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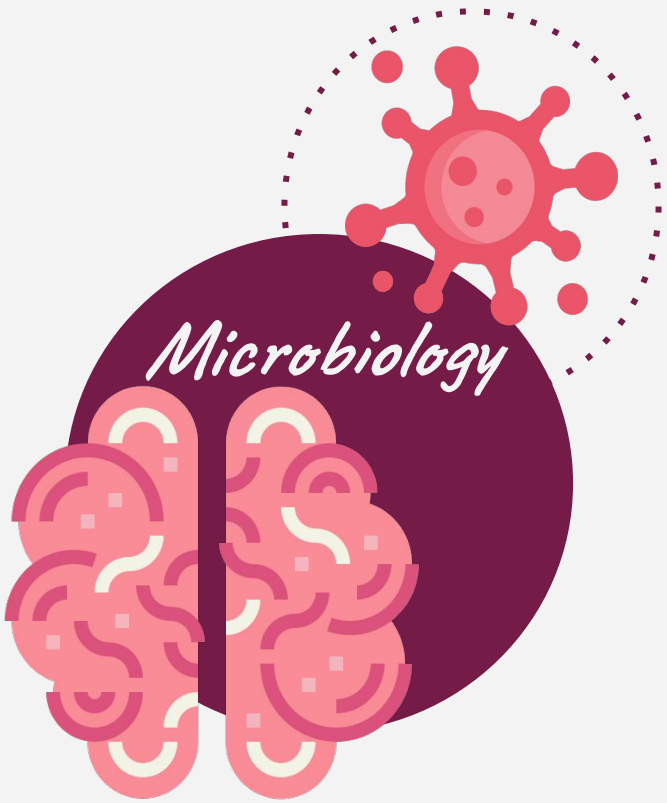

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MED439
KING SAUD UNIVERSITY

MICROBIOLOGY
TEAM 439

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Otitis media

Otitis Media is inflammation of the middle ear .
Middle ear is the area between the tympanic membrane and the inner ear including the Eustachian tube .

Epidemiology	1- Most common in infants 6 to 18 months of age (2/3 of cases) 2- Improve with age, why? The Eustachian Tube which vents the middle ear to the nasopharynx , is horizontal in infants:-Difficult to drain -Its surface is cartilage ,and the lymphatic tissue lining is an extension of adenoidal tissue from the back of the nose. 3-Often preceded by viral upper respiratory infection (URTI)
Pathogenesis	1- URTI or allergic condition cause edema or inflammation of the tube 2-Functions of the tube (ventilation, protection and clearance) disturbed 3- Oxygen lost leading to negative pressure 4- Pathogens enter from Nasopharynx into the middle ear 5- Colonization and infection result
Risk factors	1- Anatomic abnormalities 2- Medical conditions such as Cleft palate, obstruction due to adenoid or Nasogastric tube or malignancy, immune dysfunction 3- Exposure to pathogens from day care 4-Exposure to smoking
Classification of OM	1- Acute 2- Chronic OM 3-Secretory (serous) OM
Complications	**Extracranial** (intratemporal) **Hearing loss / Tympanic Membrane Perforation / Mastoiditis** /Cholesteatoma / Labyrinthitis & others **Intracranial** **Meningitis** / **Extradural abscess /** Subdural empyema / Brain abscess & others

Types	Acute	Chronic	Serous
Bacterial cause	**< 3 months of age: Group B Streptococcus** / H.influenzae (non typable) / S.pneumoniae,(40%) /Gram negative bacteria including Pseudo.aeruginosa, E.coli **> Than 3 months of age:** H.influenzae / S.pneumoniae / Others (S.pyogenes, Moraxella catarrhalis, S.aureus)	Mixed flora in 40% of cases **Pseudo.aeruginosa / Anaerobic bacteria /** H.influenzae / S.aureus / Proteus species / K.pneumoniae / Moraxella catarrhalis	Same as chronic OM, but most of the effusions are sterile with a few acute inflammatory cells.
Viral cause	1- RSV (Respiratory Syncytial Virus) 74%. 2- Rhinovirus. 3- Parainfluenza virus. 4- Influenza virus		
Clinical presentation	Mostly Bacterial →Severe and continuous Pain Often a complication of viral URTI. **First 1-2 days: Fever**/hyperthermia (39 C), irritability, earache (otalgia). / muffled nose. / Bulging tympanic membrane, **(Pain)** **After 3-8 days:** Pus and ear exudative discharge released spontaneously (otorrhea) → then pain and fever begin to decrease. **After 2-4 weeks:** Healing phase, discharge clears and hearing becomes normal.	Usually result from unresolved acute infection / Involves perforation (rupture/hole formation) of tympanic membrane and active bacterial infection for long period. / Pus may drain to the outside (otorrhea). / Results in destruction of middle ear structures and significant risk of permanent hearing loss.	Collection of fluid within the middle ear as a result of negative pressure produced by altered Eustachian tube function. / Represents a form of chronic otitis media or allergy related inflammation. **Over weeks to months**: Thickening of middle ear fluid (glue ear) / Tends to be chronic with non–purulent secretions. / Cause conductive hearing impairment.
Management	**Empirical** antimicrobial therapy depending on the most likely bacterial pathogens, usually to cover **S.pneumoniae** and **H.influenzae. / Amoxicillin +/- Clavulanic acid, or cefuroxime /** Careful follow up / Drainage of exudates may be required.	○ Need complex management, Possibly surgical.	
How to diagnose	○ Clinical examination ○ Tympanometry (detect the presence of fluid) ○ Gram stain & culture of aspirated fluid to detect the etiologic agents.		

Acute Pyogenic Meningitis

Pyogenic Meningitis	
Definition	A serious infection that causes inflammation of the meninges affecting the pia, arachnoid and subarachnoid space, and it is associated with marked inflammatory exudation
Characteristics	-Acute onset -Usually caused by bacterial infection -May be preceded by URTI -Can be fatal if left untreated
Common etiologic agents	-Neisseria Meningitidis -Streptococcus Pneumoniae -Haemophilus Influenzae
Epdimiology of Meningities	- A worldwide disease, about 1.2 million cases annually and 135,000 deaths. - Bacterial meningitis is one of the top ten infections that causes death worldwide. - Half of the survivors suffer neurological damage, and/or permanent side effects afterwards.

★ Causes according to the age	
Age	**Pathogens**
Newborns	**Group B Streptococcus** (strept.agalactiae), E. coli (and other gram negative bacilli), Listeria monocytogenes.
Infants / Children	**S. pneumoniae, N. meningitidis, H. influenzae.**
Adults	**S. pneumoniae, N. meningitidis, Listeria Monocytogenes** also if the patient >50y
Special circumstances	**S. aureus**, S. epidermidis, **S. pneumoniae**, anaerobes, P. aeruginosa.

Signs & Symptoms of Acute Meningitis		
Most common (children and adults)	-Fever -Severe Headache -Stiff neck. - **Sensitivity to light** - Nausea & vomiting - Confusion	
In infant (Neonates and young children)	-Inactivity -Vomiting -Irritability -Poor feeding	
Advanced cases	Bruises under skin (rapidly spread).	
Advanced disease	- Brain damage -Coma -Death	
Physically demonstrable symptoms of meningitis	**Brudzinski's sign**	Severe **neck stiffness** (due to the inflammation of the meninges) causes the patient's hips and knees to flex when the neck is flexed.
	Kernig's sign	Severe stiffness of the hamstrings cause an inability to straighten leg when the hip is flexed to 90 degrees.

Acute Pyogenic Meningitis

Morphology

Listeria Monocytogenes	○ Gram +ve rods (diphtheroids like) ○ Small Rods (basilli) Aerobes ○ Human intestinal colonization (2-12%) ○ Facultative intracellular ○ Tumbling motility
S. Pneumoniae	○ Gram +ve diplococci ○ Catalase -ve ○ **Diplococci** ○ Coagulase -ve ○ **Alpha-hemolytic** ○ **Optochin sensitive**
Group B Streptococcus agalactiae (GBS)	○ Gram +ve cocci in chains ○ Beta hemolytic ○ Coagulase -ve ○ Catalase -ve ○Bacitracin Resistant ○Resident bacteria in **GIT & vagina** (10-30%)
N. Meningitidis	○ Gram -ve diplococci oxidase-positive present in the nasopharynx of 10% of people (potentially pathogenic) ○ Kidney bean shaped diplococci ○ Latex particle agglutination ○ **Utilises maltose and glucose** ○ Grows on thayer-martin agar ○ **Catalase and Oxidase +ve** ○Grows on chocolate agar
E. Coli	○ Gram -ve bacilli ○ Most common cause of neonatal meningitis ○ Many features similar to GBS (Group B Streptococcus) ○ Oxidase -ve ○ **Lactose fermenter**
H.Influenzae (B)	○ Small gram -ve coccobacilli ○ Has polysaccharide **capsule**, other H. Influenza species has no capsule. ○ Need blood for optimal growth, Hematin (**factor X**) and NAD (**factor V**) ○ Found in the nasopharynx normal flora ○ Major cause of lower RTI; occasionally invade deeper tissues and cause bacteremia. ○ Bacteremia : bacteria spread to the CNS ,bones or other organs ○ **Coccobacilli**

Pathogenesis

Listeria Monocytogenes	○ Widespread among animals in nature including those associated with certain foods (cheese and meat) ○ Spread to fetus following hematogenous spread in mother or from birth canal. ○ Has tropism to the CNS
S. Pneumoniae	○ S. Pneumococcal meningitis may follow Pneumococcal Pneumonia or other infections caused by this bacteria ○ **Capsule** is a polysaccharide polymer ○ **Pneumolysin** toxin decreases inflammatory immune response and leads to severe infection.
Group B Streptococcus agalactiae (GBS)	○ Gain access to amniotic fluid during delivery or colonize newborn during passage through birth canal ○ Causes **sepsis** and meningitis in the first few days of life and after 4 weeks
N. Meningitidis	○ **Colonization of nasopharynx** → **Septicemia** → crosses **blood brain barrier** → **endothelial damage** → activation of coagulation cascade → thrombosis and platelets aggregation → bleeding : skin rash and adrenal hemorrhage Shortly: **Colonization of nasopharynx** → **Septicemia** → crosses **blood brain barrier** → **Meningitis** ○ It stimulates antibody production in carriers ○ **Pili** attach to microvilli of **nasopharynx** → invasion → bacteremia **endotoxin LPS** (lipopolysaccharide) produced which spreads to the meninges ○ **Capsule** resists **phagocytosis**
E. Coli	○ Vaginal E.coli colonize infant via rupture of amniotic membrane or during birth. ○ Failure of preterm maternal IgM to cross placenta & special susceptibility of newborn. ○ K1 sialic acid capsule of some strains invade brain microvascular endothelial cells.

Acute Pyogenic Meningitis

Serotypes

N. Meningitidis	○ B,C,Y,W135 cause isolated ,sporadic small epidemics in close population. ★ **Serotype A** has an epidemic potential in Sub-Saharan Africa **(meningitis belt)**
H.Influenzae (B)	○ Many serotypes a-f ○ H.influenzae **Type B** has a **capsule** made of a polymer of **PRP (Polyribosylribitol Phosphate)** that causes acute life threatening invasive infections

Risk Factors

Listeria Monocytogenes	○ Causes meningitis in newborns and immunosuppressed patients and elderly.
S. Pneumoniae	○ **Skull Trauma** ○ Unvaccinated patients (infection rate decreased with vaccination)
Group B Streptococcus agalactiae (GBS)	○ Premature rupture of membrane ○ **Prematurity** ○ Low infant innate immunity
N. Meningitidis	○ Susceptible individuals Unvaccinated people

Prognosis

S. Pneumoniae	○ Recovered cases develop sustained (long period) learning disabilities ○ High mortality rate >30% due to invasive disease
N. Meningitidis	○ 11-20% of recovered patients suffer permanent hearing loss, mental retardation while 10-14% of cases are fatal
H.Influenzae (B)	○ 3-6% mortality rate ○ 1/3 of survivals have significant neurological sequelae ○ Infection rate decreased since the routine use of Hib vaccine

N. Meningitidis

Transmission	○ Inhalation of aerosolized droplets & close contact
Prevalence	○ Common in children who are younger than 6 and young adults

Diagnosis

- **Clinically:** Sign & symptoms
- **Specimens:** CSF analysis acquired through lumbar Diagnosis of puncture and blood specimen for Meningitis culture.
- CSF is analyzed for cells, proteins, glucose and chloride in addition to culture and antimicrobial susceptibility testing.

Acute Pyogenic Meningitis

CNS PARAMETERS

Normal CSF			Pyogenic Meningitis
Adults	○ WBC =0-5 /cmm3 ○ PMN= 0 % ○ glucose = > 60 % of blood ○ protein =< 30 mg/dl ○ chloride = 115-130mmol/l		○ ↑WBC= 5 - 5000/cmm3 ○ ↑PMN[1]= > 60% ○ ↓Glucose[2] = < 45 % of blood ○ ↑Protein[3] = >60 mg/dl ○ ↓Chloride = 110 mmol/l
Neonates	**Term (mature):** WBC =0-32 /cmm3 PMN=>60 % glucose = >60 % of blood protein= 20-170 mg/dl	**Preterm (premature):** WBC=0-29/cmm3 PMN= <60 % glucose = >60 % of blood protein= 60-150 mg/dl	

CSF Evaluation

Condition	WBC	Protein (mg/dL)	Glucose (mg/dL)
Normal	<5, ≥75% lymphos	20-45	>50 (or 75% serum glucose)
Bacterial, acute	100-10,000 or more; usually 300-2,000; **Neutrophils predominate**	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)
Bacterial, partially treated	5-10,000	Usually 100-500	Low to normal
TB	10-500 Lymph	100-3000	<50
Viral or meningoencephalitis	Rarely > 1000 Lymph	Usually 50-200	Generally normal; may Viral or be decreased

Abnormal findings of CSF in some pathological conditions

Parameter	Bacterial Meningitis	Tuberculous Meningitis	Viral Meningitis	Brain Tumor
Protein	↑↑	↑↑	**Normal**	↑
Glucose	↓↓	↓↓	**Normal or slightly ↓**	↓
Chlorides	↓↓	↓↓	**Normal or ↓**	**Normal or ↓**

Management

○ A medical emergency. ○ Antibiotics given after taking specimens for lab diagnosis. ○ Parenteral administration

Children & Adults	★ **Ceftriaxone** (or Cefotaxime) **+ Vancomycin** (covers the main 3 pathogens). ○ Add ampicillin if the patient age is > 50 or at risk for Listeria.
Neonates	★ **Ampicillin + Gentamicin + Cefotaxime** ○ Modify treatment after lab results (as needed)
Duration	○ 10-14 days (or more) according to the medical condition
Prevention	○ Vaccination ○ Prophylactic antimicrobial agent for contacts (Hib & N. meningitidis)

Cerebral infections

Chronic meningitis	
Definition	Meningeal inflammation that persists for more than 4 weeks
General causes	1. Infectious: ○ **Bacterial including TB** ○ Viral ○ Fungal ○ Parasitic 2. Neoplasm 3. Chemical 4. Parameningeal 5. Autoimmune 6. Idiopathic

Causes of Chronic Cerebral infection and Meningitis	
Bacterial,	**Common in Saudi Arabia:** Not common in Saudi Arabia : Lyme disease-caused by Borrelia burgdorferi . Others: ○ Partially treated acute meningitis. ○ Syphilis-caused by Treponema Pallidum. ○ Liptosporosis- caused by L.Icterohaemorrhagiae. ○ Nocardiosis-caused by Nocardia species .g N. Asteroids. ○ Actinomycosis caused by actinomycetes. These organisms can also cause Cerebral abscesses,, preferred as chronic infection
Risk factors	○ Age and Gender (listeria, brucella and SLE) ○ Regional preponderance. ○ Occupation and Recreational activities. ○ Immune status. ○ Sexual exposure ○ Animals or ticks contact.
Can produce	○ Neurological disability ○ May be Fatal if not treated
They usually have	○ Slow insidious onset ○ With progression of signs and symptoms over a period of weeks
They differ from those of acute infection which have	○ Rapid onset of symptoms and signs

- They are usually diagnosed ,if the neurological syndrome exists for > 4 weeks ,
- Should differentiated from recurrent aseptic meningitis , aseptic meningitis symptoms are less than 4 weeks
- Chronic meningitis affects about 10% of patients diagnosed with meningitis

Cerebral infections

Clinical Presentation of chronic cerebral & meningitic infection	
Symptoms	-Chronic headache. -Neck or back pain. -Changes in the personality -Facial weakness -Double vision -Leg & arm weakness -Clumsiness
Signs	-+/-Papilloedema -BrudZinski or Kerning 'positive (sign of meningeal irritation) -Altered mental status, memory loss, etc -Seventh nerve palsy -3,4,6th,Nerve palsy -Ataxia -Hydrocephalus
They should differentiated on the basis of:	-Clinical History -Occupation -Clinical symptoms -CSF findings -Clinical signs in other organism
Diagnosis of chronic cerebral & meningeal infections	-History for brucellosis & TB -Clinical examination -Laboratory findings -Imaging (X-ray, MRI or Ultrasound)

Tuberculous Meningitis		
Diagnostic Features	**Clinical**	- Fever and headache (for more than 14 days). - Vomiting. - Altered sensorium or focal. - Neurological deficit.
	CSF	- Pleocytosis (more than 20 cells, more than 60% lymphocytes) - Increased protein (more than 100 mg/dl) - Low sugar (less than 60% of corresponding blood sugar) - India ink studies and microscopy for cryptococcus Neoformans - Malignant cells should be negative
	Imaging	- Exudates in basal cisterns or in sylvian fissure - Hydrocephalus - Infarcts (basal ganglionic) - Gyral enhancement - Tuberculoma formation
Complications		○ **Hydrocephalus** due to obstruction of the foramina of Luschka and Magendie or the aqueduct of Sylvius ○ Vasculitis, sometimes causing arterial or venous occlusion and stroke ○ **Cranial nerve deficits**, particularly of the 2nd, 7th, and 8th cranial nerves

Cerebral infections

	Tuberculosis	Brucellosis
Etiology	Caused by **Mycobacterium tuberculosis.**	In KSA caused by Br.melitensis.
Epidemiology	○ It the most common cause of chronic meningitis ○ It infect one third of human race.	○ It is common disease in Saudi Arabia.
Transmission	Airborne disease, the bacteria is very small and can stay in air for a long time and spread to a long distance.	It affect people who: ○ **Are in contact with domestic animals.** ○ Consume raw milk and milk products. ○ And through inhalation.
Clinical presentation	○ The patient usually presents with **fever of long duration.** ○ In some cases present as meningitis and cerebral infection presenting chronic neurological symptoms and signs. (Headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies, and raised ICP) ○ Symptoms of cough and coughing of blood (Haemoptysis) when the chest is affected.	○ It usually presents with **Pyrexia (fever) of unknown organism** of intermittent nature (rising and falling) ○ The fever is accompanied by **night sweating**, in between the attacks of fever the patient is not very ill. ○ Influenza-like symptoms.
Can cause	Parenchymal CNS involvement can occur in the form of tuberculoma or more rarely abscess. Also can cause: ○ Spinal meningitis ○ Spinal cord infarction (Pott's spine, Pott's paraplegia).	○ It can cause chronic cerebral infections & meningitis.
Prevention	Immunization with Bacille Calmette-Guerin (BCG) to newborns.	○ **Prevention in animal:** Vaccination. ○ **Eradication:** can only be achieved by test-and slaughter combined with effective prevention measures and control of animal movements ○ Cook the meat ,avoid contact with animals when they are giving birth and drink pasteurized milk
Treatment	**Total 9-12 months** For the first **2** months: - **Rifampicin** ★ **Isoniazid (INH)** - **Ethambutol** - **Pyrazinamide** For the next **(4-6)** , **(7-10)** months: - **Rifampicin** - **INH**	Two of the following 3 drugs: - Tetracycline - **Rifampicin** - **Cotrimoxazole** Usually Rifampicin and Cotrimoxazole are preferred as they have good penetration power in the Blood-Brain-Barrier

Cerebral infections

CSF and Laboratory Findings	
Tuberculosis & Brucellosis	
Biochemical investigation	-Total protein→↑ **protein** level due to presence of inflammatory substance, dead organism, protein and WBC. -Glucose level in comparison to the serum glucose level→↓ **glucose** level (Normally is 2/3 of serum glucose level).
Microscopy	-Presence of organism. -Total white cell count →↑ local white cell count but in chronic infection the differential shows **lymphocytosis** while in acute infections there is ↑of polymorph. -Gram stain can same time rarely shows causative organism. -Differential count mainly for: -Polymorphic -Lymphocytes → Neutrophil
Culture for CSF	-For Brucella, T.B Mycobacterium tuberculosis, Leptospira other Bacteria. -TB: -Media :CSF culture a solid medium L.J or fluid medium. -Stain: **Z-N** Stain can show **AFB** of T.B
PCR	Or other molecular biopsy test for presence of bacterial element
Serology	For Brucella.

CSF Findings in different cases				
Topic	**Viral meningitis**	**TB meningitis**	**Fungal meningitis**	**Bacterial meningitis**
Cell count 0-5	< 2000 cell/ mcL predominantly lymphocytes	**100-2000 cells/mcL predominantly lymphocytes**	100-500 cells/mcL predominantly lymphocytes	>1000-20000 cell/mcL predominantly Neutrophil
Protein 15-50	30-150 mg/dl	**High (100-500 mg/dl)**	40-150 mg/dl	High (>250 mg/dl)
Glucose 45-100	30-70 mg/dl	**Decreased <40 mg/dl**	30-70 mg/dl	<40 mg/dl (<40% of serum Glucose)

Fungal infections

Risk factors

- HIV/AIDS
- Hematopoietic stem cell transplant (HSCT)
- Malignancies
- Hereditary immune defects
- Solid organ transplantation
- Immunosuppressive medications
- surgery/trauma
- Indwelling catheters (e.g candidemia -> CNS seeding)
- Diabetes mellitus
- Neutropenia

How fungi reach the CNS

Traumatic introduction	○ Surgical procedures ○ Head trauma ○ Contaminated Injections ○ lumbar punctures
Local extension	From the paranasal sinuses, the ear, or the orbits.
Hematogenous spread	More common with yeast

Clinical syndromes

Meningitis	Brain abscess
A. Sub acute B. Chronic	A. With vascular invasion B. Without vascular invasion

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

Etiology

Mould / Filamentous	Dimorphic	Yeast
○ **Aspergillus spp** ○ Zygomycetes ○ Fusarium spp ○ Exophiala spp ○ Cladophialophora Bantiana ○ **Rhinocladiella Mackenziei** ○ Curvularia , Bipolarid ○ Others	○ Histoplasma spp ○ Blastomyces spp ○ Coccidioides spp ○ Paracoccidioides spp ○ Penicillium marneffei	○ **Candida spp** ○ Cryptococcus spp (Encapsulated yeast)

Cryptococcal Meningitis

Etiology	**Cryptococcus neoformans is the most common etiology** + cryptococcus gattii ○ **Capsulated** yeast cells ○ Naturally in birds droppings (Pigeon) , tree hollows and soil
Predisposing factor	**AIDS** is the leading predisposing factor
Acquired by	Inhalation
Clinical Syndrome	Mainly meningitis

Fungal infections

Candidiasis	
Candida species are the 4th most common cause of hospital acquired bloodstream infections.	
Etiology	○ **Candida albicans** & other species including : C.glabrata, C. tropicalis C. parapsilosis, & C. krusei.
Morphology	○ Hematogenously ○ Surgery, Catheters
Clinical syndrome	○ **Meningitis** ○ Cerebral abscesses
CNS Zygomycosis (mucormycosis)	
Etiology	Zygomycetes e.g: Rhizopus, Absidia, Mucor Fast growing fungi
Common risk factors	★ **Diabetes with ketoacidosis**, in addition to other risk factors.
Clinical syndrome	○ 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%) -Progression rapid-
To improve outcome	○ Rapid diagnosis ○ Early surgical debridement ○ Control the underlying disease ○ Appropriate antifungal therapy
Pheohyphomycosis	
-Fungal infections caused by dematiaceous fungi - Neurotropic fungi	
Etiology	★ **Rhinocladiella mackenziei** (Mainly reported from Middle East) ○ Cladophialophora, Exophiala , Curvularia, Fonsecaea.
Common risk factors	★ **Reported in immunocompetent hosts**
Clinical syndrome	Chronic and Usually brain abscesses
CNS Aspergillosis	
Etiology	○ **Aspergillus fumigatus** ○ A. flavus ○ A. terrus
Reach CNS by	○ Spread Hematogenously ★ May also occur via direct spread from the anatomically adjacent sinuse Dr: This is called: **Rhinocerebral aspergillosis** ○ Angiotropism (infarction and hemorrhagic necrosis)
Common risk factors	○ Hematological malignancies ○ Cancer chemotherapy ○ Transplantation
Clinical syndrome	○ Usually brain abscesses (single or multiple)
Prognosis	○ Mortality rate is high

Fungal infections

Other infections

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis

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

Diagnosis

Clinical features	(history, risk factors... ect): Not specific for fungal infection)	
Neuro-imaging	Good value in diagnosis and therapy monitoring	
Lab Investigations	**Clinical Examples**	-CSF -Biopsy -Pus -Aspirate -Blood (for serology)
	CSF Abnormalities:	-Cell count -Glucose level(↓) -Protein level (high): Not specific for Fungal infections
	Direct Microscopy	Fungal stains: -Giesma -GMS -PAS -India ink: (mostly for Cryptococcus neoformans)
	Serology	-Candida -Aspergillus -Cryptococcus -Histoplasma -Blastomyces -Coccidiodis -Paracoccidioides
	PCR	-
	Culture	Fungal media: -SDA agar -BHI agar -Other media if needed

Lab diagnosis

CNS infection	Direct microscopic	Culture	Serology
Cryptococcal Meningitis	Yeast cells capsulated **(india ink)**	Yeast	○ 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
Pheohypho-mycosis	**Brown septate hyphae**	Dematiaceous (Black) mould	No serology available

Serology: β-D- Glucan[1], for diagnosis of invasive fungal infections except cryptococcosis and zygomycosis

Treatment

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

	CNS fungal infection	Treatment
Antifungal Therapy	**Cryptococcal meningitis**	**Amphotericin B** (combination with Flucytosine)
	CNS Candidiasis	**Caspofungin, Fluconazole**, Voriconazole, Amphotericin B
	CNS Aspergillosis	**Voriconazole**, Amphotericin B (Combination of voriconazole and Caspofungin)
	CNS Zygomycosis	**Amphotericin B**

Viral infections

Etiology	
Enteroviruses	○ **Poliovirus**, Coxsackieviruses (A&B) , Enteroviruses, Echoviruses ○ Can cause 1-Aseptic meningitis. 2-Paralysis. 3-Encephalitis
Herpes simplex Encephalitis	○ **Herpes simplex virus -1 (HSV-1)**
Rabies encephalitis	○ **Rabies virus**
Arthropod borne virus	○ **West Nile Virus,** Common in middle east

Pathogenesis	
Enteroviruses	○ Fecal-oral route → replicate in the GIT mucosa and oropharynx → reaches the blood (viremia) → it targets many organs. ○ Inhalation of infectious aerosols
Poliovirus	○ **Pathway to CNS by:** - Blood (viraemia). - Peripheral nerves. ★ **Causing destruction of motor neurons AHCs** (Anterior horn cells) . ○ **Rarely affects brain stem (bulbar Poliomyelitis)** ○ **Immunity:** - IgA & IgG = Lifelong type-specific immunity.
Herpes simplex Encephalitis	○ **Primary infection:** Virus enters via cutaneous or mucosal surface → infect sensory or autonomic nerve endings → transport to the cell body in ganglia before establishing latent phase ○ **Latent phase** ○ **Reactivation (lytic phase):** deactivation of HSV in trigeminal ganglion can result in spread to temporal lobe via meningeal branch of CN-V (trigeminal nerve)
West Nile Virus	○ **West Nile Virus** spread to humans through the bite of an infected vector (**Mosquito**, Tick, & Sandfly) , the vector get the virus when they bite an infected Wild birds & Mammals . **which causes:** - Fever, Rash, & Arthralgia - Hemorrhagic fever ± hepatitis. - CNS diseases (meningitis & encephalitis)
Rabies encephalitis	○ **Route of transmission:** - **Bite of rabid animal (bats , dogs and cats)** - Inhalation while in a bat infested cave - Corneal transplant

Phases Of Rabies encephalitis

The incubation period	The prodromal phase	Neurological phase	Recovery
1-3 month	Fever, Nausea, Headache, Vomiting, Malaise, Anorexia, ★Abnormal sensation around the wound	1- Encephalitis: Nervous, lacrimation, salivation, hydrophobia (fear of water), convulsion, coma & death 2- Paralytic illness: Ascending, death, associated with Bat bite	Extremely rare

Viral infections

Diagnosis

CSF analysis	Color:Clear Cells:↑ Lymphocytes Glucose: Normal Protein:Normal or↑
Enteroviruses	- RT-PCR to detect Enteroviruses RNA in CSF. (Molecular testing) - Virus isolation (old method).Stool sample and indoculate in cell culture - Serology
Herpes simplex Encephalitis	- **PCR**: Detection of HSV-1 DNA in CSF.↑ in Lymphocytes, glucose is normal & ↑protein - **MRI**: For temporal lobe lesion - The clinical presentation: Fever, headache, vomiting, seizures & altered mental status
Rabies encephalitis	- **RT-PCR** Rabies RNA in saliva - **Rapid virus antigen detection** Neck skin biopsy ,Corneal impressions ,Brain tissue - Histopathology : Neuronal brain cell Intracytoplasmic inclusions (negri bodies) - Virus cultivation - Serology
Arthropod borne virus	- **Isolation (Gold standard)** - **IgM -AB, ELISA, IF (most used)** - Arbovirus RNA by RT-PCR

Infections

Poliovirus	○ **No illness (90-95%):** Asymptomatic ○ **Minor illness (4-8%):** Abortive poliomyelitis (No CNS involvement). ○ **Major illness (1-2%):** - Non-paralytic poliomyelitis (Aseptic meningitis). - Paralytic poliomyelitis (Flaccid paralysis). Usually affects the lower limb (no sensation loss)
Arthropod borne virus	○ Asymptomatic infections ○ Diseases: - Fever, Rash, & Arthralgia - Hemorrhagic fever ± hepatitis. - CNS diseases (meningitis & encephalitis)

Prevention

Poliovirus	○ Inactivated/killed polio vaccine (IPV), **for adults** (Salk, injection). ○ Live-attenuated polio vaccine (OPV), (Sabin, oral) → has a potential risk of reverting to its virulent form. (good **for children**).
Herpes simplex Encephalitis	○ **Treatment** : Acyclovir
Rabies encephalitis	○ Control measures against canine rabies includes -Stray animals control. -Vaccination of domestic animals ○ **Pre-exposure prophylaxis (vaccine)** for persons at risk of rabies ex, animal handlers ○ **Post-exposure prophylaxis :** - Wound treatment - Passive immunization human anti-rabies immunoglobulin - Active immunization: Human Diploid Cell Vaccine (HDCV) 5-6 doses
Arthropod borne virus	○ **Vector control :** - Elimination of vector breeding sites - using insecticides - Avoidance contact with vectors (repellants, net) ○ **Vaccines :** - Tick-borne encephalitis vaccine, Japanese encephalitis vaccine

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