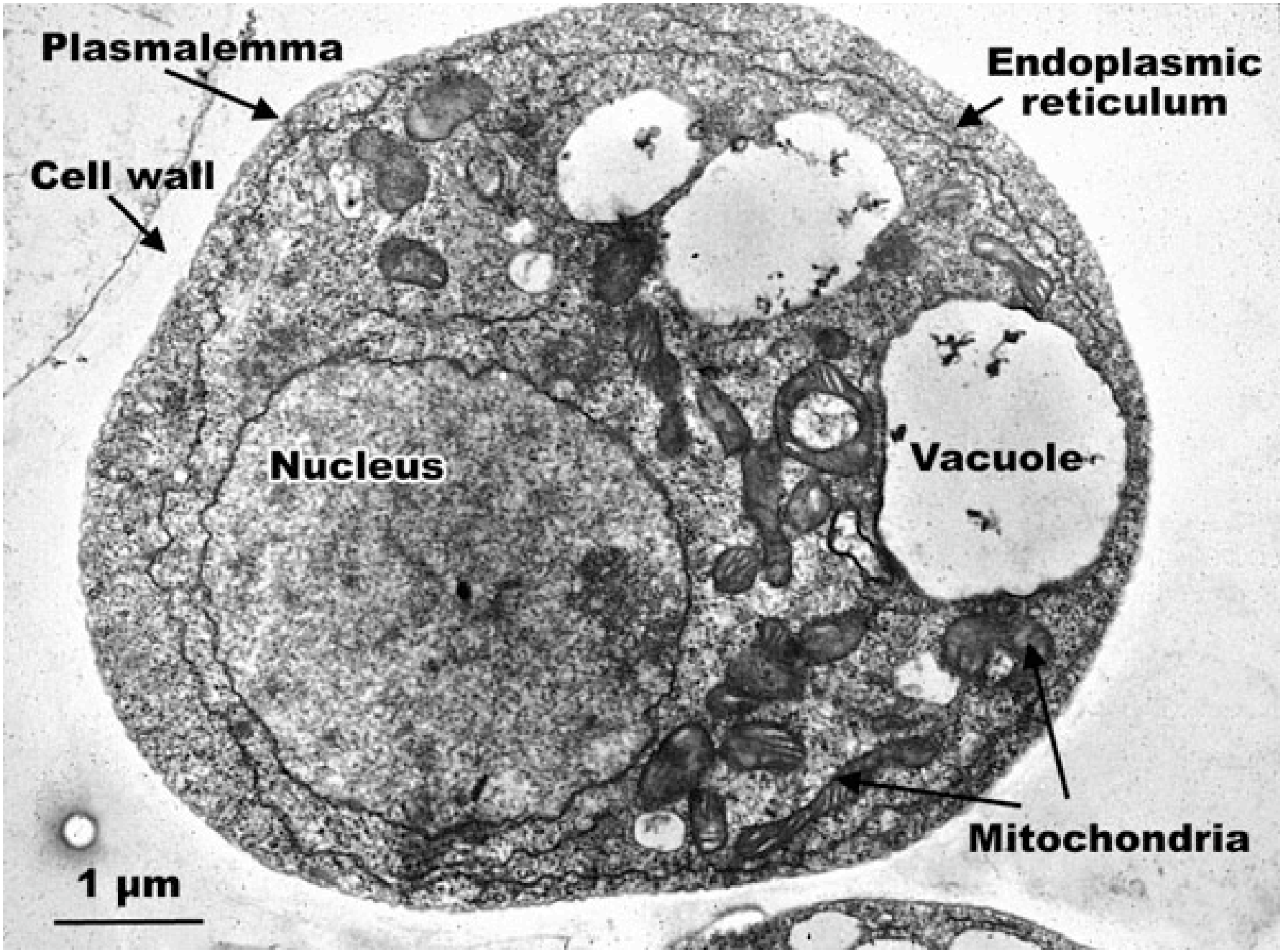
a. New antifungal agents and treatment options

b. Tremendous increase in understanding of molecular basis of pathogenesis

Lecture outline

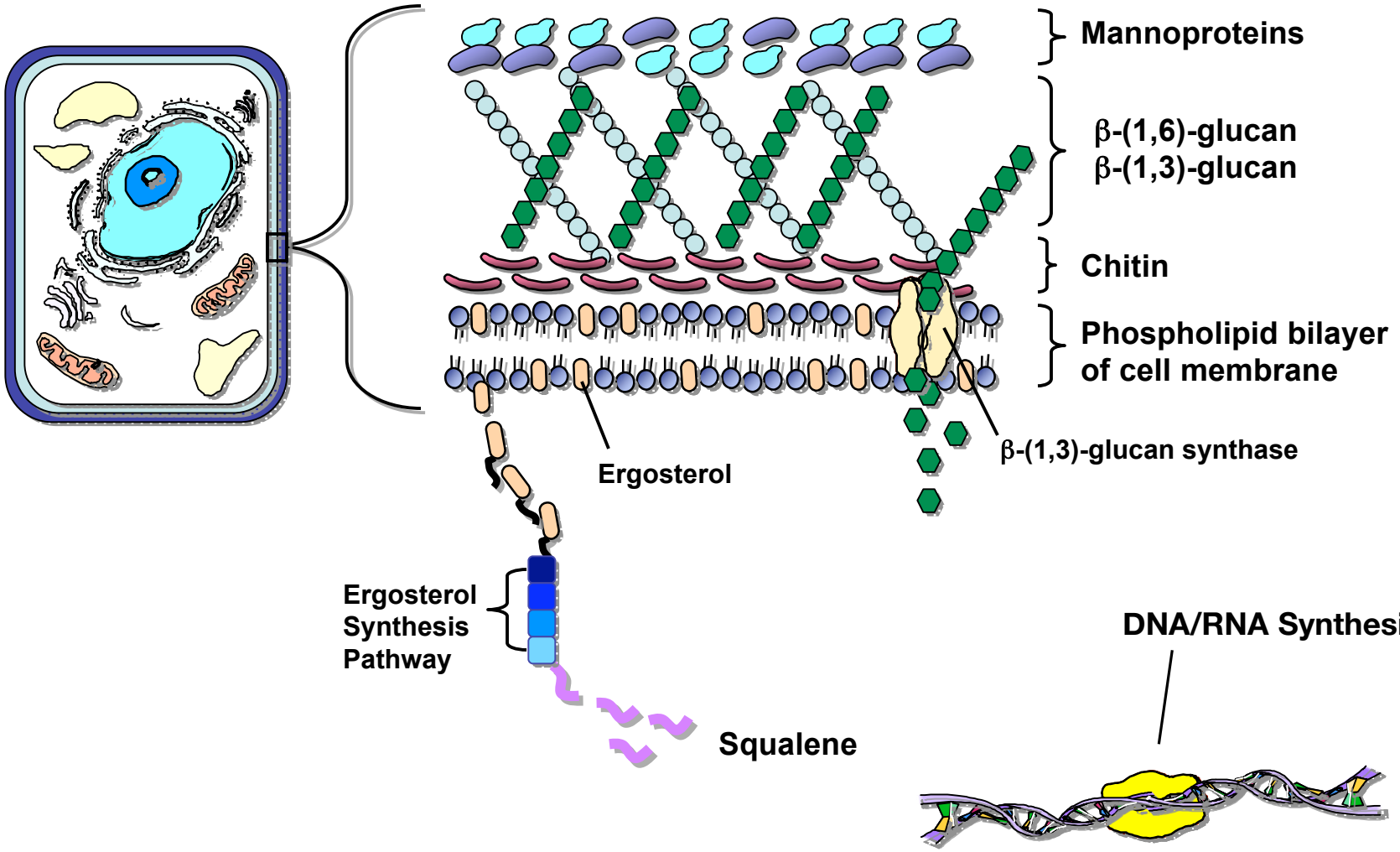
- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary


PLANTS
Eukaryotic
Autotrophic
FUNGI
ANIMALS
Eukaryotic
Heterotrophic
PROTOZOA
Eukaryotic
BACTERIA
Prokaryotic


Plasmalemma
Endoplasmic reticulum
Cell wall
Nucleus
Vacuole
Mitochondria
1 µm

Fungal cell

Cell membrane and cell wall



ANTIFUNGAL DRUGS
targets

- **Membrane disrupting agents**
  Amphotericin B, nystatin
- **Ergosterol synthesis inhibitors**
  Azoles, allylamines, morpholine
- **Nucleic acid inhibitor**
  Flucytosine
- **Anti-mitotic (spindle disruption)**
  Griseofulvin
- **Glucan synthesis inhibitors**
  Echinocandins
- **Chitin synthesis inhibitor**
  Nikkomycin
- **Protein synthesis inhibitors**
  Sordarins, azasordarins

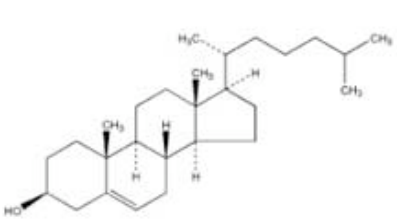
Lecture outline

- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary

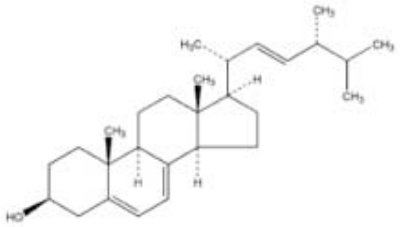
ANTIFUNGAL DRUGS classes

- **POLYENES**
  Amphotericin B, nystatin
- **AZOLES**
  Imidazoles: Ketoconazole..
  Triazoles: Fluconazole,
  itraconazole,
  voriconazole,
  posaconazole,
  ravuconazole
- **ALLYLAMINES**
  Terbinafine, butenafine
- **MORPHOLINE**
  Amorolfine
- **FLUORINATED PYRIMIDINE**
  Flucytosine
- **ECHINOCANDINS**
  Caspofungin,
  anidulafungin,
  micafungin
- **PEPTIDE-NUCLEOSIDE**
  Nikkomycin Z
- **TETRAHYDROFURAN DERIVATIVES**
  Sordarins, azasordarins
- **OTHER**
  Griseofulvin

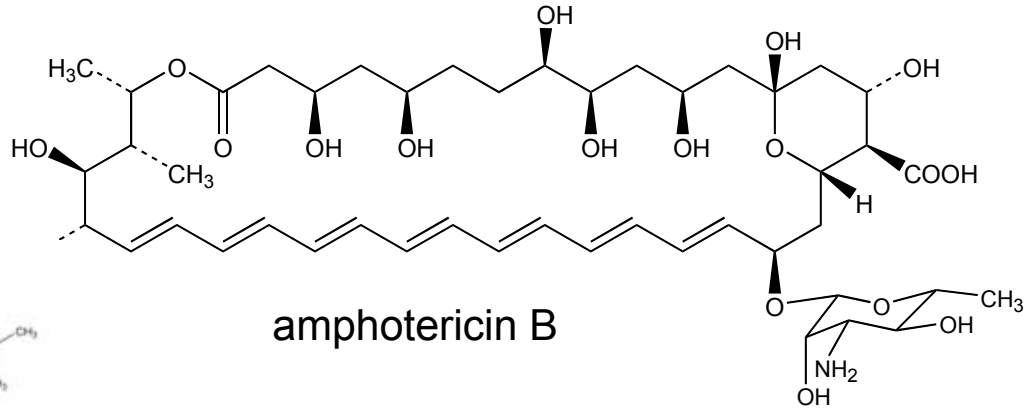
Polyenes



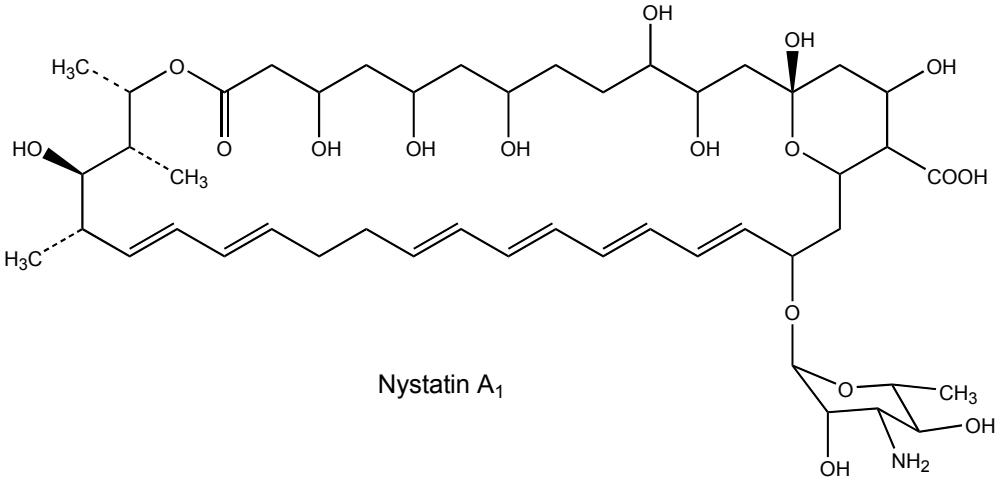
Cholesterol



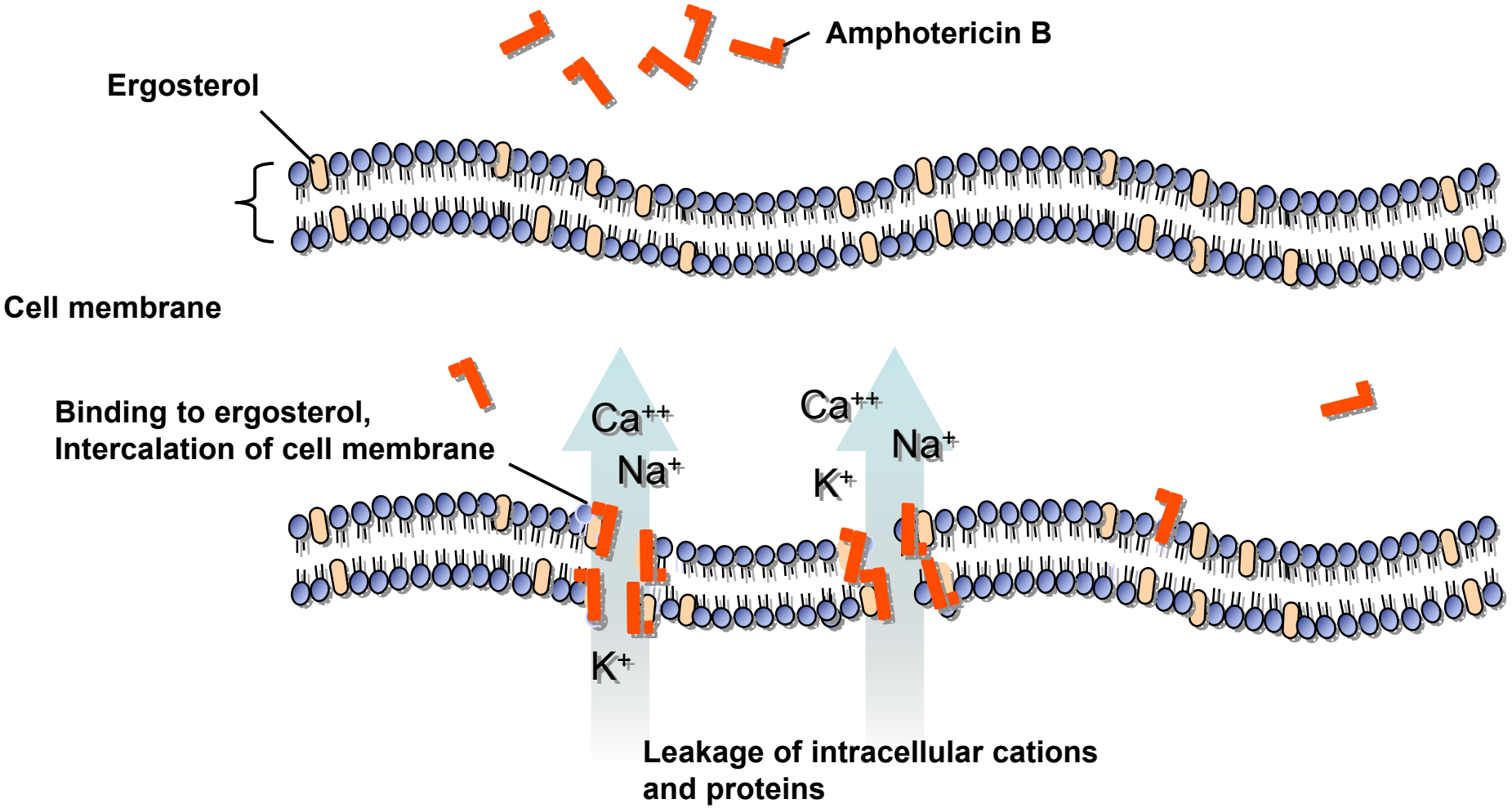
Ergosterol



amphotericin B



Nystatin A_1


Amphotericin B
Ergosterol
Cell membrane
Binding to ergosterol,
Intercalation of cell membrane
Ca++
Na+
Ca++
Na+
K+
K+
Leakage of intracellular cations
and proteins

Amphotericin B

- Mechanism: binds sterols, preferentially ergosterol, and disrupts osmotic integrity of cell membrane

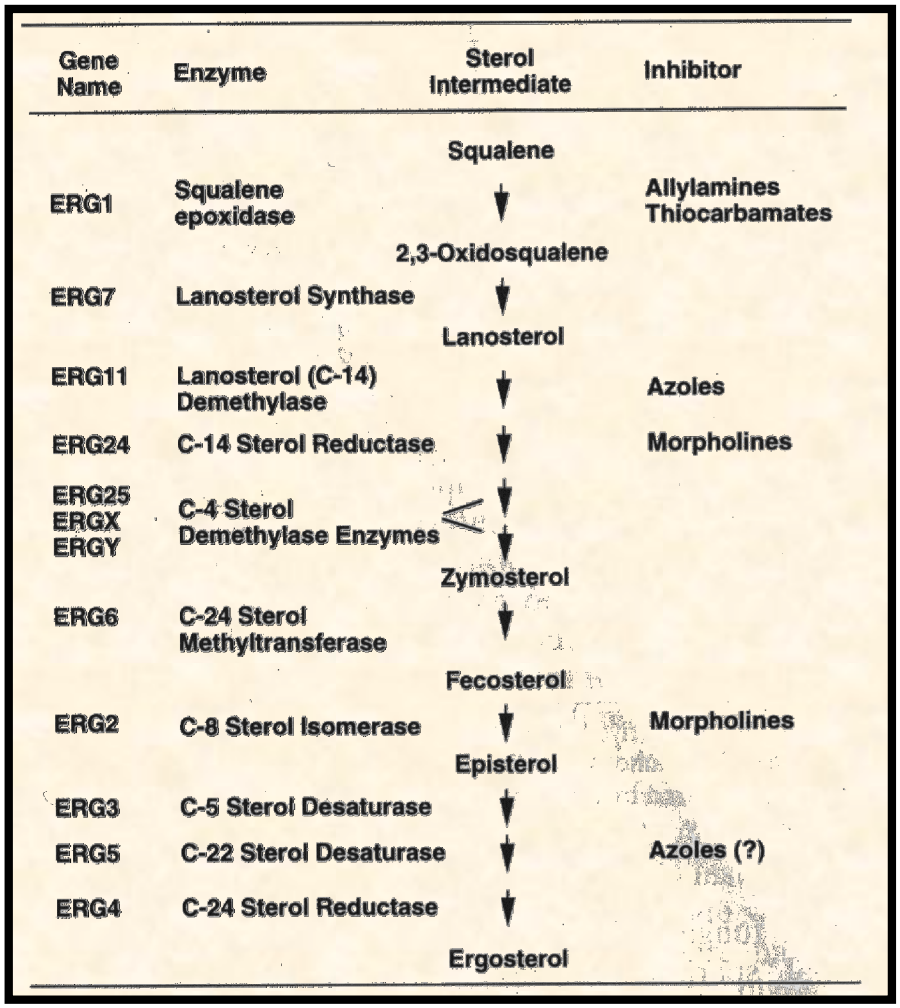
- Complications: fever, chills, myalgia, nephrotoxicity, thrombophlebitis

- Pharmacokinetics: poorly soluble in water
  - rapid uptake by RES, then redistributed
  - four formulations
    - ampho B colloidal dispersion (ABCD; Amphotec)
    - amphotericin B lipid complex (ABLC; Abelcet)
    - liposomal amphotericin B (L-AMB; Ambisome)
    - oral amphotericin B (poor absorption)

- Indications: broad range of activity, ABCD is mainstay of antifungal therapy

Azoles, allylamines & morpholines

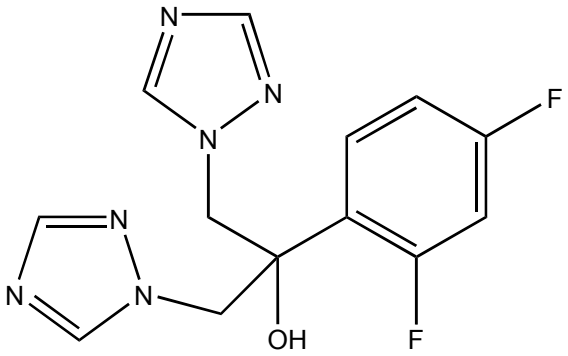
ergosterol synthesis inhibitors



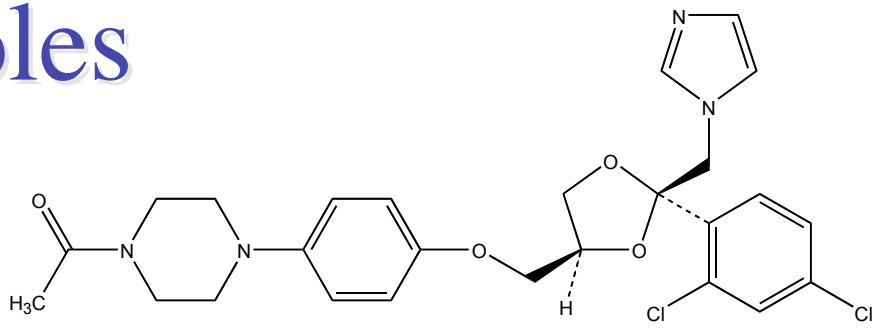
Gene Name	Enzyme	Sterol Intermediate	Inhibitor
		Squalene	
ERG1	Squalene epoxidase	↓	Allylamines Thiocarbamates
		2,3-Oxidosqualene	
ERG7	Lanosterol Synthase	↓	
		Lanosterol	
ERG11	Lanosterol (C-14) Demethylase	↓	Azoles
ERG24	C-14 Sterol Reductase	↓	Morpholines
ERG25 ERGX ERGY	C-4 Sterol Demethylase Enzymes	↓	
		Zymosterol	
ERG6	C-24 Sterol Methyltransferase	↓	
		Fecosterol	
ERG2	C-8 Sterol Isomerase	↓	Morpholines
		Episterol	
ERG3	C-5 Sterol Desaturase	↓	
ERG5	C-22 Sterol Desaturase	↓	Azoles (?)
ERG4	C-24 Sterol Reductase	↓	
		Ergosterol	

Clin Microbiol Rev
1998; 11: 382

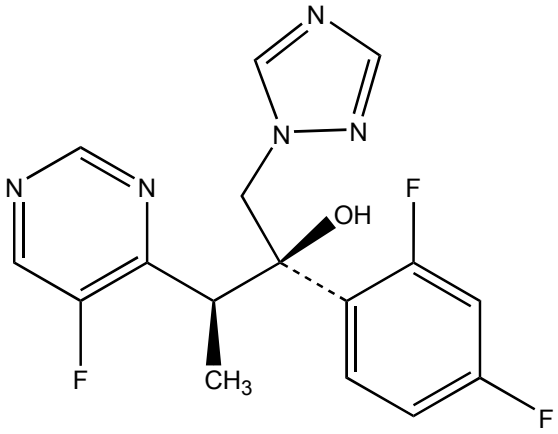
Azoles



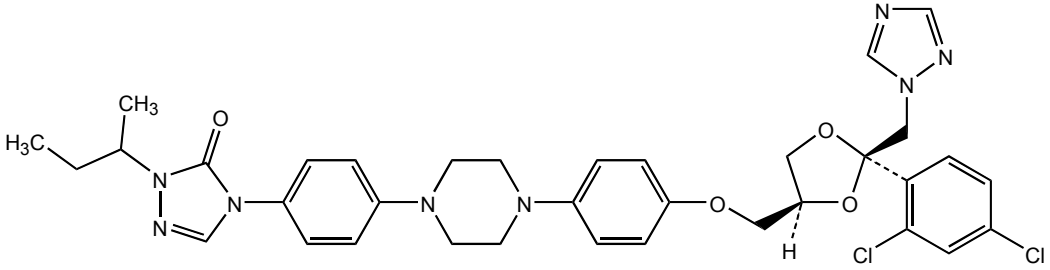
fluconazole



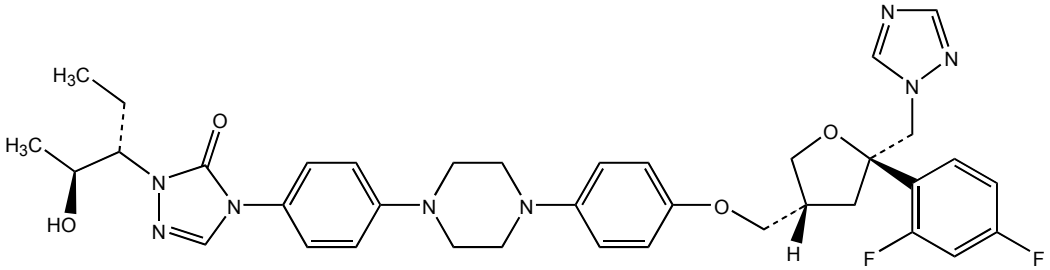
ketoconazole



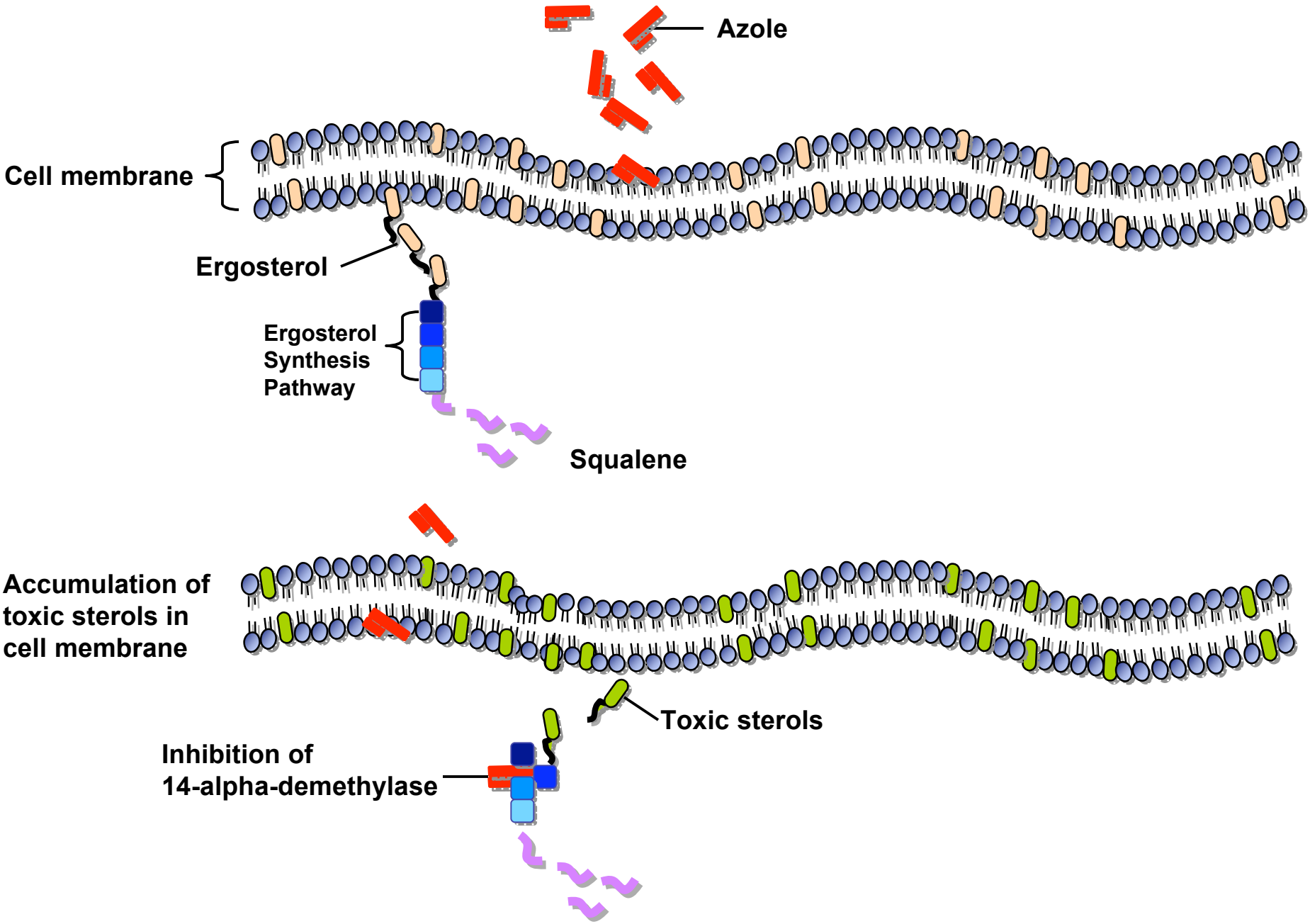
voriconazole



itraconazole



posaconazole


Azole
Cell membrane
Ergosterol
Ergosterol
Synthesis
Pathway
Squalene
Accumulation of
toxic sterols in
cell membrane
Toxic sterols
Inhibition of
14-alpha-demethylase

Azoles

- Mechanism: block ergosterol synthesis via inhibition of cytochrome P450 dependent 14α-demethylase (Erg11)

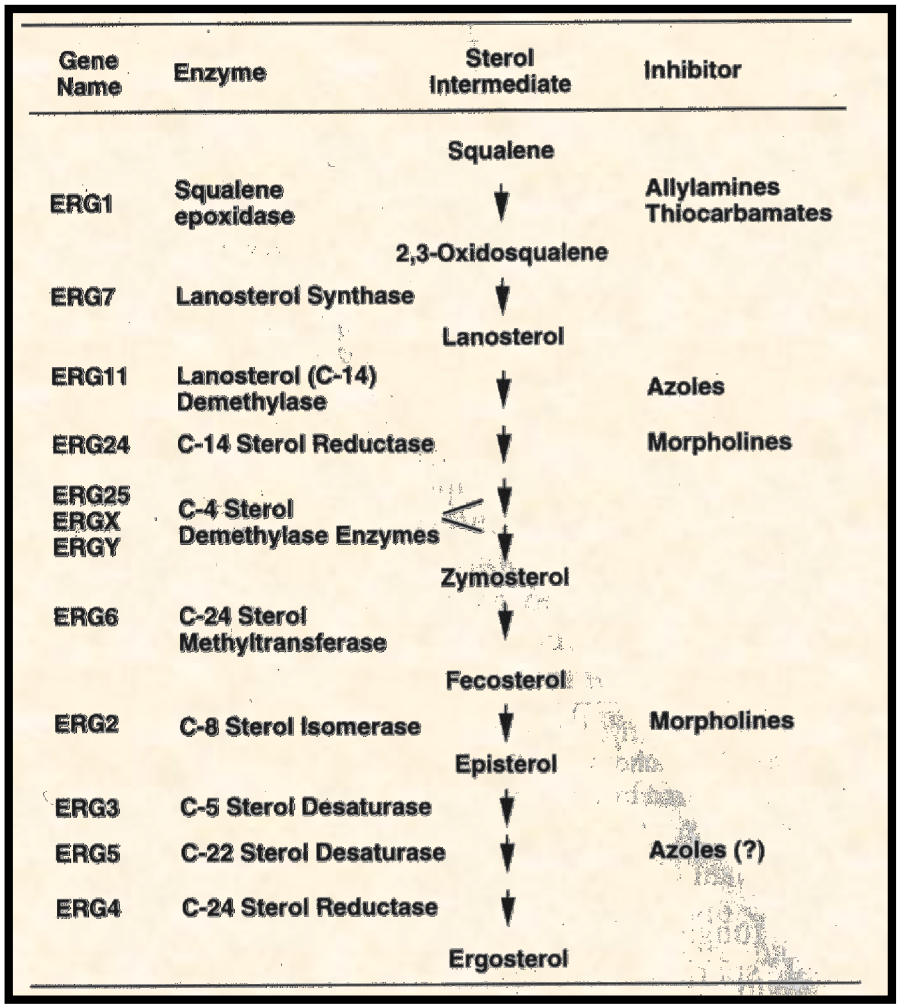
- Complications: well-tolerated, hepatotoxicity, hypertension, headache, visual disturbances, resistance

- Formulations: poorly soluble in water, fungistatic
  - Fluconazole (Diflucan)
  - Voriconazole (Vfend)
  - Ravuconazole
  - Itraconazole (Sporanox)
  - Posaconazole
  - Ketoconazole (Nizoral)

- Indications: *Candida*, *Cryptococcus*, *Coccidioides*, *Histoplasma*, *Blastomyces*, some *Aspergillus* spp.

Azoles, allylamines & morpholines

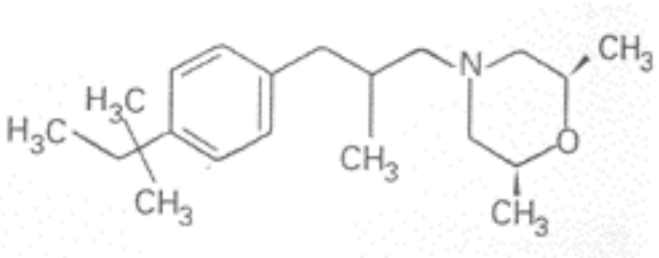
ergosterol synthesis inhibitors



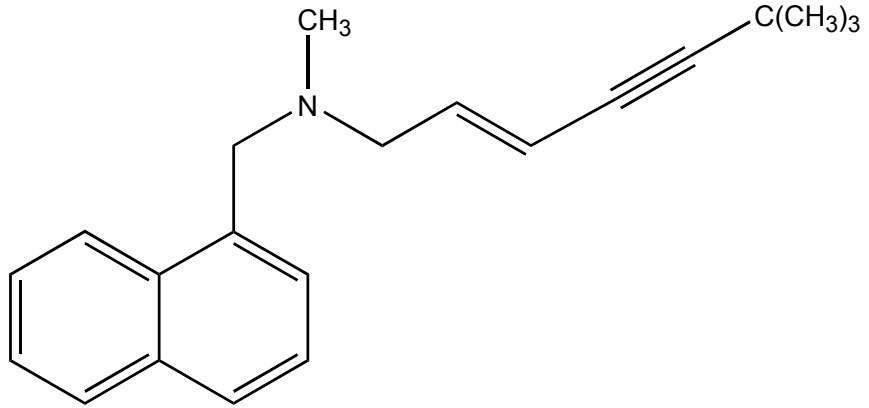
Gene Name	Enzyme	Sterol Intermediate	Inhibitor
		Squalene	
ERG1	Squalene epoxidase	↓	Allylamines Thiocarbamates
		2,3-Oxidosqualene	
ERG7	Lanosterol Synthase	↓	
		Lanosterol	
ERG11	Lanosterol (C-14) Demethylase	↓	Azoles
ERG24	C-14 Sterol Reductase	↓	Morpholines
ERG25 ERGX ERGY	C-4 Sterol Demethylase Enzymes	↓	
		Zymosterol	
ERG6	C-24 Sterol Methyltransferase	↓	
		Fecosterol	
ERG2	C-8 Sterol Isomerase	↓	Morpholines
		Episterol	
ERG3	C-5 Sterol Desaturase	↓	
ERG5	C-22 Sterol Desaturase	↓	Azoles (?)
ERG4	C-24 Sterol Reductase	↓	
		Ergosterol	

Clin Microbiol Rev
1998; 11: 382

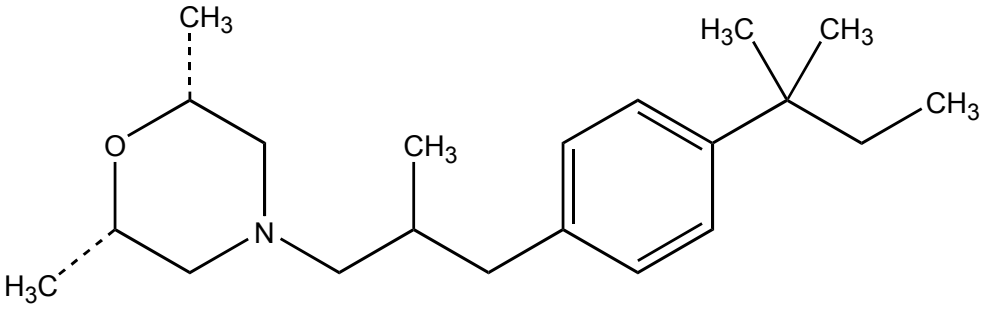
Allylamines, morpholines



Amorolfine



terbinafine



butenafine

Allylamines, morpholines

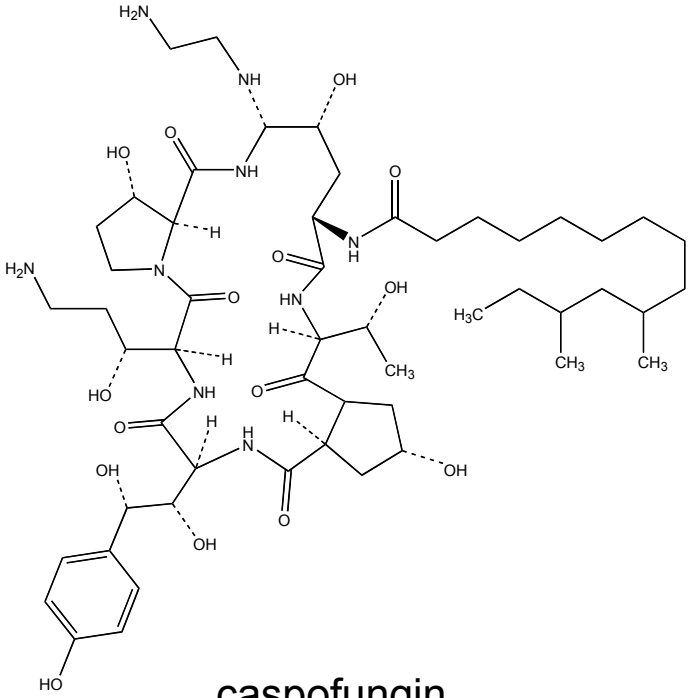
- Mechanism: block ergosterol synthesis via inhibition of squalene epoxidase (allylamines), sterol reductase and isomerase activity (morpholines)

- Complications: mild gastrointestinal and skin reactions

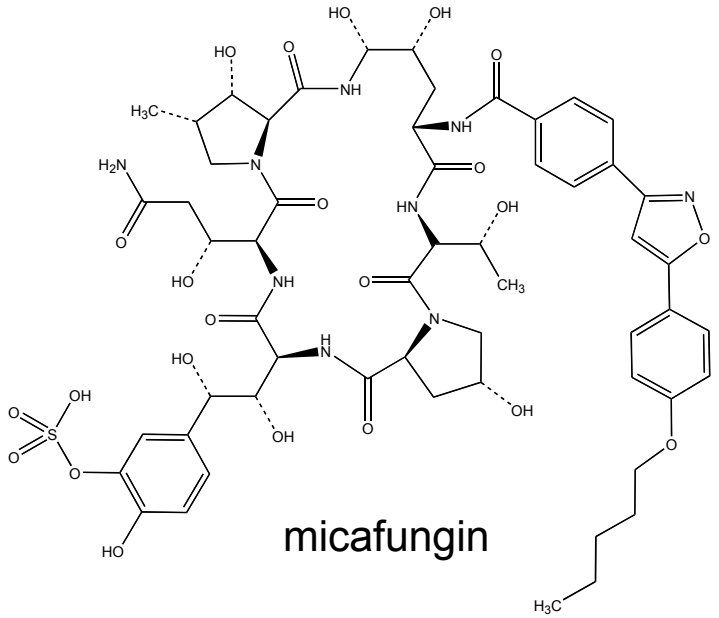
- Formulations: poorly soluble in water, oral and topical, fungicidal
  - Terbinafine (Lamisil)
  - Amorolfine (Loceryl)
  - Butenafine (Mentax)

- Indications: dermatophytes, *Candida* (Mentax)

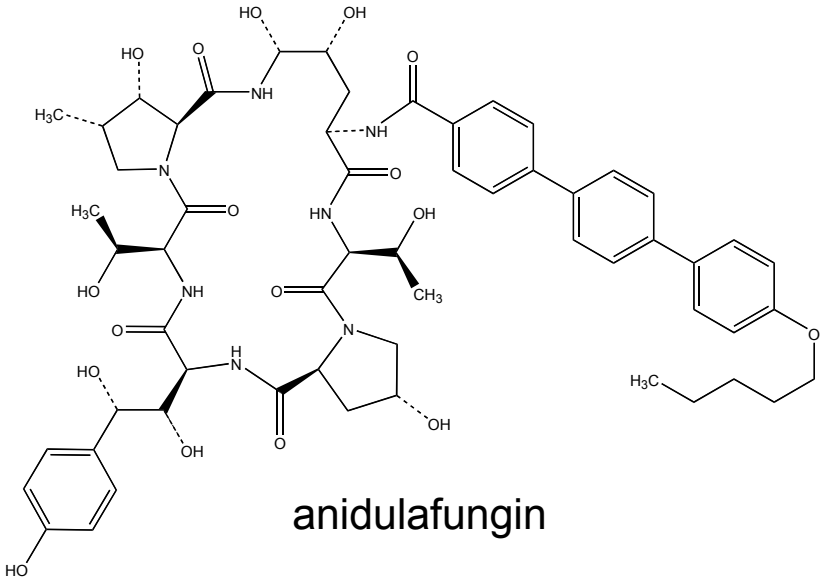
Echinocandins



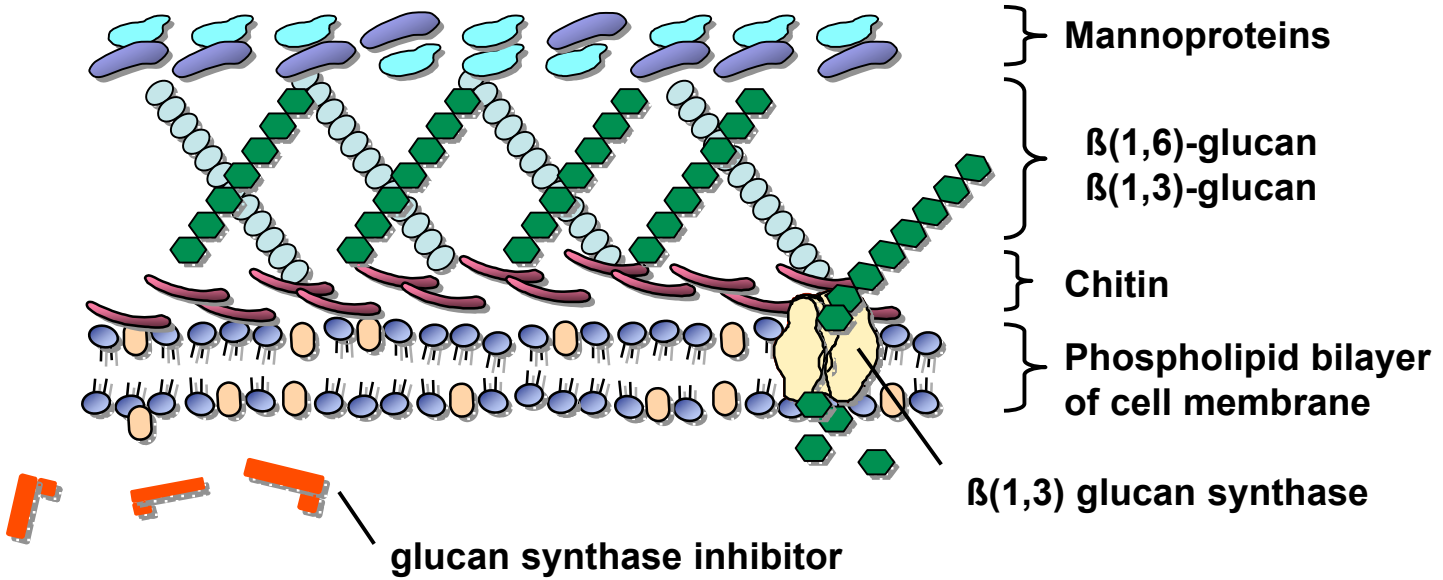
caspofungin

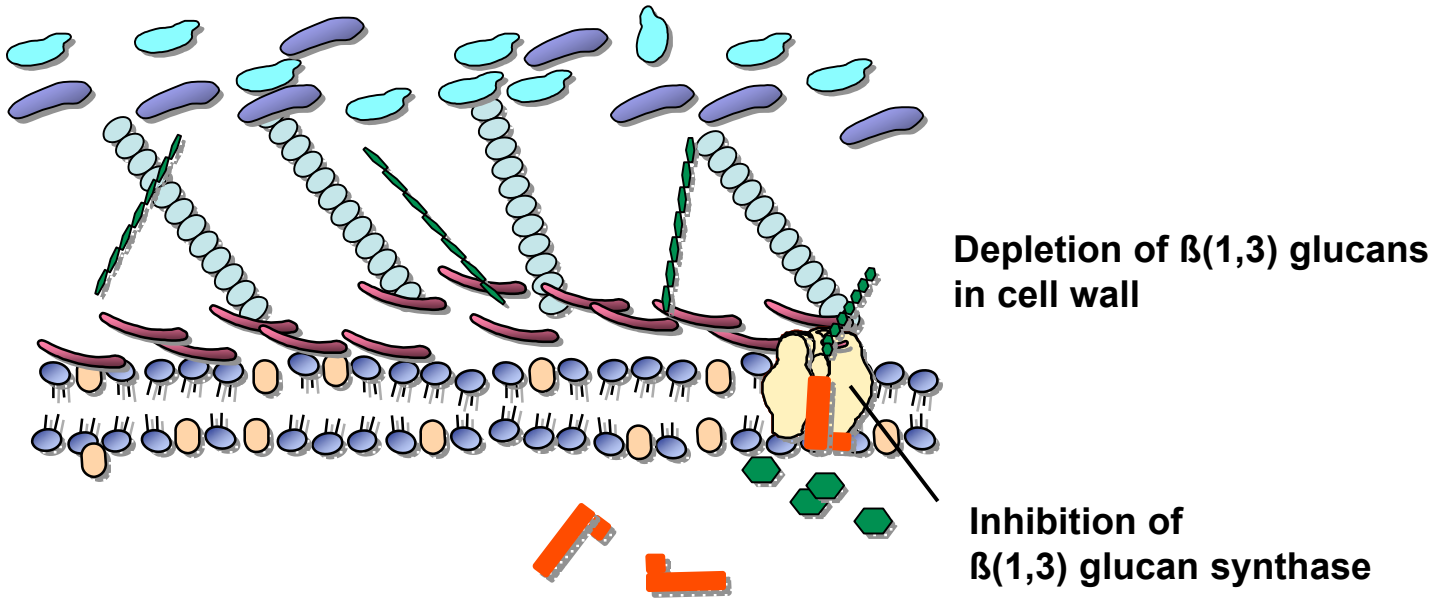


micafungin



anidulafungin


Mannoproteins
ß(1,6)-glucan
ß(1,3)-glucan
Chitin
Phospholipid bilayer
of cell membrane
ß(1,3) glucan synthase
glucan synthase inhibitor


Depletion of ß(1,3) glucans
in cell wall
Inhibition of
ß(1,3) glucan synthase

Echinocandins

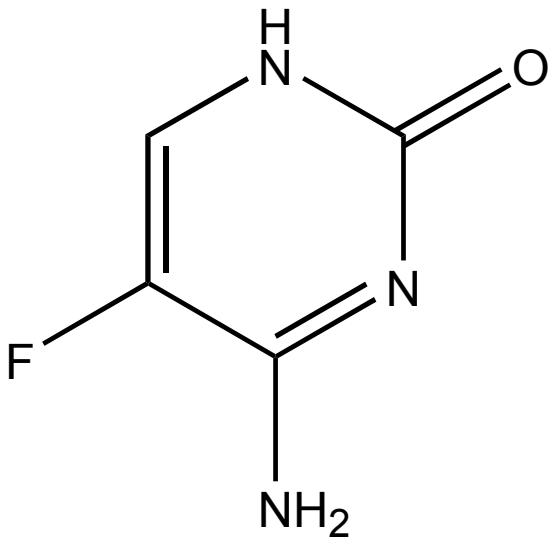
- Mechanism: block cell wall synthesis via β-1,3 glucan synthesis inhibition

- Complications: well-tolerated, histamine release, no activity against *Cryptococcus*, *Fusarium* spp.

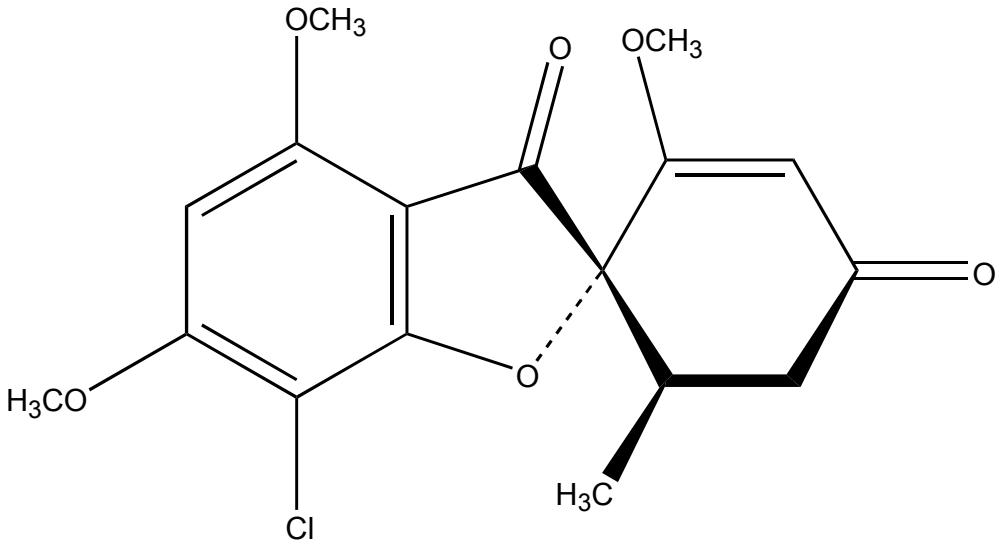
- Formulations: poorly soluble in water, fungicidal
  - Caspofungin (Cancidas)
  - Micafungin
  - Anidulafungin (Eraxis)

- Indications: *Candida*, *Aspergillus* spp.

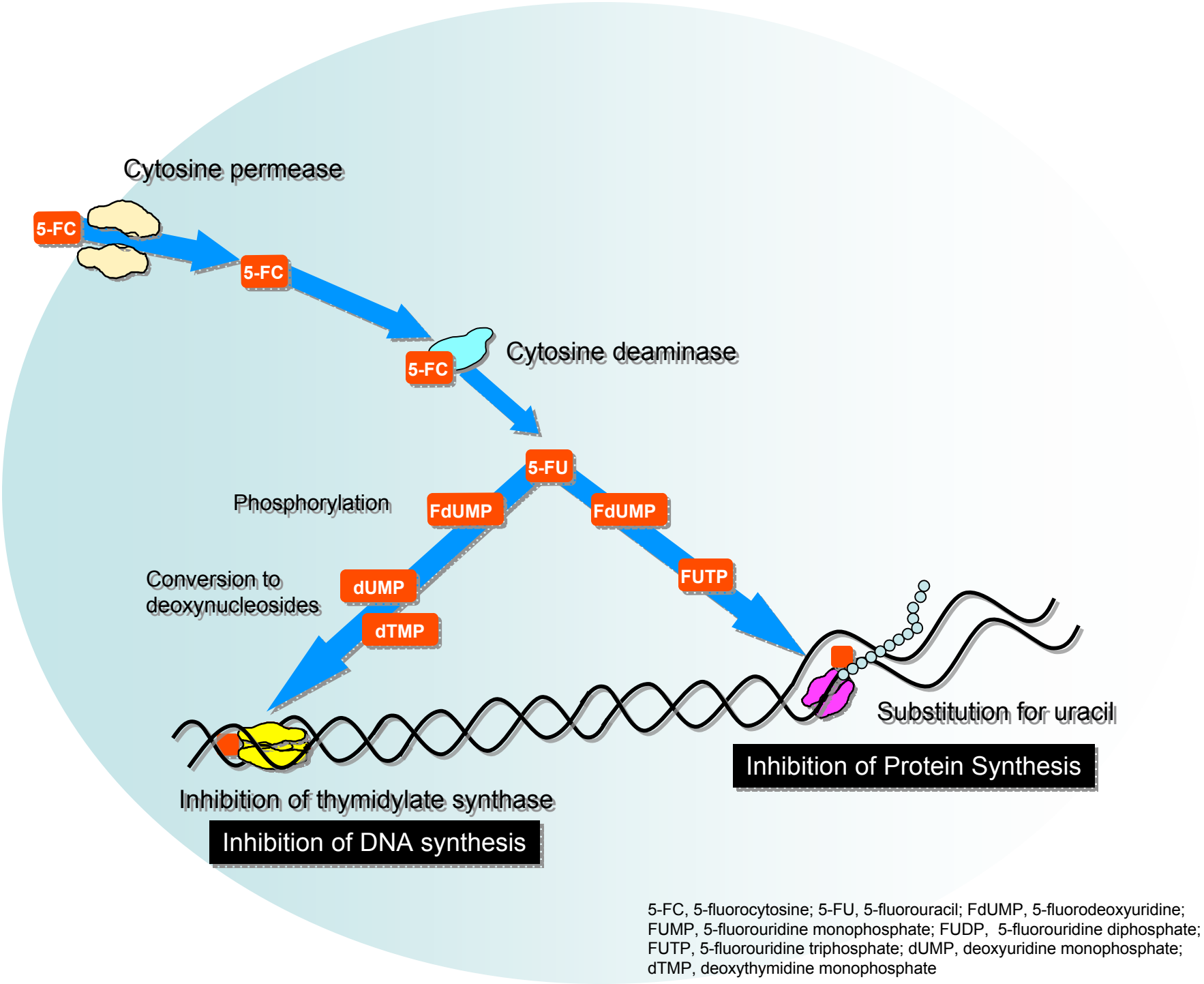
Antimetabolites



flucytosine



griseofulvin



5-FC, 5-fluorocytosine; 5-FU, 5-fluorouracil; FdUMP, 5-fluorodeoxyuridine; FUMP, 5-fluorouridine monophosphate; FUDP, 5-fluorouridine diphosphate; FUTP, 5-fluorouridine triphosphate; dUMP, deoxyuridine monophosphate; dTMP, deoxythymidine monophosphate

Antimetabolites

- Mechanism: block fungal DNA and protein synthesis (Flucytosine), fungal mitosis (Griseofulvin)

- Complications: GI intolerance, bone marrow suppression, hepatotoxicity, headache, hallucinations, sedation, nausea

- Formulations: poorly soluble in water
  - Flucytosine (Ancobon)
  - Griseofulvin (Grifulvin V, Fulvicin U/F, Grisactin, Peninol)

- Indications: (Flucytosine): for resistant *Candida*, *Aspergillus* spp. and in combination with Ampho B for *Cryptococcus*; (Griseofulvin): dermatophytes

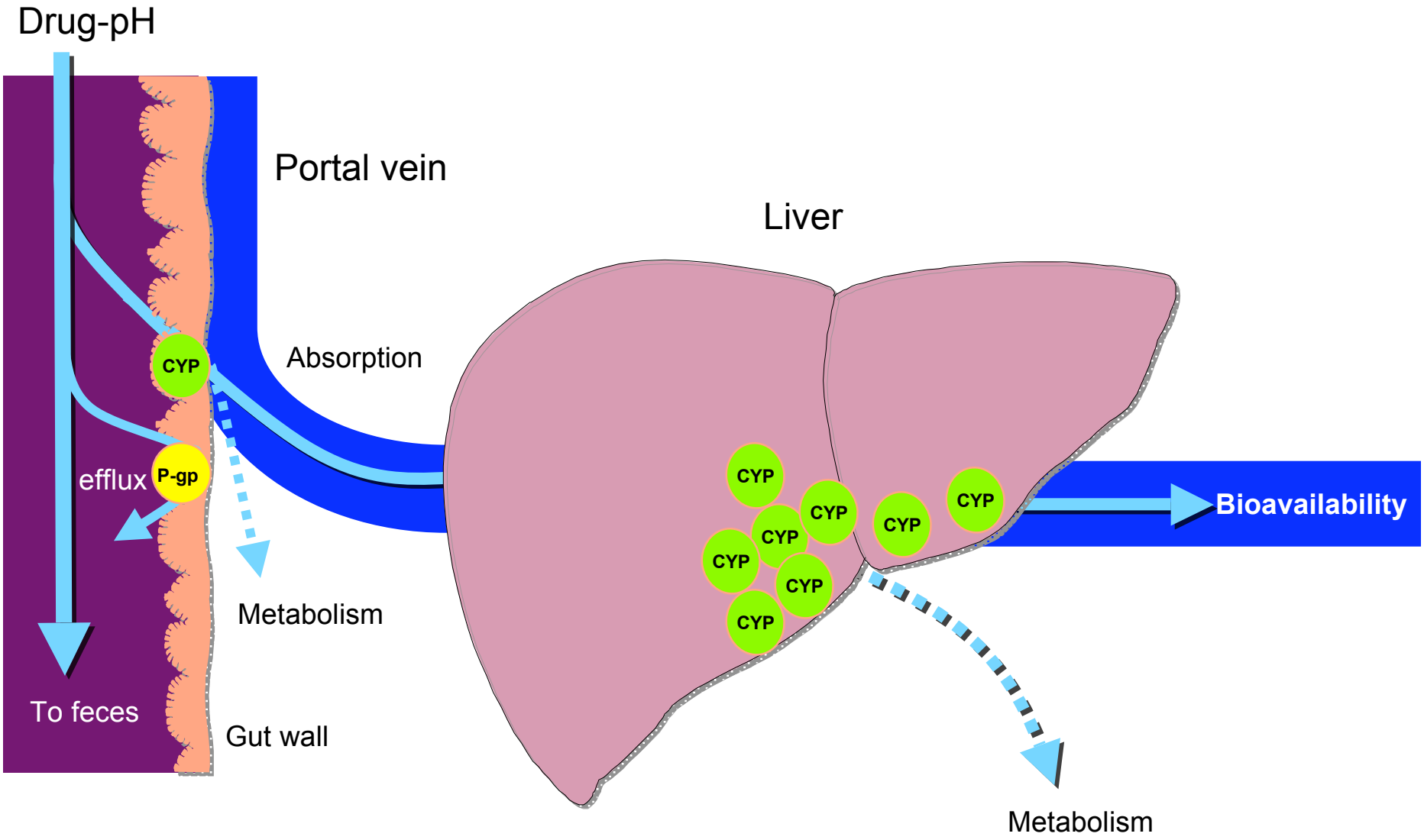
Lecture outline

- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary

Antifungal drug interactions

- Pharmacokinetic interactions: changes in absorption or elimination of interacting drug and the antifungal
  - Interactions of drug absorption
    - Ketoconazole, itraconazole require low pH for absorption (avoid antacids, vitamin supplements)
    - Pre-systemic clearance via membrane transporters (P-gp) & metabolic enzymes. Azoles can be both substrates and inhibitors of P-gp
  - Interactions of drug metabolism
    - Oxidation, reduction, hydrolysis, conjugation of lipophilic compounds
  - Interactions with cytochrome P450
    - Azoles are metabolized by CYP P450 system
    - Azoles are also reversible inhibitors of P450 enzymes
    - Co-administered metabolites are a concern

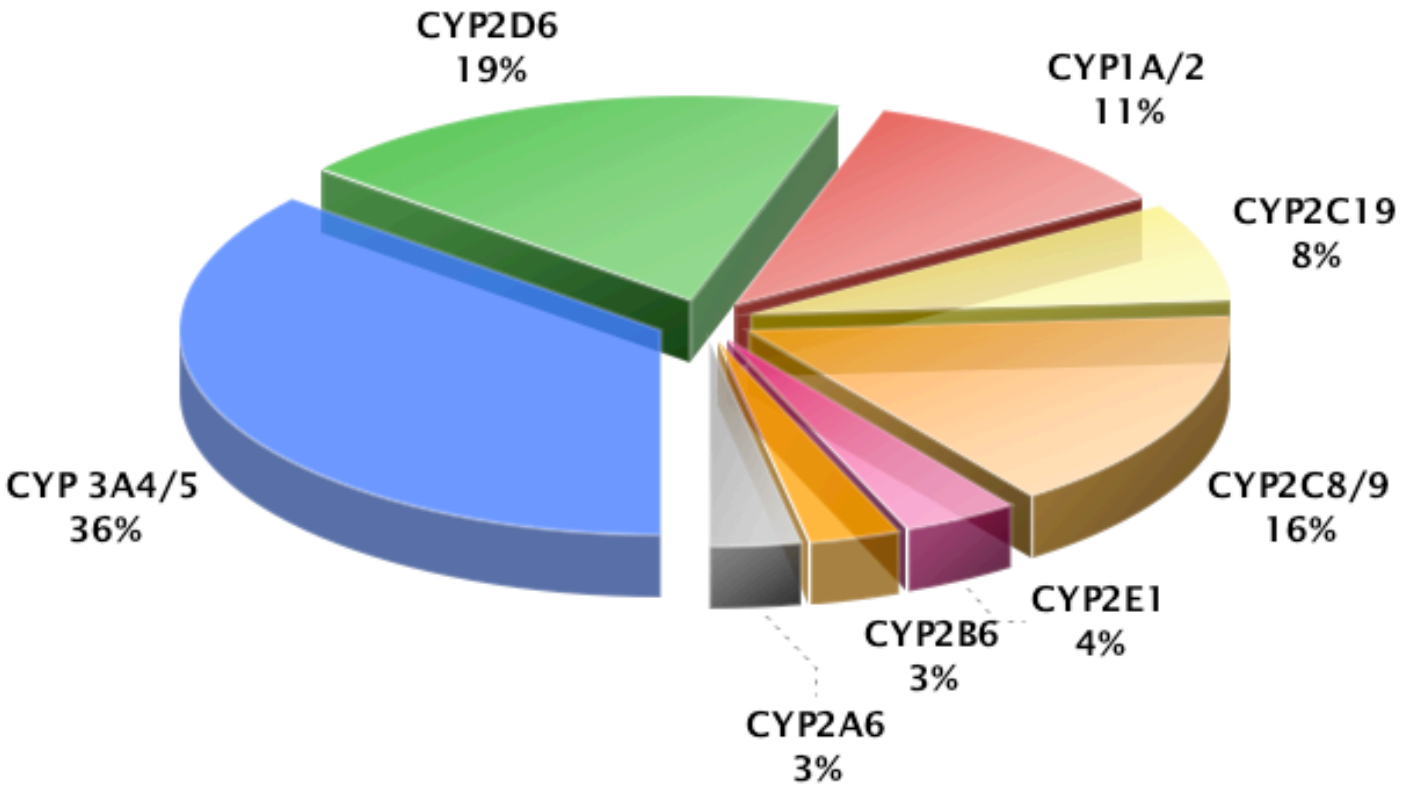
Azoles: Interactions in the GI Tract



Antifungal drug interactions

- Pharmacokinetic interactions: changes in absorption or elimination of interacting drug and the antifungal
  - Interactions of drug absorption
    - Ketoconazole, itraconazole require low pH for absorption (avoid antacids, vitamin supplements)
    - Pre-systemic clearance via membrane transporters (P-gp) & metabolic enzymes. Azoles can be both substrates and inhibitors of P-gp
  - Interactions of drug metabolism
    - Oxidation, reduction, hydrolysis, conjugation of lipophilic compounds
  - Interactions with cytochrome P450
    - Azoles are metabolized by CYP P450 system
    - Azoles are also reversible inhibitors of P450 enzymes
    - Co-administered metabolites are a concern

Proportion of Drugs Metabolized by CYP P450

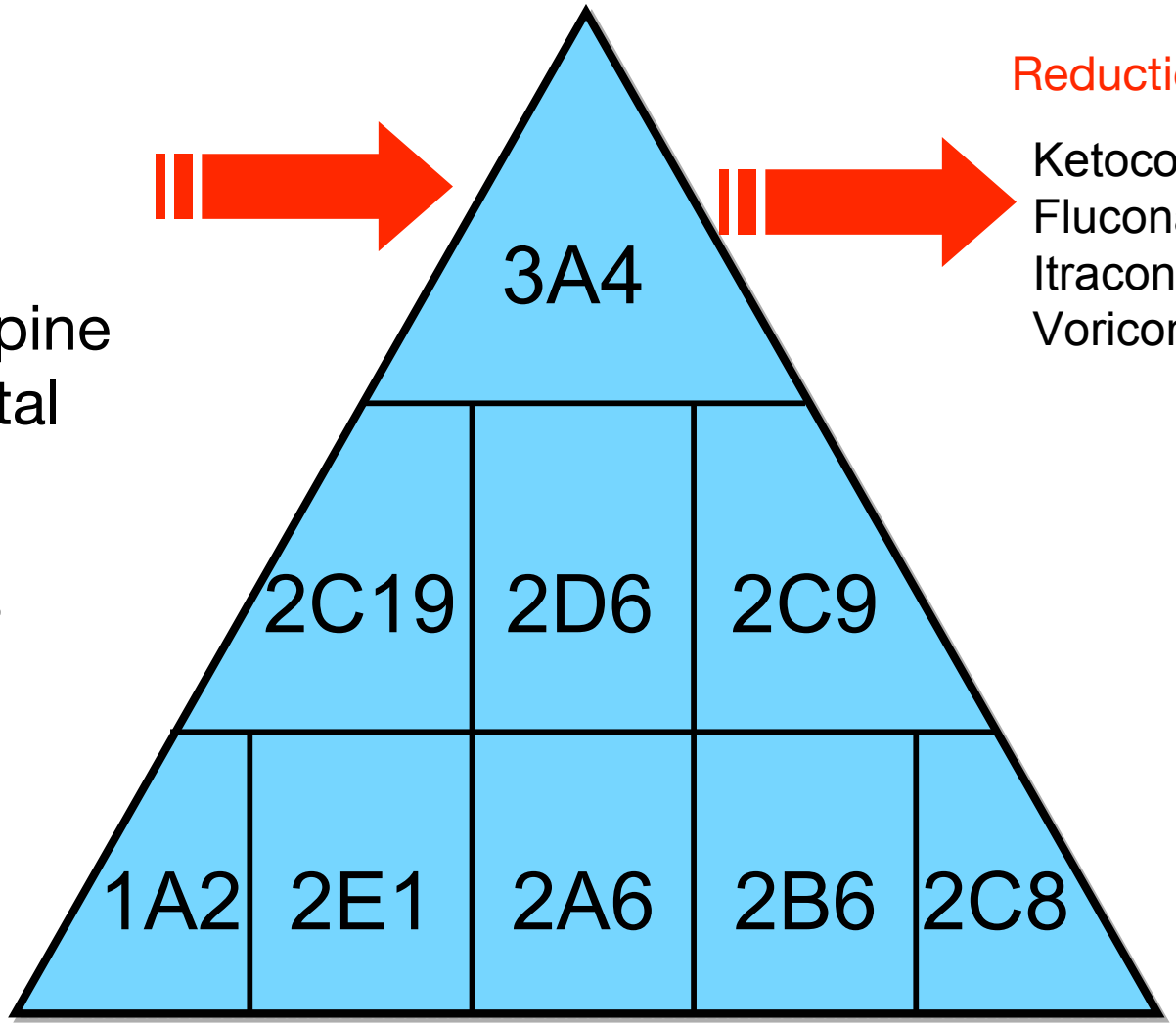


Antifungal drug interactions

- Pharmacokinetic interactions: changes in absorption or elimination of interacting drug and the antifungal
  - Interactions of drug absorption
    - Ketoconazole, itraconazole require low pH for absorption (avoid antacids, vitamin supplements)
    - Pre-systemic clearance via membrane transporters (P-gp) & metabolic enzymes. Azoles can be both substrates and inhibitors of P-gp
  - Interactions of drug metabolism
    - Oxidation, reduction, hydrolysis, conjugation of lipophilic compounds
  - Interactions with cytochrome P450
    - Azoles are metabolized by CYP P450 system
    - Azoles are also reversible inhibitors of P450 enzymes
    - Co-administered metabolites are a concern

Rifampin
Phenytoin
Carbamezepine
Phenobarbital

Ritonovir?



Reduction in levels

Ketoconazole (>90%)
Fluconazole (~ 50%)
Itraconazole (> 90%)
Voriconazole (~ 90%)

Azole Inhibition of CYP P450

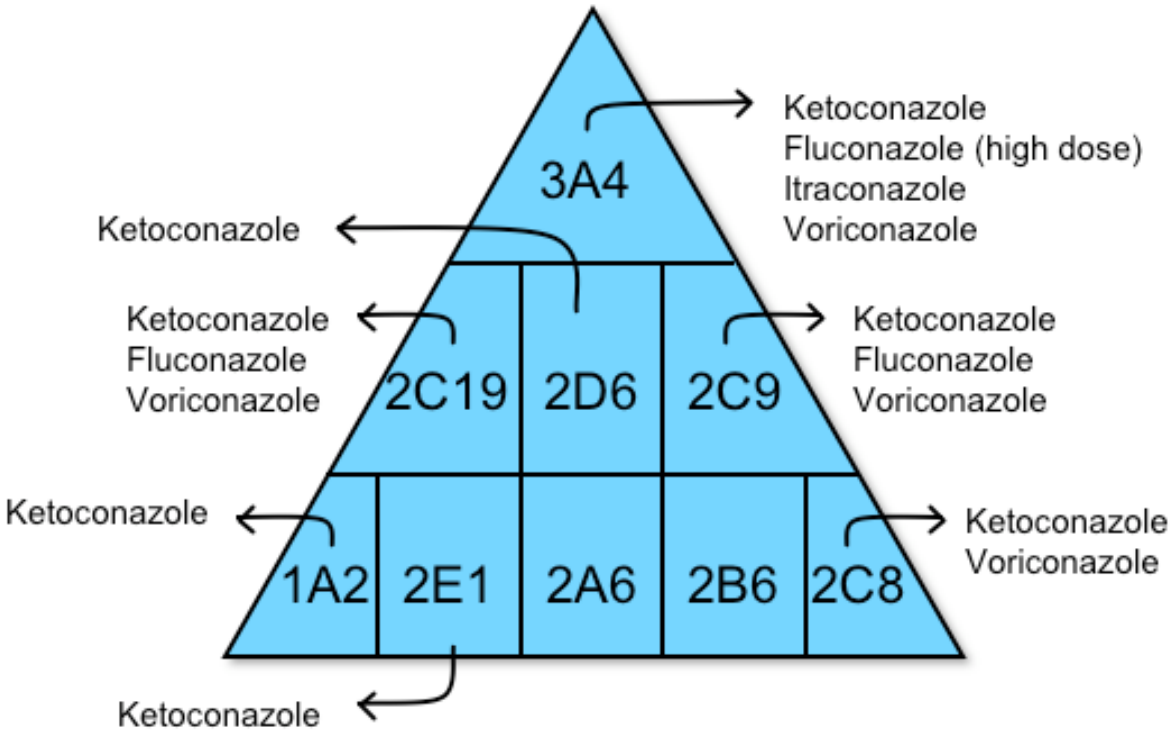


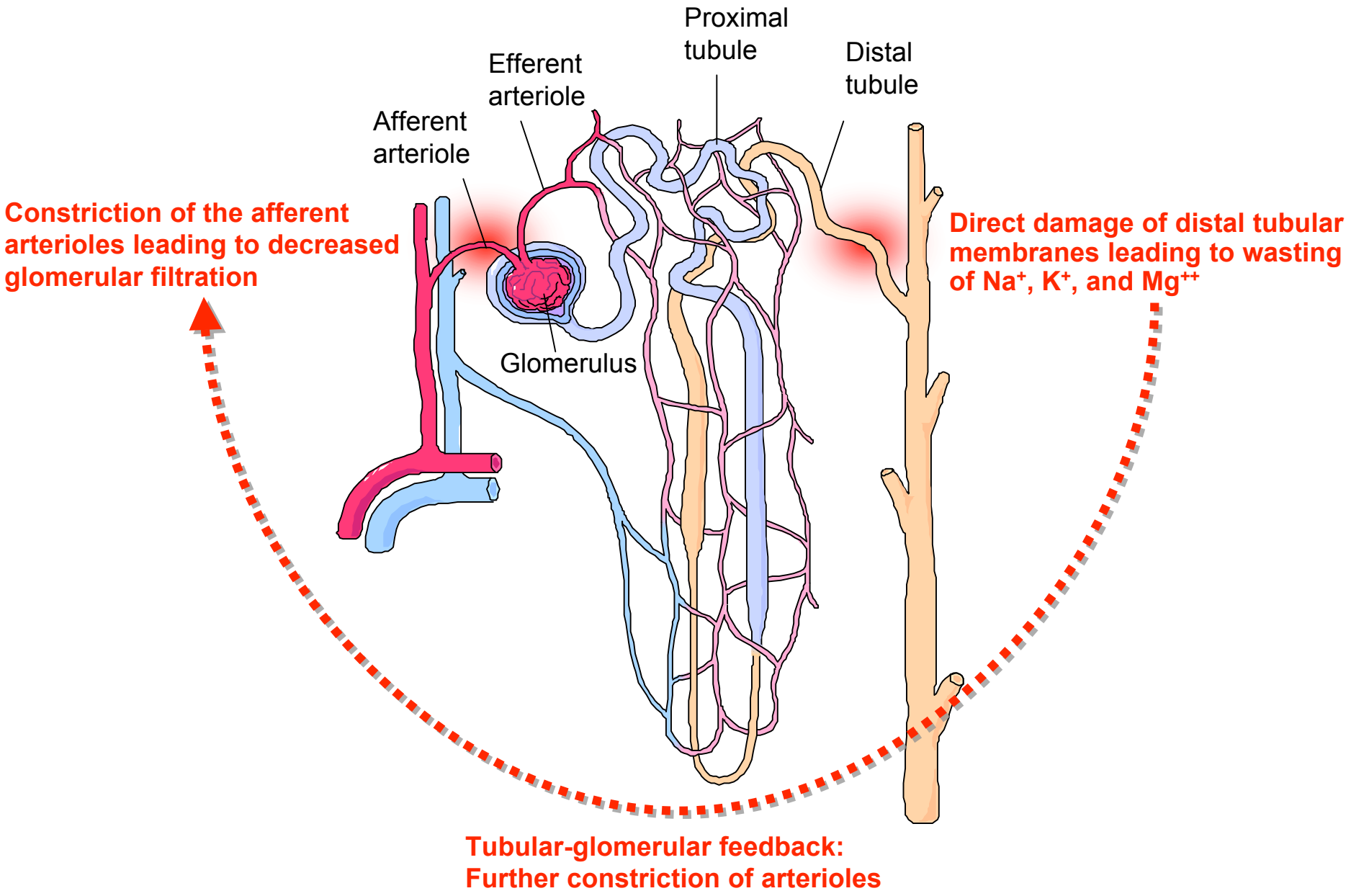
Figure concept: John Gerber, M.D. and Courtney Fletcher, Pharm.D., Univ. of Colorado
Source: AHFS Drug Facts 2003,

Increased serum concentration of co-administered drug or metabolite

- Oral hypoglycemics
- S-warfarin
- R-Wafarin
- Cyclosporin
- Tacrolimus
- Sirolimus
- Phenytoin
- Carbamezepine
- Triazolam, alprazolam, midazolam
- Diltiazem
- Lovastatin
- Isoniazid
- Rifabutin
- Quinidine
- Protease inhibitors (saquinavir, ritonavir)
- Busulfan
- Vincristine
- Cyclophosphamide
- Digoxin
- Loratidine
- and others…

Nephrotoxicity

- Primarily due to Amphotericin B
- Two mechanisms:
  - Effects of ampho B on renal blood flow and glomerular filtration
    - Constriction of afferent arterioles decreases renal blood flow and GFR
    - Subsequent increase in serum creatinine and BUN
  - Direct toxic effect on distal tubules via membrane disruption
    - Cholesterol target


Proximal tubule
Efferent arteriole
Distal tubule
Afferent arteriole
Constriction of the afferent arterioles leading to decreased glomerular filtration
Direct damage of distal tubular membranes leading to wasting of Na+, K+, and Mg++
Glomerulus
Tubular-glomerular feedback:
Further constriction of arterioles

Lecture outline

- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary

Clinical Resistance is a Multifactorial Issue

- **HOST**

Immune status

Site of infection

Severity of infection

Foreign devices

Noncompliance with drug regimen

- **FUNGUS**

Initial MIC

Cell type: Yeast/hyphae..

Genomic stability

Biofilm production

Population bottlenecks

- **DRUG**

Fungistatic nature

Dosing

Pharmacokinetics

Drug-drug interactions

Antifungal-drug-resistance mechanisms

Increased efflux

Overexpression of ABC (ATP-binding cassette) transporters or major facilitator proteins in the cell membrane. Often caused by mutations in transcriptional regulators. Represents a broad mutational target, as many non-synonymous changes in the regulators confer a resistant phenotype. See the second case study in BOX 3 for the example of the transcriptional regulator *PDR1* of *Saccharomyces cerevisiae*.

Alteration of target enzyme

Changes in target protein either prevent binding of the antifungal drug or prevent the allosteric inactivation of the target after the inhibitor binds. This is a relatively small mutational target, as only a few specific amino-acid changes confer resistance. Alternatively, the target protein might be overexpressed, resulting in sufficient activity in the presence of the drug.

Alteration of metabolism

Loss of enzyme activity prevents the accumulation of a toxic product in the presence of the drug. This is a relatively broad mutational target, as myriad amino-acid changes result in loss of function and a resistant phenotype. See experiment 2 (BOX 4) for the example of the loss of function in the sterol-biosynthesis gene *ERG3* of *S. cerevisiae*.

Several excellent reviews[1,3,4] have documented these mechanisms in detail. Known mechanisms of resistance do not account for all observed resistance. Additional mechanisms undoubtedly await discovery.

Anderson JA. (2005) Nature Reviews. 3:547-556

Resistance to Amphotericin B

- Technical difficulties in detection of resistance in vitro
- In vivo resistance is rare

C. lusitaniae, C. krusei

C. neoformans

Trichosporon spp.

A. terreus

S. apiospermum

Fusarium spp.

Mechanisms of Amphotericin B resistance

- Reduced ergosterol content (defective ERG2 or ERG3 genes)
- Alterations in sterol content (fecosterol, episterol: reduced affinity)
- Alterations in sterol to phospholipid ratio
- Reorientation or masking of ergosterol
- Stationary growth phase
- Previous exposure to azoles
- (?)

Resistance to Azoles

- Well-known particularly for fluconazole
- Data available also for other azoles
- A significant clinical problem

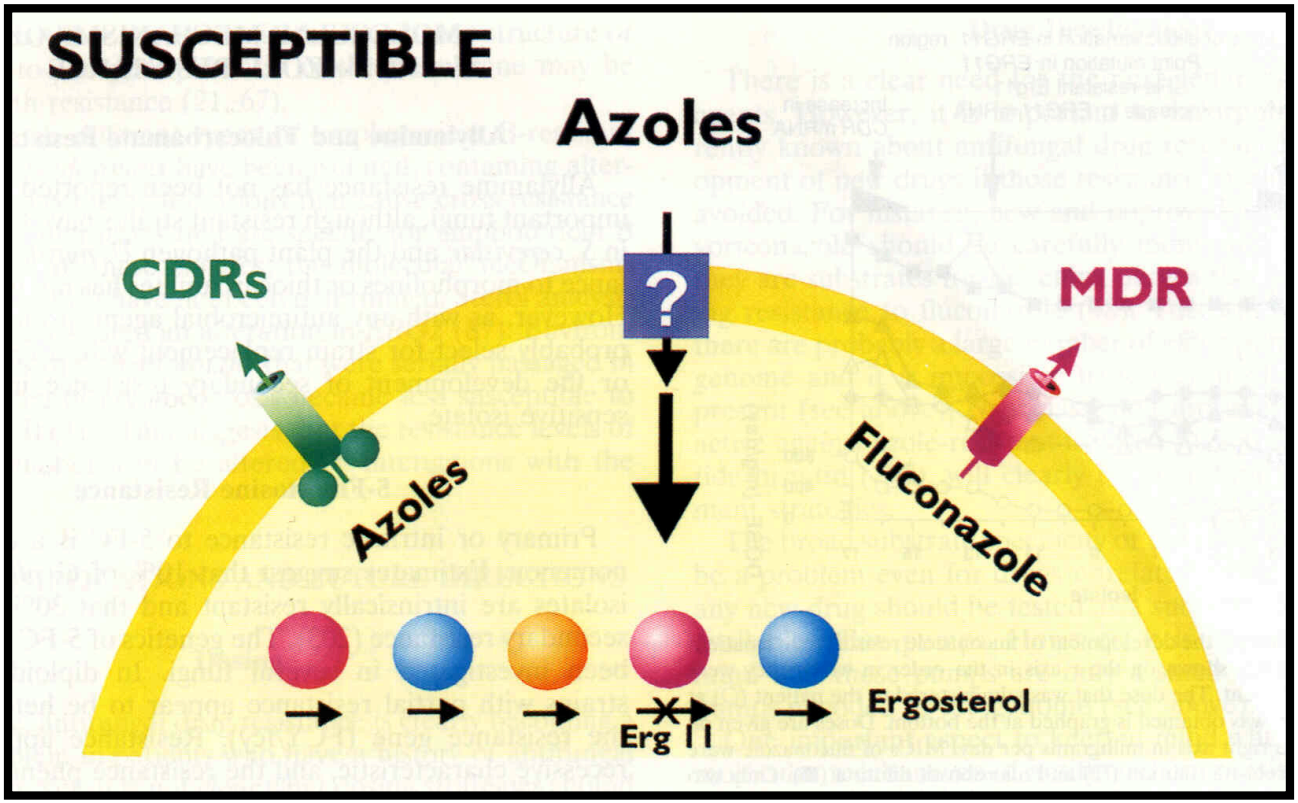
RESISTANCE TO FLUCONAZOLE

PRIMARY	*C. krusei*
	Aspergillus
	C. glabrata
	C. norvegensis...
SECONDARY	*C. albicans*
	C. dubliniensis...

Azole Resistance

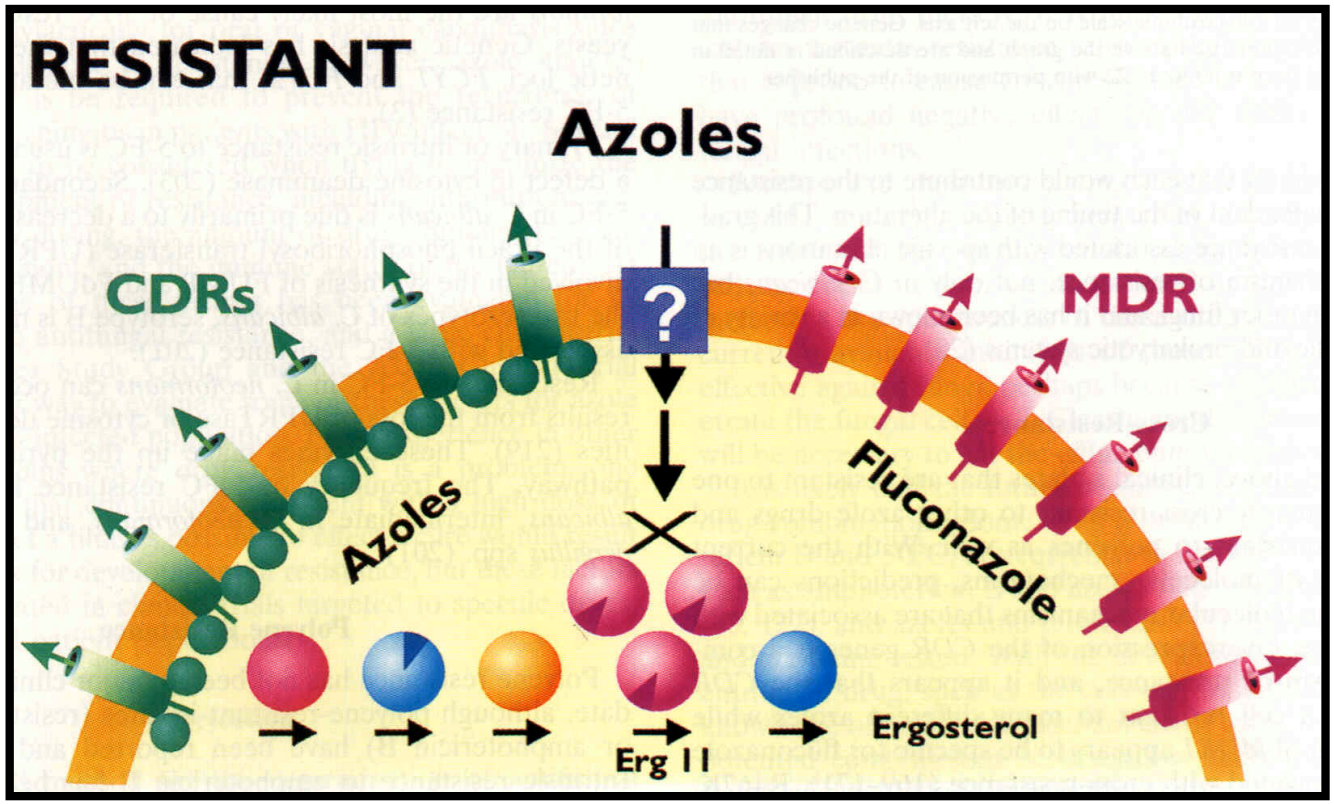
- Single point mutation of ERG11 gene
  - Altered lanosterol demethylase
- Overexpression of ERG11 gene
  - Increased production of lanosterol demethylase
- Alterations in ERG3 or ERG5 genes
  - Production of low affinity sterols
- Increase in mRNA levels of CDR1 or MDR1 genes
  - Decreased accumulation of the azole in fungal cell
- Changes in sterol and/or phospholipid composition of fungal cell membrane (decreased permeability)

If your fungus is susceptible to azoles..



Clin Microbiol Rev 1998; 11: 382

If it is azole-resistant..



Clin Microbiol Rev 1998; 11: 382

Resistance to Flucytosine

- **PRIMARY** non-*albicans Candida*
  C. neoformans
  Aspergillus (highest)

- **SECONDARY** *C. albicans*
  C. neoformans

❁Secondary resistance develops following flucytosine MONOtherapy.

Mechanisms of Resistance to Flucytosine

- Loss of permease activity
- Loss of cytosine deaminase activity
- Decrease in the activity of UPRTase

Resistance to Echinocandins

PRIMARY	*C. neoformans*
	Fusarium spp.
SECONDARY	(?) Candida spp.

Echinocandin Resistance Molecular Aspects

- FKS1 encodes glucan synthase
- GNS1 encodes an enzyme involved in fatty acid elongation
- Resistance is observed following laboratory derived mutations in FKS1 or GNS1

- Other mechanisms (?)

Future Directions to Avoid Development of Resistance

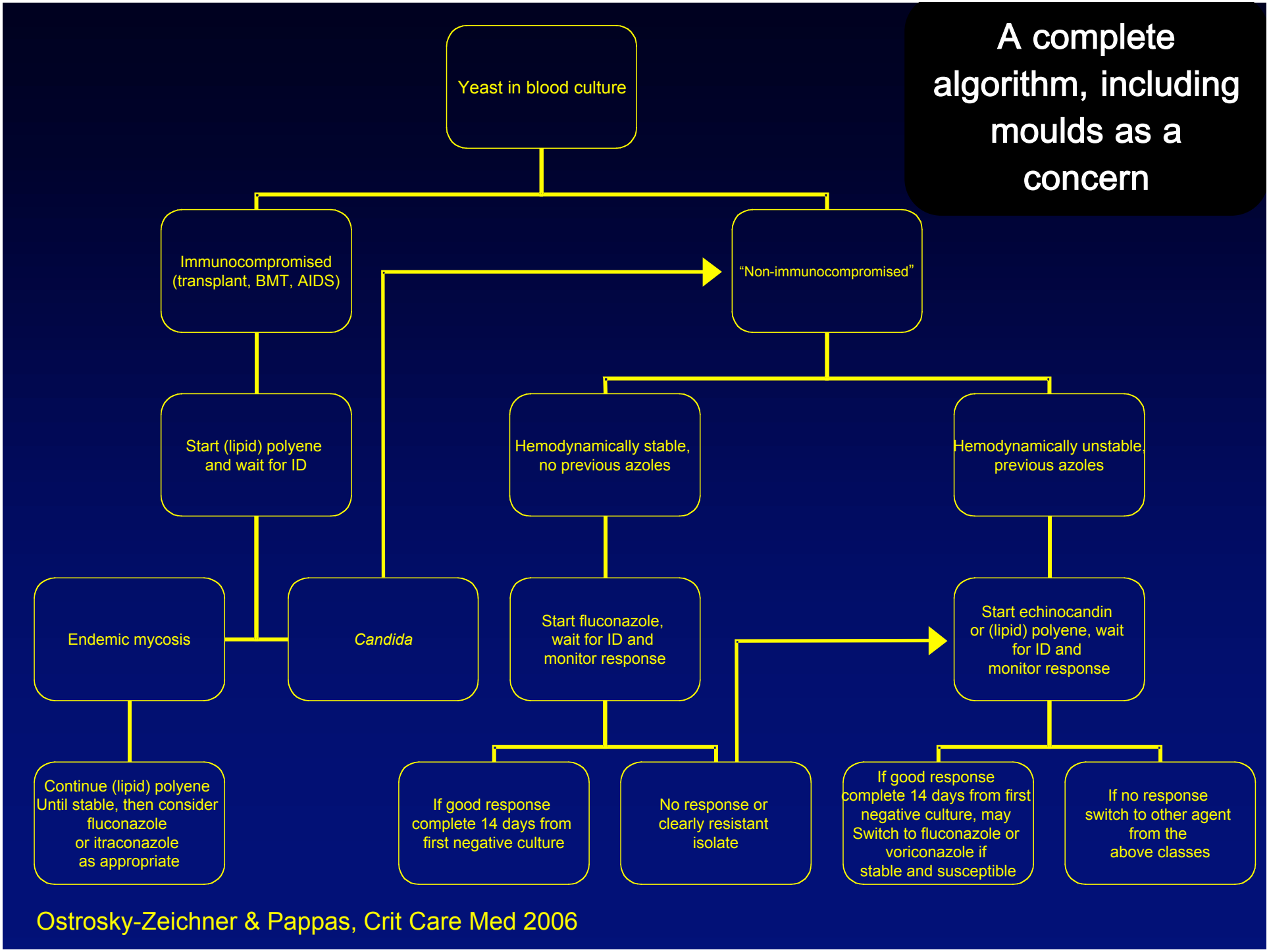
- Proper dosing strategies
- Combination therapies
- Restricted and well-defined indications for prophylaxis with azoles

❁ Fungi will continue to develop NEW resistance mechanisms!..

Lecture outline

- Clinical significance of fungal infection
- Fungal cell structure and targets
- Antifungal agents and mechanism of action
- Antifungal drug interactions & nephrotoxicity
- Mechanisms of antifungal resistance
- Summary

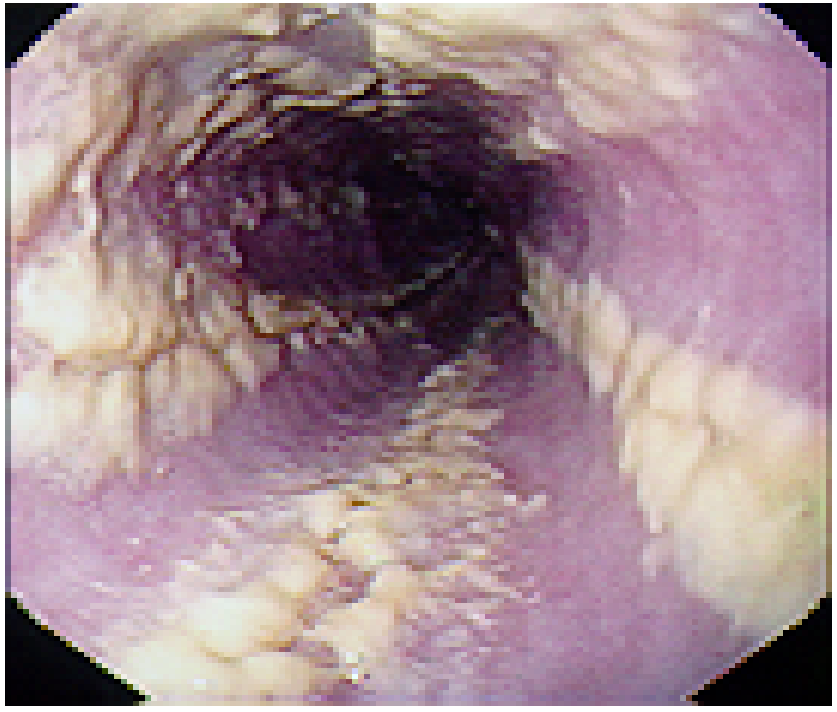
A complete algorithm, including moulds as a concern



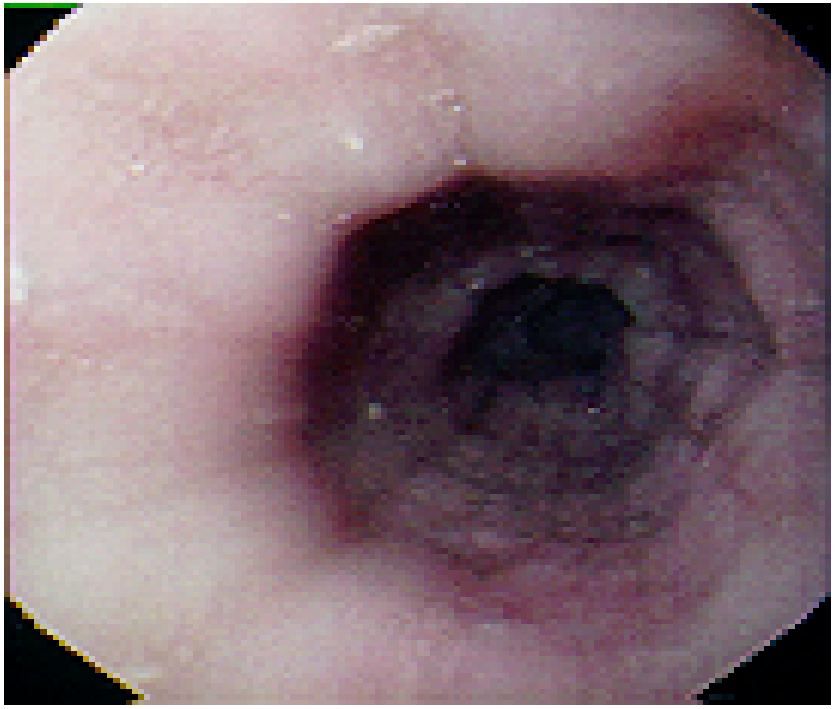
Ostrosky-Zeichner & Pappas, Crit Care Med 2006

This AIDS patient failed fluconazole, amphotericin B, and itraconazole…

Echinocandins: No cross-resistance



Baseline



After caspofungin

Courtesy of John Rex, MD

Recommendations

Table 1 Challenges of managing invasive fungal infections

Challenge	Recommendation
Rapid and accurate diagnosis is important, but difficult to achieve	Clinicians should aggressively pursue an accurate diagnosis, but pre-emptive therapy based on clinical criteria and diagnostics can be helpful
Too much or too little of a host immune response can be problematic	Individualized approaches are necessary to balance restoration of host immunity with risks of immune reconstitution inflammatory syndrome
Poor drug bioavailability, pharmacokinetic variability, drug interactions and toxicities can contribute to clinical failures	Clinicians should anticipate and manage these problems proactively to reduce risks of drug failure, toxicity and resistance
Removal of infected tissue can be critical to achieving clinical success, particularly in mould infections	Not all patients are candidates for surgery, but debridement of devitalized tissue and debulking large fungal burdens may be helpful for patients with mould infections
For many patients, fungal infection is a catastrophic event that renders them unable to receive treatment for their underlying disease such as chemotherapy	Prophylaxis with antifungal agents should be considered for high-risk patients. If break-through infections occur, an accurate diagnosis should be aggressively pursued and consistent antifungal drug strategies employed
Combination therapy of invasive fungal infections is attractive from the perspective of synergistic potential, relative safety, and lack of overlapping toxicities. Randomized, controlled clinical trial data of combination antifungal therapy for mould infections are lacking	Single agents have been effective in treating the majority of invasive fungal infections if the patient's underlying disease can be controlled; combination therapy with amphotericin B and flucytosine should be routinely employed in patients with cryptococcal meningitis; combination therapies for other fungal infections should be considered on a case-by-case basis until additional studies demonstrate benefits of this approach

Combination antifungal therapy: what can and should we expect?

MD Johnson[1,2] and JR Perfect[1]

Bone Marrow Transplantation (2007) 40, 297–305

[1]*Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, NC, USA and* [2]*Campbell University School of Pharmacy, Buies Creek, NC, USA*

Ideal antifungal?

Not yet…

TABLE 3

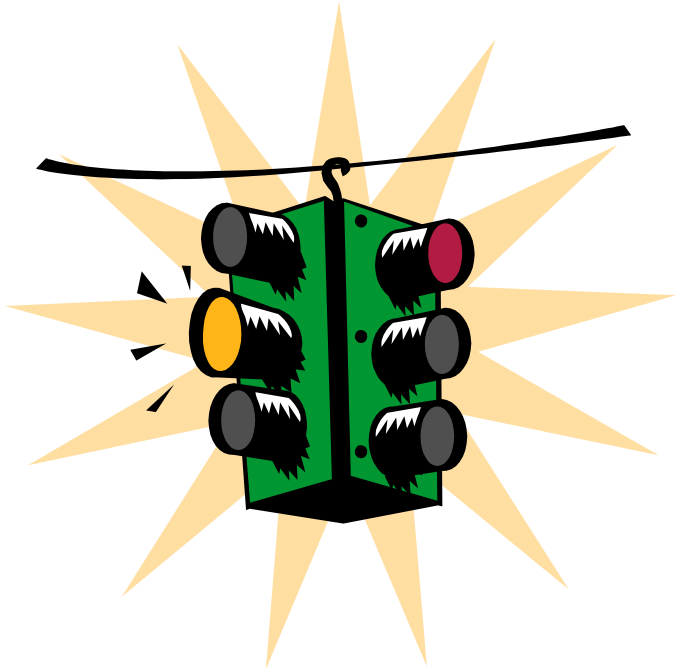
The Holy Grail. Characteristics of the Ideal Antifungal Agent

Broad antifungal activity
Fungicidal
Low frequency of resistance
Intrinsic resistance
Acquired resistance
Available in IV and PO preparations
Ease of administration
Low frequency of adverse events
Minimal drug interactions
Reasonable cost

The future of antifungals

TABLE 4
Search for the Ideal Antifungal Agent

A more complete understanding of the pathogenesis of invasive fungal infections
Virulence factors (e.g., adhesins) as targets for new antifungals and vaccines
Identification of new compounds (natural and synthetic)
Traditional screening against fungal pathogens
Identification of new targets by genomic analysis (signature)
Enhance efficacy and reduce toxicity of older antifungal drugs
Improved delivery systems (Lipid AMB, aerosols)
High-throughput and reproducible susceptibility testing
A better understanding of the mechanisms of resistance to antifungal drugs
Intrinsic vs Acquired
Combination therapy - synergy
AMB + 5FC for cryptococcal meningitis
AMB + voriconazole for aspergillosis
Echinocandins + voriconazole for filamentous moulds
Immune enhancement therapy
Monoclonal antibodies
Manan binding lectins replacement



Sample Exam Question

The effectiveness of the azole class of antifungals is based upon what structural feature of the fungus?

A. the chitin composition of the cell wall
B. the cholesterol composition of the cell membrane
C. the protein components of the cell membrane
D. the ergosterol composition of the cell membrane

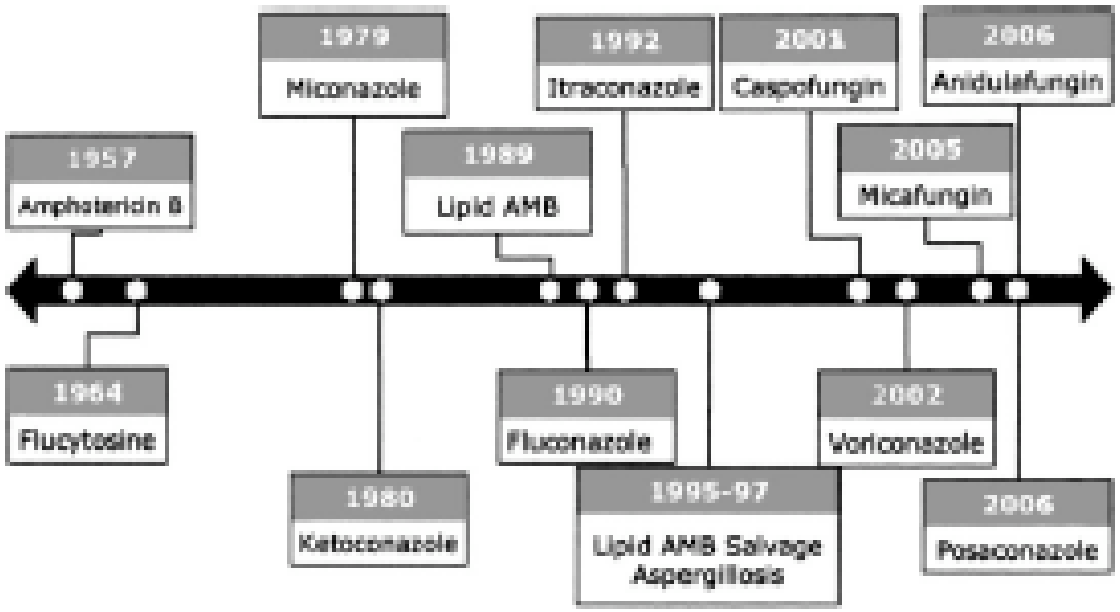


FIG. 1. Timeline of development of antifungal agents.