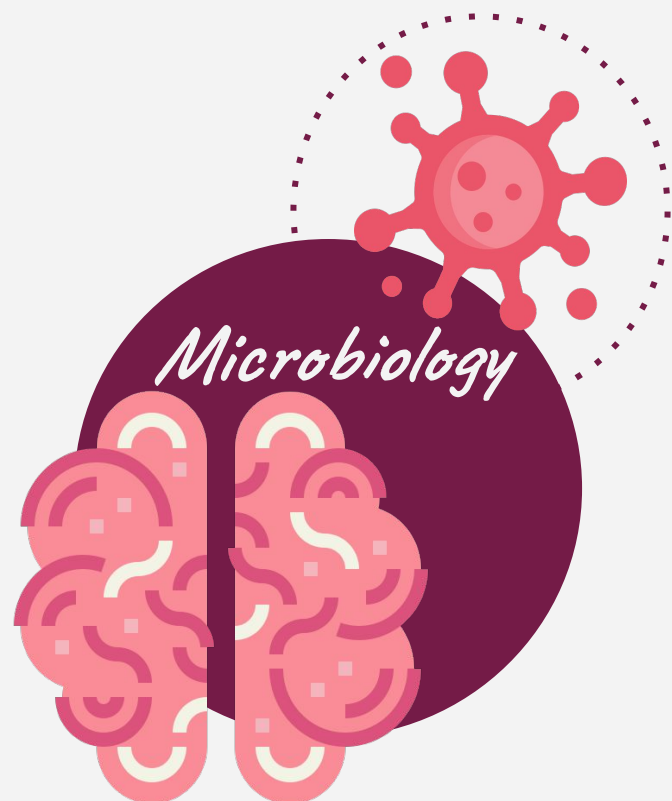


Fungal infections

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



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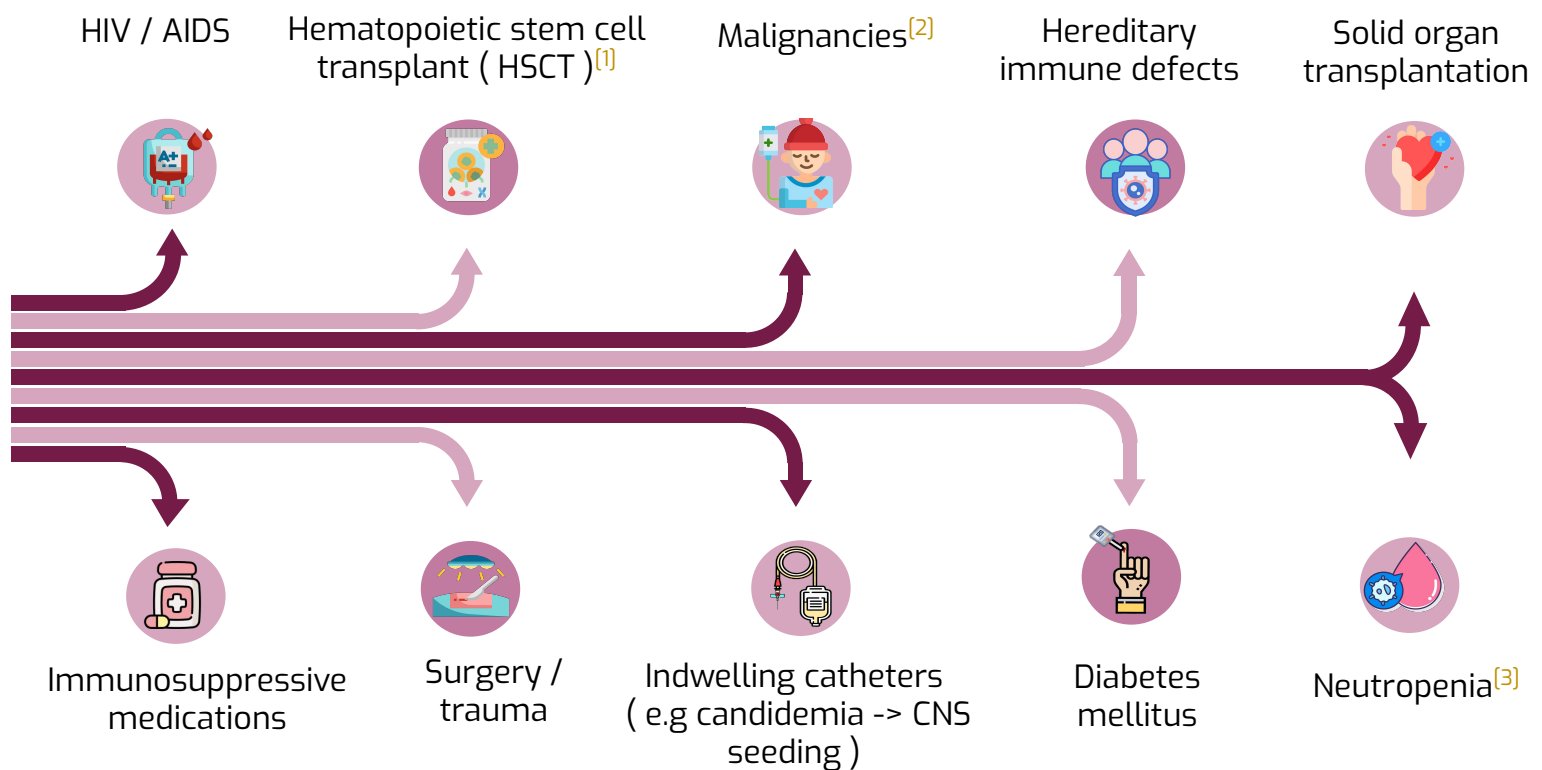


Fungal infections

Fungal Infections of Central Nervous System

- CNS infections are both diagnostic challenge & medical emergency.
- Delay in diagnosis & 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

Risk factors



^[1] Because patients must be given immunosuppressant drugs

^[2] due to usage of chemotherapy

^[3] abnormally low number of neutrophils, could be caused by chemotherapy, cancers, malnutrition or some infections

How fungi reach CNS ?

1

Traumatic introduction

- Surgical procedures (neurosurgery , major abdominal surgery)
- Head trauma
- Contaminated Injections
- lumbar punctures

2

Local extension

From the paranasal sinuses, the ear, or the orbits.

3

Hematogenous spread

More common with yeast

Clinical syndromes

- These clinical syndromes can occur either alone or in combination
- Certain clinical syndromes are specific for certain fungi

Meningitis

(Mostly caused by yeast)
A. Sub acute
B. Chronic usually

Brain abscess

Mostly cause by filamentous
A. With vascular invasion
B. Without vascular invasion

Etiology



Mould / Filamentous

- **Aspergillus spp**^[1]
- Zygomycetes
- Fusarium spp
- Exophiala spp
- Cladophialophora Bantiana
- **Rhinoctadiella Mackenziei**
- Curvularia , Bipolarid
- Others

Dimorphic^[2]



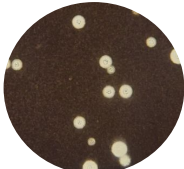

- Histoplasma spp
- Blastomyces spp
- Coccidioides spp
- Paracoccidioides spp
- Penicillium marneffeii



Yeast

- **Candida spp**^[1]
- Cryptococcus spp (Encapsulated yeast)

Cryptococcal Meningitis

| | | |
|----------------------------|--|--|
| Etiology | Cryptococcus neoformans is the most common etiology + cryptococcus gattii <ul style="list-style-type: none"> ○ Capsulated yeast cells^[3] ○ Naturally in birds droppings (Pigeon) , tree hollows and soil | |
| Predisposing factor | AIDS is the leading predisposing factor | |
| Acquired by | Inhalation | |
| Morphology |  <p>India ink preparation stains the background, not the fungal cells</p> |  <p>Mucoïd appearance of cryptococcus in the media culture is due to its capsule.</p> |
| Clinical Syndrome | Mainly meningitis, it almost never causes brain abscesses | |

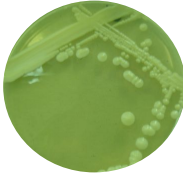
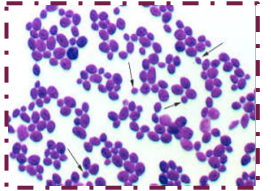
^[1] Candida is the first common cause of CNS fungal infection and aspergillus is the second

^[2] Fungi that can grow as yeast and filamentous



^[3] The capsule is useful to differentiate between candida and cryptococcus

Candidiasis

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

| | | |
|--------------------------|--|---|
| Etiology | <ul style="list-style-type: none"> ○ Candida albicans^[1] & other species including : ○ C.glabrata, C. tropicalis C. parapsilosis, & C. krusei. | |
| Reach CNS by | <ul style="list-style-type: none"> ○ Hematogenously ○ Surgery, Catheters | <ul style="list-style-type: none"> ○ Indwelling catheter & fever unresponsive to broad antibacterial agent^[2] (sign of candida infection) ○ Septicemia caused by candida |
| Morphology | <p>Culture.</p> <p>*Not mucoid</p>  | <p>Direct microscopy.</p> <p>Candida has budding yeast cells</p>  |
| Clinical syndrome | <ul style="list-style-type: none"> ○ Meningitis (Mostly) ○ Cerebral abscesses | <ul style="list-style-type: none"> ○ Cerebral microabscesses ○ Vascular complications (infarcts, hemorrhage) |

CNS Zygomycosis (mucormycosis)

| | | |
|----------------------------|--|--|
| Etiology | Zygomycetes e.g: Rhizopus, Absidia, Mucor Fast growing fungi (all of them are Mucorales) | |
| Common risk factors | ★ Diabetes with ketoacidosis ^[3] , in addition to other risk factors. ^[4] | |
| Clinical syndrome | <ul style="list-style-type: none"> ○ The rhinocerebral form is the most frequent presenting clinical syndrome in CNS zygomycosis ○ 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. ○ Facial edema, pain, necrosis, eye infection, loss of vision, black discharge Angiotropism due to blood vessel invasion; As angio-invasion is very frequent ○ Usually brain abscesses | |
| Prognosis | Mortality rate is High (80- 100%) ^[5] -Progression rapid- | |
| To improve outcome | <ul style="list-style-type: none"> ○ Rapid diagnosis ○ Control the underlying disease ○ Early surgical debridement ○ Appropriate antifungal therapy |   |

[1] Normal flora in skin, GIT and oropharynx

[2] Ex. A patient was catheterized for long time then he got a fever his doctors gave him multi broad spectrum antibiotics but he didn't respond to it, why? Because it's a candida infection not bacterial

[3] Because it can thrive in high acidic condition

[4] HIV/AIDS, (HSCT), Solid organs transplantation, Malignancies, Neutropenia, Hereditary immunosuppression (hereditary or by medications), Diabetes mellitus, Surgery, trauma and Indwelling catheters.

[5] It can kill the patient within three weeks

CNS Aspergillosis

| | |
|----------------------------|---|
| Etiology | <ul style="list-style-type: none"> ○ Aspergillus fumigatus^[1] ○ A. flavus^[2] ○ A. terreus |
| Reach CNS by | <ul style="list-style-type: none"> ○ Spread Hematogenously ★ May also occur via direct spread from the anatomically adjacent sinuses Dr: This is called: Rhinocerebral aspergillosis ○ Angiotropism (infarction and hemorrhagic necrosis) |
| Common risk factors | <ul style="list-style-type: none"> ○ hematological malignancies ○ cancer chemotherapy ○ transplantation |
| Clinical syndrome | <ul style="list-style-type: none"> ○ Usually brain abscesses (single or multiple) |
| Prognosis | <ul style="list-style-type: none"> ○ Mortality rate is high^[3] |

Pheohyphomycosis

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



Extra Picture

| | |
|----------------------------|--|
| Etiology | <ul style="list-style-type: none"> ★ Rhinoctadiella mackenziei (Mainly reported from Middle East) ○ Cladophialophora, Exophiala, Curvularia, Fonsecaea. |
| Common risk factors | <ul style="list-style-type: none"> ★ Reported in immunocompetent hosts |
| Clinical syndrome | Chronic and Usually brain abscesses |
| Prognosis | Mortality is high almost 100% |

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis

Other infections

Can be caused by:

- Cause by primary pathogens
- Subacute or chronic Meningitis (common), & brain abscess
- Following a primary infection, mainly respiratory

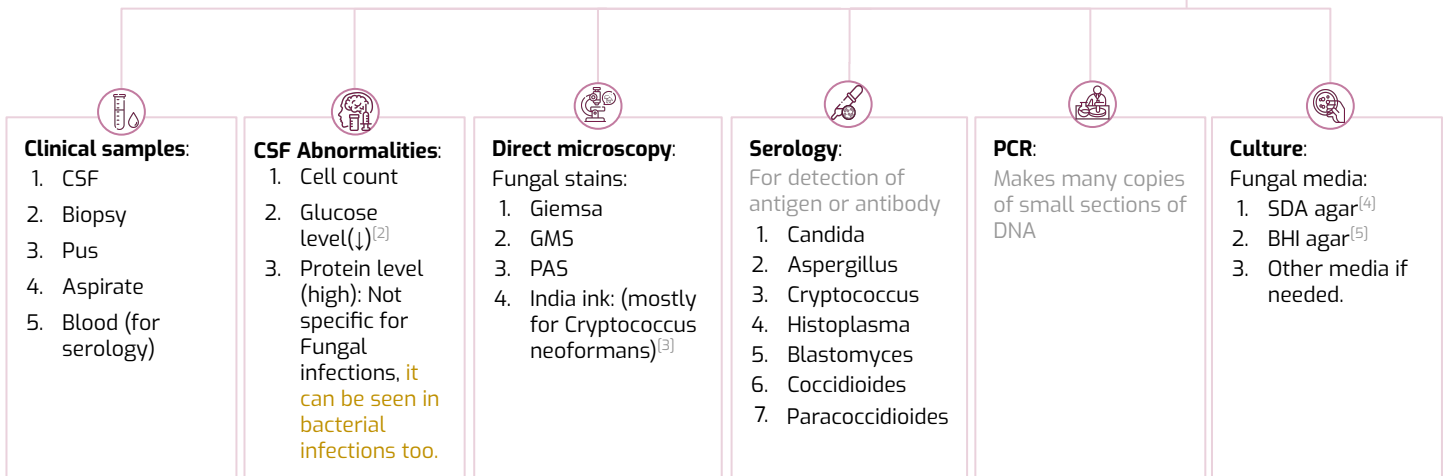
^[1] Most common/virulent globally

^[2] Most common in our region due to environmental factors and climate

^[3] Regardless of the medical treatment (nearly always).

Diagnosis

- 1 Clinical features**
(history, risk factors... ect): Not specific for fungal infection
- 2 Neuro-imaging**
Good value in diagnosis and therapy monitoring
- 3 Lab investigations^[1]**
CSF examination (cell count, chemistry), Histopathology, Microbiology.



Lab diagnosis

| CNS infection | Direct microscopic | Culture | Serology |
|-------------------------|---|---|--|
| Cryptococcal Meningitis | Yeast cells capsulated (india ink) | Yeast (mucoïd because of the capsule) | <ul style="list-style-type: none"> ○ Cryptococcal Ag (capsule) ○ Latex agglutination |
| Candidiasis | Budding yeast cells and pseudohyphae | Yeast | Manann Ag (cell wall) |
| Aspergillosis | Septate branching hyphae | Hyaline mould | Galactomannan Ag (specific for aspergillus) |
| Zygomycosis | Broad non-septate hyphae | Hyaline mould Fast growing | No serology available |
| Pheohyphomycosis | Brown septate hyphae | Dematiaceous (Black) mould | No serology available |

Serology:

β-D- Glucan^[6], for diagnosis of invasive fungal infections except cryptococcosis and zygomycosis

^[1]We start with CSF, direct microscopy and culture then we go for PCR if needed

^[2]Because it is consumed by the organism.

^[3]Because of the presence of polysaccharide capsule.

^[4]Sabouraud dextrose agar

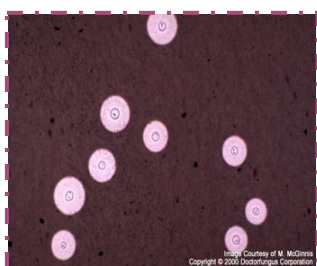
^[5]Brain & heart infusion agar

^[6]An attractive antigen in that it is found in a broad range of fungal agents



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 (abscesses)
5. Key of treatment is early diagnose



| | CNS fungal infection | Treatment |
|---------------------------|-------------------------|---|
| Antifungal therapy | Cryptococcal meningitis | Amphotericin B ^[1] (combination with Flucytosine) |
| | CNS Candidiasis | Caspofungin, Fluconazole, Voriconazole, Amphotericin B (The best drug depends on the age group and the case itself) |
| | CNS Aspergillosis | Voriconazole ^[2] , Amphotericin B (Combination of voriconazole and Caspofungin) |
| | CNS Zygomycosis | Amphotericin B (in high dose followed by surgery) |

^[1] It is the best treatment to be use in case of cryptococcal meningitis (drug of choice)

^[2] Drug of choice

- All are considered as a medical emergency and considered to be a diagnostic challenge.
- Early diagnosis & antimicrobial treatment of CNS infections is extremely important to avoid complications.
- Fungal infections of CNS are being increasingly diagnosed because the population of immunocompromised people has increased due to increased incidence of many diseases, malignancy, transplantation, usage of immunosuppressant drugs, chemotherapy, and things as such.
- A good example of traumatic introduction of fungi into the CNS is neurosurgery.
- Pathophysiology of cryptococcal meningitis in AIDS patient is: The patient inhales fungal element, it will go to the lung, patient develops asymptomatic disease in the lung, and finally it will disseminate to CNS and presents as cryptococcal meningitis (note that cryptococcus almost never cause brain abscess)
- Humans are very colonized with candida (it is a normal flora of skin, oral cavity, GIT, and vagina). It can reach the CNS in many ways; one of which is surgery, especially abdominal surgery. Also, if the patient has a risk factor already (e.g. surgery), and he does not respond to anti-bacterial treatment, we must think of candida.
- We have two classes of zygomycetes; entomophthorales and mucorales. Most zygomycosis CNS infections are caused by mucorales, and hence the name mucormycosis
- Pathophysiology of mucormycosis: Rapid dissemination from sinuses to nearby regions such as nose and eye (it disseminates from the eye to the brain through the optic nerve). Early diagnosis of mucormycosis (in the sinusitis stage or eye infection before reaching the brain) is the key to survive this infection. Once it reaches the brain, mortality is quite high. .
- Pathophysiology of CNS Aspergillosis: Patient inhales the fungal spores of aspergillus, (1st scenario: Hematogenous) is that it might colonize lungs and disseminate to blood and cause a CNS infection. (2nd scenario: Rhinocerebral aspergillosis) is that it can colonize the sinuses and either cause chronic rhinosinusitis, or it will form a mass in the sinuses (Fungal ball), and finally it will extend locally to brain and nearby regions like the eye. Also, Aspergillus might also invade the blood vessels and cause haemorrhage (nearly always fatal).
- The other infections: Histoplasmosis, Blastomycosis, Coccidioidomycosis, and Paracoccidioidomycosis are endemic mycoses in other countries (US/Canada/South America), but almost never seen in our region.
- In case of meningitis, the best sample is CSF, whereas the best sample in abscesses is biopsy or aspirate.
- In PCR we detect the DNA of the fungi, but it is only used if all other lab diagnosis methods were negative.
- In antifungal therapy of CNS Aspergillosis, the drug of choice is Voriconazole. Alternatively, amphotericin B can be used if treatment with voriconazole failed.

Quiz

Click on the icon to check out the team's summary and extra case

MCQ

Q1: A 23 years old patient with no history of any disease or predisposing factor (immunocompetent) was diagnosed with a CNS fungal infection. Which one of the following is the possible causative agent?

- A- *Aspergillus fumigatus*
- B- *Rhinoctadiella mackenziei*
- C- *Candida albicans*
- D- *Zygomycetes (Rhizopus/Mucor)*

Q2: What is the drug of choice in treatment of CNS Aspergillosis?

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

Q3: A 72 years old patient with uncontrolled diabetes and facial edema. Laboratory and microscopy revealed non-septate hyphae. Which one of the following is the causative organism?

- A- *Aspergillus fumigatus*
- B- *Rhinoctadiella mackenziei*
- C- *Candida albicans*
- D- *Zygomycetes (Rhizopus/Mucor)*

Q4: A 55 years old patient was suspected to have a fungal CNS infection that is caused by *aspergillus fumigatus*, which one of the following microscopic features must be seen to confirm the diagnosis?

- A- Budding yeast cells
- B- Broad non-septate hyphae
- C- Septate brown hyphae
- D- Septate branching hyphae

Q5: Which one of the following is the laboratory method that is used to diagnose cryptococcal meningitis?

- A- india ink
- B- Galactomannan Ag
- C- Manann Ag
- D- Dematiaceous mould appearance

Q6: Which one of the following is the drug of choice in treatment of zygomycosis?

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

Answers: Q1:B | Q2:C | Q3:D | Q4:D | Q5:A | Q6:C

SAQ

CASE: 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.

Q1: What is the most likely diagnosis?

A: CNS Zygomycosis

Q2: What is the most important risk factor in this case?

A: Diabetics ketoacidosis

Q3: Describe the prognosis and how you can improve it?

A: -progress rapidly with high mortality rate (80-100%)
-rapid diagnosis, control underlying disease, early surgical debridement, appropriate antifungal therapy

Q4: What is the appropriate treatment for this patient?

A: Amphotericin B

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