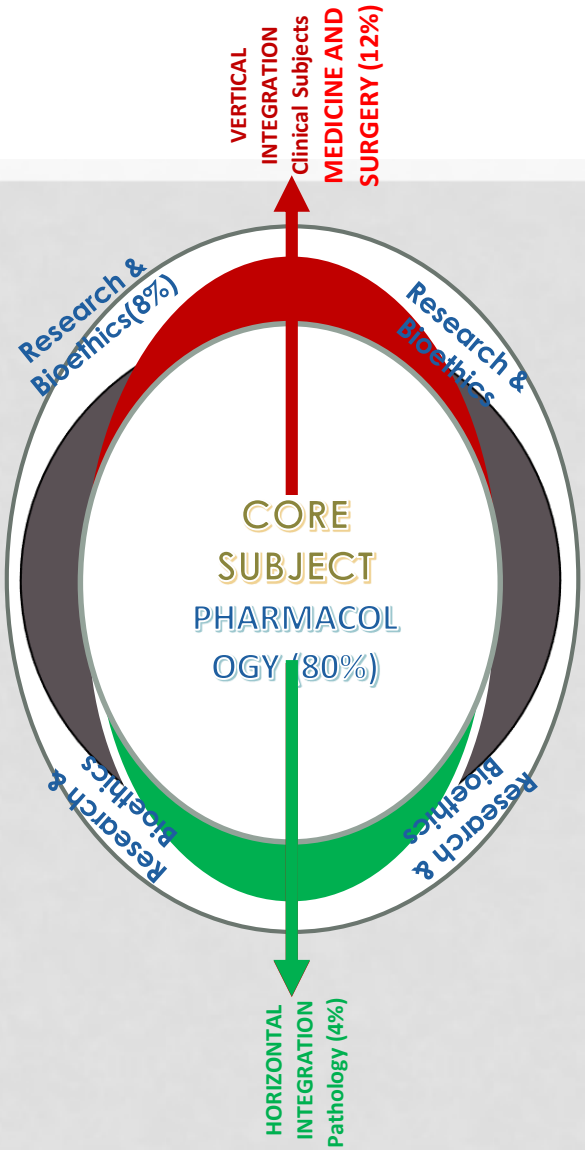

بسم الله الرحمن الرحيم

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology LGIS(56 slides)	
Core Subject –45 slides(80%)	
Horizontal Integration pathology 2 slides –(4%)	
Vertical integration (Clinical Subjects)	(Medicine) - 7slides(12%)
Research & Bioethics	2 slide(4%)

Anti Fungal Agents

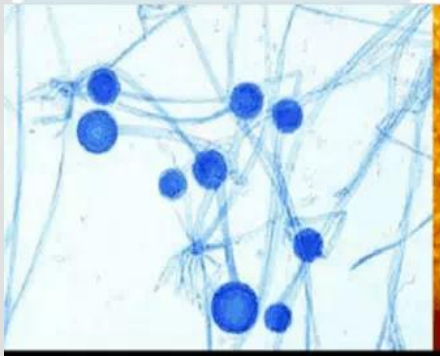
DR UZMA UMAR

LEARNING OBJECTIVES

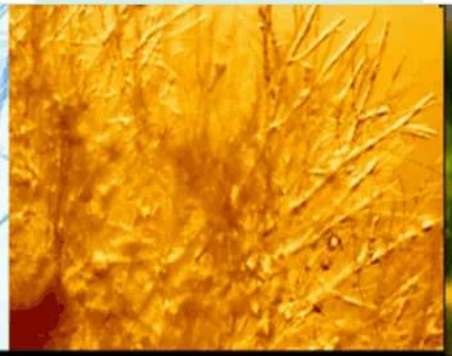
- At the end of the session, the students should be able to
- Enumerate various antifungal agent
- Describe mechanism of action and antimicrobial spectrum of amphotericin B.
- Discuss pharmacokinetics and unwanted effects of amphotericin B.
- Describe mechanism of action of azoles , echinocandins and other antifungal drugs
- discuss clinical uses and adverse effects of various antifungal drugs.

HORIZONTAL INTEGRATION – PATHOLOGY(MICROBIOLOGY)

Phycomycetes (Lower Fungi)	Ascomycetes (Sac Fungi)	Basidiomycetes (Club Fungi)	Deuteromycetes (Fungi imperfecti)
• Saprolegnia	• Yeast	• Agaricus	• Cercospora
• Rhizopus	• Aspergillus	• Polyporus	• Collectotrichum
• Mucor	• Pencillium	• Puccinia	• Trichoderma
• Albugo	• Neurospora	• Ustilago	• Pyricularia
• Pythium	• Peziza	• Lycoperdon	• Fusarium

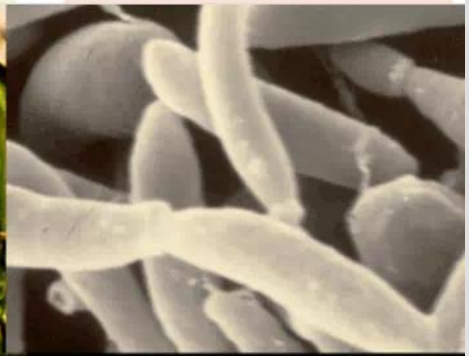


Rhizopus



Neurospora

Agaricus



Fusarium

CORE SUBJECT
(PHARMACOLOGY)

CLASSIFICATION

According To Route Of Administration

Systemic antifungal drugs

For systemic infections

- amphotericin B
- flucytosine
- azoles (ketoconazole,itraconazole,fluconazole ,posaconazole)
- echinocandins(caspofungin,micafungin ,anidulafungin)

For mucocutaneous infections

- griseofulvin
- terbinafine

Topical antifungal drugs

- Nystatin
- Topical azoles(clotrimazole ,miconazole)
- Allylamines(terbinafine ,neftifine)

CHEMICAL CLASSIFICATION

Polyenes macrolides .

Amphoteracin B

Pyrimidine analogue

Flucytosine (5-FC)

Azoles:

Ketoconazole, itraconazole , Fluconazole , voriconazole , posaconazole

Allylamine

Terbinafine

Echinocandins

Caspofungin, Anidulafungin, Micafungin

Classification: Mechanism of Action

- **Drugs that disrupt the Fungal cell membrane**
  - Polyenes..Amphoteracin B
  - Azoles:
    - Imidazoles..Ketoconazole
    - Trizoles…Fluconazole
  - Allylamines…Terbinafine
- **Drugs that disrupt the Fungal cell wall**
  - Echinocandins:Caspofungin, Anidulafungin, Micafungin
- **Drugs that inhibit mitosis**
  - Griseofulvin
- **Drugs that inhibit DNA synthesis**
  - Flucytosine

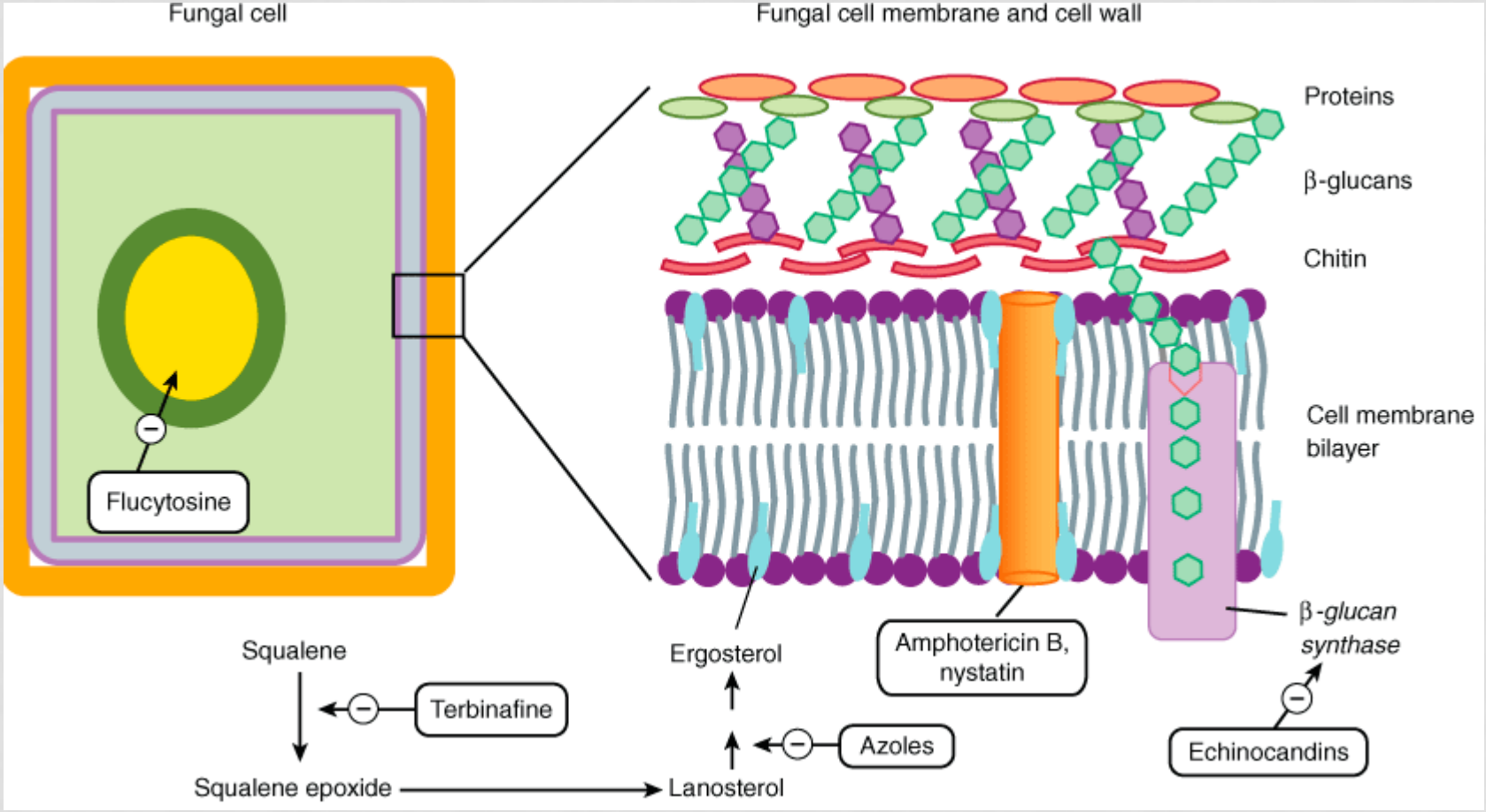
Amphotericin B

- Amphotericin A & B are antifungal antibiotics.
- Amphotericin A is not used clinically.
- It is a natural polyene macrolide
- (polyene = many double bonds)
- (macrolide = containing a large lactone ring)

PHARMACOKINETICS

- **Oral route-----**Poorly absorbed orally so effective for fungal infection of gastrointestinal tract.
- **Parentral route---**For systemic infections given as slow I.V
- **Wide distribution bt only 2-3% of the blood level is reached in csf.**
- **Highly bound to plasma protein**
- **Metabolized in liver**
- **Excreted slowly in urine over a period of several days.**
- **Half-life 15 days**

MECHANISM OF ACTION



Resistance To Amphotericin B

Impairing binding with ergosterol by

1. Decreasing the membrane concentration of ergosterol.
2. modifying the sterol target molecule.

Antifungal Activity

broadest spectrum of activity

- Candida albicans
- Cryptococus neoformans
- Histoplasma capsulatum
- Blastomysis dermatidis
- Aspergillus fumigatus
- mucor

CLINICAL USES

- **broad spectrum of activity & fungicidal action.**
- **I/V therapy**
  - Drug of choice for life-threatening mycotic infections.
  - initial induction therapy for serious fungal infection -----then replaced by one of newer azoles for chronic therapy & prevention of relapse esp in immunosuppressed pts
- **Intrathecal therapy**
  - for fungal meningitis----in pts who don't respond to other drugs
- **Local or topical therapy**
  - Mycotic corneal ulcers and keratitis---drops or subconjuctival injection
  - Fungal arthritis---local injection
  - Candiduria---via bladder irrigation

ADVERSE EFFECTS

1. **Infusion–related toxicity**

   Fever, muscle spasm, vomiting ,headache, hypotension.

2. **Cummulative toxicity**

   - Renal toxicity
   - Liver toxicity
   - Anaemia
   - Intrathecal therapy-----seizures and chemical subarachnoiditis

FLUCYTOSINE

- Synthetic pyrimidine antimetabolite (cytotoxic drug) often given in combination with amphotericin B or itraconazole.
- Oral formulations
- Poorly protein bound
- Well penetration into all body fluids including CSF
- Elimination by glomerular filtration

MECHANISM OF ACTION

- Taken via cytosine permease
- Converted from 5-FU to 5-fluorodeoxyuridine monophosphate (FdUMP) and FUTP
- Inhibit DNA and RNA synthesis

Mechanism of resistance

altered metabolism of flucytosine

Antifungal Activity

- Narrow spectrum
- C neoformans
- Candida species
- Dematiaceous molds

CLINICAL USES

- Narrow spectrum
- Cryptococcal meningitis alongwith amphotericin
- Chromoblastomycosis alongwith itraconazole

ADVERSE EFFECTS

- Narrow therapeutic index
- Adverse effects related to 5-Fu formed by intestinal organisms
- Bone marrow toxicity--- anemia, leukopenia and thrombocytopenia
- Derangement of hepatic enzymes
- Toxic enterocolitis
- Use in combination----dec resistance and toxicity

AZOLES

- Imidazoles (ketoconazole ,miconazole and clotrimazole)
- Triazoles(fluconazole , itraconazole ,voriconazole and posaconazole)

Pharmacokinetics of systemic azoles

	Water Solubility	Absorption	CSF: Serum Concentration Ratio	$t_{1/2}$ (hours)	Elimination	Formulations
Ketoconazole	Low	Variable	< 0.1	7–10	Hepatic	Oral
Itraconazole	Low	Variable	< 0.01	24–42	Hepatic	Oral, IV
Fluconazole	High	High	> 0.7	22–31	Renal	Oral, IV
Voriconazole	High	High	—	6	Hepatic	Oral, IV
Posaconazole	Low	High	—	25	Hepatic	Oral

MECHANISM OF ACTION

- Inhibit synthesis of ergosterol by inhibiting fungal cytochrome P450 enzymes
- Selective for fungal p450 enzymes
- Imidazoles less selective than triazoles -----so higher drug interactions

Antifungal Activity

- **Broad spectrum**
- Candida species
- C neoformans
- Endemic mycoses (blastomycosis , coccidioidomycosis , histoplasmosis)
- Dermatophytes
- Aspergillus(itraconazole ,voriconazole)
- Intrinsically amphotericin-resistant organism

CLINICAL USES

- **KETOCONAZOLE**
  - First oral azole
  - Broad spectrum bt toxicity restricts to topical therapy
- **ITRACONAZOLE**
  - Drug of choice for diseases d/t histoplasma ,blastomyces and sporothrix
  - Active against aspergillus bt mainly replaced by voriconazole
- **VORICONAZOLE**
  - Similar to itraconazole in spectrum
  - Excellent activity against candida and dimorphic fungi
  - Drug of choice for aspergillus

CLINICAL USES

- **FLUCONAZOLE**
  - High oral BA,less effect on microsoma; eznyme ,wide therapeutic index and few GI intolerance ----aggressive dosing against fungal infections
  - Azole of choice for treatment and prophylaxis of cryptococcal meningitis
  - i/v form----equivaent to amphotericin B for candidemia in ICU pts
  - Mucocutaneous candidiasis
  - Coccidiodal diseases
  - Prophylaxis----reduce fungal infections in bone marrow transplant recipients and AIDS

CLINICAL USES

- **POSACONAZOLE**
  - Only azole active against zygomycosis and mucormycosis
  - Salvage therapy in invasive aspergillosis
  - Prophlyaxis of fungal infections during induction chemotherapy for leukemia and allogenic bone marrow transplant with graft versus host disease

ADVERSE EFFECTS

- Relatively nontoxic
- Minor GI upset
- Abnormalities in liver enzymes

Drug Interactions

- **Ketoconazole**
  - cytochrome P450 inhibitor
  - Less selective for fungal p450
- **Itraconazole**
  - Absorption increased by food and gastric Ph
  - Decreased bioavailability when taken with rifamycins
- **Voriconazole ,posaconazole**
  - CYP3A4 enzyme inhibitor

ECHINOCANDINS

- Caspofungin
- Micafungin
- anidulafungin

Pharmacokinetics

- Only available in I/V forms
- Dose adjustment required only in severe hepatic insufficiency

MECHANISM OF ACTION

- Inhibits the synthesis of fungal cell wall by inhibiting the synthesis of β(1,3)-D-glucan, leading to disruption of cell wall & cell death.

Antifungal Activity

- Only candida and aspergillus
- NOT active against C neoformans or agents of zygomycosis and mucormycosis

CLINICAL USES

- **Caspofungin**
  - Disseminated mucocutaneous candida infection
  - Empiric antifungal therapy during febrile neutropenia
  - As salvage therapy in invasive aspergillosis who failed to respond to amphotericin
- **Micafungin**
  - Mucocutaneous candida ,candidemia and candida prophylaxis in bone marrow transplant
- **Anidulafungin**
  - Esophageal candidiasis and invasive candidiasis inc candidemia

ADVERSE EFFECTS

- Extremely well tolerated
- Minor GIT sideffects
- Flushing
- Elevated liver enzymes when caspofungin used in combination with cyclosporine
- Micafungin-----increases levels of nifedipine ,cyclosporine and sirolimus
- Anidulafungin-----histamine release during i/v administration

GRISEOFULVIN

- Fungistatic, has a narrow spectrum
- Given orally (Absorption increases with fatty meal)
- Half-life 24 hours
- Taken selectively by newly formed skin & concentrated in the keratin.
- Induces cytochrome P450 enzymes

Uses

1. dermatophyte infections (ring worm of skin, hair, nails).
2. Should be given for 2-6weeks for skin & hair infections to allow replacement of infected keratin by the resistant structure
3. Nail infections

Adverse effects ;

- Serum sickness
- Hepatitis
- Drug interaction with warfarin and phenobarbital

TERBINAFINE

- Inhibits fungal squalene epoxidase, decreases synthesis of ergosterol .(Accumulation of squalene ,which is toxic to the organism causing death of fungal cell).
- Fungicidal ,its activity is limited to candida albicans & dermatophytes.
- Effective for treatment of onychomycoses (12 weeks therapy)

- Rare side effects
- No significant drug interaction reported till todate

TOPICAL ANTIFUNGAL AGENTS

NYSTATIN

- It is a polyene macrolide ,similar in structure & mechanism to amphotericin B.
- Too toxic for systemic use.
- Used only topically.
- Available as creams, ointment , suppositories & other preparations to skin & mucous membrane
- Most active agent against candida sp

USES

- Local candidal infection
- Oropharyngeal thrush ,vaginal candidiasis and intertrginous candidal infections

TOPICAL AZOLES

- Miconazole, Clotrimazole ,ketoconazole

CLOTRIMAZOLE

- Oral form-----oral thrush -------pleasant tasting alternative to nystatin
- Cream form------vulvovaginal candidiasis, dermatophytic infections (tinea pedis , tinea corporis and tinbea cruris)

MICONAZOLE

- Cream form------vulvovaginal candidiasis, dermatophytic infections (tinea pedis , tinea corporis and tinbea cruris)

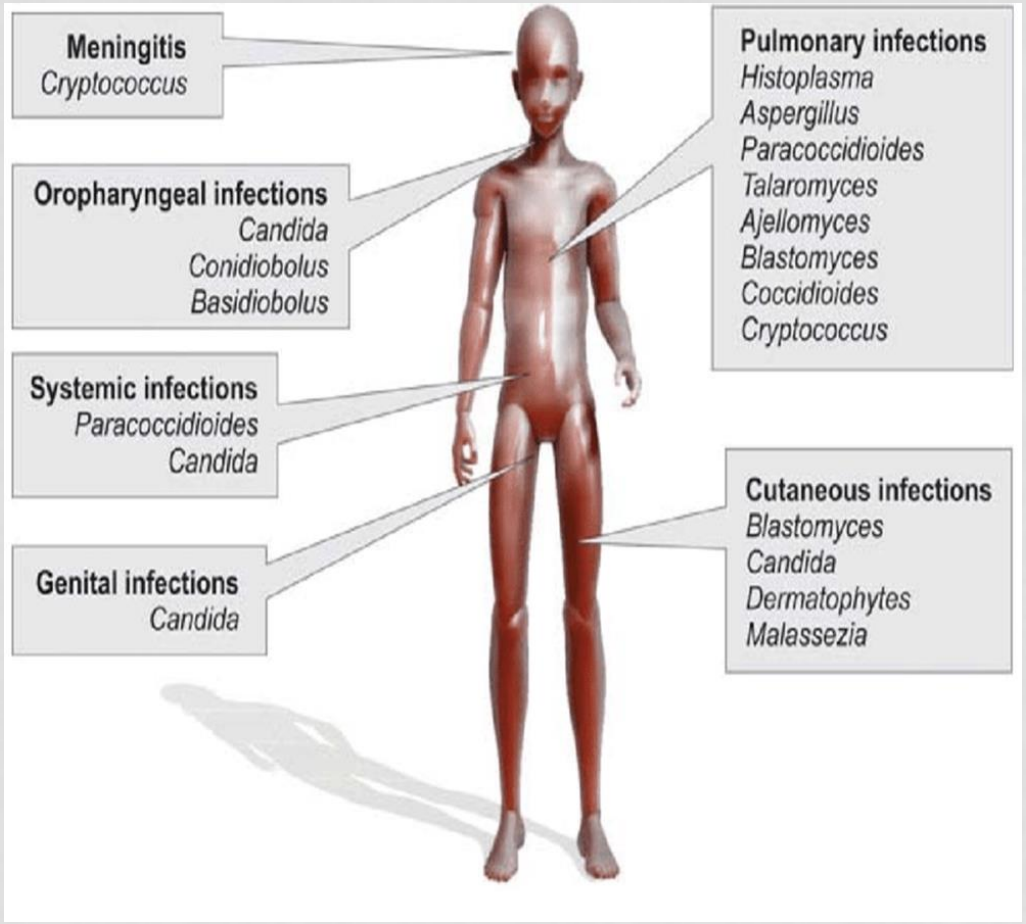
KETOCONAZOLE

Topical &shampoo------seborrheic dermatitis and pitryiasis versicolor

TOPICAL ALLYLAMINES

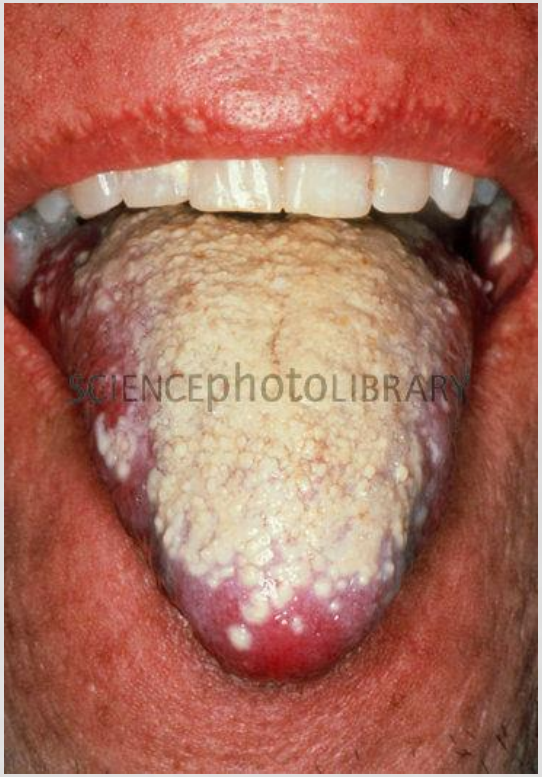
- Terbinafine ,neftifine
- Tinea corporis and tinea cruris

VERTICAL INTEGRATION - MEDICINE

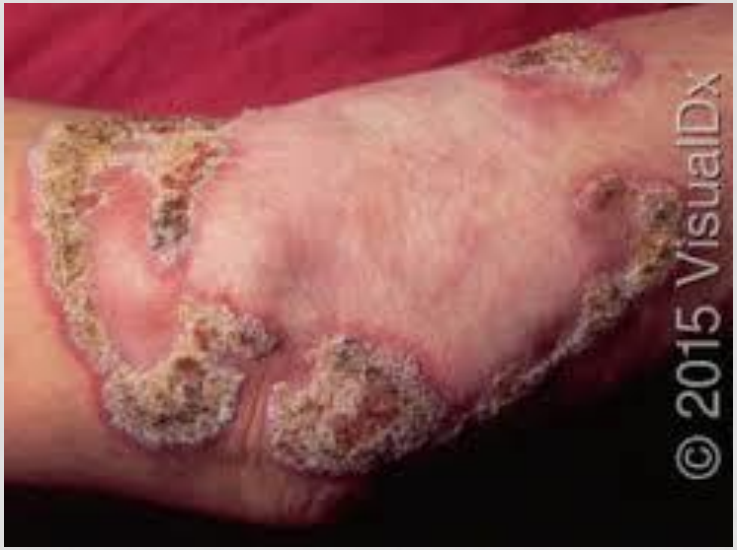

Meningitis
Cryptococcus
Oropharyngeal infections
Candida
Conidiobolus
Basidiobolus
Systemic infections
Paracoccidioides
Candida
Genital infections
Candida
Pulmonary infections
Histoplasma
Aspergillus
Paracoccidioides
Talaromyces
Ajellomyces
Blastomyces
Coccidioides
Cryptococcus
Cutaneous infections
Blastomyces
Candida
Dermatophytes
Malassezia

FUNGAL INFECTIONS

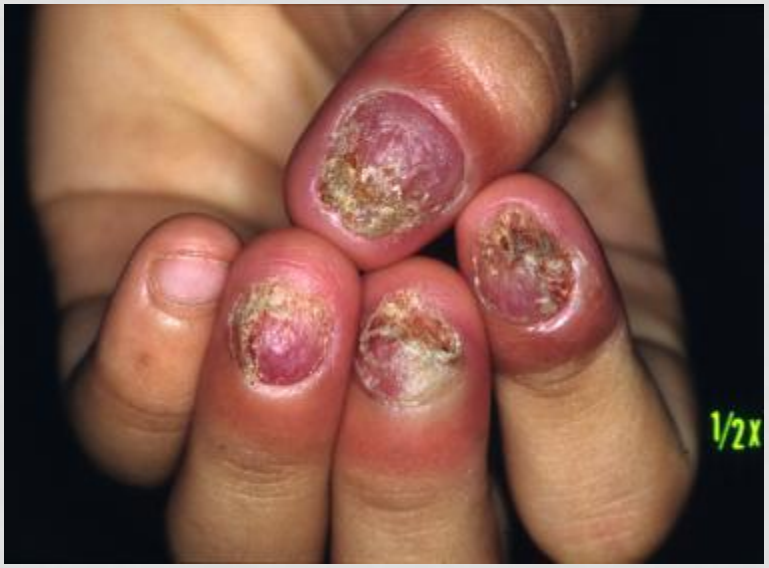
Figure – White, curd-like, discrete plaques are evident on the tongue and palate of this otherwise healthy 3-month-old girl. No diaper rash was noted.



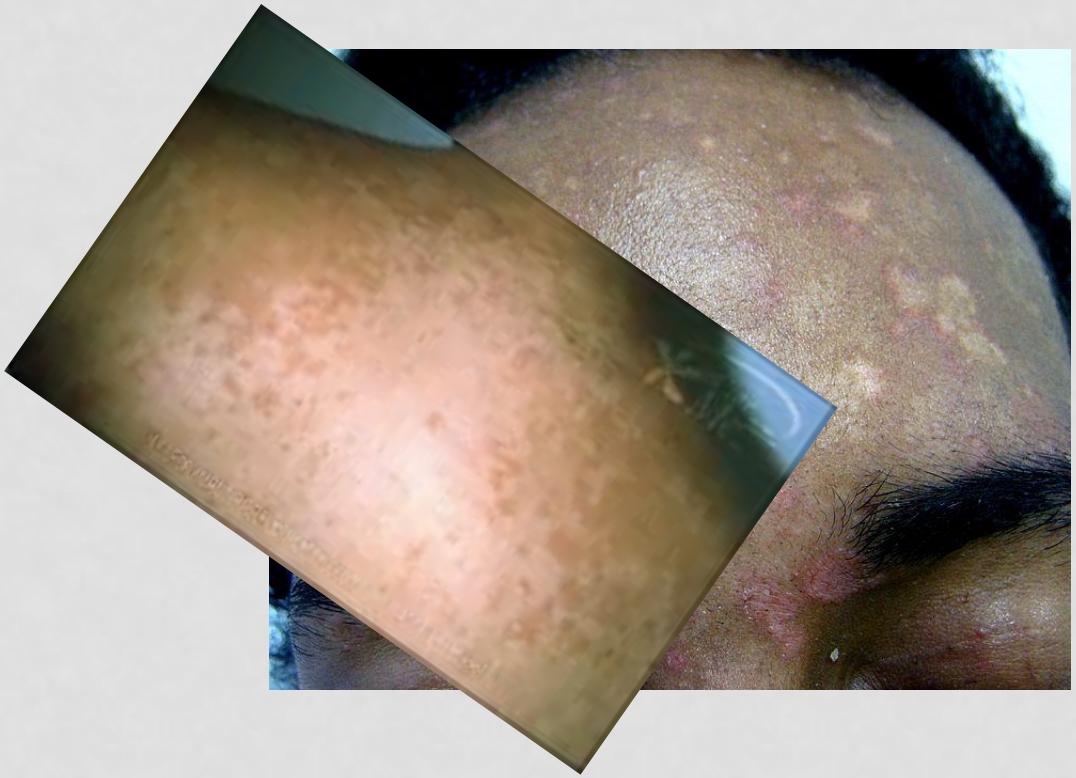
BLASTOMYCOSIS



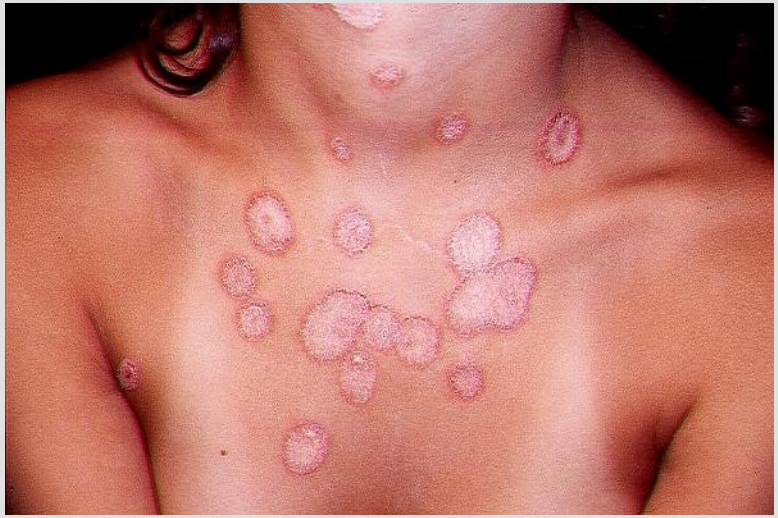
ONCHOMYCOSIS

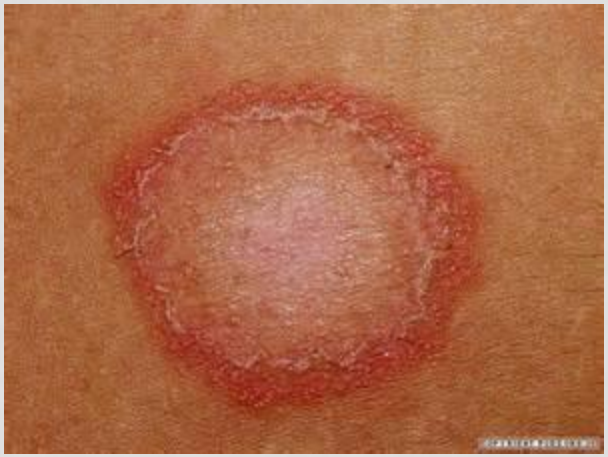


TINEA VERSICULAR



TINEA CORPOROS





RESEARCH

. 2005 Sep;366(9490):1013-25.

Advances and challenges in management of invasive mycoses

Thomas F Patterson [1]

Clin microbiol rev. 1999 jan;12(1):40-79.

Current and emerging azole antifungal agents

D J sheehan 1, C A hitchcock, C M sibley

BIO ETHICS

Vertical integration

Beneficence

The principle of beneficence is the obligation of physician to act for the **benefit of the patient** and supports a number of moral rules to protect and defend the right of others, prevent harm, remove conditions that will cause harm, help persons with disabilities, and rescue persons in danger.

It is worth emphasizing that, the language here is one of positive requirements. The principle calls for not just avoiding harm, but also to benefit patients and to promote their welfare.

TAKE HOME MESSAGE

END OF LECTURE ASSESSMENT

1- Interactions between this drug and cell membrane components can result in the formation of pores lined by hydrophilic group present in the drug molecule.

a) Caspofungin
b) Flucytosine
c) Griseofulvin
d) Nystatin
e) Terbinafine

2- A 14 yrs-old patient has experienced severe headache and double vision for a month. His temperature is 38.6 C. His CSF culture was positive for cryptococcal antigen. Which of the following drugs would be appropriate to treat this patient systemically (not intrathecally)?

a) Amphotericin B
b) Fluconazole
c) Itraconazole
d) Ketoconazole
e) Nystatin

3- Which drug is least likely to be effective in the treatment of esophageal candidiasis if it is used by the oral route?

a) Clotrimazole
b) Griseofulvin
c) Ketoconazole
d) Intraconazole
e) Nystatin

REFERENCES

- Lange: Katzung Basic & Clinical Pharmacology for literature
- Google for bioethics , research and images

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