

# Diversity of Fungi and fungal infections

Dr. Ahmed M. Al-Barrag

# Mycotic diseases

Hypersensitivity (Allergy)

Mycotoxicoses

Mycetismus

Infections

# Types of fungal infections ( Mycoses)

- **Superficial mycoses**
- **Cutaneous mycosis**
- **Subcutaneous mycoses**
- **Systemic mycoses**
- **Opportunistic mycoses**

# Types of fungal infections - Mycoses

- **Superficial mycoses**

- Affect the outer layer of the skin or hair shaft
- No immune response

- **They are:**

- Tinea versicolor
- Tinea nigra
- Black Piedra
- White piedra

## **Etiology**

*Malassezia furfur*

*Exophiala spp*

*Piedraia hortae*

*Trichosporon beigelii*

# Types of fungal infections - Mycoses

- **Cutaneous mycosis**

- Dermatophytosis

- Infection of the skin, hair or nails caused by a group of keratinophilic fungi, called dermatophytes
- Primary pathogens
- Contagious
- Tinea or Ringworm
- Examples

|               |                       |
|---------------|-----------------------|
| Tinea capitis | Scalp                 |
| Tinea pedis   | Foot (Athlete's foot) |
| Tinea manuum  | Hand                  |

Etiology

|                       |                  |
|-----------------------|------------------|
| <i>Microsporum</i>    | Skin , Hair      |
| <i>Epidermophyton</i> | Skin, nail       |
| <i>Trichophyton</i>   | Hair, skin, nail |

# Types of fungal infections - Mycoses

## Subcutaneous mycosis

Fungal infections involving the dermis, subcutaneous .tissues, muscle and may extend to bone

.Usually they are initiated by trauma to the skin

Are difficult to treat and surgical intervention (excision or .amputation) is frequently required

Disease in healthy host, more severe in immunocompromised .host

# Types of fungal infections - Mycoses

## Subcutaneous mycoses

**Mycetoma**

**Subcutaneous zygomycosis**

**Sporotrichosis**

**Chromoblastomycosis**

**Pheohyphomycosis**

**Rhinosporidiosis**

**Lobomycosis**

# Types of fungal infections - Mycoses

## Primary Systemic Mycosis

Histoplasmosis

Blastomycosis

Coccidioidomycosis

Paracoccidioidomycosis

- **Caused by primary pathogens**
- **Contracted by inhalation, Start as respiratory disease**
- **Geographically restricted (endemic), north and south America**



# Types of fungal infections - Mycoses

## Opportunistic fungal infections

- Diseases in immunocompromised host
- Risk factors

### Etiology

*Candida spp*

*Cryptococcus spp*

*Aspergillus spp*

*Zygomycetes*

Many others

# Opportunistic fungal infections

## Predisposing factors of the host

HIV/AIDS

Hematopoietic stem cell transplant (HSCT)

Solid organs transplantation

Malignancies

Neutropenia

Hereditary immune defects

Graft versus host disease (GvHD)

Chronic granulomatous disease (CGD)

Immunosuppressive medications

Diabetes mellitus

surgery or trauma

Indwelling catheters

# The Fungi

## Opportunistic fungi

### – Normal flora

*Candida spp.*

Other yeast

## Ubiquitous in our environment

*Aspergillus spp.*

*Cryptococcus spp.*

*Zygomycetes spp.*

## Primary pathogens

- Dermatophytes

*Microsporum*

*Tricophyton*

*Epidermophyton*

- Endemic geographically restricted

- *Histoplasma spp.*

- *Blastomyces spp.*

- *Coccidioides spp.*

- *Paracoccidioides spp.*

## Other fungi

*Fusarium spp.*

*Scedosporium spp.*

*Exophiala*

*Bipolaris*

*Cladosporium*

*Madurella spp.*

*Cladophialophora spp.*

and many others

# Diagnosis of fungal infection

Clinical features (history, risk factors, etc)

Imaging

Good value in diagnosis and therapy monitoring

Lab Investigations

Histopathology

Microbiology

# Lab Diagnosis

## Direct Microscopy

1. Potassium Hydroxide (10-20% KOH)

## 2. Fungal stains:

Giemsa Stain

Grocott's Methenamine Silver stain (GMS)

India ink (for Capsulated yeast, *Cryptococcus neoformans*)

## Culture:

Fungal media: SDA, BHI, other media if needed.

## Serology:

Candida

Aspergillus

Cryptococcus

Histoplasma

Blastomyces

Coccidioides

Paracoccidioides

## PCR

# Antifungal agents

# Targets for antifungal agents

## Cell membrane

- **Polyene**
  - Amphotericin B, lipid formulations
  - Nystatin
- **Azole**
  - Ketoconazole
  - Itraconazole
  - Fluconazole
  - Voriconazole
  - Posaconazole,
  - Miconazole, clotrimazole
  - Ravuconazole,
  - Albaconazole

# Targets for antifungal agents

## DNA/RNA synthesis

- Pyrimidine analogues
  - Flucytosine

## Cell wall

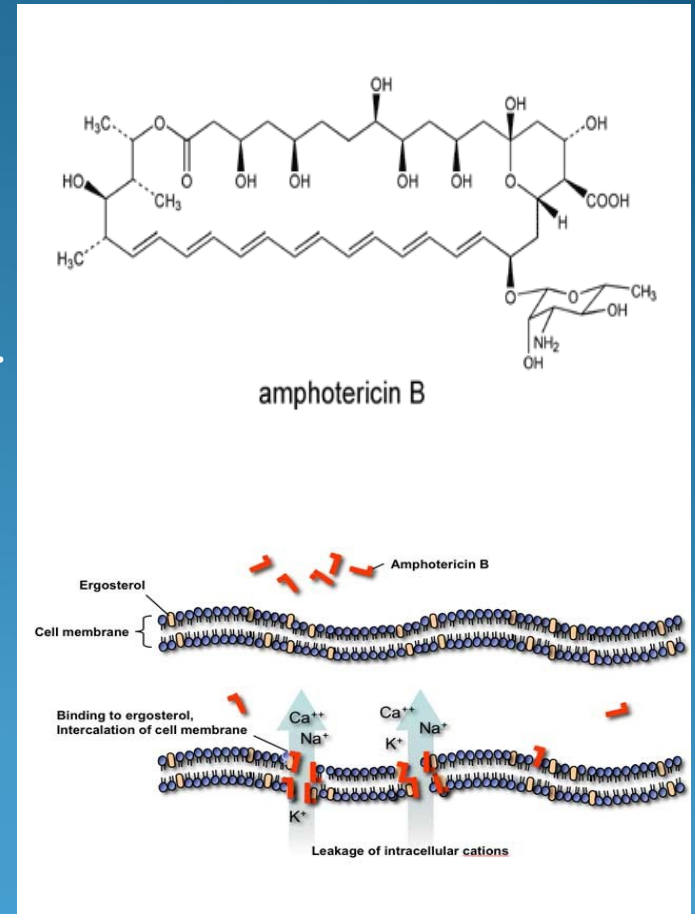
- Echinocandins
  - Caspofungin
  - Micafungin
  - Anidulafungin



# Polyenes—Amphotericin B

## Mechanism of Action (MOA):

Binds to ergosterol within the fungal cell membrane resulting in formation of pores. Which permit leakage of intracellular contents, and death .



# Amphotericin B

## Formulations

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

### Less toxic preparations:

|                                     |                   |
|-------------------------------------|-------------------|
| Liposomal amphotericin B            | (Ambisome® L-AMB) |
| Amphotericin B lipid complex        | (Abelcet® ABLC)   |
| Amphotericin B colloidal dispersion | (Amphotec® ABCD)  |

## Amphotericin B - Clinical Uses

Amphotericin B has a broad antifungal spectrum which includes most fungi that cause human disease

With the exception of

*Aspergillus terreus*, *Scedosporium* spp., some isolates of *Candida lusitanae*, and few others.

The drug of choice for:

Cryptococcal meningitis

Mucormycosis (zygomycosis)

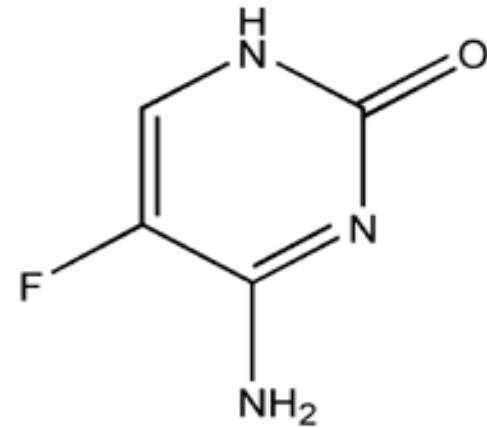
Invasive fungal infection, not responding to other therapy

# Flucytosine

## MOA

Fungal RNA miscoding

Interfering with DNA synthesis



flucytosine

Fluorinated pyrimidine

# Flucytosine

Spectrum of Activity (Restricted spectrum of activity)

Active against

*Candida* species

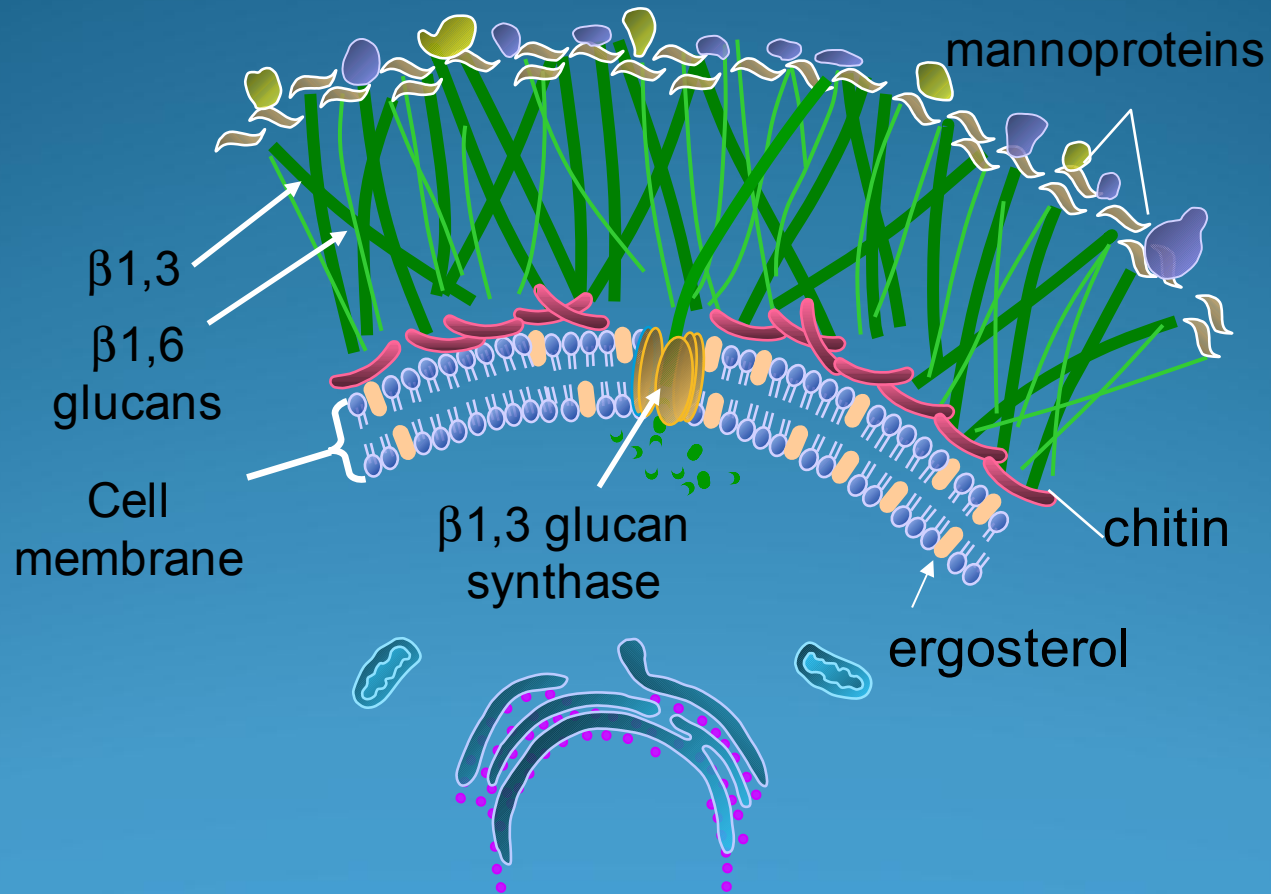
*Cryptococcus neoformans*

Monotherapy : now limited

Resistance

use as combination therapy for Cryptococcal meningitis (Synergy with amphotericin B )

# The Fungal Cell Wall

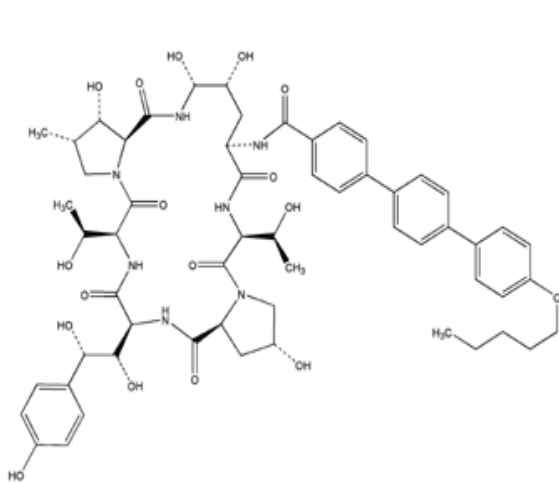


# Echinocandins

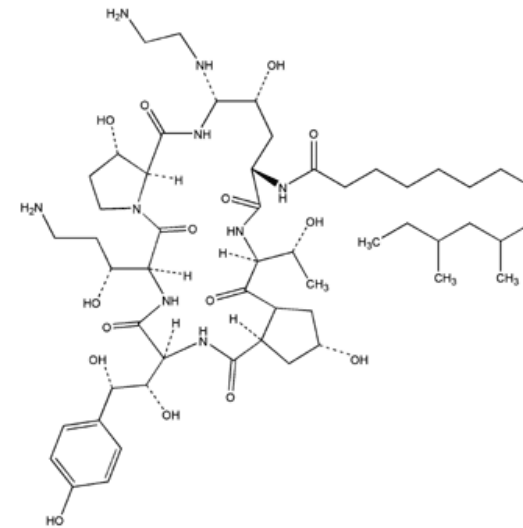
## MOA

Inhibits B-1,3 -D glucan synthase, the enzyme complex that forms glucan polymers in the fungal cell wall.

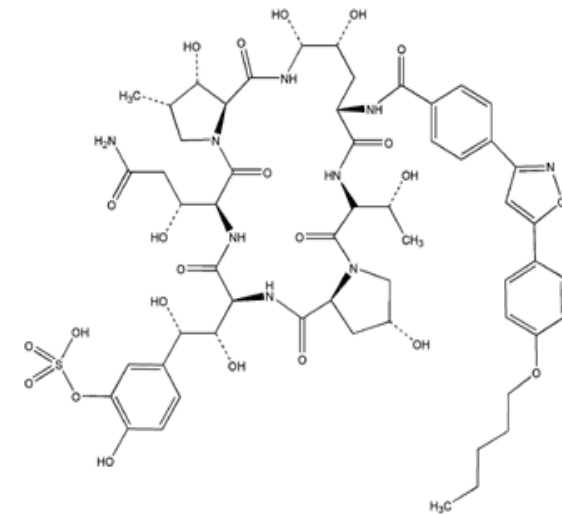
Glucan polymers are responsible for providing rigidity to the cell wall.



anidulafungin



caspofungin



micafungin

# Echinocandins—Spectrum of Activity

## Good activity against

*Candida spp*

*Aspergillus spp*

## Not active against

*Cryptococcus*

*Fusarium*

*Zygomycetes*

*Scedosporidium*

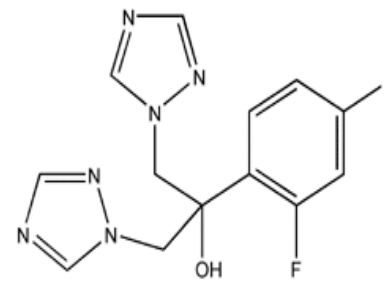


# AZOLES

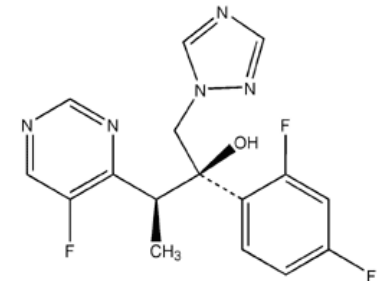
- **MOA:**

Inhibits 14- $\alpha$ -sterol demethylase, which is a microsomal CYP450 enzyme.

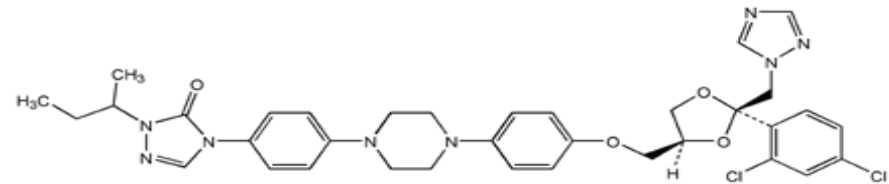
This enzyme is responsible for conversion of lanosterol to ergosterol, the major sterol of most fungal cell membranes



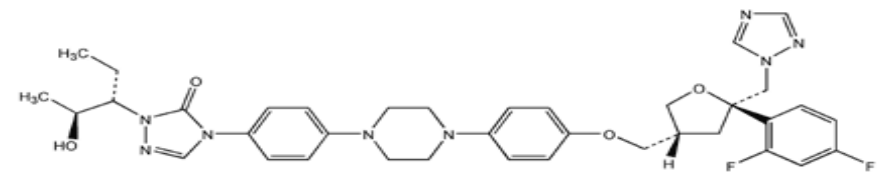
fluconazole



voriconazole



itraconazole



posaconazole

## Azoles—Spectrum of Activity

|                        | Fluconazole | Itraconazole | Voriconazole | Posaconazole |
|------------------------|-------------|--------------|--------------|--------------|
| <i>C. albicans</i>     | +++         | ++           | +++          | +++          |
| <i>C. glabrata</i>     | +           | +            | ++           | ++           |
| <i>C. krusei</i>       | --          | +            | +++          | ++           |
| <i>C. tropicalis</i>   | +++         | ++           | +++          | +++          |
| <i>C. parapsilosis</i> | +++         | ++           | +++          | +++          |
| <i>Cryptococcus</i>    | +++         | +++          | +++          | +++          |
| <i>Coccidioides</i>    | +++         | +++          | +++          | +++          |
| <i>Blastomyces</i>     | ++          | +++          | ++           | +++          |
| <i>Histoplasma</i>     | +           | +++          | ++           | +++          |
| <i>Aspergillus</i>     | --          | ++           | +++          | +++          |
| <i>Fusarium</i>        | --          | --           | ++           | ++           |
| <i>Zygomycetes</i>     | -           | -            | -            | ++           |



# Azoles

- Common Adverse Effects
  - Examples: Rash, Hepatotoxicity, Visual disturbance, Fever
- Serious Adverse Events
- Drug Interactions

