



TEAM443  
MICROBIOLOGY

# Fungal infections of the CNS

LECTURE 3



# Objectives



To know the main fungi that affect the central nervous system and the clinical settings of such infections.



To acquire the basic knowledge about fungal meningitis and brain abscess : Clinical Features , Etiology , Diagnosis , And Treatment.

Any future corrections will be in the editing file, so please check it frequently

## Color Index:

Main text

Important

Notes

Boys slides

Girls slides

Extra

# Fungal Infections

## Fungal infection of CNS

- CNS infections are both diagnostic challenge & medical emergency.
- Delay in diagnosis and initiation of appropriate therapy will lead to high mortality rate or in permanent, severe neurological damage.
- Fungal infections of the CNS are not common. However, they are being increasingly diagnosed. Why? **because there is a population who are at risk of developing fungal infection because they have risk factors** (next topic)

## Risk Factors

- ◆ **HIV/AIDS**
- ◆ Diabetes mellitus
- ◆ Solid organs transplantation
- ◆ Malignancies
- ◆ Neutropenia
- ◆ Hematopoietic stem cell transplant (HSCT)
- ◆ Hereditary immune defects
- ◆ Immunosuppressive medications
- ◆ Surgery or trauma
- ◆ Indwelling catheters (e.g. candidemia → CNS seeding)

## How fungi reach CNS ?

- Hematogenous spread
- Local extension from the paranasal sinuses, the ear, or the orbits.
- **Traumatic introduction:** Surgical procedures, head trauma, injections & lumbar punctures

## Clinical Syndromes

- ◆ The following clinical syndromes can occur either alone or in combination.
- ◆ Certain clinical syndromes are specific for certain fungi.



### Meningitis

- Sub acute
- Chronic



### Brain abscess

- With vascular invasion
- Without vascular invasion



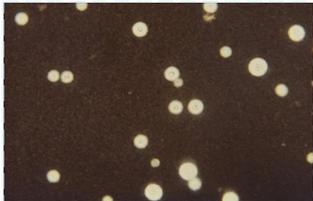
# Etiology

Yeast	Mould	Dimorphic
<ul style="list-style-type: none"> <li>◦ <b>Candida spp</b></li> <li>◦ <b>Cryptococcus spp</b></li> </ul>	<ul style="list-style-type: none"> <li>◦ <b>Aspergillus spp</b></li> <li>◦ <b>Zygomycetes</b></li> <li>◦ Fusarium spp</li> <li>◦ Exophiala spp</li> <li>◦ Cladophialophora bantiana</li> <li>◦ Curvularia</li> <li>◦ Bipolaris</li> <li>◦ <b>Rhinoctadiella mackenziei</b></li> <li>◦ Others</li> </ul>	<ul style="list-style-type: none"> <li>◦ Histoplasma spp</li> <li>◦ Blastomyces spp</li> <li>◦ Coccidioides spp</li> <li>◦ Paracoccidioides spp</li> <li>◦ Penicillium marneffeii</li> </ul>



# Fungal Infections

## 1. Cryptococcal Meningitis

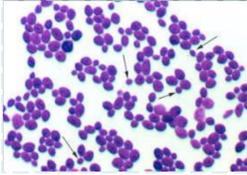
<b>Etiology</b>	<ul style="list-style-type: none"> <li>▶ <b>Cryptococcus neoformans</b> is the most common etiology + <b>cryptococcus gattii</b></li> <li>▶ Capsulated yeast cells</li> <li>▶ Naturally in birds droppings ( Pigeon ) , tree hollows and soil.</li> </ul>	
<b>Predisposing Factor</b>	<b>AIDS</b> is the leading predisposing factor.	
<b>Acquired by</b>	<b>Inhalation</b> then go to the lung but cause meningitis rarely lung disease	
<b>Morphology</b>	 <p>★<b>India ink preparation</b> stains the background, not the fungal cells</p>	 <p>Mucoïd appearance of cryptococcus in the media culture is due to its capsule</p>
<b>Clinical Syndrome</b>	Mainly meningitis, it almost never causes brain abscesses.	



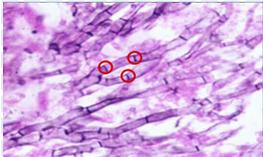
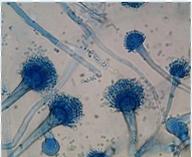
# Fungal infections

## 2. Candidiasis

Candida species are the 4th most common cause of hospital acquired **bloodstream infections**.

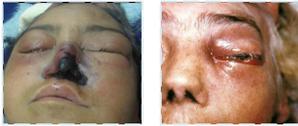
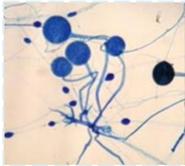
<b>Etiology</b>	<ul style="list-style-type: none"> <li>▶ <b>Candida albicans</b> &amp; other species including : <ul style="list-style-type: none"> <li>◦ C.glabrata</li> <li>◦ C.tropicalis</li> <li>◦ C.parapsilosis</li> <li>◦ C.krusei</li> </ul> </li> </ul>	
<b>Reach CNS through</b>	<ul style="list-style-type: none"> <li>▶ <b>Hematogenously (Candidemia)</b></li> <li>▶ Surgery, <b>Catheters</b></li> </ul>	<ul style="list-style-type: none"> <li>▶ Indwelling catheter &amp; fever unresponsive to broad antibacterial agent (sign of candida infection)</li> <li>▶ Septicemia caused by candida</li> </ul>
<b>Morphology</b>	 <p><u>Direct microscopy</u> Candida has budding cells</p>	 <p><u>Culture</u> Not mucoid</p>
<b>Clinical Syndrome</b>	<ul style="list-style-type: none"> <li>▶ Meningitis (Mostly)</li> <li>▶ Cerebral abscesses</li> <li>▶ Cerebral microabscesses</li> <li>▶ Vascular complication (infarcts, hemorrhage)</li> </ul>	

## 3. CNS Aspergillosis

<b>Etiology</b>	<ul style="list-style-type: none"> <li>▶ <b>Aspergillus fumigatus</b> (the most common/virulent globally)</li> <li>▶ <b>A.flavus</b> (the most common in our region due to environment &amp; climate)</li> <li>▶ <b>A.terrus</b></li> </ul>	
<b>Reach CNS through</b>	<ul style="list-style-type: none"> <li>▶ Hematogenously</li> <li>▶ May also occur via direct spread from the <b>anatomically adjacent sinuses</b>, This is called: <b>Rhinocerebral aspergillosis</b></li> <li>▶ Angiotropism (infarction and hemorrhagic necrosis)</li> </ul>	
<b>Common Risk Factors</b>	<ul style="list-style-type: none"> <li>▶ Hematological malignancies</li> <li>▶ Cancer chemotherapy</li> <li>▶ Transplantation</li> </ul>	
<b>Clinical Syndrome</b>	<p>Usually <b>brain abscesses</b> (single or multiple)</p>	
<b>Prognosis</b>	<p>Mortality rate is high (nearly always regardless of the medical treatment )</p>	
<b>Morphology</b>	 <p><b>Septate</b> (Fungal hyphae)</p>	 

# Fungal infections

## 4. CNS Zygomycosis (Mucormycosis)

<b>Etiology</b>	<i>Zygomycetes</i> e.g: <b>Rhizopus</b> , Absidia, <b>Mucor</b> Fast growing fungi (all of them are Mucorales), the black fungus in india during COVID-19 it's this fungus.		
<b>Risk factors</b>	★ <b>Diabetes with ketoacidosis</b> , in addition to other risk factors.		
<b>Clinical Syndrome</b>	<ul style="list-style-type: none"> <li>▶ The <b>rhinocerebral</b> form is the most frequent presenting clinical syndrome in CNS zygomycosis</li> <li>▶ The clinical manifestations of the rhinocerebral form start as sinusitis, rapidly progress and involve the orbit, eye and optic nerve and extend to the brain.</li> <li>▶ <b>Facial edema</b>, pain, necrosis, <b>eye infection</b>, <b>loss of vision</b>, <b>black discharge</b> Angiotropism due to blood vessel invasion; As angio-invasion is very frequent.</li> </ul>		
<b>Prognosis</b>	Mortality rate is high (80-100 %), <b>Progression is rapid</b> .		
<b>Improved Outcome by</b>	<ul style="list-style-type: none"> <li>▶ Rapid diagnosis Because it only takes weeks to kill the patient</li> <li>▶ Control the underlying disease</li> <li>▶ Early surgical debridement</li> <li>▶ Appropriate antifungal therapy</li> </ul>		
<b>Morphology</b>	 <p>Rhizopus species يشبه جذور الشجرة</p>	 <p>Broad <b>Non-septate</b> hyphae</p>	

## 5. Pheohyphomycosis

- Fungal infections caused by **dematiaceous fungi Black pigmented fungi**, due to melanin pigment.
- Neurotropic fungi, they love to infect the brain.

<b>Etiology</b>	<ul style="list-style-type: none"> <li>★ <b>Rhinoctadiella mackenziei</b> (Mainly reported from <b>Middle East</b>)</li> <li>◦ Cladophialophora, Exophiala, Curvularia, Fonsecaea.</li> </ul>
<b>Risk Factor</b>	Reported in <b>immunocompetent</b> hosts
<b>Clinical Syndrome</b>	CNS infections are usually brain abscesses, and chronic
<b>Prognosis</b>	Mortality rate is almost 100%

## Other Infections

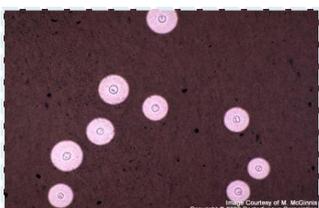
<b>Caused by</b>	<ul style="list-style-type: none"> <li>◦ Primary pathogens</li> <li>◦ Sub acute or chronic Meningitis (common), and brain abscess</li> <li>◦ Following a primary infection, mainly respiratory</li> </ul>	
<b>Examples</b>	<ul style="list-style-type: none"> <li>▶ Histoplasmosis</li> <li>▶ Blastomycosis</li> </ul>	<ul style="list-style-type: none"> <li>▶ Coccidiomycosis</li> <li>▶ Paracoccidiomycosis</li> </ul> <p>NOTE: we don't see these infections in our community</p>

# Diagnosis

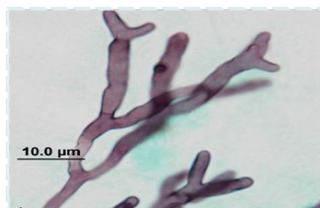
<b>Clinical features</b>	<ul style="list-style-type: none"> <li>◦ Include history, risk factors, etc</li> <li>◦ Not Specific</li> </ul>				
<b>Neuro imaging</b>	Good value in diagnosis and therapy monitoring				
<b>Lab Investigations</b>	<ul style="list-style-type: none"> <li>◦ CSF examination (cell count, chemistry), Histopathology &amp; Microbiology</li> <li>◦ <b>Clinical Samples:</b> CSF, Biopsy, Pus, aspirate &amp; Blood (for serology)</li> </ul>				
	<b>CSF abnormalities</b>	<b>Direct Microscopy</b>	<b>Culture</b>	<b>Serology</b>	<b>PCR</b>
	<ul style="list-style-type: none"> <li>◦ Cell count</li> <li>◦ Glucose level (↓)</li> <li>◦ Protein level (↑)</li> <li>◦ Not specific for Fungal infections</li> </ul>	<b>Fungal stains:</b> <ul style="list-style-type: none"> <li>◦ Giemsa</li> <li>◦ GMS</li> <li>◦ PAS</li> <li>◦ India ink (Cryptococcus neoformans)</li> </ul>	<b>Fungal media:</b> <ul style="list-style-type: none"> <li>◦ SDA</li> <li>◦ BHI</li> <li>◦ other media if needed</li> </ul>	<ul style="list-style-type: none"> <li>◦ Candida</li> <li>◦ Aspergillus</li> <li>◦ Cryptococcus</li> <li>◦ Histoplasma</li> <li>◦ Blastomyces</li> <li>◦ Coccidioides</li> <li>◦ Paracoccidioides</li> </ul>	-

<b>Lab diagnosis</b>			
<b>CNS infection</b>	<b>Direct microscopic ★</b>	<b>Culture</b>	<b>Serology*</b>
<b>Cryptococcal Meningitis</b>	Yeast cells <b>capsulated (india ink)</b>	Yeast (Mucoid because of the capsule)	<ul style="list-style-type: none"> <li>◦ Cryptococcal Ag (capsule)</li> <li>◦ Latex agglutination</li> </ul>
<b>Candidiasis</b>	Budding yeast cells & pseudohyphae	Yeast (Non - mucoid)	<b>Manann Ag (cell wall)</b>
<b>Aspergillosis</b>	<b>Septate</b> branching hyphae	Hyaline mould	<b>Galactomannan Ag</b> (specific for aspergillus)
<b>Zygomycosis</b>	Broad <b>non-septate</b> hyphae	Hyaline mould Fast growing	No serology available
<b>Pheohyphomycosis</b>	<b>Brown septate hyphae</b>	Dematiaceous ( <b>Black</b> ) mould	-

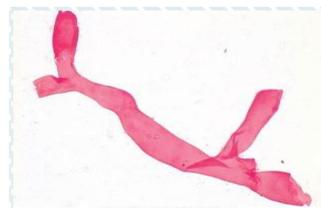
\* **Serology:** β-D- Glucan, for diagnosis of invasive fungal infections except cryptococcosis & zygomycosis



Indian ink



Septate hyphae Aspergillosis



Non-Septate hyphae Zygomycosis





# Management

1 Control of the underlying disease

2 Reduce immunosuppression, restore immunity if possible

3 Start antifungal therapy promptly: Polyenes, Azoles, Echinocandins

4 Consider surgery in certain situations



# Antifungal Therapy

CNS fungal infection	Treatment
Cryptococcal meningitis	<b>Amphotericin B</b> (combination with Flucytosine)
CNS Candidiasis	<ul style="list-style-type: none"><li>◦ Caspofungin</li><li>◦ Voriconazole</li><li>◦ Fluconazole</li><li>◦ Amphotericin B</li></ul>
CNS Aspergillosis	<ul style="list-style-type: none"><li>◦ <b>Voriconazole</b> drug of choice</li><li>◦ Amphotericin B</li><li>◦ Combination of voriconazole &amp; Caspofungin</li></ul>
CNS Zygomycosis	<b>Amphotericin B</b>



**Q1. Which of the following is a widely accepted way to stain a CSF sample for Cryptococcus neoformans ?**

A- India ink      B- Modified Gram stain      C- Giemsa      D- GMS

**Q2. A patient has a fungal infection and biopsy showed septate branching hyphae. What's the organism?**

A- Cryptococcus gattii      B- Zygomycosis      C- Cryptococcus neoformans      D- Aspergillosis

**Q3. Which one of the following has no treatment ?**

A- Candidiasis      B- Phaeohyphomycosis      C- Cryptococcal meningitis      D- Aspergillosis

**Q4. A 56 year old cancer patient came to the hospital complaining of sinusitis and neurological symptoms , what is the most likely organism ?**

A- Aspergillus fumigatus      B- Cladophialophora      C- Cryptococcus neoformans      D- Candida albicans

**Q5. A 33-year-old HIV positive man complains of headache , fever, neck stiffness , inability to tolerate light. Which one of the following microorganisms is most likely responsible for his illness ?**

A- Aspergillus fumigatus      B- Candida albicans      C- Cryptococcus neoformans      D- Zygomycetes

**Q6. Which of the following is the drug of choice for treatment of aspergillosis ?**

A- Fluconazole      B- Caspofungin      C- Amphotericin B      D- Voriconazole

**Q7. A 55 year old diabetic male with ketoacidosis recently removed a nasal polyp with sinusitis. After 2 days from surgery he came back to the emergency department with left periorbital swelling and pain. A biopsy was taken from the patient and lab diagnosis was done. Direct microscopy showed broad non-septate hyphae. The patient is most likely infected by ?**

A- Candida albicans      B- Aspergillus fumigatus      C- Zygomycetes      D- Rhinocladiella mackenziei



# Cases/SAQs 441

## Q1

**A 34 y/o woman come to ER suffering from swelling of her eye and her nose become black in clinical manifestations we found fungal infection start as sinusitis, rapidly progress and involve the orbit, eye and optic nerve and extend to the brain, past medical history: diabetes with ketoacidosis**

- A- What is the diagnosis?
- B- What is the treatment of cryptococcal meningitis?

## Q2

**A 43 years old male came to the ER complaining from loss of vision, The patient history indicated that he had sinusitis recently physical examination indicated facial edema and black discharge, a blood sample was taken from the patient and the laboratory report indicated increase in blood glucose level and increase in blood acidity also they detected ketone.**

- A- What is the most likely diagnosis?
- B- What is the most important risk factor in this case?
- C- Describe the prognosis and how you can improve it?
- D- What is the appropriate treatment for this patient?

## Q3

**A 42 saudi men come to the ER complaining of nausea, severe headache, dizziness for 2-3 months CT scan show lesions in the brian, culture shows black fungus and the direct microscopic show a brown septate hyphae**

- A- What is your diagnosis?
- B- What the most likely organism?
- C- Describe the prognosis?

### A1

A-CNS Zygomycosis  
B-Amphotericin B (combination with flucytosin)

### A2

A: CNS Zygomycosis  
B: Diabetics ketoacidosis  
C: - progress rapidly with high mortality rate (80-100%)  
- rapid diagnosis, control underlying disease, early surgical debridement, appropriate antifungal therapy  
D: Amphotericin B

### A3

A: phaeohyphomycosis  
B: Rhinocladiella mackenziei  
C: almost 100%



TEAM 443  
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## Team leaders



Aishah Boureggah



Nazmi M Alqutub

## Team Members

Sara Alharbi

Rafan Alhazzani

Sara Alajaji

Zahra Alhazmi

 Aroub Almahmoud

Maryam Alghannam

Wajd Almutairi

Moath Alhudaif

Haya Alzeer

Lama Alotaibi

Rahaf Alslimah

Omar Almogren

Mansour Alotaibi

 Faris Alzahrani

Remaz Almahmoud

Mohammed Alqutub

Abdullah Alammar

Khalid Alatar

Nazmi A Alqutub

Raghad Almuslih

Farah Abukhalaf

Aseel Alshehri

Abdulrahman Almusallam



Contact us through  
[Microbiologyteam443@gmail.com](mailto:Microbiologyteam443@gmail.com)