ANTIFUNGAL DRUGS

Fungal infections are termed as mycoses

Fungal infectious occur due to :

- 1- Overuse of broad spectrum antibiotics
- 2- Decrease in the patient immunity

Types of fungal infections

1 Superficial : Affect skin, mucous membrane, hair, nails

- Malassezia furfur –Tinea versicolor
- Dermatophytes : ring worm infection/Tinea
  Tricophyton, Microsporum, Epidermophyton
  Fungi that affect keratin layer of skin, hair, nails.
  e.g. tinea pedis
- Candidia : Yeast-like
  oral thrush, vulvo-vaginitis ,

2- Deep infections

- Affect internal organs as : lung ,heart , brain leading to pneumonia , endocarditis , meningitis.
- 3 types of fungi cause deep mycosis
- 1. Yeast like-divide by hyphae-Candida, Cryptococcus

2. Moulds - divide by spores- Aspergillus niger

3 Dimorphic-by both-. Histoplasma

- Immunocompromised patients

Classification

1. **Drug acting on cell membrane**

i. Polyene antibiotics

Amphotericin B, Nystatin, Hamycin, Natamycin

ii. Azoles

- **Imidazoles**
- Ketoconazole ,Clotrimazole, Econazole, Miconazole,, Butaconazole, Oxiconazole, Sulconazole, Sertaconazole, Isoconazole, Luliconazole
- **Triazoles**
- Fluconazole, Itraconazole , Terconazole ,Voriconazole, Posaconazole, Ravuconazole,

iii. Allyamines

-Terbinafine, Naftifine

2. Drug acting on cell wall(inhibit cell wall synthesis)

- Pneumocandins / echinocandins –caspofungin, micafugin, anidulafungin

3.Drug acting on nucleus (inhibit protein synthesis)

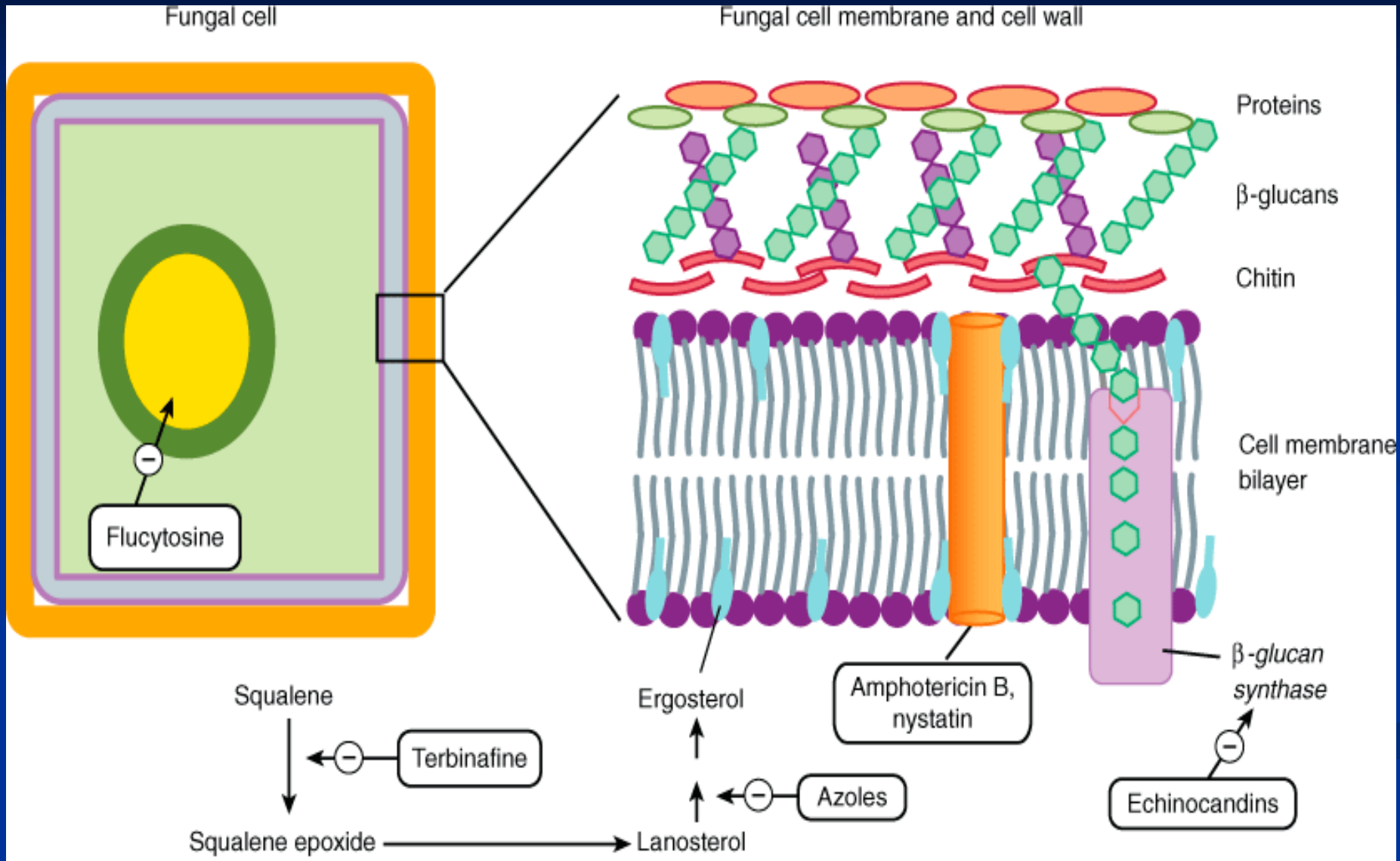
-Griseofulvin

-Flucytosine

4. Other topical agents

- Tolnaftate, Indecylenic acid , benzoic acid, Salicylic acid, selenium sulfide, ciclopirox olamine.

Targets of antifungal drugs



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Amphotericin B

- Amphoteric behaviour, It is polyene macrolide
- Broad Spectrum, Most effective
- Kala azar
- Source- bacteria- streptomyces nodusus
- Mechanism of action – Fungicidal
- Fungal cell membrane contain ergosterol – High affinity for it – Combine with ergosterol – micro pore (sponge like action)- in cell permeability – ions, amino acids move out – damage to fungal cell.

- Pharmacokinetics
- Water insoluble – Not orally

- I.V.-in 5% dextrose-0.5mg/kg over 4 hrs.
- Not in saline-insoluble-precipitate-crystals

- Amphotericin B + bite salt -(50mg) + (4mg)

- Test dose-1mg-To gauge the severity of reaction
- 0.5 – 0.6 mg/ kg/ day – Infusion over 4-6 hrs.

- Metabolism – Liver

- New formulations- Amphotericin B is packaged in a lipid- associated delivery system to reduce binding to human cell membrane , so reducing renal toxicity, acute reaction, Targeted delivery
- AMB-doc-De oxy cholate-most nephrotoxicity
- AMB-CD- colloidal dispersion-Infusion reaction
- AMB-LC-lipid complex
- L-AMB– Liposomal-Best-Safest, least nephrotoxicity, infusion reactions, anemia
- better penetration in cell
- high cost
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- Adverse reactions
- Acute reaction(infusion reaction) – Not dose dependent

- Fever with chills, Nausea, vomiting, headache..
- Subsides despite continuation of drip
- d/t Release of IL -1 , TNF
- **Can be avoided by**

A. Slowing the infusion

B. Decreasing the daily dose

C. Premedication with antipyretics,antihistaminics, corticosteroids.

D. Test dose.

- Thrombophlebitis

- Nephrotoxicity

  Renal tubular acidosis-loss of K^+ and Mg^{++}

  Dose related

  To prevent – 1-2 L. N. S. for 2 hrs. before giving Amphotericin B

- Anemia – Normocytic normochromic- decrease production of erythropoietin

- Arachnoiditis-Intrathecal injection

Uses –serious fungal infection, for induction of treatment

Systemic mycoses ……., mucormycosis

i. immunocompromised patients

ii. Spreading rapidly

iii. CNS involvement

Cryptococcal meningitis, mucormycosis

Not effective

1-pneumocystis jiroveci

2-eumycetoma

3 Microsporidia

Status-

1.Toxic

2.Parenteral

Flucytosine

- Spectrum – Cryptococcus neoformans, Candida

- Mechanism of action
- Antimetabolite

  Converted within the fungal cell to 5- fluorouracil(not in human cell) by deaminase, that inhibits thymidylate synthetase enzyme that decreases thymidylic acid synthesis- component of DNA

- PK- Good CSF con., Renal excretion

- A/E
- GIT-Nausea, vomiting , diarrhea, severe enterocolitis
- Bone marrow depression- Reversible neutropenia
  thrombocytopenia

- Uses
  Cryptococcal meningitis
  Candidial meningitis
- Along with Amphotericin reduce the dose

- Amphotericin B increases cell permeability - more 5-FC to penetrate the cell- synergistic.
- Never given alone-resistance

Griseofulvin

Source-Penicillum griseofulvum

Spectrum – Dermatophytes :- Epidermophyton , Trichophyton, Microsporum.

Not against C. albicans

- **Mechanism of action**
- **Fungistatic**
- **Dermatophytes actively concentrate it**
- **Disorients microtubules, interfere with mitosis-cell division**

Pharmacokinetics

- Absorption – Better after food (Fatty food)
- Ultra microfine particle preparation
- Deposited in keratin precursor cells
- Making resistant to fungal invasion
- Treatment till infected keratin sheds of
- Metabolized in liver

Adverse effects

- Headache
- Nausea, Vomiting, Diarrhea
- Photosensitivity

Interactions

- Enzyme inducer
- Antabuse like reaction with alcohol

Cross sensitivity with penicillin

- Uses– Dose – 500 mg/day after meals ,Duration
- Tinea capitis -DOC- 4-6 wks
- Tinea cruris /corporis- 3 wks
- Tinea pedis , manus – 4-6 wks
- Onychomycosis – Finger nails – 4-6 M.
  Toe Finger nails 8-12 M.

Status- Narrow spectrum, Duration of treatment long, Resistance since 2 years

AZOLES

Spectrum – Broad

- Superficial / Deep mycoses

Mechanism of action – Fungistatic

1) Inhibit ergosterol biosynthesis – by inhibiting 14 – α demethylase ,prevent conversion of lanosterol to ergosterol
2) Inhibitory action on peroxidase, other enzyme

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Accumulation of H_2O_2

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Autodigestion of cell

Ketoconazole -Orally active

- Less toxic
- Broad spectrum

PK

- Absorption – Acidic environment
- Metabolism – Extensive hepatic
- **Poor CNS Penetration**

Adverse effects

1. GIT - Nausea, vomiting
2. Endocrine- they inhibit gonadal steroid synthesis- testosterone- Impotence, gynecomastia, menstrual irregularities
3. Hepatitis
4. Adrenal failure-inhibit glucocorticoid and & mineralocorticoid synthesis

CI-Pregnancy

Interactions

- Antacids / H2 blockers - decrease absorption
- Inhibit human CYP-450 hepatic enzyme- Elevate Terfenadine , Astemizole con - prolonging QT Int.

Uses -400 mg /day

1) Dermatophytosis
2) Systemic mycoses
3) Seborrhoea of scalp/Dandruff-Topical-shampoo

- Triazoles

1 more selective effect on fungal cell membrane

2 less toxic-endocrine, liver

3 long acting

4 more efficacy

5 less enzyme inhibition

6 good CNS penetration

7 parenteral formulation

Itraconazole

- 100 – 400 mg/day
- Use –Maintenance therapy- Histoplasmosis ,Aspergillosis , Blastomycosis, Paracoccidiomycosis, sportrichosis
- Induction & maintenance- eumycetoma, pseudoallescheria

- ADR- endocrine side effects, hepatitis, heart failure

Fluconazole

- Completely absorbed, better G.I tolerance
- Maximum CSF penetration
- Absorption not altered by food or gastric acidity
- Excretion – kidney –only azole

Uses

- **Candidial infection-DOC –esophagitis, Oropharyngeal, cutaneous**
- Vaginal candidiasis – Single dose 150 mg
- Cryptococcal meningitis-maintenance-DOC
- Coccidioidal meningitis-induction & maintenance
- Fungal keratitis-eye drops
- Dermatophyte

Not effective in dimorphic (Aspergillus) & Moulds (mucormycosis)

ADR-

Reversible alopecia

CI-pregnancy-increase risk of fallott's tetralogy

Voriconazole

- Used for the induction and maintenance treatment of invasive aspergillosis & serious infections.
- Not effective in mucormycosis
- Reversible visual disturbances, QT interval prolongation
- Contain fluorine-Florosis

- Posaconazole
- Oral
- Mucormycosis

- Isavuconazole

Ketoconazole	Itracoazole	Fluconazole
Azole	Azole	Azole
Imidazole	Triazole	Triazole
All Fungi	Histoplasmasis Blastomycosis	Candidiasis Crytococcal inf. Ringworm
Oral, Shampoo Food – absn	Oral , I.V	Oral , I.V, eye drops
Acidic PH-	Same	No effect Better bioavailability
CSF Con –	+	++
Hepatic metabolism	+	Renal excretion

t ½ - 10 hrs	24 hrs	24 hrs
GIT S/E ++	+	-
Endocrine S/E ++	+	-
Enzyme inhibition ++	+	-
Drug interactions ++	+	-
Hepatitis ++	+	-

Terbinafine

- Keratinophilic medication

- Mechanism of action
- Fungicidal
- Inhibit squalene epoxidase – involved in ergosterol synthesis
- Accumulation of squalene – toxic to fungus
- Dermatophytes

- As compared to azoles
  - Fungicidal
  - Efficacy more
  - Relapse rate low
  - Cure rate high -80%
  - Duration of treatment – less

Uses

Oral-250 mg OD, Topical 1% cream

Tinea corporis /cruris/pedis,
Pityriasis versicolor, candidiasis
Topical treatment – Twice daily 1%-3 wks.

Tinea capitis
Onychomycosis ORAL DOC

ADR- Hepatotoxic, Steven Johnson syndrome

Echinocandins

Caspofungin

Micafungin i.v.

Andulafungin

Mechanism of action-fungicidal

-Inhibit cell wall synthesis

Inhibit 1-3 β glucan synthase –glucose polymer – maintains integrity of cell wall

Effective in invasive Aspergillus & Candida infections- Resistant to azoles, amphotericin B

- Very expensive
- Good tolerability, no nephrotoxicity

Topical Antifungals

Indications

- Ringworm/ Dermatophyte
- Pityriasis versicolor
- Mucocutaneous Candidiasis
- Otomycosis

Topical antifungals not useful in

1.Tinea capitis

2.Onychomycosis

Preparations

- Creams, Lotions, Ointments, Powders – Skin
- Vaginal – Creams, Tab, Pessary
- Scalp – Shampoo

AZOLES

Clotrimazole

- Dermatophytes- Tinea pedis, cruris, corporis- 1% cream
- Vaginal candidiasis- pessary– 200 mg OD – 3 days or 500 mg once or 100 mg OD- 7 days –Long lasting residual effect
- Oral candidiasis--troche
- Cutaneous candidiasis
- Otomycosis
- Tinea versicolor

ECONAZOLE –Same as Clotrimazole

- Less useful in vaginal candidiasis

MICONAZLE – More vaginal irritation

Nystatin-

- It is a polyene macrolide.
- Too toxic for systemic use.
- Used only topically-for Candidial infections
    1. Vaginitis-less effective than azoles-
    2. Dirrhoea- Bad taste
    3. Oral candidiasis-thrush-paint, d/t glucocorticoids
    4. intestinal candidiasis-suspension-not absorbed
    5. corneal,conjuctival- ointment
    6. Cutaneous

Natamycin-topical eye drops- keratomycosis- other drugs-solution of amphotericin B, silver nitrate

Hamycin

-Developed by HA in Pimpri

-Otomycosis

-Candidiasis

Other topical agents

Cyclopirox olamine

Tolnaftate –

Whitfield oinment-

Naftifine-

Butenafine

Selenium sulfide-Dandruff