

# FUNGAL INFECTIONS AND MASSES IN CENTRAL NERVOUS SYSTEM: DIAGNOSIS AND MANAGEMENT

# Introduction

Fungi are saprophytes


- **Yeast** - candida, cryptococcus , trichosporon
- **Filamentous** – rhizopus, rhizomucor, mucor
- **Dimorphic Fungi**- blastomyces , histoplasma, coccidoïdes , paracoccidoïdes

# INFECTIVE PHASES OF FUNGI

ORGANISM	CLASSIFICATION	PATHOGENIC PHASE
PATHOGENIC		
BLASTOMYCES	DIMORPHIC	YEAST
COCCIDOIDES	DIMORPHIC	SPHERULES
HISTOPLASMA	DIMORPHIC	YEAST
PARACOCCIDOIDES	DIMORPHIC	YEAST
OPPORTUNISTIC		
ASPERGILLUS	MOULD	HYPHAL
CANDIDA	YEAST	YEAST
ZYGOMYCETES	MOULD	HYPHAL
CRYPTOCOCCUS	YEAST	YEAST

# Introduction

- Commonly seen in tropical countries
- Incidence is increasing world wide
  - Immune suppression
  - Broad spectrum antibiotic
  - Steroids
  - Drug abuse
  - AIDS , malignancy
  - International travel

- 
- Mode of infection
    - Hematogenous spread
    - Direct inoculation
    - Adjacent contiguous spread

# Pathology

- Depends on size forms
  - a. Small size - yeast enter microcirculation  
micro-abscess, meningitis
  - b. Larger hyphal forms-invade vasculature  
cause infarcts
  - c. Host immune response

# CNS MANIFESTATIONS

- Meningitis
- Meningoencephalitis
- Space occupying lesion
- Hemorrhage, infarction,
- Myelopathy

# CLINICAL FEATURES

- Meningeal syndromes- headache, nausea, vomiting, neck stiffness , fever, cranial nerve paresis, focal signs due to arteritis
- Meningitis is subacute/ chronic
- Meningoencephalitis
- Hydrocephalus



# Clinical features

- Space occupying lesions-  
granulomas  
abscesses
- Spinal cord compression
- Rhinocerebral syndromes
- Skull base syndromes
- Stroke syndromes

## MURTHY: CLINICAL SYNDROMES OF CNS MYCOSES

<b>FUNGAL INFECTIONS OF THE CNS: CLINICAL SYNDROMES</b>						
<b>FUNGAL INFECTION</b>	<b>MENINGITIS</b>	<b>INTRACRANIAL MASS LESION</b>	<b>SKULL-BASE SYNDROME</b>	<b>RHINOCEREBRAL FORM</b>	<b>STROKE SYNDROME</b>	<b>SPINAL SYNDROME</b>
ASPERGILLOSIS	+	++	+++	+	+	+
ZYGOMYCOSIS	±	++	-	+++	+	-
CRYPTOCOCCOSIS	+++	+	-	-	+	+
PHEOHYPHOMYCOSIS	+	+++	-	-	-	-
CANDIDIASIS	+	-	-	-	+	-
PENICILLIOSIS	+		-	-	-	+

### **FUNGAL INFECTIONS OF CNS: SKULL-BASE SYNDROMES**

ORBITAL APEX SYNDROME

CAVERNOUS SINUS SYNDROME

PROPTOSIS WITH OR WITHOUT OCULAR PALSY

POLYNEURITIS CRANIALIS

ORBITO-CRANIAL SYNDROMES

## HIGH INDEX OF SUSPICION

### **DIAGNOSIS OF FUNGAL INFECTIONS OF THE CNS**

IMMUNOCOMPROMISED HOST AND DIABETES MELLITUS

HIV INFECTION

TRANSPLANT PATIENT

PROSTHETIC VALVES

PARANASAL SINUS INFECTION

# INVESTIGATIONS

Routine

CSF proteins, sugar

- Cell examination

- Biochemical- count

- Cytological examination- India ink

- Cultures

- Immunoassay/ PCR

# Investigations

Blood cultures

Imaging in CNS

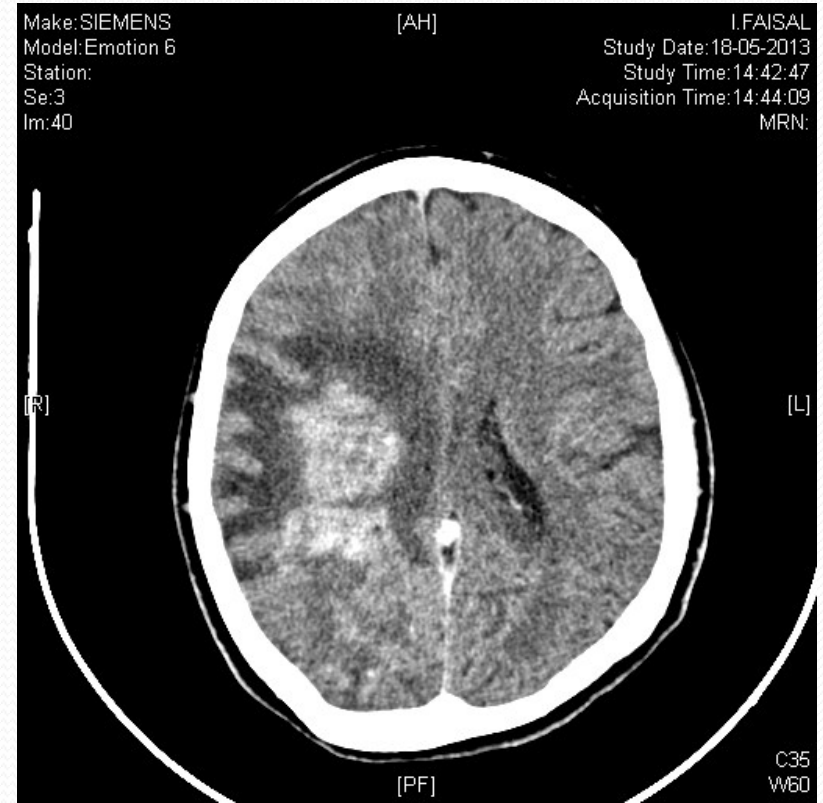
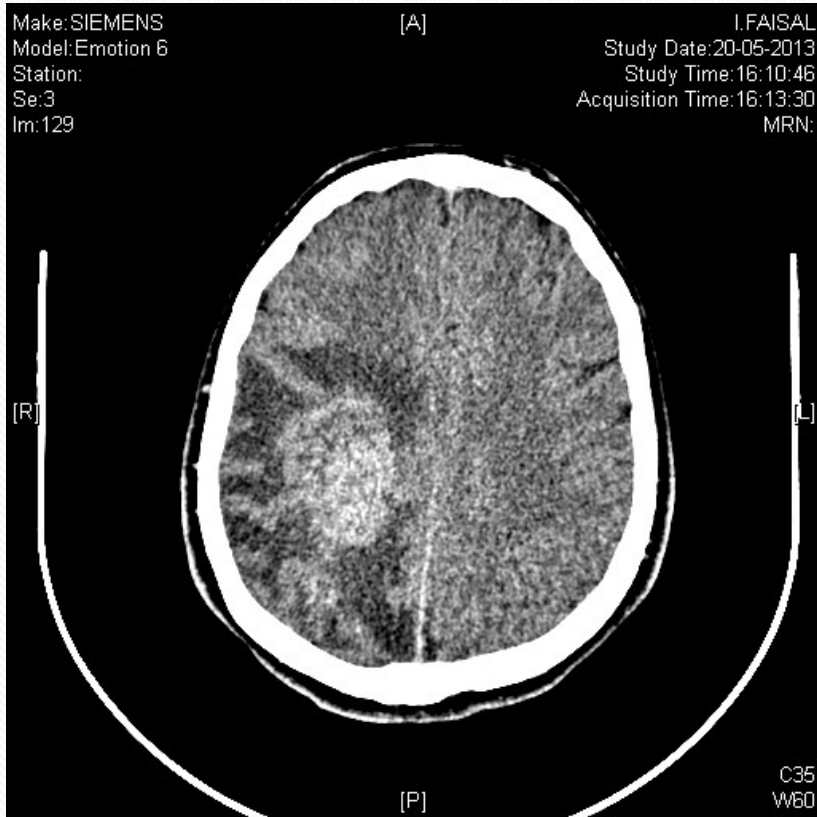
MRI

CT SCAN

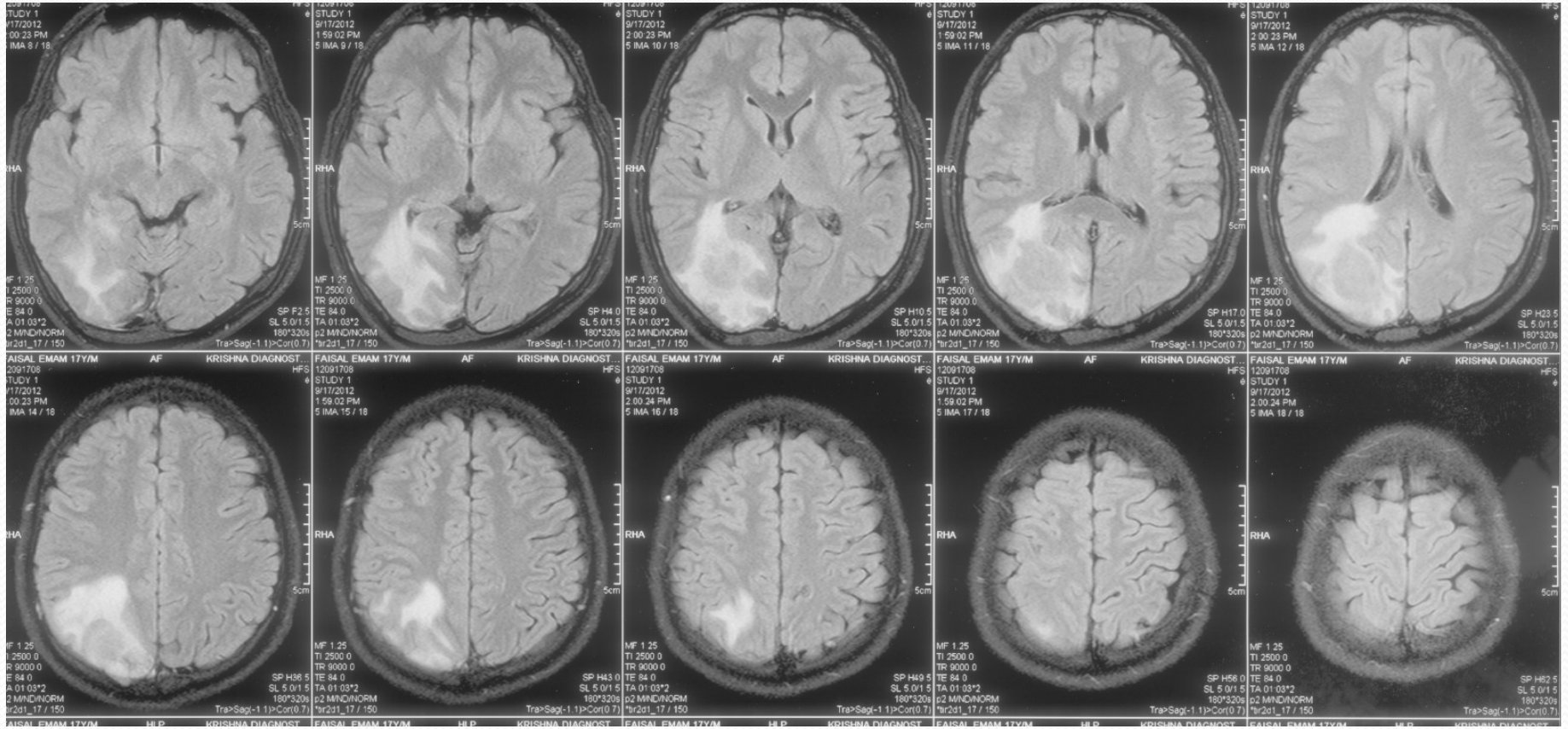
Biopsies

Evidence of infection elsewhere

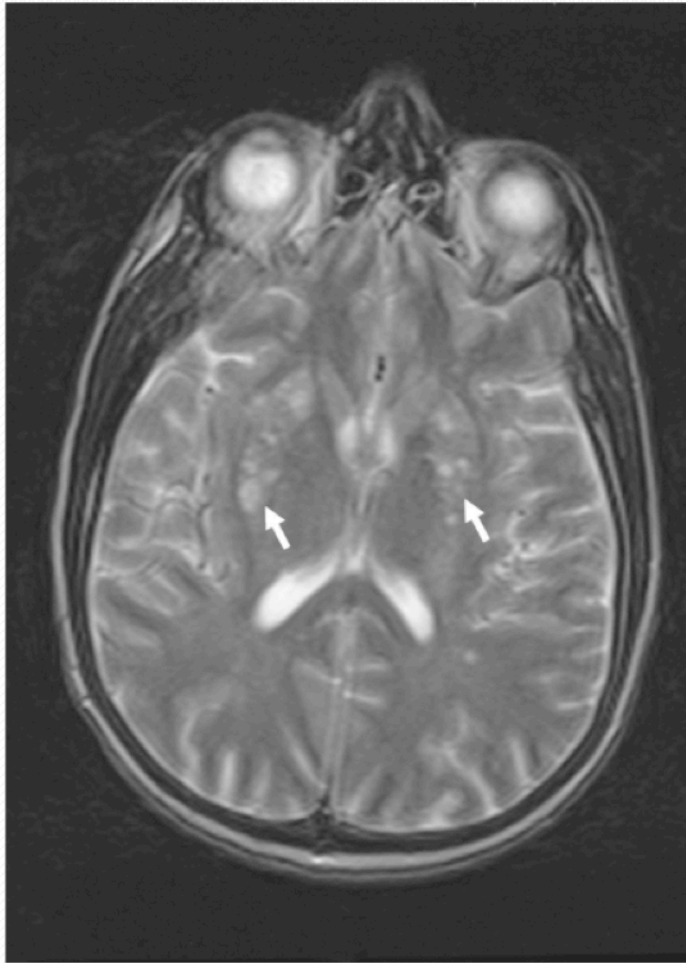
# ASPERGILLUS GRANULOMA



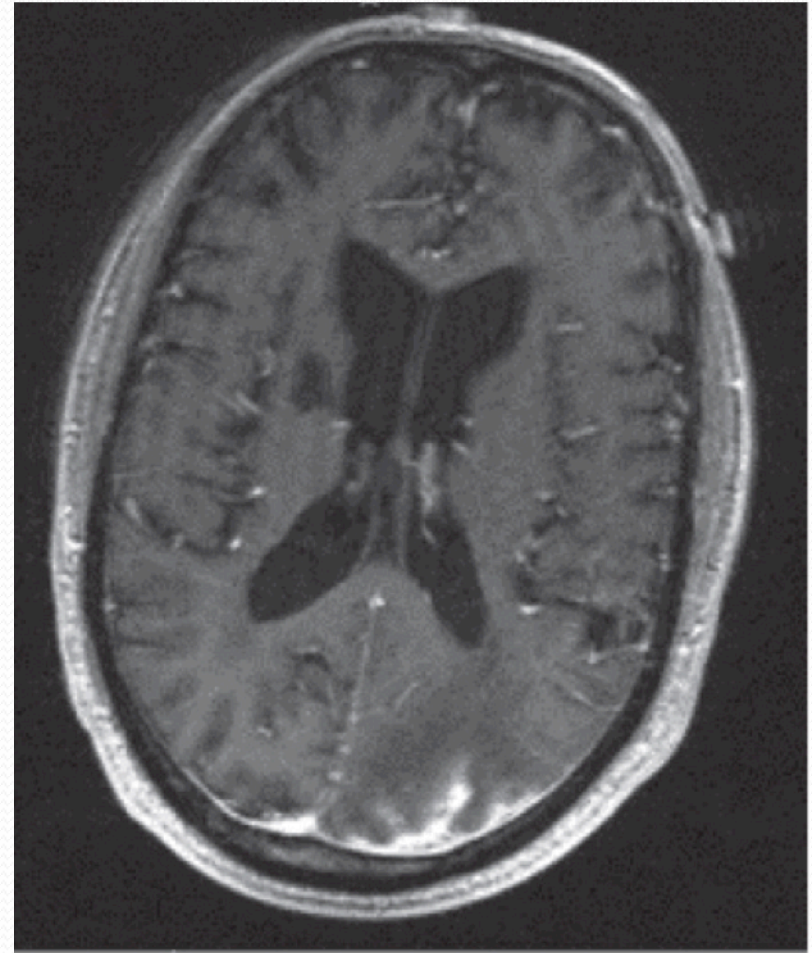
# ASPERGILLOSIS



# CRYPTOCOCCUS MENINGITIS



pseudocyst T2w



T1w contrast

# Treatment

- Nonspecific measures
  - Raised ICT – mannitol, frusemide
- Antifungal agents
- Surgical management
  - Biopsy
  - surgical excision
    - abscess drainage
    - insertion of ommaya chamber
  - Shunt



# Management of fungal intracranial fungal masses

Most commonly- *Aspergillus* sp

Divided into

- a. Rhinocerebral /sinocranial
- b. primary intracranial-
  1. extra axial
  - 2.intra axial

frontal lobes most commonly involved

fungal aneurysms – very rare

# Management of fungal intracranial fungal masses

- Differential diagnosis- Tuberculoma, Lymphoma, Gliomas, Soft tissue malignancy

Intracerebral – soft, suckable with pockets of pus

Rhinocerebral- firm fibrous

## Surgical management

stereotactic biopsy/aspiration- deep seated lesions/  
eloquent area, multiple lesions, frail patient

Craniotomy – for easily accessible areas

PNS lesion- otolaryngorhinological surgery (FESS)

Shunt surgery

Endovascular coiling for fungal aneurysms

Antifungal therapy

# Cryptococcus

Soil enriched pigeon droppings

Route of entry- respiratory system

affects RE system

Basal meningitis, Meningoencephalitis,

Granulomas and cysts- subependymal regions of thalamus  
and basal ganglia- single or grouped in jelly like mass

Spinal cryptococcosis- mass lesions, spinal arachnoiditis

- Treatment of Cryptococcus (immunocompetent )

Amphotericin B -0.7-1mg/kg/d +

5-flucytosine 100mg/kg/d for 6-10 weeks

OR

Amphotericin B -0.7-1mg/kg/d +

5-Flucytosine -100mg/kg/d for 2 weeks

Fluconazole -400mg/d for 10 weeks can be continued for 6-12 months

# Cryptococcosis: Treatment

- Preferred: (immunocompromised)
  - Induction ( $\geq 2$  weeks):
    - Amphotericin B 0.7 mg/kg IV + flucytosine 25 mg/kg PO QID
    - Lipid formulation amphotericin B 4-6 mg/kg IV + flucytosine 25 mg/kg PO QID
  - Consolidation (8 weeks):
    - Fluconazole 400 mg PO
  - Chronic maintenance: fluconazole 200 mg PO QD

# Cryptococcosis: Treatment (3)

- Flucytosine increases rate of CSF sterilization during induction therapy
- Consolidation therapy should not be started until  $\geq 2$  weeks of successful induction therapy:
  - Significant clinical improvement
  - Negative CSF culture on repeat lumbar puncture
- Fluconazole more effective than itraconazole for consolidation therapy

# Cryptococcosis: Preventing Recurrence

- Secondary prophylaxis:
  - Lifelong suppressive treatment (after completion of initial therapy), unless immune reconstitution on ART
  - Preferred: fluconazole 200 mg /d
- Consider discontinuing maintenance therapy in asymptomatic patients on ART with sustained increase in CD4 count to  $>200$  cells/ $\mu$ L for  $\geq 6$  months
- Restart maintenance therapy if CD4 count decreases to  $<200$  cells/ $\mu$ L



# Prognostic factors

- Cryptococcus

Positive india ink test

High opening pressure

Low CSF leucocyte

Extraneural cryptococcosis

Absent antibody

Initial CSF/serum cryptococcal titre 1:32

Corticosteroid

# Aspergillosis

- Saprophyte in soil

Hematogenous spread from GI tract/ Pulmonary

High affinity to blood vessels

Abscesses or Granulomas in CNS

Treatment consists of surgery + antifungal

# Aspergillosis: Treatment

- Preferred: Voriconazole -6 mg/kg IV Q<sub>12</sub>H for 1 day, then 4 mg/kg IV Q<sub>12</sub>H until clinical response, then 200 mg PO Q<sub>12</sub>H
  - Not well studied in HIV-infected patients; significant interactions with protease inhibitors and efavirenz
- Alternative:
  - Amphotericin B 1 mg/kg IV/d or amphotericin B lipid formulation 5 mg/kg IV /d
  - Caspofungin 70 mg IV for 1, then 50 mg IV /d
  - Posaconazole 400 mg PO BID

# Mucormycosis

- Rhizopus, rhizomucor and absidia

CNS -entry is by direct extension through paranasal sinuses along nerves, blood vessels and cartilage

Periorbital pain

Nasal discharge

Poorly controlled diabetic

Black necrotic mass

External ophthalmoplegia and vision loss

- Diagnosis –biopsy  
surgical excision + antifungal therapy such as  
amphotericin- b

# Candidiasis

- Gut commensal

Through blood to CNS

Immunosuppressed ,  
iv access,  
neutropenic patients,  
parenteral nutrition  
neurosurgical procedures

Small intraparenchymal micro abscesses in anterior  
and middle cerebral territory

# Prognostic factors

- Candidal meningitis  
diagnosis delay >2 weeks  
CSF glucose <35mg/dl  
raised ICT  
focal deficits

# Blastomycosis

- Inhalation of airborne spores
- Spread to CNS via hematogenous route  
or bony involvement , vertebrae are commonly involved
- Mimics tuberculosis of spine
- Treatment  
surgery + antifungal treatment



# coccidioidomycosis

- Soil saprophyte
- Route of entry of spore- lung  
chronic meningitis , granulomas in basal meninges  
mimicking tuberculous meningitis  
infects vertebral bodies
- Diagnosis by- subcutaneous nodules, csf antibodies,  
biopsy
- Treatment- amphotericin b or azoles

# Nocardiosis

- Not a true fungi
- Soil saprophyte
- route of entry- lung/skin
- CNS-abscesses, granulomas, meningitis
- Treatment- sulphonamides

# Antifungal drugs

- **Polyenes-** Amphotericin B
- **Azoles-** ketocanazole, voriconazole, fluconazole, itraconazole
- **Heterocyclic** – Griseofulvin
- **Antimetabolite-** Flucytosine
- **Echinocandins** – Caspofungin



- Polyenes

- Fungicidal
- Increasing the permeability of the cell membrane by targeting ergosterol in the membrane
- Include nystatin and AmB

- Amphoteriin -B

binds to ergostrol and disrupts fungal cell membrane

Initial test dose of 1 mg in 100ml of 5% d over 1 hr

Preloading - 500ml of saline

Amphotericin B dissolved in 500ml 5% dextrose and

started at a small dose transfused over 4-6hrs

dose increased in small increments to

0.3mg-1mg /kg

Dose concentration for infusion <0.1mg/ml



- Intrathecal administration

initial dose-0.025mg

gradually increased-0.25mg-0.5mg three times a week

### Adverse effects-

chills and rigors, hypotension

Nephrotoxicity

Thrombophlebitis

Bone marrow suppression

Electrolyte imbalances

# Lipid formulations of polyenes

- Lipid formulations of polyenes
  - Improve the therapeutic index for polyene macrolides
  - AmB lipid complex
  - AmB colloidal dispersion
  - Liposomal AmB
    - invasive fungal infections in patients refractory or intolerant to standard AmB
  - Liposomal nystatin
    - phase III clinical trials

# Lipid formulations of polyenes

- In vivo testing of liposomal AmB (1 or 3 mg/kg/d)
  - Significantly higher success rate than conventional AmB
  - Twofold to six fold decrease in drug-related adverse events
  - Lower incidence of severe drug-related side effects
  - Fewer nephrotoxicity





- Flucytosine

interferes with protein synthesis

dose- 100mg-150mg/kg/d

adverse effect- GI upset, hepatotoxic  
pancytopenia



- AZOLES

interfere with ergosterol synthesis by binding to lanosterol 14-demethylase

e.g.- voriconazole, fluconazole, itraconazole

Dose 200mg-1200mg/day

Adverse effect- nausea, loss of hair, gynecomastia, hepatotoxic

- Fluconazole given 400mg/d 8-12 weeks
- Itraconazole, ketaconazole- poor CSF penetration
- Voriconazole - 6 mg/kg IV Q<sub>12</sub>H for 1 day,  
4 mg/kg IV Q<sub>12</sub>H for 2weeks  
200mg oral 12hrly for 8-12 weeks
- Posaconazole salvage therapy for aspergillosis and candida

## ANTIFUNGAL AGENTS

### LIKELY INTRINSIC RESISTANCE TO ANTIFUNGAL AGENTS

AMPHOTERICIN B

ASPERGILLUS TERREUS, CANDIDA LUSITANIAE, TRICHOSPORON BEIGELLI, SCEDOSPORIUM PROLIFICANS

FLUCYTOSINE

NOT TO BE USED AS SINGLE AGENT BECAUSE OF RESISTANCE. MOLDS, ZYGOMYCETES, DIMORPHIC FUNGI, DEMATIACIOUS FUNGI, TRICHOSPORON BEIGELLI

FLUCONAZOLE

ALL MOLDS, CANDIDA KRUSEI

ITRACONAZOLE

CANDIDA KRUSEI

VORICONAZOLE

ZYGOMYCETES, CRYPTOCCOCUS NEOFORMANS, TRICHOSPORON SPP., FUSARIUM SPP.

ECHINOCANDINS

ZYGOMYCETES, CRYPTOCCOCUS NEOFORMANS, TRICHOSPORON SPP., FUSARIUM SPP.



- **New antifungal agents**

- **Pradimicins-benanomicins**

- bind to cell wall mannoproteins causing osmotic sensitive lysis and cell death

- **Nikkonycins**

- competitive inhibitors of fungal chitin-synthase enzymes

- **Allylamines/thiocarbamates**

- non-competitive inhibitors of squalene epoxidase

- **Sordarins**

- inhibit protein synthesis, i.e. elongation factor 2

- **Cationic peptides**

- bind to ergosterol and cholesterol and lead to cell lysis

# Experimental immunotherapy

- Increase neutrophil , stimulate neutrophils and macrophages - G-CSFs and GM-CSFs
- Increase cellular immunity- IFN-gamma
- Increase humor immunity- vaccines

# Literature review

- Intracranial fungal granuloma

Prof B.S.Sharma et al Dept of neurosurgery PGI  
chandigarh. Surgical neurology 1997,47:489-97



Thank you