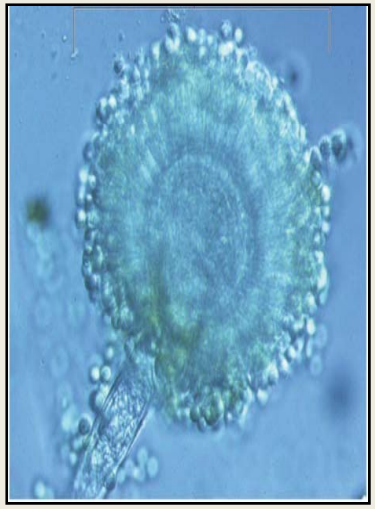
FUNGAL INFECTIONS IN NEUROSURGERY



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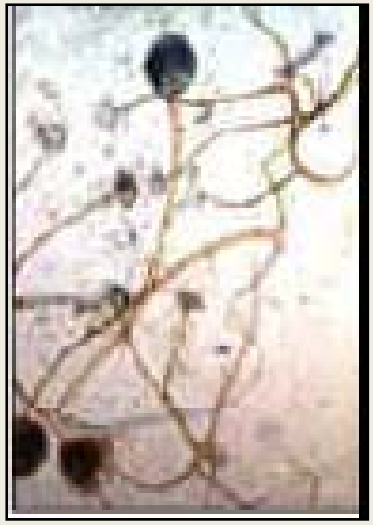


Introduction

- Fungi common in environment but only few pathogenic
- 1 million species : 200 pathogenic to man : 20 invasive systemic infections
- Uncommon or rare infections of CNS
- Since non-notifiable disease, exact incidence unknown
- Importance : Wide spectrum of neurologic manifestations, many lethal
- Preponderance in the 4^{th} decade *
- Male predominance : due to increased exposure of males to various environmental hazards as compared to females*

*Chakrabarti A. et al Otolaryngol Head Neck Surg 1992;107:745-750

Historical aspects

- 1892 : A. Dosadas & R. Wernicke – described coccidiomycosis
- 1894: Busse – described cerebral cryptococcosis
- 1897: Oppe – 1st case of cerebral aspergillosis extending from sphenoid sinusitis
- 1905: Van Hanseman – 1st demonstrated Cryptococcus in CSF
- 1933: Smith & Sano – 1st case of candida meningitis
- 1943 : Gregory – described Rhinocerebral zygomycosis.

- 1903: Antifungal CT – KI used for sporotrichosis
- 1953: 1st useful polyene drug Nystatin
- 1956: 2nd polyene drug Amphotericin B (AMB) “Standard”

FUNGI

Yeast	**Filamentous**	**Dimormhic Fungi**
Candida	Aspergillus	Blastomyces
Cryptococcus	Rhizopus	Histoplasma
	Rhizomucor	Coccidoides
	Mucor	Paracoccidoides

- Eukaryotic plants
- Saphrophytes: devoid of chlorophyll and depend on hosts
- Rigid cell wall: stains with Periodic Acid Schiff' (PAS) or Gomori methenamine Ag stain.
- Most are weakly Gram-positive except Candida.

BROAD CATEGORIES OF FUNGI

ORGANISM	CLASSIFICATION	PATHOGENIC PHASE
PATHOGENIC : - infect a healthy host.		
BLASTOMYCES	DIMORPHIC	YEAST
COCCIDOIDES	DIMORPHIC	SPHERULES
HISTOPLASMA	DIMORPHIC	YEAST
PARACOCCIDOIDES	DIMORPHIC	YEAST
OPPORTUNISTIC: - can not infect a healthy volunteer but can do so when host defenses are compromised		
ASPERGILLUS	MOULD	HYPHAL
CANDIDA	YEAST	YEAST
ZYGOMYCETES	MOULD	HYPHAL
CRYPTOCOCCUS	YEAST	YEAST

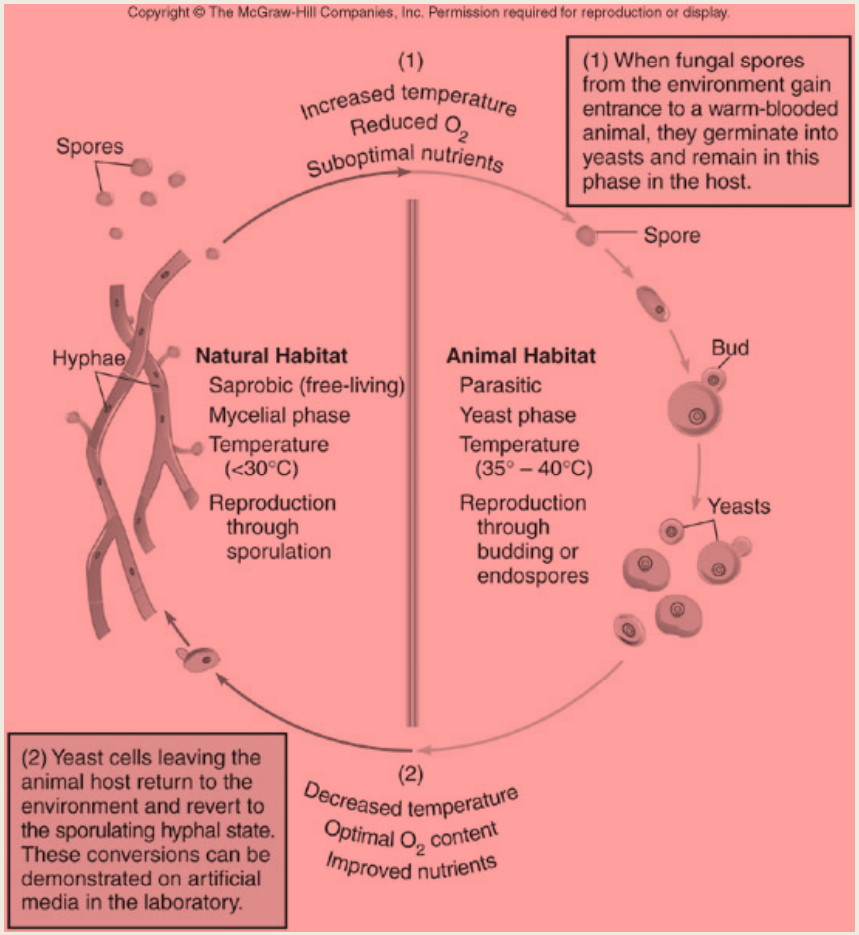
True or **primary** fungal pathogen can invade and grow in a healthy, noncompromised host

Bennett JE. Principles and practice of Infectious diseases,Churchill Livingstone, 2000:2654-2656

Most striking adaptation to survival and growth in the human host is the ability to switch from hyphal cells to yeast cells.

Thermal Dimorphism

25°C - Hyphal state



37°C – Yeast State

Thermal dimorphism is a property of true fungal pathogens but is uncommon for opportunistic pathogens

Increasing incidence

- Increased awareness of the condition
- Improved diagnostic techniques
- Widespread use of:
  - Steroids
  - Broad spectrum antibiotics
  - Cytotoxic & immunosuppressive drugs
- Increased survival of the patients with multiple risk factors
  - Immune suppression/ immunocompromised: Diabetes, AIDS , malignancy

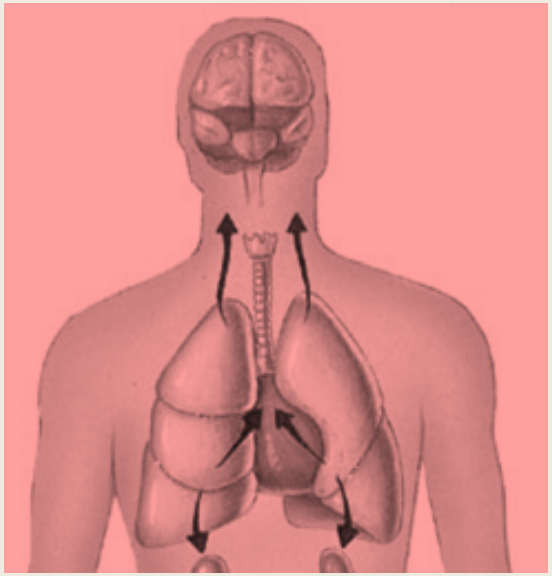
Singh N. J Antimicrob Chemother 2000;45(6):749-755

In about half of the patients no cause for immunosuppression can be found

Nadkarni TD, Goel A ,et al. J Postgrad Med 1993; 39:43-44
Rajshekhar V. Neurology India. July-Sept 2007, Vol 55, Issue

Mode of infection to the CNS

- Adjacent contiguous spread
- Hematogenous spread: pulmonary, GIT, prosthetic heart valves
- Direct inoculation



Routes of dissemination

- Candida:
  - Endogenous : digestive tract, female genitalia
  - Colonization of artificial prosthesis, implants, i.v. lines, peritoneal dialysis catheters, VP / VA shunts, EVD
  - Direct co-relation of risk with extent of *neutropenia*
- Aspergillus and Zygomycosis:
  - Structures adjacent to cranial cavity eg. Sinuses, nasopharynx, middle ear cavity, mastoid air cells
  - Zygomcosis : diabetes
- Histoplasma and Cryptococcus:
  - Hematogenous from often subclinical pulmonary focus
  - Rarely: direct inoculation- trauma, surgery, lumbar puncture

CNS MANIFESTATIONS

- Meningitis
- Meningoencephalitis
- Hydrocephalus
- SOL: Granuloma formation, Abscesses
- Vasculitis
- Infarction
- Hemorrhage
- Myelopathy

Diamond RD. Ann Intern Med 1974;80:176-181
Jamjoom AB. Acta Neurochir (Wien) 1995;137(1-2):78-84

CNS MANIFESTATIONS OF FUNGAL INFECTIONS

Fungal infections	Meningitis	Intracranial masses	Skull base syndrome	Rhinocerebral form	Stroke syndrome	Spinal syndrome
Aspergillosis	+	++	+++	+	+	+
Zygomycosis	+/-	++	-	+++	+	-
Crytococcosis	+++	+	-	-	+	+
Candidiasis	+	-	-	-	+	-

Murthy JMK, Neurology India, Jul- Sept 2007, Vol 55, Issue 3

Meningitis and meningoencephalitis

- Subacute / chronic
- But as lethal as bacterial if untreated
- Most yeasts: Crytococcus, Blastomyces, Coccidiomyces, Paracoccidoides, Sporotrichium, Histoplasma and Candida
- Access to microcirculation: seed subarachnoid space
- Meningitis most significant complication of Coccidiodes infection

Meningitis and meningoencephalitis

- Cryptococcal meningitis:
  - 5-10% of HIV pts have it as AIDS defining ilness
  - 40% initial manifestation of HIV infection
  - Histoplasma meningitis
  - 5-10 % cases of disseminated ds
- Rx:
  - Cryptococcal: Amphotericin B (AMB) + flucytosine
  - Candida: AMB
  - Coccidiodal: IV + Intrathecal/intraventricular
  - Blasto- & Histoplasmosis: AMB + Fluconazone

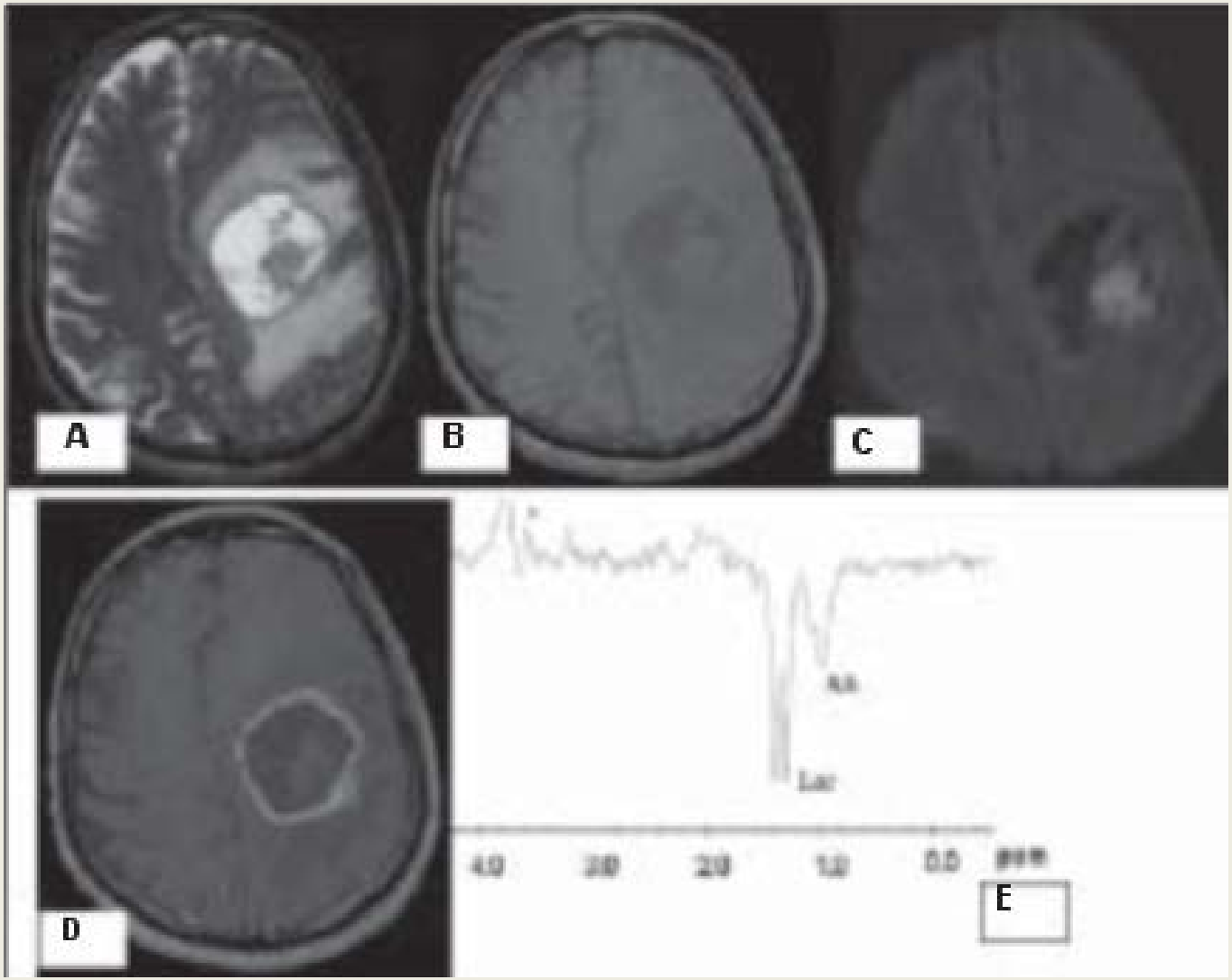
Increased ICP

- Due to
  - (1) HCP &/or (2) SOL: abscess, granuloma, cysts, co-existing brain tumors.
- Symptomatic HCP: meningitis / ventriculitis
- 2° to arachnoid scarring esp in basal region
- Obstruction in the ventricular system
- Management: Surgical decompression / VP shunt unilateral / bilateral

Fungal Abscess

- Common : Candida, aspergillus, cladosporium, mucormycosis, fungus like bacteria (nocardiosis and actinomycosis)
- Multiple areas of infection within the brain
- Meningoencephalitis with vasculitis thromboisis → hemorrhagic infarct → abscess forms
- 70 % neonates with systemic fungal infections.
- Candidal: small, multiple, round, hypoechoic lesions with echogenic areas in periventricular region.
- Aspergillosis: few large echogenic in periventricular areas.
- Stereotactic /USG guided aspiration with antifungal drugs with excision whenever possible/ needed

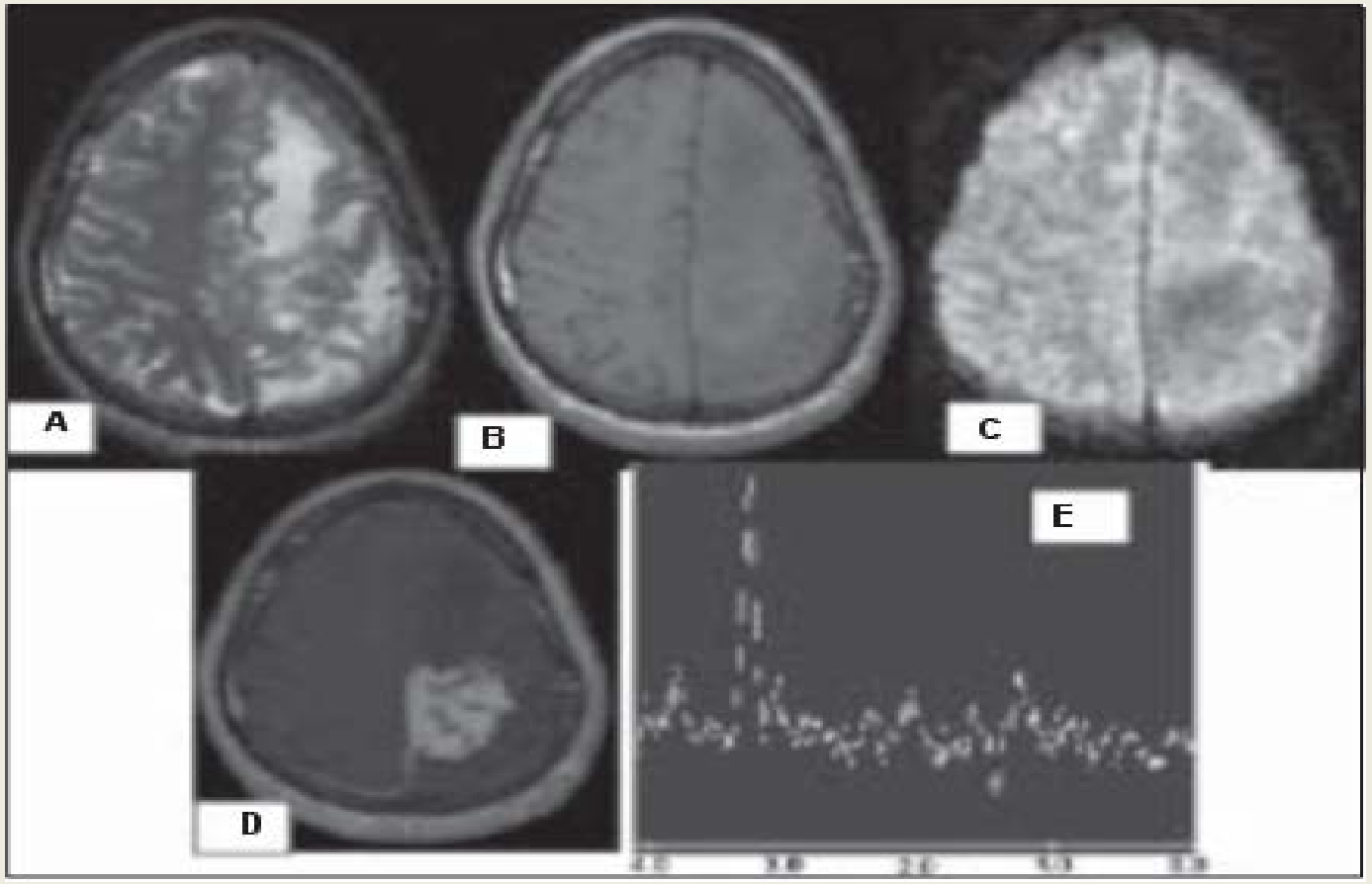
Fungal abscess



Fungal granulomas

- Common: Aspergillus, Histoplasma, Blasto-, Paracoccidio-, Cryptococcus, Actinomycosis.
- Resemble tuberculomas, but are
  - More fibrous – often cut with knife or scissors as they resist curretting.
  - Clear plane of cleavage as in tuberculomas and meningiomas is not present.
  - Adherence to dura is firmer.
  - Should be completely excised f/b antifungal Rx

ASPERGILLUS GRANULOMA



Management of fungal intracranial fungal masses

Most commonly- Aspergillus, Mucor sp

Divided into

a. Rhinocerbral /sinocranial

b. Primary intracranial- 1. extra axial

2.intra axial

frontal lobes most commonly involved

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

Management of fungal intracranial fungal masses

- Surgical management
  - Stereotactic biopsy/aspiration- deep seated lesions/ eloquent area, multiple lesions, frail patient
- Craniotomy – for easily accesible areas
- Combined Approaches with ENT surgeon
- PNS lesion- otolaryngorhinological surgery (FESS)
- Shunt surgery- if associated HCP
- Endovascular coiling for fungal aneurysms
- Antifungal therapy

Intracranial fungal granuloma.

Sharma BS, Khosla VK, Kak VK, Banerjee AK, Vasishtha RK, Prasad KS, Sharma SC, Mathuriya SN, Tewari MK, Pathak A.

Surg Neurol. 1997 May;47(5):489-97.

- Thirty-two cases: Rhinocerebral group (22cases) Primary intracranial group (10 cases)
- The granulomas were soft, suckable, and contained pus or necrotic material.
- Postoperative and overall mortality were 37.5% and 50%,
- Meningoencephalitis was the most common cause of death.
- Altered sensorium, pus in the granuloma, and/or severe brain edema were poor prognostic factors.
- All survivors except four have symptomatic residual or recurrent lesions.
- CONCLUSION:
- Early diagnosis with MRI or stereotactic biopsy, radical surgery, and high dose and chronic suppressive chemotherapy may improve overall results in these cases.

Intracranial Fungal Granuloma In Immunocompetent Children: A Ten Year Clinicopathological Study.

F U Ahmad, V Naik, A Gupta, A Suri, C Sarkar, A K Mahapatra, B S Sharma

AANS Nov 2007

- 8 Patients : Age ranged from 7 years to 17 years.
- 5 males and 3 females.
- Headache, proptosis and seizures were common presenting complaints
- Five had anterior cranial fossa lesions, 3 had middle fossa lesions and 1 in CP angle
- Two patients expired due to meningoencephelitis and infarcts.
- Rest all had good clinical outcome.
- Conclusions: ICFG is rare in children, is often misdiagnosed before surgery
- high morality rate unless managed properly.
- Poor neurological status at presentation and opening of ventricles during surgery are poor prognosticators.
- Prompt therapy with antifungal drugs and radical surgery can lead to good outcome.

Fungal infections of CNS: Skull Base Syndromes

- Invasive Aspergillus /Mucormycosis sinusitis.
- Basifrontal and basitemporal granulomas in immunocompetent.
  - Orbital Apex syndrome
  - Cavernous sinus syndrome
  - Proptosis ± ocular palsy
  - Polyneuritis cranialis
  - Orbito-cranial syndromes

Murthy JMK, Neurology India, Jul- Sept 2007, Vol 55, Issue 3

Orbitorhinocerebral syndrome

- Fungal infections of nasal cavity, paranasal sinuses, orbit, cranial bones and mandible: l/t intracranial infection
- Most common: Aspergilllosis and zygomycosis

Features of Orbitorhinocerebral ds *(Rhinocerebral syndrome)*

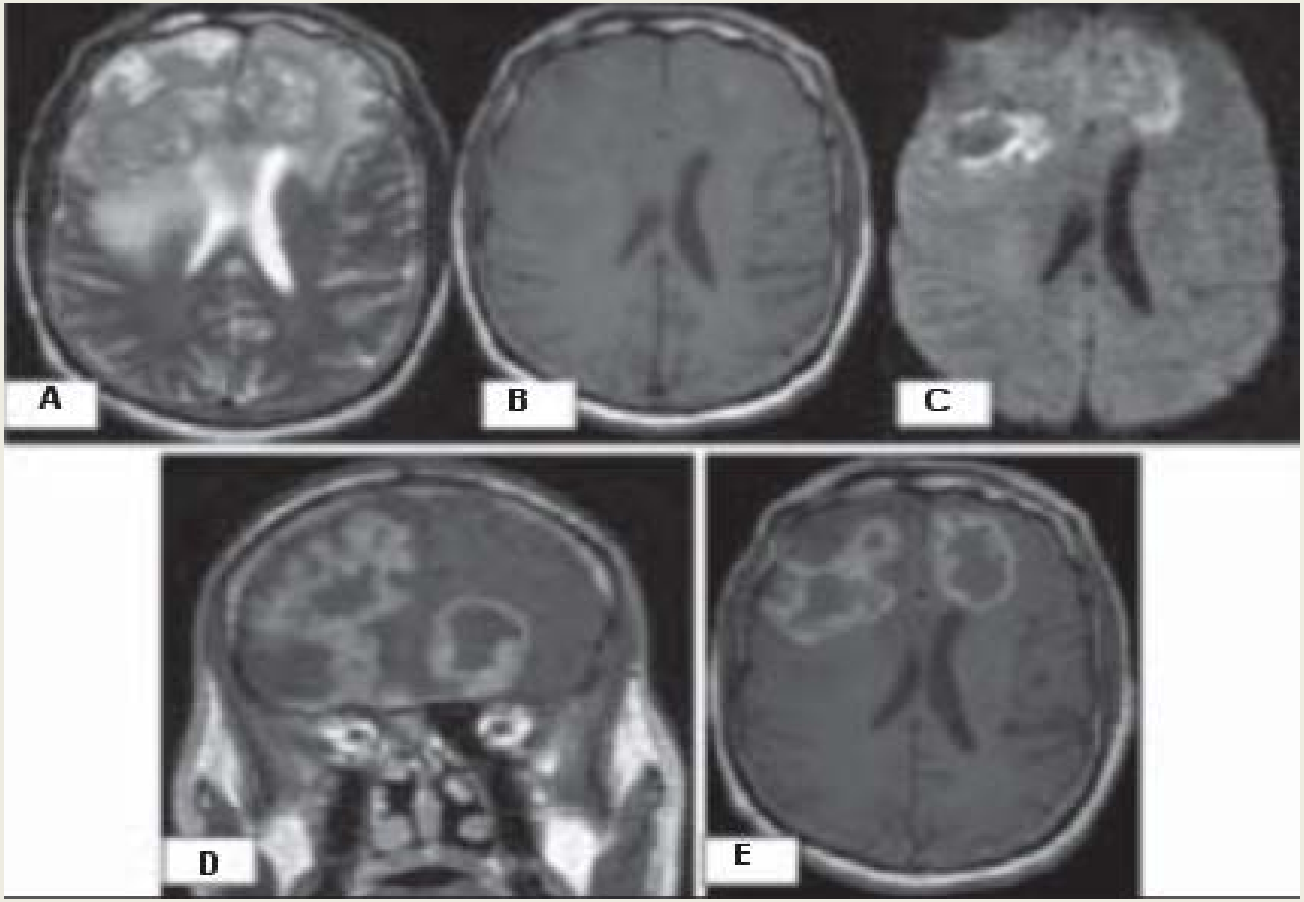
Periorbital pain, proptosis, chemosis

Nasal discharge, black necrotic mass

External opthalmoplegia, loss of vision (central retinal artery) and sensation over forehead

Retro-orbital venous obstruction (cavernous sinus) and ICA involvement (stroke)

RHINOCEREBRAL ASPERGILLOSIS



•Murthy JM. J Assoc Physicians India 2000;48(7):677-681

Feature	Rhinocerebral	1° Intracranial
Paracranial focus	PNS, orbit, ear	None
Age	>30 years in 50% cases	<30 years in 80% cases
Duration of Illness	>3 months	<3 months
Mode of spread	Direct extension	Hematogenous/ retrograde thrombosis
Common symptoms	PNS symptoms, Raised ICT	Raised ICT, seizures
Common Signs	Cranial nerve deficits	Focal deficits
CT findings	Hyperdense, mild enhancement	Mixed density, patchy or rim enhancement
Location	Basal	parenchymatous

Feature	Rhinocerebral	1° Intracranial
SAH	Nil	Present
D/D	Malignancy	Tuberculosis
Diagnosis	Early by PNS biopsy	Delayed till craniotomy
Dural involvement	Common	Uncommon
Gross appearance	Tough, fibrous	soft
Surgical resection	Mostly partial	Total
Prognosis	High morbidity	High Mortality
Reccurrence	Common	Uncommon

Acute cerebrovascular events

- Sudden cerebrovascular event:
  - Arteritis causing occlusion mainly of ICA and its branches
  - Aneurysms causing SAH.
- Aspergillosis and Zygomycosis mainly obstruct large and medium sized arteries, hgic infarcts may convert into septic.
- Rx : direct surgery inappropriate, antifungals and supportive.
- Fungal aneurysms:
  - Commonly present with sudden severe SAH
  - Aspergillus is the most common causative fungus.
  - Uncommon: Penicillium, Coccidiodes, Zygomycetes.
  - Warning symptoms and signs are absent
  - Rx: if aneurysm recognized- excision

Spinal Fungal Infections

- Common: Coccidiomycosis, blastomycosis, histoplasmosis, aspergillosis
- Upper thoracic spine mc involved (contiguous spread of infection from lungs)
- Presentation
  - Intramedullary lesions: granuloma, abscess
  - Spinal arachnoiditis
  - Paradural infections
  - Vertebral osteomyelitis
  - Compressive myelopathy is very rare
- CT/MRI: non-specific- spondylitis, paraspinal abscess, granulomas
- Diagnosis:
  - Biopsy, pus culture
- Treatment:
  - Antifungals + NSx : Paraspinal abscess, spinal granuloma & vertebral lesions Spinal deompression and stabilization
- Prognosis : poor

Investigations

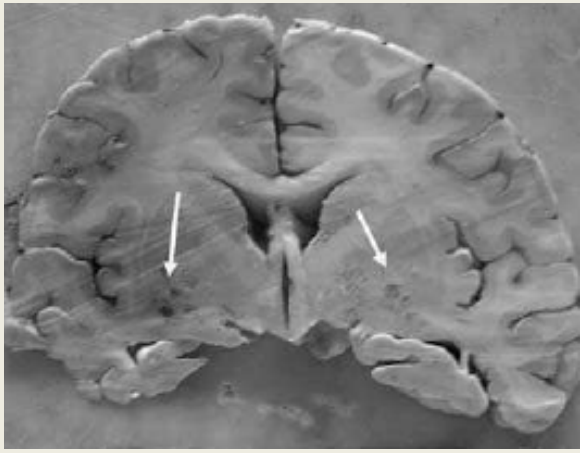
- Fungal : CSF/ Blood cultures
- Imaging in CNS
  - MRI : hypo- or iso- intense on T2WI with hyperintense perilesional edema
  - CECT SCAN
- Biopsies : specimen in normal saline
  - stained with Periodic Acid Schiff's stain/ Gomori methenamine silver stain (especially for Aspergillosis or Zygomycoses)
  - or with hematoxyllin and eosin stain (for Cladosporium and other dermatiaceous fungi).
- Evidence of infection elsewhere
- Immunocompromise : status of DM/ AIDS/ steroids

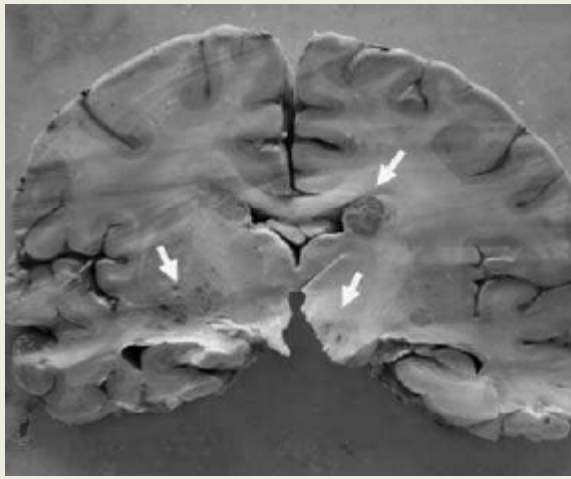
Cryptococcosis (European Blastomycosis)

- Ubiquitous – soil and bird excreta
- Pigeon-breeders – special risk
- Spherical budding capsulated yeast (5-20 µ)
- Route of entry- respiratory system: affects RE system
- Primary focus : lungs
- Secondary dissemination: hematogenous
- 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 arachanoiditis
- One of the mc CNS infections in immunocompromised, children, elderly

Cryptococcosis : Neuropathology

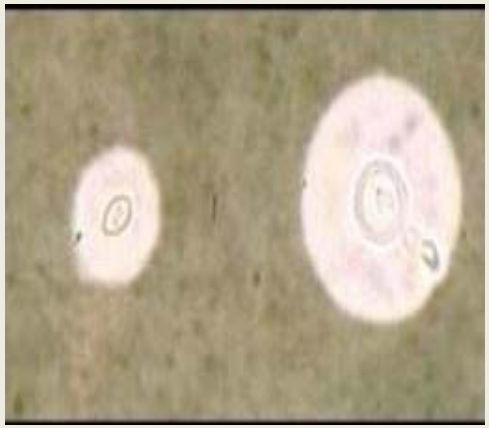
- Leptomeninges: infiltrated, thickened & opaque
- Virchow-Robin spaces: distended with organisms
- Granulomatous lesions in parenchyma
- Spinal arachnoididtis
- Chronic fibrosing leptomeningitis may l/t HCP
- Basal ganglionic pseudocysts (less common): exuberant capsular material produced by prolifertaing crytococci
- Rarely aggregate: Cryptococcoma, Toruloma
- Meningitis:
  - minimal inflammation: capsule masks surface ag
  - Glial reaction & cerebral edema –minimal
  - Slimy exudate over surface and base of brain





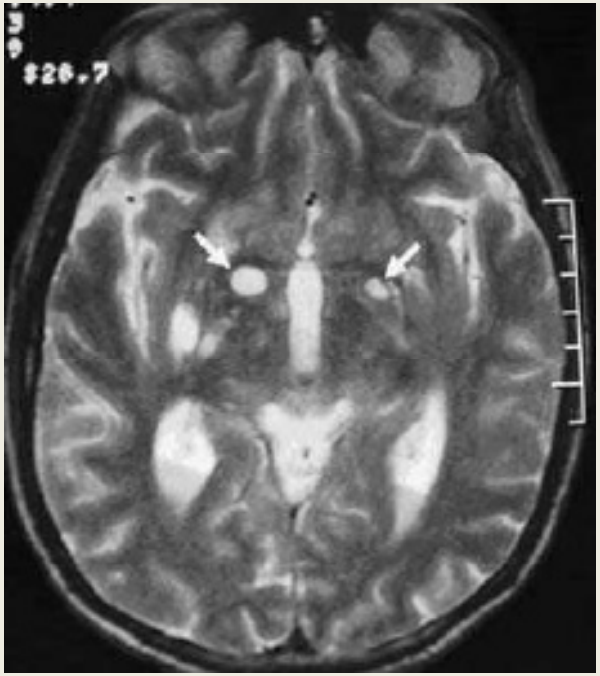
Cryptococcosis : Diagnosis

- CSF clear (as capsule transparent), xanthochromic
- India-ink prep: demonstrates mucoid capsule
- Mucicarmine and Alcian blue better show capsule
- Tissue stains : PAS & methenamine silver
- Antigen titer : CSF
- CSF culture: at 30° C x 5 days
- Positive serum latex agglutition test with ↑ titers: prognostic value.
- Chest x-ray: pulmonary lesion



Cryptococcosis : Patterns on CT & MRI

- Ventricular dilatation
- Virchow- Robin space dilatation
- Leptomeningeal enhancement
- No difference d/t immunity level

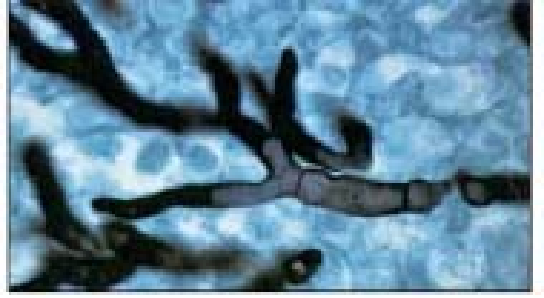


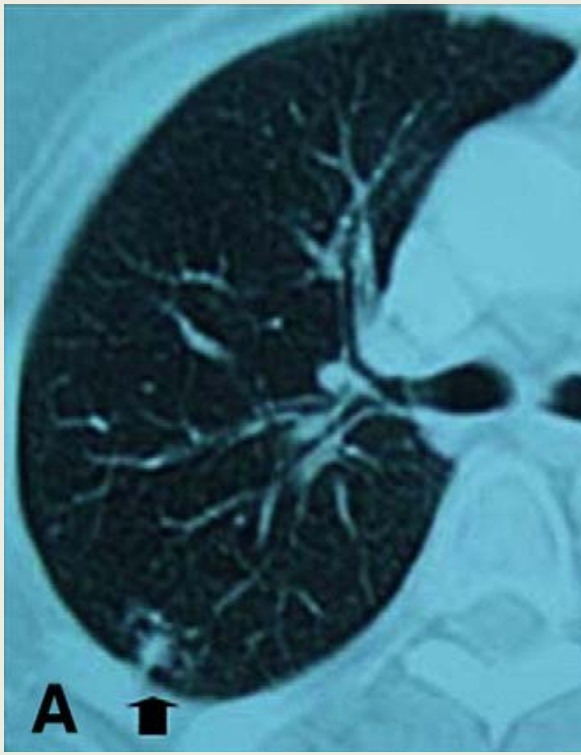
Cryptococcosis : Treatment

- Untreated : fatal
- Immunocompetent
  - AMB -0.7-1mg/kg/d + 5-flucytosine 100mg/kg/d for 6-10 weeks or
  - AMB -0.7-1mg/kg/d x 6 weeks + Fluconazole - 400mg/d for 10 weeks can be continued for 6-12 months
- Immunocompromised
  - Induction (≥2 weeks):
    - AMB 0.7 mg/kg IV + flucytosine 25 mg/kg PO QID
    - Lipid formulation AMB 4-6 mg/kg IV + flucytosine 25 mg/kg PO QID
  - Consolidation (8 weeks):
    - Fluconazole 400 mg PO
  - Chronic maintenance: Fluconazole 200 mg PO OD

Aspergillosis

- Temperate climate, constant exposure to high spore content
- Moldy work environment
- Species causing CNS infection:
  - A. fumigatus, A. niger, A.flavus, A. oxyzae
- Saprophytic, ubiquitous, opportunistic: soil, plants and decaying matter
- Branching septate hyphae 4-12 µ in width
- Primary portal of entry: respiratory tract
- Infection of brain:
  - Directly : nasal sinuses via vas channels
  - Blood born : lungs , GIT
  - Airborne: contaminating neurosurgical operative field.



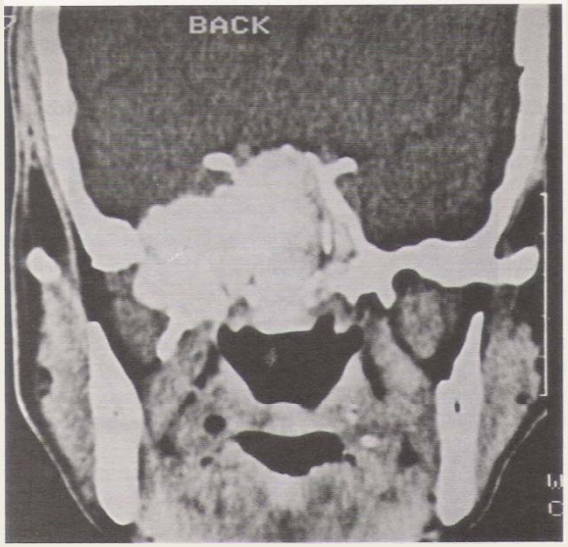


Aspergillosis : Neuropathology

- Sinocranial in origin is MC
- 1° focus- paranasal sinuses
- Chronic mycoses of paranasal sinuses:
  - Orbital, cranial, intracranial (extradural, dural, intradural)
- Angiotropic – marked tendency to invade vs: most striki *vascular invasion with thrombosis*.
  - Necrotizing angitis, 2° thrombosis & hemorrhage
  - Acute manifestations of FND in ACA & MCA distribution
- Hemorrhagic infarcts may convert to septic infarcts with associated cerebritis and abscesses
- Hyphae in blood vs of all sizes with invasion through walls into adjacent tissues; reverse invasion can occur.
- Purulent lesions: chronic , tendency for fibrosis and granuloma formation.

Aspergillosis : Presentation

- Suspected : acute onset FND due to suspected vascular or SOL, esp in immunocompromised.
- Paranasal sinus disease patients: orbital extension with proptosis, ocular palsies, visual deterioration and chemosis (Orbitorhinocerebral syndrome)
- Intracranial SOL with ↑ ICP
- Acute stroke*
- Aneurysms**
- Meningitis: very few cases

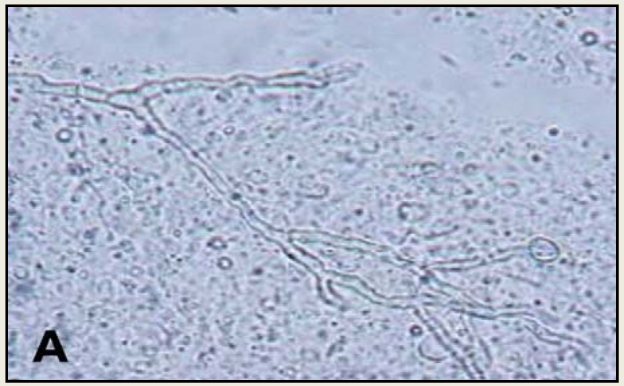


*Hurst RW et al. AJNR 2001;22(5):858-863

**Ishikawa T et al. Surg Neurol 2002;58(3-4):261-265

Aspergillosis : Diagnosis

- Direct exam & culture
- CSF: pleocytosis – 600 cells/mm³, mod ↑ proteins but sugar is normal.
- Rarely found in CSF: Methenamine Ag stain
- Serologic test Double diffusion CIE, IF, ELISA
- Spinal disease: image-guided aspiration, vertebral biopsy, histological examination and culture



Branched hyphae at 45° C
In 15 % KOH

Colonies on Sabraud's agar

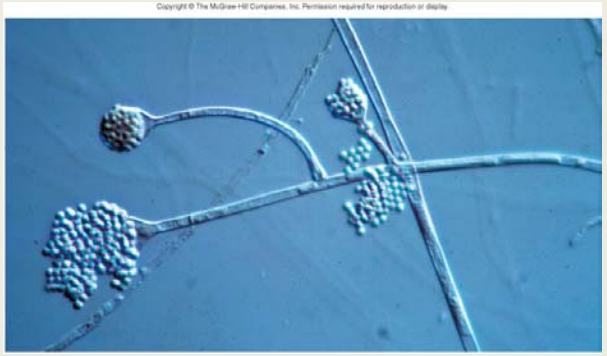
Conidial head

M. Turgut et al. / Surgical Neurology 69 (2008) 169– 174

Aspergillosis : Treatment

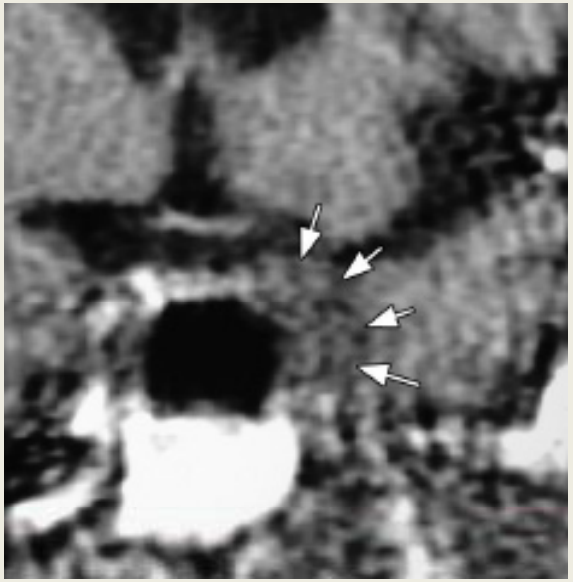
- Aggressive NSx intervention: abscess, granuloma, focally infarcted brain.
- Correction of underlying risk factors and source of infection
- AMB + Flucytosine combinaion used
- Preferred: Voriconazole -6 mg/kg IV Q12H for 1 day, then 4 mg/kg IV Q12H until clinical response, then 200 mg PO Q12H
  - Not 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
  - Itraconazole high dose 880 mg/d x 4 months f/b 400 mg/d x 5 months
  - Caspofungin 70 mg IV for 1, then 50 mg IV /d
  - Posaconazole 400 mg PO BID

CNS Mucormycosis



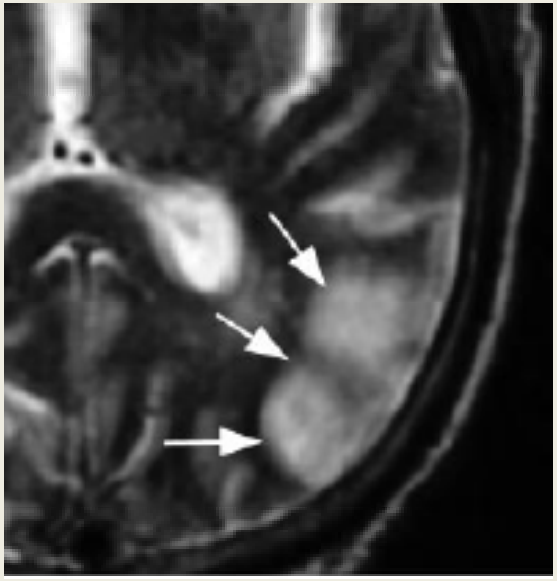
- Rhizopus, mucor and absidia genera
- R. arrhizus, R. oryzae - 95 % cases
- Ubiquitous in soil, manure, decaying vegetation
- Airborne infection in rhinosino-orbital region, resp system, GI

- CNS infection by direct invasion through paranasal sinuses along nerves, blood vessels, cartilage or hematogenous
- Associated with diabetic ketoacidosis, iv drug abuse, renal transplant, malignancy, steroid Rx
- Rhinocerebral syndrome



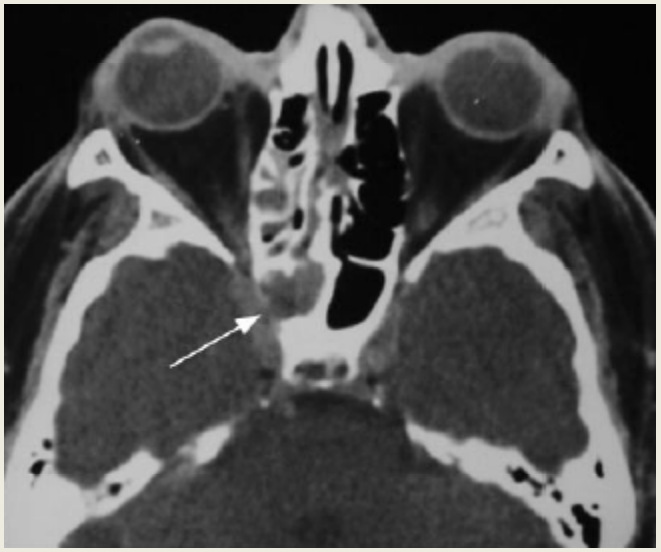
Coronal T1WI: soft-tissue thickening in the region of the left cavernous sinus (arrows) secondary to invasion by the sphenoid sinus disease.

T2WI shows min mucosal thickening in left sphenoid sinus. The normally expected flow void of left carotid artery is absent (arrow).

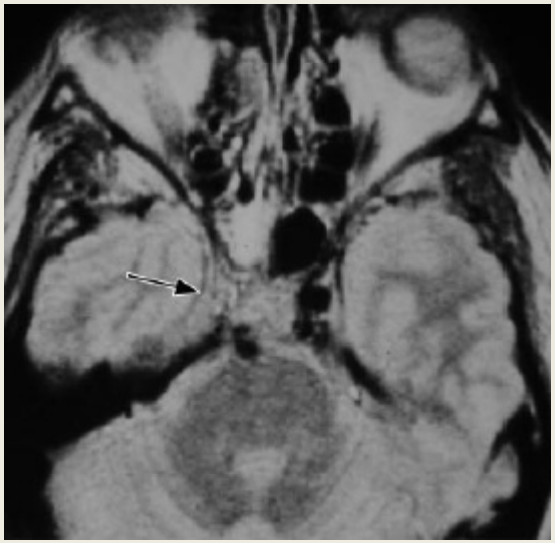


T2WI acute infarct involving the left temporal lobe (arrows).

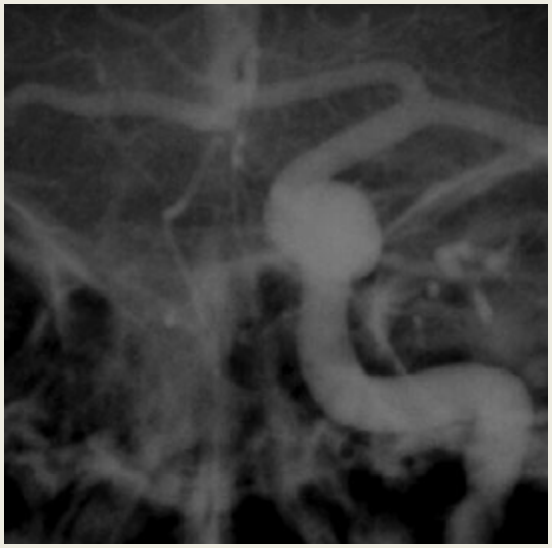
CNS Mucormycosis



CECT scan right ethmoid & sphenoid sinusitis with destruction of the lateral wall of the right sphenoid sinus



Proton DWI:occlusion of right internal carotid artery more clearly, with absence of the normal flow void in the artery (arrow).



DSA with injection of the left ICA shows cross flow to the right carotid circulation.

CNS Mucormycosis

- Angiotropic : Occlude vessels- thrombosis and associated infarction
- Hemorrhage into infarcted brain or from mycotic aneurysm
- Fronatal lobe abscess and infarct
- Predominatly neutrophilic response – granulomas not seen
- Orbitorhinocerebral ds is potentially lethal with rapid progression and high mortality
- Diagnosis : biopsy of necrotic material or nasal mucosa
- Sabouraud's agar: grows rapidly
- Rx: control diabetes and predisposing conditions
- AMB+ septran x 10-12 wks with radical debridement to reduce mass with irrigation of paranasal sinuses with antifungal agents

Bilateral ACA aneurysm due to mucormycosis.

- *M K Kasliwal, V Reddy, S Sinha, B S Sharma, P Das, V Suri*
- *Journal of clinical neuroscience (2009) Vol16, Issue: 1, Pages: 156-159*

- True mycotic aneurysms are extremely rare
- dismal prognosis.
- mostly follow fungal meningitis or septicemia

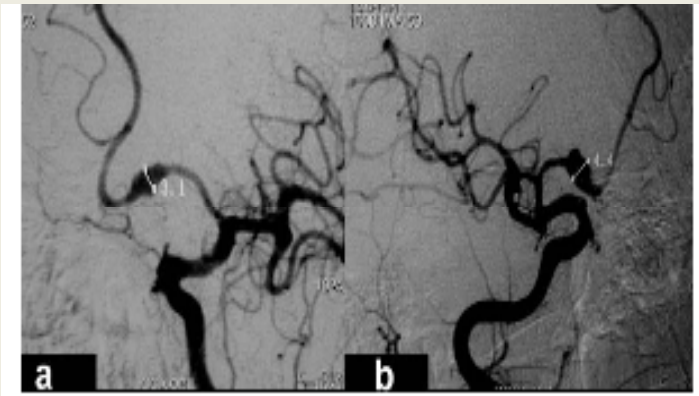
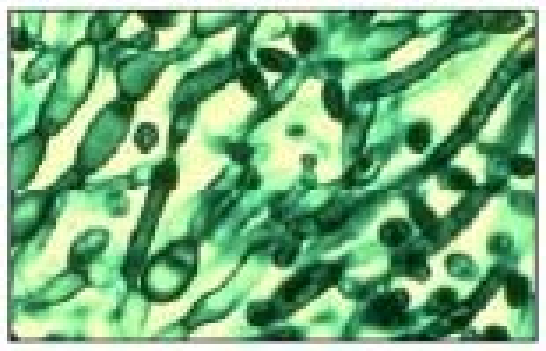


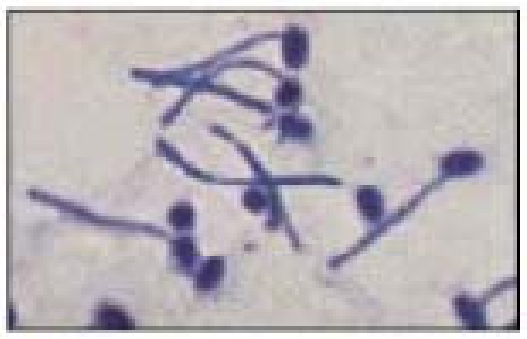
Fig. 2. Digital subtraction angiograms showing bilateral almost mirror image-like symmetrical fusiform aneurysms of the (a) left and (b) right anterior cerebral arteries on oblique internal carotid artery projections with no obvious necks.

•highlights an atypical presentation of fungal infection that can perplex the best of clinicians and thus delay diagnosis.
•high index of suspicion should be maintained when a neurosurgical patient is predisposed to fungal infection.

Candidiaisis

- Most common cerebral mycoses in autopsy studies
- Ubiquitous present as epithelial infections when balance with host is altered in favor of yeast
- Primary focus: infects GIT – oral cavity, esophagus
- Spread to CNS- hematogenous: also from colonized *ventricular drains, shunt tubings & central venous lines*
- Direct inoculation via infected wound
- Neutropenic patients esp susceptible

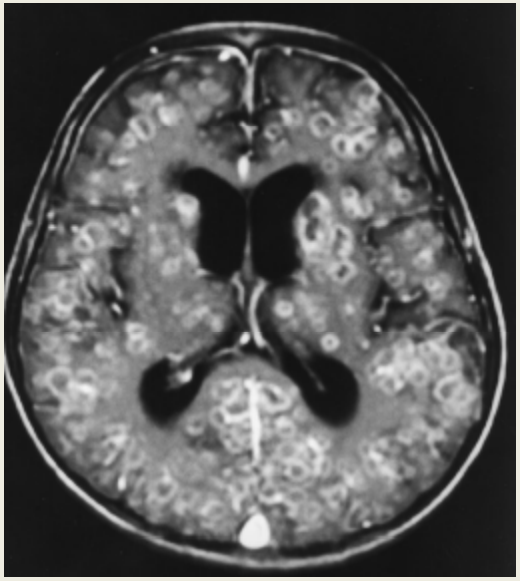




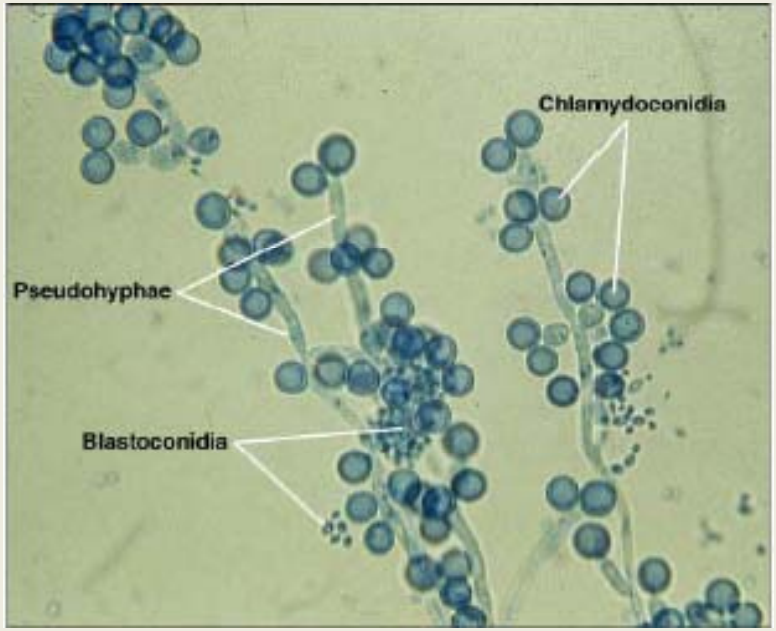
AJNR 18:1303–1306, Aug 1997

Candidiaisis : Neuropathology

- Invasion of small blood vs: thrombosis & infarct
- Disseminated meningitis or focal encephalitis
- Multiple micro abscesses & microgranuloma in ACA & MCA territory.
- Abscesses evolve to granuloma after a week
- Intensely stain with PAS & methenamine Ag,
- Faintly basophilic with H & E
- Prognostic factors
  - Diagnosis delay >2 weeks
  - CSF glucose <35mg/dl
  - Raised ICT
  - Focal deficits



CE T1WI



Candidiaisis : Symptomatology

- Cranial:
  - Low grade meningitis
  - Marked basal infiltrates
  - Multiple cranial nerve palsies, ↓ consciousness, HCP
- Spinal : rare – vertebral body or disc
  - Hematogenous
  - Local invasion: post-op complication of spine surg
  - Persistent low back ache , neurological deficits
  - Imaging: nonspecific spondylitis and discitis

Candidiasis: Diagnosis

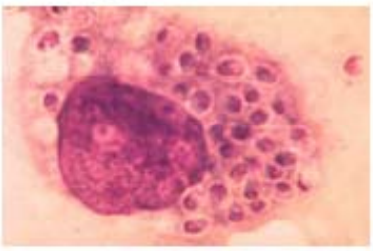
- Suspected : EVD or blocked shunts
- CSF exam and culture
- Serology: double diffusion CIE, IF, Latex agg test
- Fundus exam: endopthalmitis before permanent visual loss

Candidiasis : Treatment

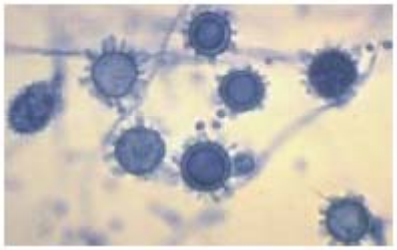
- Removal of infected artifacts
- Correction of predisposing factors
- NSx for abscess
- AMB ± Flucytosine

Histoplasmosis (Ohio Valley Fever)

- H. capsulatum: dimorphic ubiquitous
- Found in soil
- Inhaled with dust contaminated by bird, chicken or bat excreta
- Invades RES: lesions in spleen, liver, lymph nodes
- 1° focus : lungs – calcified, also in mouth, GIT, skin
- 2 peaks of incidence: early childhood & middle age



Yeast within histiocyte



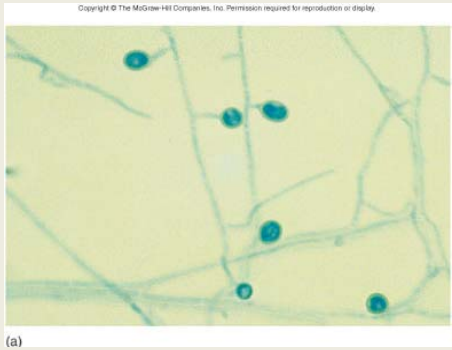
Hyphae, micro- and macroconidia

Histoplasmosis

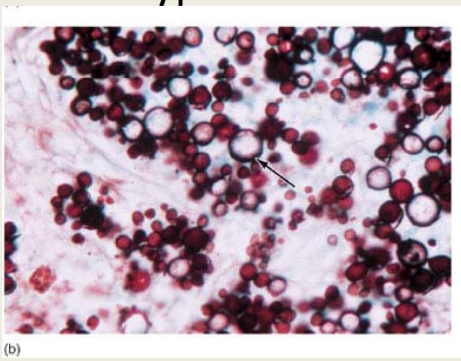
- CNS involvement in < 1 % of active ds
- Diffuse leptomeningitis, periventricular / parenchymal/ choroid plexus granulomata, granulomatous arteritis
- Diffuse basilar leptomeningitis: thick yellow exudates with miliary granulomas along vs. Central noncaseating granulomas – mimics sarcoidosis and other fungal and tubercular granulomas
- Presents as chronic meningitis with or without HCP
- Mass lesions are rare
- Chorioretinitis seen occaisionally
- Diagnosis:
  - Culture of sputum, CSF (50%) and serum or histology
  - Peripheral blood and bone marrow exam
- CT: ring enhancing lesions
- MRI: hypointense rims on T1WI with edema on T2WI
- Rx: AMB + NSx

Blastomycosis (North American Blastomycosis)

- Blastomyces dermatidis: found in soil, dog reservoir
- Endemic : in south east US and Africa
- Inhalation of airborne spores
- Mainly granulomatous (blastomycomas) – begin as pulmonary lesion
- Pulmonary macrophages phagocytoze and disseminate disease
- 2° lesions in skin, bone, urinary tract, CNS rarely
- Chronic leptomeningitis, granulomas & abscess in brain and spine, fibrosis l/t HCP
- Bone and vertebral disc destruction with paraspinal abscess mimics TB spine
- CSF : predominantly lymphocytic >1000/mm^3
- Rx: Antifungals + NSx
- Prognosis: poor if untreated but much better with appropriate management



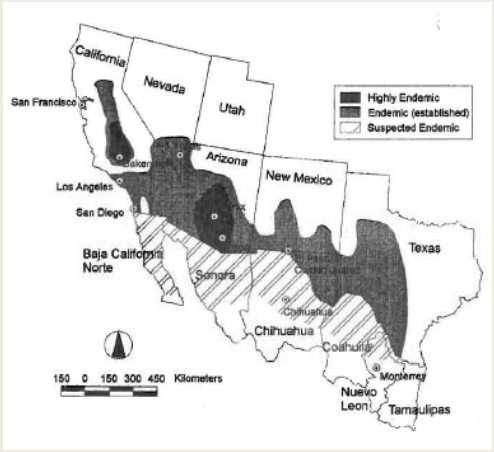
Hyphal state



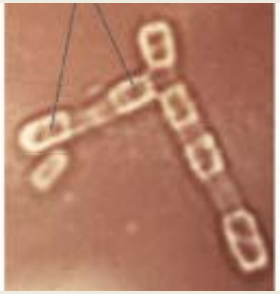
Yeast state

Cutaneous blastomycosis

Coccidiodomycosis (Modeling valley fever)

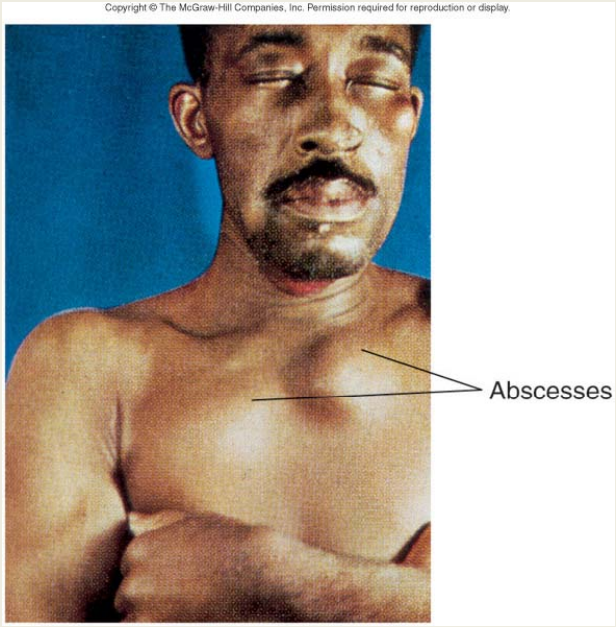


- Coccidiodes immitis-
  - *most virulent fungus* causing human mycoses
- Geographically restricted in semiarid climate of southwest US
- Soil saprophyte: carried by wind or rodents
- Pulmonary infection by inhalation- most self-limited
- Considered both pathogen and opportunist
- Hematogenous spread to CNS in 50 % as terminal even



- Meningeal inflammation: exudate, opacification of membranes, obliteration of sulci with caseous nodules at base of brain
- Invasion of blood vs: multiple aneurysms

Coccidiodomycosis



Microscopic picture : TBM

Symptoms

Acute/subacute/chronic meningitis

Transient focal deficits (aphasia, hemiparesis)

Basal meningitis/ mass: Multiple cranial nv palsies, ↑ ICP, HCP

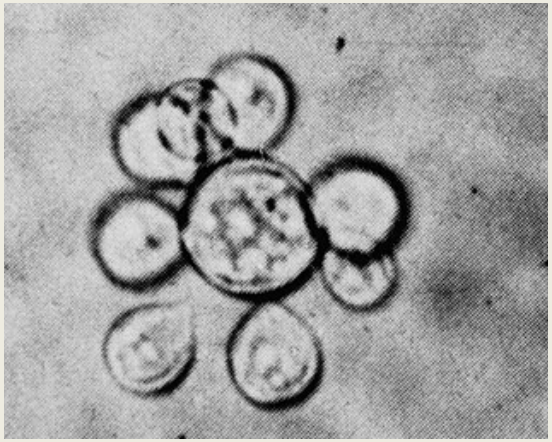
Diagnosis by- subcutaneous nodules, CSF antibodies, biopsy

Treatment- AMB or azoles

Rx: IV AMB- most promising drug: intrathecal infiltration in seriously ill.

Paracoccidiomycosis (South American blastomycosis)

- Paracoccidioides brasiliensis: dimorphic - soil and vegetation
- Chronic progressive granulomatous disease spreading from external nares to lungs and local lymph nodes
- CNS involved in 1/8 th of systemic disease
- Male >> female
- Epilepsy is MC neurologic presentation
- Granulomas and basal leptomeningitis
- Diagnosis: serology and biopsy
- Polarized light: stained with bright green rings
- CT: hypointense with annular or nodular involvement
- Rx: NSx + AMB: Septran or itraconazole for maintenance

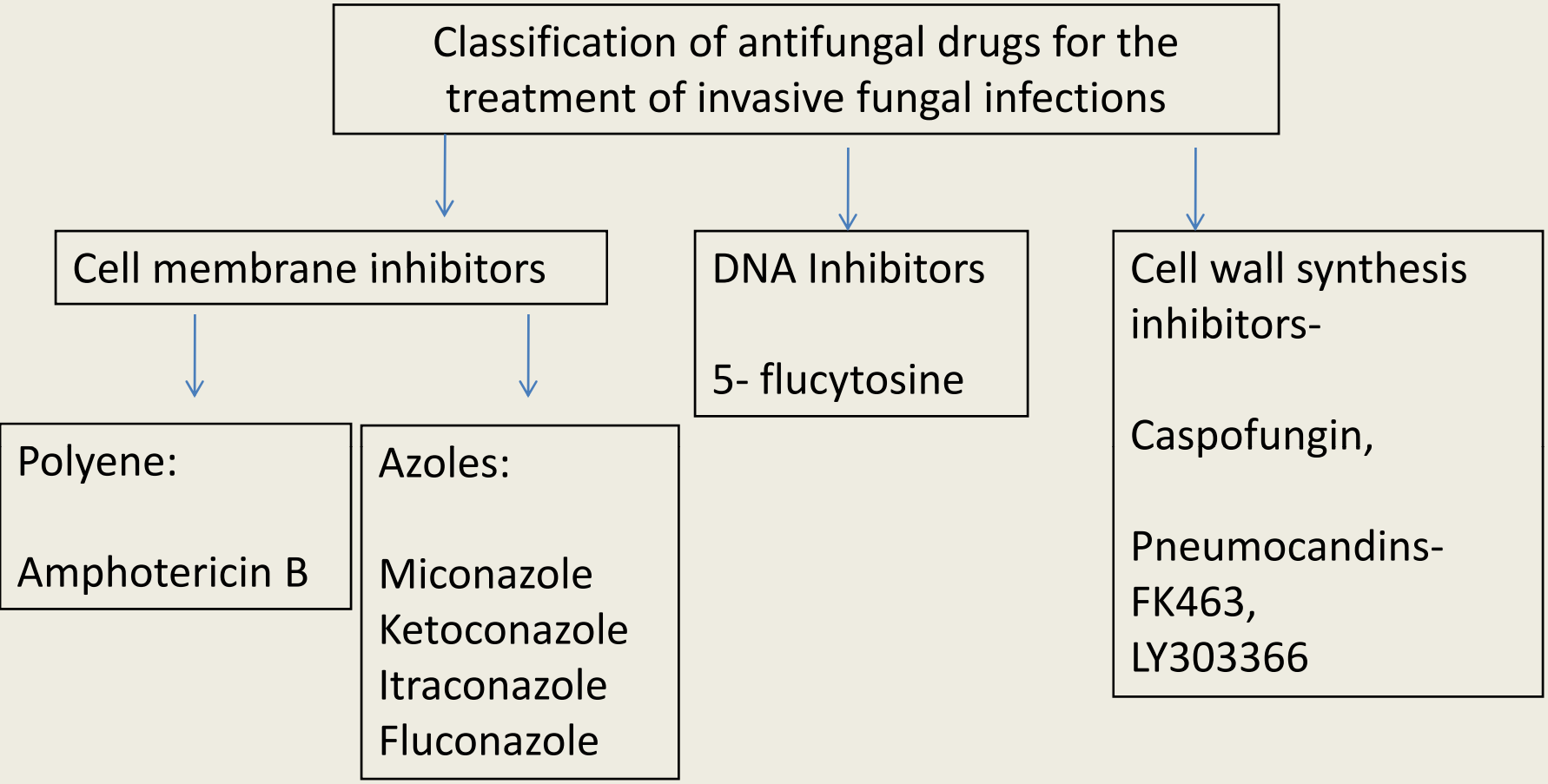


Principles of Management of CNS Fungal infections

1. Correction of underlying pathogenic risk factor:
   - Immunosupression
   - Neutropenia
   - Diabetes
   - Ketoacidosis
   - Steroid use
2. Removal of source of infection:
   - Drains, shunts, i.v. lines
   - Radical sx of orbit and paranasal sinuses: irrigation with antifungals
3. Antifungal drugs
4. NSx intervention

Antifungal Therapies

- Mycoses: among the most difficult diseases to heal
  - Resist the oxidative damage of T cells during CMI responses
  - Fungi are biochemically similar to human cells and antifungal drugs can harm human tissues
- Fungi have ergosterol in their membranes rather than cholesterol and it is often a target for antifungal treatment
  - Side effects can still result, especially with long-term use



Often the therapy is started with an i.v. agent such as AMB
Changed to oral azoles once the patient's clinical condition improves.
Also used in combination: The most widely used combination used is 5-flucytosine and AMB.

Amphotericin B (AMB):

- Mainstay of treatment of all intracranial fungal infections
- Effective against all the fungi except dermatiaceous .
- MOA:
  - binds to ergosterol the principal steroid of fungal cell membrane, and disrupts the cell membrane.
  - Immunoadjuvant: ↑ both the humoral and CMI.
- *Dosage:*
  - 1 mg test dose in 25-50 ml of 5% D infused over 1-2 hours.
  - Started at 0.25 mg/kg on Day-1
  - Daily increments of 5 mg or 0.1 mg/kg: until max dose of 0.5- 0.75 mg/kg/day is achieved.
  - In severe infections & in immunocompromised patients: the total daily dosages of 1mg/kg may be administered.
  - Total cumulative dose upto 3 gm can be given

Amphotericin B (AMB):

- Poorly crosses BBB: intraventricular/ intrathecal or intracavitary administration is also recommended.
  - Intrathecal therapy is started at 0.025 mg and gradually increased to 0.25-0.5 mg.
- *Duration of therapy:* continued for 6-12 weeks.
- *Side-effects:*
- a) Acute- Chills, Fever, headache, thrombophlebitis, myalgia, arthalgia in >50% of the patients.
- b) Chronic- Renal toxicity (most significant), hypokalemia, hypomagnesemia, normochromic normocytic anemia and rarely thrombocytopenia.
- The combination therapy with flucytosine may results in enhanced bone marrow suppression.
- Use in pregnancy is to be deferred because of possible teratogenicity.

Lipid formulations of polyenes

- Improve the therapeutic index for polyene macrolides
- AMB lipid complex or AMB colloidal dispersion
- Liposomal AMB
  - invasive fungal infections in patients refractory or intolerant to standard AmB
  - AMB incorporated into the phospholipid bilayer membrane, rather than in closed aqueous phase.
  - In vivo testing of liposomal AmB (1 or 3 mg/kg/d)
    - *Significantly higher success rate*
    - *Twofold to sixfold decrease in adverse events*
    - *Lower incidence of severe drug-related side effects*
    - *Fewer nephrotoxicity*
- Liposomal nystatin
  - phase III clinical trials

Flucytosine (5-FC)

- Pyrimidine analogue, converted inside the cell into 5 fluoro-uracil, which inhibits DNA synthesis.
- Crosses BBB: esp useful for Cryptococcus, Candida, Aspergillus and Chromoblastomycosis infections.
- Works synergistically with AMB and reduces it's toxicity.
- Solitary use results in early resistance.
- *Dosage:* 100-150 mg/kg/day in four divided doses.
- Monitored according to the creatinine clearance.
- Decreased to ½ - 25-50 mL/min & to ¼ - 12-25 mL/min.
- *Side-effects: Rash, GI discomfort, diarrhea*, reversible elevations in hepatic enzymes and *thrombocytopenia, leucopenia* or enterocolitis in patients with co-existent renal dysfunction or concomitant AMB therapy.

AZOLES

- Interfere with ergosterol synthesis by binding to lanosterol 14-demethylase

Ketaconazole:
Oral - imidazole effective against most , except Aspergillus.
Dosage: High dose of 1.2 gm/day for invasive intracranial fungal infections as BBB penetration is poor.
Side-effects: Dose-related GI discomfort; adrenal axis suppression, gynecomastia, decreased libido, oligospermia, impotence and sterility due to decreased testosterone.
The drug should not be used in pregnancy.

Itraconazole:
Broad spectrum of activity. It poorly crosses BBB.
Dosage: 200 mg once or twice daily.
Side-effects: similar to ketaconazole, but with a lower frequency.
Potentially teratogenic and should not be used in pregnancy.

Fluconazole:

Unique pharmacokinetics: almost complete and rapid absorption after oral administration.
Used specifically in Cryptococcosis in patients with AIDS.
Dosage: 400mg/d 8-12 weeks
Side-effects: well tolerated in many patients. The majority complain of gastro-intestinal complaints, headache and rash.
Contra-indicated in pregnancy

Voriconazole:

Has activity against Aspergillus and fluconazole resistant strains of Candida

	Loading dose (day 1)	Maintenance dose
i.v. formulation	6 mg/kg/12hrs	4 mg/kg/12hrs
Oral formulation ≥ 40 kgs	400 mg/12hrs	200 mg/12hrs
Oral formulation < 40 kgs	200 mg/12hrs	100 mg/12hrs

Posacanazole: salvgae therapy for aspergillosis and candida

- **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 & macrophages by ↑ G-CSF & GM-CSF
Increase cellular immunity- IFN-gamma
Increase humor immunity- vaccines

Spectrum of Activity of Select Antifungal Agents

Organism	Ampho B	5-FC	Ketoconazole	Fluconazole	Itraconazole
Candida albicans	S	S	S	S	S
Candida, non albicans	S	S	S/V	S/V	S/V
Candida krusei	S		R	R	V/R
Blastomyces dermatitidis	S	R	S	S	S
Histoplasma capsulatum	S	R	S	S	S
Coccidioides immitis	S	R	S	S	S
Cryptococcus neoformans	S	S	S	S	S
Aspergillus spp.	S	V	R	R	S
Fusarium spp.	S/V	R	R	R	R
Zygomycetes (Mucor)	S	V	R	R	R
Sporothrix schenckii	V	R	V	V	S

http://www.lumen.luc.edu

Surgical Treatment:

- Stereotactic biopsy-
- to establish the diagnosis and identification of the organism
- mass is deep seated, is in eloquent location
- in case of multiple lesions when the diagnosis is in question
- possibility of being performed even under local anesthesia
- attractive option especially in patients who do not have much mass effect mandating significant decompression of the lesion.

Surgical Treatment

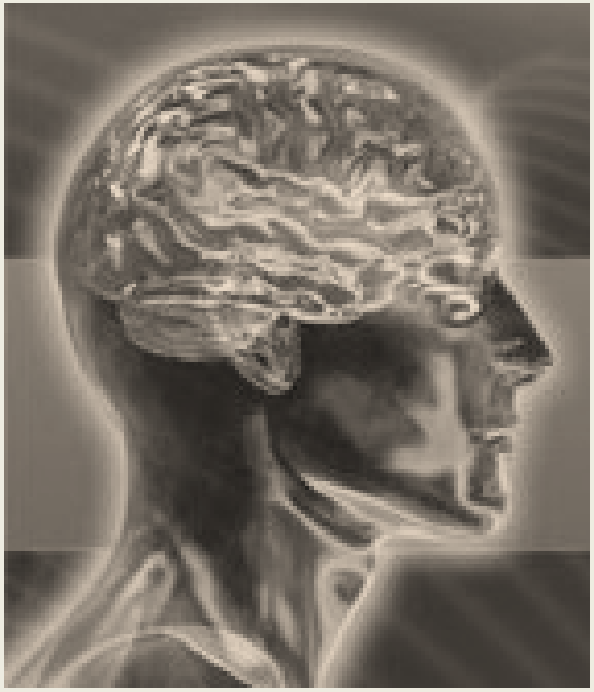
- Surgical excision-
- helps in establishing the diagnosis as well as reducing the mass effect
- improving the efficacy of the antifungal therapy.*
- radical excision of the granuloma with minimal contamination of the CSF spaces is the preferred treatment modality. **
- Basal arteritis or cavernous sinus thrombosis is a major deterrent in the good outcome of the skull base granulomas in the Rhinocerebral group.
- procedure should only be undertaken when it can be performed without causing much morbidity or incurring fresh neurological deficits.

*Khanna N et al. J Med Microbiol 1996;45:376-379
*Yanai Y et al. Surg Neurol 1985;23:597-604
**Ramos-Gabatin A.J Neurosurg 1981;54:839-41.

Surgical Treatment

- Ventriculo-peritoneal shunt –
  - for hydrocephalus which is often communicating, the block being present at the basal cisterns due to basal archnoiditis. *
- Intracavitary administration of AMB **
  - In fungal abscesses: reported to have good outcomes.
  - Can also be done via ommaya reservoirs, which can be used to instill the antifungals drug.

*Khanna N et al. J Med Microbiol 1996;45:376-379
*Ramos-Gabatin A.J Neurosurg 1981;54:839-41.
**Haran RP, Chandy MJ. Br J Neurosurg 1993;7:383-388
**Camarata PJ et al. Neurosurgery 1992;31(3):575-579



Thank you