Fungal & Amoebic Meningitis
NS1 Module
2022-2023

Dr. Mohammad Odaibat
Mutah University
Faculty of Medicine

Objectives

- An overview of the protozoa classification.
- The protozoa associated with the CNS infections.
- The fungal infections of the CNS infections.
- Their mode of transmission.
- Treatment .
- Prevention.

The phylum Sarcomastigophora (Protozoa)

The phylum Sarcomastigophora belongs to the Protista kingdom and it includes many unicellular autotrophic or heterotrophic organisms. It is characterized by having flagellae, pseudopodia, or both.

The phylum classification

The amoeba groups

Entamoeba histolytica
Entamoeba dispar
Naegleria fowleri
Acanthamoeba spp.
Balamuthia spp.

The Flagellates group

Trichomonas vaginalis
Giardia duodenalis
Leishmania spp.
Trypanosoma brucei gambiense and rhodesiense
Trypanosoma cruzi

The amoeba groups

- Amoeba are single celled protozoa.
- Most protozoa are free-living and have little or no impact on human health.
- They are found throughout the environment, particularly in soil and water.
- However, there are three free-living amoeba that have been associated with serious human infections.
- *They are: Acanthamoeba* spp., *Balamuthia mandrillaris, and Naegleria fowleri*

Pathogenic free living amoeba are

Naegleria fowleri

Causative parasite of

Primary amoebic meningo-encephalitis (PAM).

Acanthamoeba species

Causative parasite of

- **Granulomatous amoebic encephalitis (GAM)**
- **keratitis**
- **Chronic granulomatous infection of the skin.**

Distribution

Acanthamoeba species are found worldwide:

- Most commonly in soil, dust, fresh water, marsh, and sea water.
- In swimming pools, hot tubs and drinking water systems (e.g., slime layers in pipes and taps)
- In heating, ventilating and air conditioning (HVAC) systems and humidifiers.

Balamuthia mandrillaris:

- Found in soil.

Naegleria fowleri:

- Is a heat-loving (thermophilic).
- Commonly found around the world in warm fresh water (e.g., lakes, rivers, hot springs).
- In soil.

Transmission

N. fowleri:

- Occurs when water containing amebae enters the nose.
- Trophozoites penetrate the nasal tissue and migrating to the brain via the olfactory nerves causing PAM.

Acanthamoeba spp:

- The trophozoites are the infective forms.
- Through eye, the nasal passages, cuts or skin wounds or by being inhaled into the lungs, it can invade the CNS by hematogenous dissemination in individuals with **compromised immune systems**. .
- When enter the eye they can cause severe keratitis in **healthy individuals,** particularly contact lens users.

Balamuthia mandrillaris:

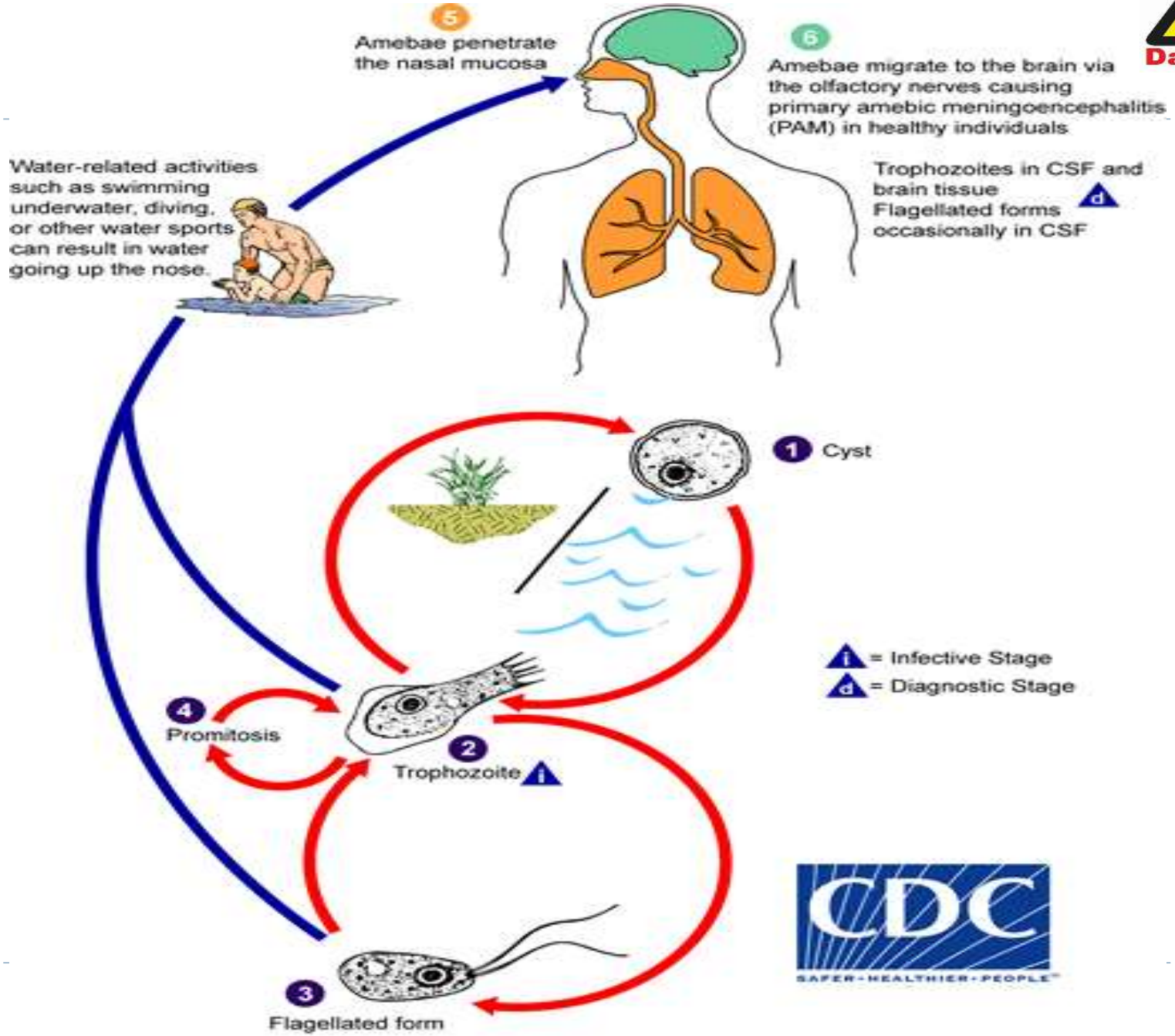
- When dust containing the trophozoites enter the respiratory system or through the skin, it can invade the CNS by hematogenous dissemination causing GAE or disseminated disease, or skin lesions in individuals with **compromised immune systems.**

N. fowleri

Epidemiology

- This parasite largely affects children and young adults through **full-body contact with** warm fresh water, **and is almost always fatal.**
- The organism exists in trophozoite, flagellate, and cyst forms.
- It enters the nasal passages and traverses the nasal mucosa and the cribriform plate as an ameboid form to the olfactory nerves of the CNS.
- Amoeba are the only form found in tissue.

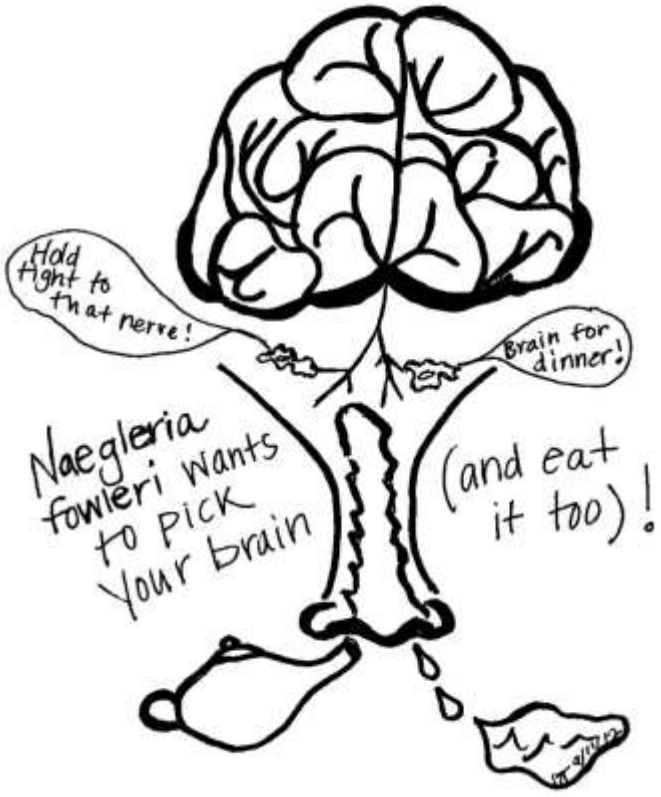
Transmission- N. fowleri



Incubation Period and Illness Duration

Naegleria fowleri:

- Incubation period: symptoms start 1-14 days (median 5 days) after exposure.
- Death: occurs 1-18 days (median 5 days) after symptoms begin



Clinical Illness-(PAM)

Primary Amebic-Meningoencephalitis (PAM)

- **Clinical Case Definition:**
  - An infection presenting as meningoencephalitis or encephalitis.
  - The clinical course:
    - **Stage 1 Symptoms**: begin within 1 to 14 days post amebic exposure and include severe **headache, fever, nausea and vomiting.**
    - **Stage 2 Symptoms:** include stiff neck, confusion, lack of attention to people and surroundings, loss of balance, seizures, and hallucinations.
- After the start of symptoms, death usually occurs within 1 to 18 days (median 5 days) of onset of stage 2 symptoms. Final cause of death is brain swelling and deterioration of tissue.

Treatment- (PAM)

Medical:

- Amphotericin B intrathecally in severe cases +Miconazole (IV injection) + Rifampicin (orally).

Surgical:

- Hydrocephalus may necessitate shunting.

Laboratory Diagnosis- (PAM)

Head CT scanning or MRI

↓

Should precede lumber puncture if signs of increased intracranial pressure were found.

Lumber puncture for CSF analysis

↓

The primary diagnostic tool

↓

1- CSF is purulent (no bacteria), ↑ neutrophils, RBCs, protein levels & ↓ glucose level.
2- Trophozoite and flagellate form were found in CSF.

Culture of CSF

↓

Trophozoite & cyst

Fluorescent antibodies test

↓

Help in detection of the numerous trophozoites in brain tissue

PCR

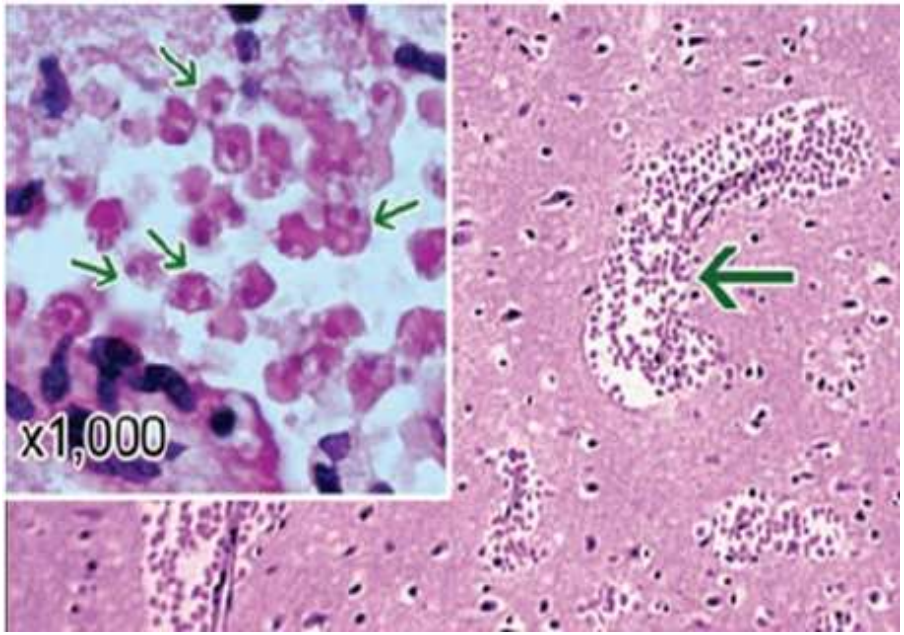
↓

sensitive diagnostic test

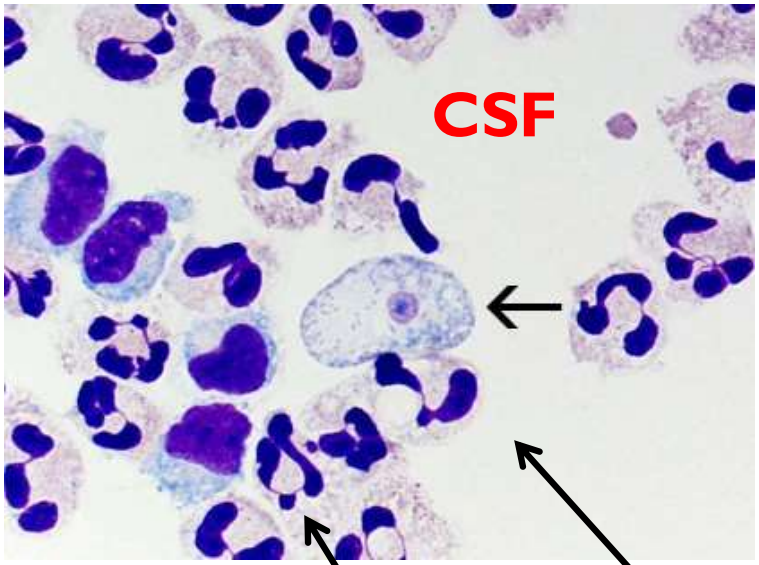
N. fowleri

Diagnosis:

- The protein level is elevated and the glucose level decreased.
- Staining to confirms the identification.



Trophozoites in brain tissue



N. fowleri (KEY CONCLUSIONS)

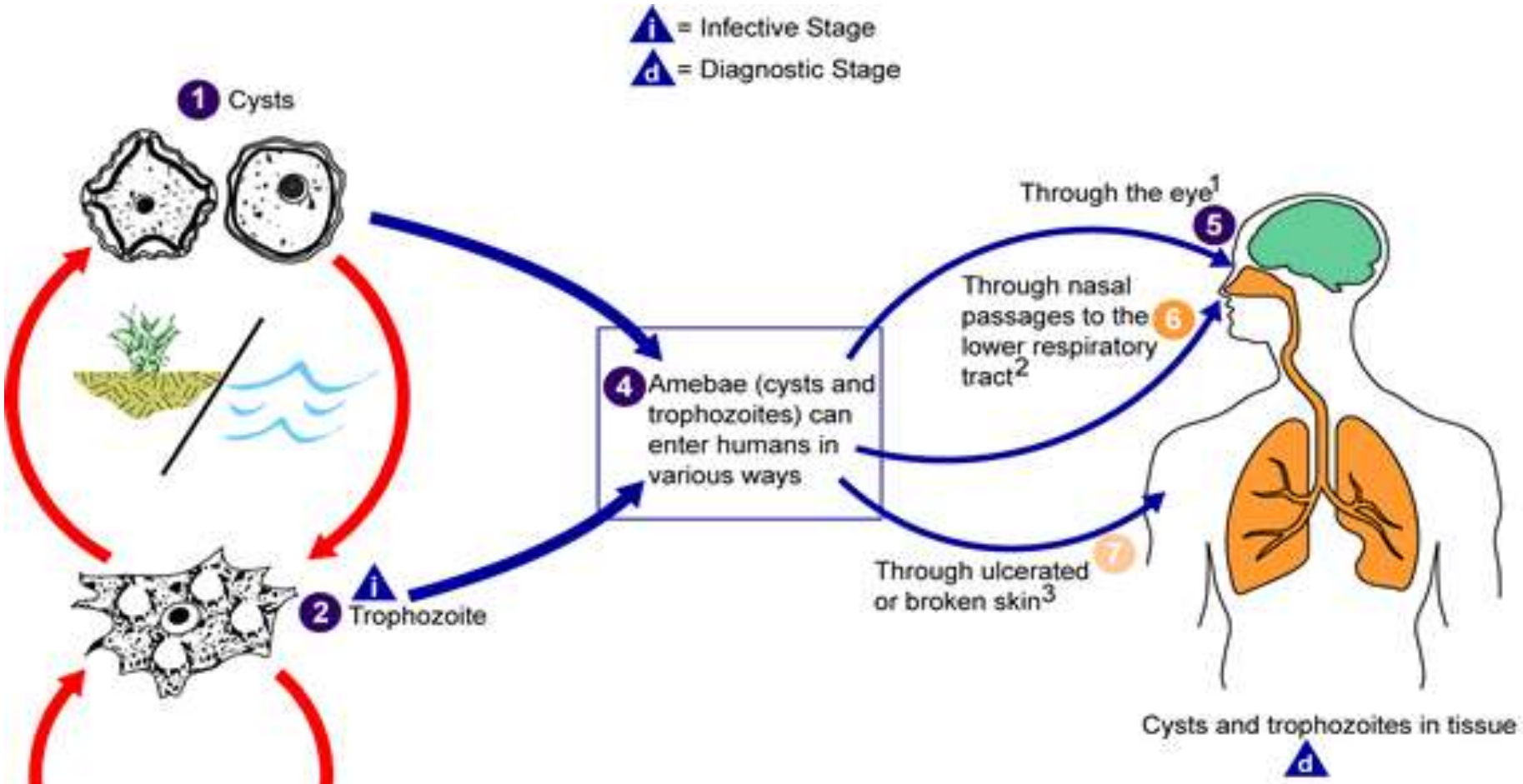
- N. fowleri infections are acquired by full body contact with warm (greater than 40°C) water sources.
- Infections are caused by flagellated trophozoites contacting the nasal mucosa and migrating to the brain.
- Dealth due to meningoencephalitis usually follows in 5 to 6 days.
- Presumptive diagnosis is usually bacterial or viral meningoencephalitis.
- It is imperative for the physician to obtain information regarding the contact with water within the past few days to differentiate it form bacterial or viral meningoencephalitis

Acanthamoeba & B. mandrillaris

Epidemiology

- The caustve agents of GAE.
- They are ubiquitous in soil, fresh and salty water, heating, ventilating and air conditioning units, humidifiers, Jacuzzis, dialysis machines, and dust.
- Infections usually involve older, immunocompromised persons.
- The ameba probably reaches the brain by hematogenous dissemination from an unknown primary site, possibly the respiratory tract, skin, or eye.
- History of freshwater swimming is generally absent.

Acanthamoeba spp & Balamuthia mandrillaris



[1] Results in severe keratitis of the eye. 8

[2] Results in granulomatous amebic encephalitis (GAE) and/or disseminated disease 10 in individuals with compromised immune systems. 9

[3] Results granulomatous amebic encephalitis (GAE), disseminated disease 10, or skin lesions 11 individuals with compromised immune systems. 9

Acanthamoeba & B. mandrillaris

The clinical course

- The clinical course of is more prolonged than that of Naegleria and occasionally ends in spontaneous recovery.
- The disease in immunocompromised hosts is always fatal.
- Histologically, infections produce a diffuse, necrotizing, granulomatous encephalitis.
- Both cysts and trophozoites can be found in the lesions.

Incubation Period and Illness Duration

B. mandrillaris and Acanthamoeba spp:

- Incubation period: Weeks to months (or longer).
- Duration of illness: Weeks to months

Laboratory Diagnosis- (GAM)

1- CSF:

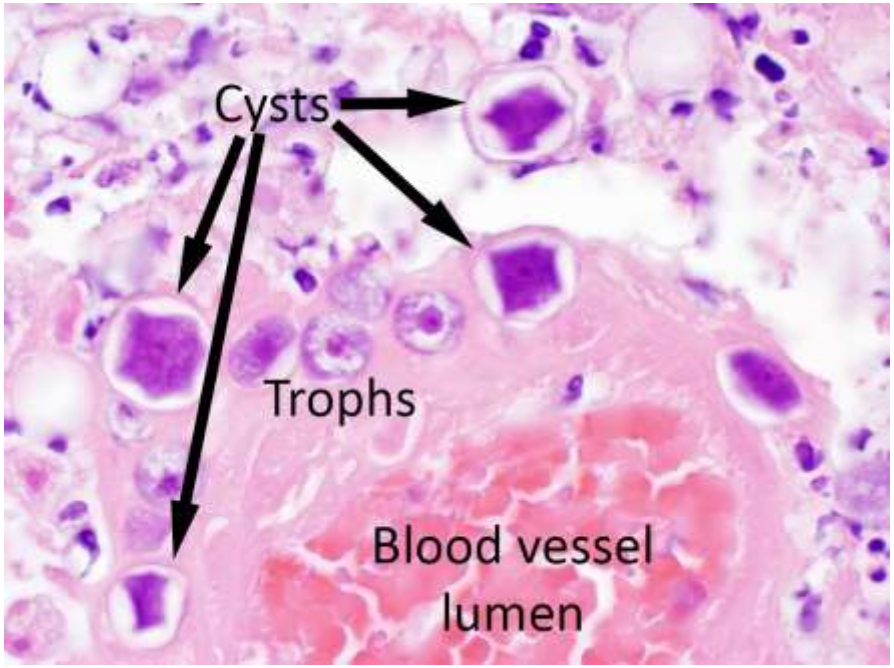
- Trophozoites and/or cysts are rarely seen in the CSF.
- A negative test on CSF does not rule out infection because the organisms are not commonly present in the CSF.
- Every effort should be made to obtain brain tissue in order to diagnosis GAE.

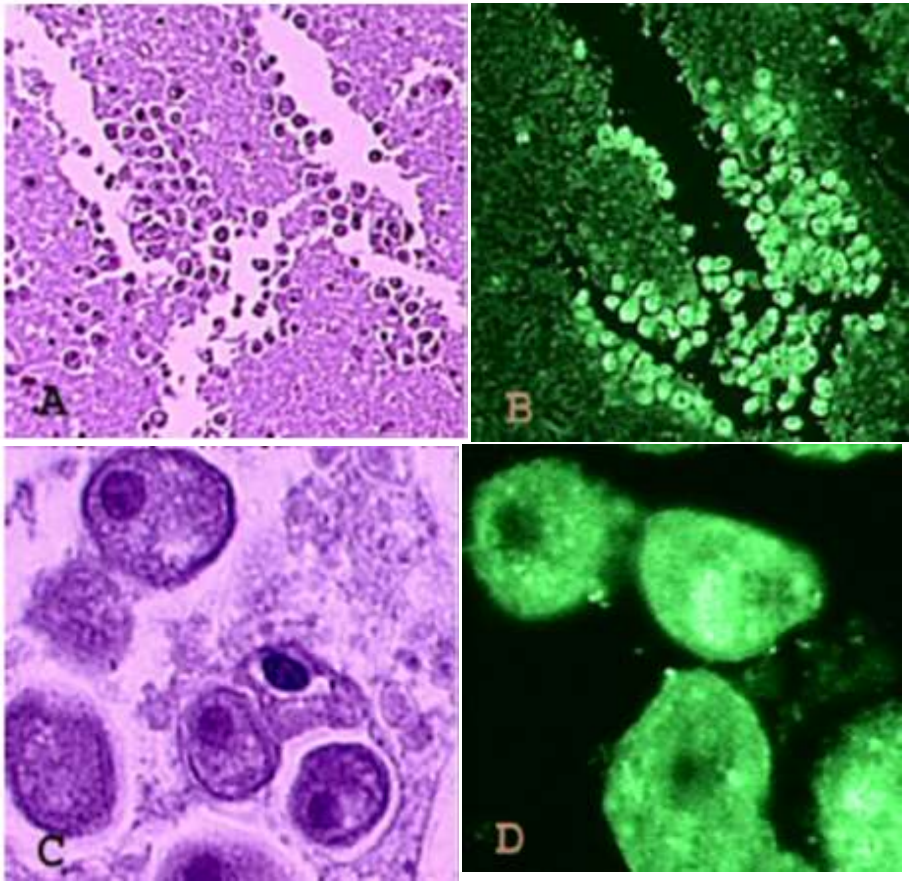
2- Tissue:

- The diagnosis can be made by microscopic examination of tissue sections from biopsy specimens (skin lesions or brain tissue) stained with hematoxylin and eosin (H&E) or periodic acid-Schiff (PAS) which might demonstrate trophozoites and/or cysts.

3- PCR or immunohistochemical or IF.

Trophozoites and Cysts of *Acanthamoeba* species/*Balamuthia mandrillaris*





The diagnosis can be made from microscopic examination of stained smears of biopsy specimens (brain tissue, skin, cornea) or of corneal scrapings, which may detect trophozoites and cysts.

Tissue staining **IF staining**

Clinical Illness

Granulomatous amebic encephalitis (GAE)

- **Clinical Case Definition**
  - An infection presenting as meningoencephalitis or encephalitis.
  - GAE can include general symptoms and signs of encephalitis.

Laboratory Confirmation:

- **Same as *Naegleria* but differs in:**
  - **In lumber puncture: No trophozoites appear in the CSF.**

Acanthamoeba & B. mandrillaris

KEY CONCLUSIONS

- The primary routes of exposure is not well defined by may be oral or through the skin and rarely involve water contact.
- Infections with these parasites are more prolonged than those involving Naegleria.
- Granulomatous encephalitis, keratitis, and skin lesions are most commonly reported.

Treatment- (GAE)

Medical:

- Ketoconazole and amphotericin B (alone or in combination).
- Sulfadiazine may be indicated.

Surgical:

- Same as *Naegleria*.

Control Measures

Naegleria fowleri

- Avoid water-related activities in bodies of warm freshwater during **periods of high water temperature** and low water levels.
- Hold the nose shut or use nose clips when taking part in water-related activities.

Balamuthia mandrillaris and Acanthamoeba spp. :

- There are no specific prevention and control measures.
- Recommend that anyone experiencing symptoms be evaluated by a physician.
- They mainly affects those who are immunocompromised.

Communicability of Amebic meningitis/encephalitis

Amebic meningitis/encephalitis is not spread from person-to-person (except in the case of transmission through transplantation of organs from an infected donor).

Fungal meningitis (Cryptococcosis)

- **It is a fatal fungal disease caused by *Cryptococcus neoformans*.**
- **General characters of *C. neoformans*:**
  - **Yeast cells, oval in shape with a gelatinous capsule.**
  - **Found in soil contaminated with the excreta of birds specially pigeons' feces.**
  - **It is an opportunistic fungus affecting mainly immunosupressed persons specially AIDS patients.**

Fungal meningitis (Cryptococcosis)

- **PATHOGENESIS**
- After being inhaled, cryptococci reach the alveoli, where production of the polysaccharide capsule (many immunosuppressing actions).
- If engulfed by macrophages, C neoformans is able to survive and multiply by altering its metabolic pathways and by inducing melanin production, which interferes with oxidative killing mechanisms.
- C. neoformans cross the blood–brain barrier using macrophages (Trojan horse model) or by the interaction between the components on the microbial surface and the proteins on the endothelial cells of the brain microvasculature.
- Infections in immunologically normal people are very rare,
- Person-to-person transmission has not been documented

Cryptococcosis-Risk groups

- Diseases as AIDS, lymphoma, sarcoidosis, liver cirrhosis, lung & heart diseases.
- Long term corticosteroids therapy.
- Diabetes.
- Pregnancy.

Cryptococcosis-Pathogenesis & Symptomatology

- Depending on the virulence of the yeast strain and the immune status of the host, *C. neoformans* can either cause latent infection (in which the yeast cells remain dormant in the body) or symptomatic disease.

Treatment

Combination of amphotericin B and flucytocine.

Clinical pictures

Respiratory symptoms (pneumonia like illness)

Fever, cough, chest pain & dyspnea

Dissemination of the infection mainly with AIDS

To CNS causing meningoencephalitis

- **Headache, fever.**
- **Neck pain.**
- **Nausea and vomiting.**
- **Sensitivity to light**
- **Mental status range from confusion to coma.**
- **If left untreated, cryptococcal meningoencephalitis may lead to brain damage, hearing loss & hydrocephalus**

To skin, eyes, bones & joints

Diagnosis

Specimens: Sputum, CSF, blood

- **Microscopic Examination** → CSF examination by using India ink showing the oval yeast surrounded by unstained capsule.
- **Blood or CSF culture**
- **Detection of *Cryptococcous* antigen in CSF by** → Latex agglutination test & ELISA. → Rapid & sensitive methods for diagnosis
- **PCR**
- **Dipstick test** → A new method for detecting *Cryptocoocal* antigen in patient's serum → Rapid (takes 10 minutes), sensitive & inexpensive