MEDICINE
KING SAUD UNIVERSITY

MICROBIOLOGY436

Review File

- Important

Editing File

"لا حول ولا قوة إلا بالله العلي العظيم" وتقال هذه الجملة إذا داهم الإنسان أمر عظيم لا يستطيعه ، أو يصعب عليه القيام به

LECTURE: Microbiology of Middle Ear Infections

Characteristics	Otitis media		
Definition	Inflammation of the middle ear		
Classification	Acute OM*	Chronic OM	Secretory(serous) OM
Epidemiology	Most common in infants 6 to 18 months of age (2/3 of cases) Often preceded or accompanied by viral upper respiratory infection (URTI).		
Pathogenesis	❖ In normal situation, the Functions of the eustachain tube *(ventilation, protection and clearance)* when they are disturbed they may lead to OM. ❖ During this process the Oxygen lost leading to negative pressure ❖ Pathogens enter from nasopharynx into the middle ear. ❖ Colonization and infection result.		
Risk factors	❖ URTI or allergic condition ❖ Anatomic abnormalities ❖ Medical conditions such as Cleft palate ,obstruction due to adenoid or nasogastric tube or malignancy, immune dysfunction. ❖ Exposure to pathogens from day care ❖ Exposure to smoking		

OM*: Otitis media
URTI**: Upper respiratory tract infection

Classification	OM bacterial causes (MOST CASES ARE BACTERIAL, MORE SERIOUS)	
Acute OM	< 3 months of age	❖ S.pneumoniae,(40%) *(most common)* ❖ group B Streptococcus ❖ H.influenzae ❖ Gram negative bacteria
	> 3 months of age	❖ S.Pneumoniae *(the most common)* ❖ H.influenzae ❖ others eg. S.aureus
Serous OM	❖ Mixed flora in 40% of cases ❖ P.aeruginosa , K.pneumoniae, anaerobic bacteria.	
Chronic OM	❖ Same as chronic OM, but most of the effusions are sterile (no bacteria culture) ❖ Few acute inflammatory cells	

OM-Viral causes	**1)** RSV(Respiratory Synsechial Virus) -74% **2)** Rhinovirus

<table>
<tr><th>Classification</th><th colspan="2">Clinical presentation</th></tr>
<tr><td rowspan="4">Acute OM</td><td colspan="2">❖ Mostly Bacterial ,often a complication of viral URTI.</td></tr>
<tr><td>First 1-2 days</td><td>❖ Fever (39 C), irritability, earache , muffled nose.
❖ Bulging tympanic membrane ,poor mobility and obstruction by fluid or inflammatory cells on otoscopic examination.</td></tr>
<tr><td>3-8 days</td><td>❖ Pus and ear exudative discharge released spontaneously
❖ Pain and fever begin to decrease</td></tr>
<tr><td>2-4 weeks</td><td>Healing phase, discharge dies up and hearing becomes normal</td></tr>
<tr><td>Serous OM (with effusion)</td><td colspan="2">❖ Collection of fluid within the middle ear as a result of negative pressure produced by altered Eustachian tube function.
❖ Represent a form of chronic OM or allergy-related inflammation.
❖ Over weeks to months, middle ear fluid become very thick and glue like (glue ear)
❖ Tends to be chronic , with non –purulent secretions.
❖ Cause conductive hearing impairment and hearing deficit.</td></tr>
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Classification	Clinical presentation
Chronic OM	❖ Usually result from unresolved acute infection due to inadequate treatment or host factors that perpetuate the inflammatory process. ❖ Involves perforation of tympanic membrane and active bacterial infection for long period. ❖ Pus may drain to the outside (otorrhea). ❖ Result in destruction of middle ear structures and significant risk of permanent hearing loss.

Diagnostic approach of OM	Management	Complications	
		Extracranial	**Intracranial**
❖ Clinical examination ❖ Tympanometry (detect the presence of fluid) ❖ Gram stain and culture of aspirated fluid to determine the etiologic agents.	❖ Acute OM requires antimicrobial therapy & careful follow up. ❖ Antimicrobial* usually empirical depending on the most likely bacterial pathogens, usually to cover S.pneumonia and H.influenzae. ❖ Drainage of exudate may be required. ❖ Chronic or serous OM need complex management, possibly surgical.	❖ Hearing loss ❖ Tympanic membrane perforation ❖ Mastoiditis ❖ Cholestatoma	❖ Meningitis (most dangerous complication) ❖ Extradural abscess ❖ Subdural empyema ❖ Brain abscess

LECTURE: VIRAL INFECTION OF THE CNS

Viral meningitis	Bacteria meningitis
• Aseptic meningitis • Caused by virus. • Less severe • Resolves without specific treatment within a week or two	• Septic meningitis •Caused by bacteria •Quite severe and may result in **a)** brain damage **b)** hearing loss **c)** learning disability • It would also causes death!

	Normal	Aseptic meningitis	Septic meningitis
Colour	Clear	Clear	Cloudy
Cells/mm^3	< 5	increase 100-1000 Lymphocytes	High/v. high 200-20,000 Neutrophils
Glucose mg/dl	45-85	Normal	Low<45*
Protein mg/dl	15-45	Normal/high 50-100	High>100
Causes		Viruses , others	Bacteria

Enteroviruses:

Nonenveloped , icosahedral , ss (+) RNA	
Include:	•Poliovirus(1, 2&3 types) •Coxsackieviruses (A&B) •Echoviruses
Epidemiology:	
Reservoir:	Human
Spread :	•Fecal - oral route (mainly) •Inhalation of Infectious aerosols (Crowded, Poor hygiene & Sanitation)
Age :	children > adults
Seasonal distribution:	summer & fall

Enteroviral infections:
Asymptomatic infections

Neurologic diseases	Non-neurologic diseases
Aseptic meningitis Paralysis encephalitis	Respiratory tractinfections – skin &mucosa infections – cardiac infections – acute hemorrhagic conjunctivitis

Poliovirus infections

No illness 90-95%	Asymptomatic
Minor illness 4-8%	Abortive poliomyelitis (No CNS involvement)
Major illness 1-2%	1- Nonparalytic poliomyelitis (Aseptic meningitis) 2- Paralytic poliomyelitis: (Flaccid paralysis)

Immunity: IgA & IgG = Lifelong type-specific immunity

- **Lab Diagnosis of Enteroviruses**:
  CSF in aseptic meningitis : EV(enteroviruses) RNA detected in CSF by RT-PCR

- **Management**: (No antiviral)
- **Prevention:**

Sanitation ,Hygienic measures & Poliovirus vaccines:

a- Inactivated polio vaccin (IPV) (Salk, Killed) (S/C or IM)- for adult

b- Live-attenuated polio vaccine (OPV) (Sabin, oral)- for children

•Important Features of Polio Vaccines:

Attribute	Killed (IPV)	Live (OPV)
3 types (trivalent)	Yes	Yes
Prevents disease	Yes	Yes
Induces humoral IgG	Yes	Yes
Induces intestinal IgA	No	Yes
Duration of immunity	Shorter	Longer

Viral encephalitis	Inflammation of the brain caused by a virus		
Virus all of them enveloped	Herpes Simplex Virus-1	Rabies	Arboviruses : Arthropod Borne Virus: west nile v
Features	dsDNA Icosahedral	Bullet shaped virus , ss (-) RNA	+ssRNA , flaviviridae (family)
Reservoir & Transmission	-	R:Raccoons, foxes, wolves, bats, cats ,dogs. T: bite of a rabid animal	Vector: mosquitos R: birds T: bite of an infected vector
Clinical features	Fever, headache, vomiting, seizures and altered mental state.	4 phases : **1-incubation:** 3 mths depend on bite **2-prodromal:** fever ,anorexia,headache **3-neurological:** 1. Encephalitis(most common) : nervous,lacrimation,hydrophobia, coma death 2. Paralytic illness: ascending, death **4-Recovery**: rare	**(West Nile Fever)** **Distribution:** Europe, Africa, Middle East, Asia,America. **Cause febrile illness eventually meningitis and encephalitis.**
Laboratory diagnosis *PCR is useful for all of them to detect the genome	CSF: Lymphocytes, normal glucose, high protein	• **Histopathology:**intracytoplasmic inclusions (Negri bodies) • Rapid virus antigen detection (IF)	**IgM** → ELISA and Immunofluorescence. Isolation is the gold standard
Prevention	**treatable** but not preventable by Acyclovir (antiviral)	1-Vaccination of domestic animals. 2-**Pre**-exposure(prophylactic vaccine) 3-**Post**-exposure: wound treatment and (passive & active) immunization	**Vector Control** by using insecticides **Vaccines:** -Tick-borne & Japanese vaccine
Infection	Encephalitis	Encephalitis(most common): fatal acute encephalitis Paralytic illness	-Asymptomatic Infections→80% -West Nile Fever → 20%

LECTURE: cerebral TB and chronic infection

Bacteria: (most sever) **Most Important.**	Common in saudi :	Brucella-Brucellosis , TB-Tuberculosis
	Partially treated acute meningitis:	*Neisseria Meningitidis , Streptococcus Pneumoniae , Haemophilus influenzae.*
	Others:	Syphilis by Treponema Pallidum, Leptospirosis by L. Ictero haemorrhagica, Lyme Disease by Borrelia burgdorferi - Lyme Disease (not common in Saudi Arabia), Nocardiosis by Nocardia Asteroids e.g. N. Asteroids, Cerebral abscess can also same – preferred as chronic infection.
Fungal:	Cryptococcus neoformans (Aids patients), Candida species (in Saudi Arabia species mainly Candida albicans in immunocompromised patients) , Aspergillus species (cancer patients + very common) , Histoplasma capsulatum.	
Parasitic:	Toxoplasma gonodii (most common , from kittens) , Trypanosoiasis (caused by Trypanosoma brucei gambiense , Trypanosoma brucei rhodesiense , Trypanosoma cruzi Acanthamoeba spp (Rare causes).	
Virus: (less sever)	Some virus can some present as chronic meningitis these include: üMumps , Herpes simplex , HIV.	

brucellosis

Etiology	Brucella Species | Gram -ve Coccobacilli | Brucella Melitensis is the most common in Saudi Arabia
Transmission	Contact with domestic animals or consumption of raw milk and dairy products (camels)
Presentation	● It usually presents with Pyrexia (fever) of unknown organism of intermittent nature. ● The fever is accompanied by night sweating, however, in between the attacks of fever the patient is not very ill. ● Because the symptoms are not specific and flu-like, untreated Brucilla can invade the CNS, causing chronic cerebral infection and meningitis.
Laboratory	CSF culture and Serology.
Treatment	**Two of the following 3 drugs** ● Tetracycline ● Rifampicin ● Cotrimoxazole **Rifampicin and Cotrimoxazole are preferred as they have good penetration power in the BBB.**

Tuberculosis

Etiology:	Mycobacterium Species (Resist Staining) Mycobacterium tuberculosis which infected 1\3 the human race
Presentation:	•The patient usually presents with fever of long duration You will never have TB without fever. •Symptoms of cough, and coughing blood (Haemoptysis) when the chest is affected. •It can present as meningitis or cerebral infection with chronic neurological symptoms and signs. •Parenchymal CNS involvement can occur in the form of tuberculoma or, more rarely, abscess. •Spinal meningitis,radiculomyelitis, spondylitis, or spinal cord infraction pott's spine and pott's paraplegia

Diagnosis	
Clinical	**CSF**
•Fever and headache for >14 days. •Vomiting. • Altered sensorium or •focal neurological deficit. •Mantoux test (Tuberculin skin test) •occupying lesions (Tuberculoma). •Tuberculoma with Miliary Tuberculosis. •Tuberculous abscess	•Microscopy: Z.N. Stain. •Culture: on L.J. or Fluid Medium. •PCR. •Pleocytosis : >20 cells, >60% lymphocytes. •Increased proteins : >100 mg/dl. •Low sugar: <60%. •Malignant cells: should be -ve. (because tb formation a granuloma which a mass so it be confuse with tumor)

Treatment:

For the first 2 months: Rifampicin + Isoniazid (INH) + Ethambutol + Pyrazinamide

Then, for 4-6 months: Rifampicin + Isoniazid (INH)

•Diagnosis of chronic cerebral and meningeal infections

•History for Brucellosis and Tuberculosis

•Clinical examination

•Imaging by x- ray or MRI or ultrasound

• Laboratory findings

CSF Findings
• Increased CSF pressure indicating increased intra cranial pressure. • Increased protein level due to presence of inflammatory substance, dead organism, protein and WBC. •Reduced glucose level (Normally it is 2/3 of serum glucose level). •Increased local white cell count but in chronic infection the differential shows lymphocytosis while in acute infections there is increased % of polymorphonuclear leukocytes. • Gram stain can sometimes show the causative organism. •Z-N Stain (Ziehl-Neelsen stain) can show AFB (acid-fast bacilli) of T.B while modified Z-N can show Nocardia

LECTURE: Acute pyogenic meningitis

•Causes According to the Age

Age Group	Common Causative Agents
Newborns	Group B Streptococcus, E.coli (and other gram negative bacilli) , Listeria monocytogenes, •
Infants / Children •	Strep.pneuomiae, N.meningitidis, H.influenzae
Adults	Strep.pneumoniae, N.meningitidis
Elderly	•Strep .pneumoniae, N.meningitidis •Listeria monocytogenes,

•Pyogenic meningitis is an inflammation of the meninges affecting Pia, Arachnoid and subarachnoid space.
•Acute in onset, serious infection, associated with marked inflammatory exudation.
•Usually caused by bacterial infections.
•May be preceded by URTI.
•Can be fatal if untreated.
Three main capsulated bacterial species:
1. Neisseria meningitidis
2. Sterptococcus pneumoniae
3. Hemophilus influenzae

Neisseria Meningitides	
General info.	Gram negative Diplococci – Present as normal flora of nasopharynx n 10% of people
Transmission	By inhalation of aerousal droplets
Prevalence	Common in children below 6 years
Risk Factors	Susceptible individuals (with no antibodies)
Serotypes	•**B,C,Y,W135** cause isolated ,sporadic small epidemics in close population. •Serotype **A** has an epidemic potential in sub-saharan Africa (meningitis belt).
Pathogenisis	•In some individuals , the bacterial pili attach to the nasopharungeal microvilli àinvasion à bacteremia àendotoxin Lipopolysaccharide (LPS) produced à meninges. •In case of carriers it stimulates antibody production •its capsule resists phagocytosis
Prognosis	•11-20 % of recovered patients suffer permanent hearing loss, mental retardation. •10-14% of cases are fatal.

Streptoccous pneumoniae	
General info.	Gram positive Diplococci
Risk Factors	•May develop after trauma to the skull •None vaccinated patients
Pathogenisis	• May follow a Pneumococcal pneumonia, or any other site infected with the organism. • Pneumolysin decreases inflammatory immune response and leads to severe infection. •Capsule is polysaccharide polymer.
Prognosis	•High mortality rate more than 30% (due to invasive disease) •Recovered patients develop learning disabilities.

Haemophilus Influenzae	
General info.	• Small gram negative coccobacilli in the nasopharynx normal flora • Has a polysaccharide capsule, other species have no capsule. • Need blood for optimal growth, Hematin (factor X) and NAD (factor V). • Major cause of LRTI. • Occasionally invade deeper tissues and cause bacteremia. •Infection rate decreases since the routine use of Hib vaccine .
Serotypes	• Has many serotypes (from A to F). • HIB has a capsule made of a polymer of Polyribosylribitol Phosphate that cause acute life threatening invasive infections.
Prognosis	• 3-6% mortality rate32. • 1/3 of survivals have significant neurological sequelae. •

Group B Streptococcus	
General info.	•Gram positive cocci in chains , Catalase –ve , Resident Bacteria in GIT and vagina (10-30%)
Risk factors	•premature rupture of membrane •prematurity, •low infant innate immunity
Pathogenesis	•Gain access to the amniotic fluid during delivery → Colonize the newborn as it passes the birth canal → Cause sepsis and meningitis in the first few days of life or after 4 weeks.

Escherichia Coli	
General info.	•Gram negative bacilli , Catalase +ve , Oxidase +ve , Lactose Fermenter •Similar to Group B Streptococcus •Most common cause of neonatal meningitis
Pathogenesis	•Vaginal Escherichia Coli colonize the infant via a rupture of the amniotic membrane or during birth. •Failure of preterm maternal IgM to cross the placenta, leading to a special susceptibility of the newborn to infections. •K1 sialic acid capsule of some strains invade the brain microvascular endothelial cells.

Listeria Monocytogenes	
General info.	•Gram positive rods , Catalase +ve •Human intestinal colonization (2-12%) •
Pathogenesis	•Widespread among animals in nature including those associated with food supply. •Spread to fetus following hematogenous spread in the mother, or from the birth canal35. •Has tropism to the CNS.

•Diagnosis of Meningitis

Clinically (symptoms , signs , history)
Specimen : CSF acquired through lumbar puncture and blood for :
1. Analysis of cells.
2. protein.
3. glucose .
Culture and antimicrobial susceptibility testing.

CSF Findings
• Increased protein level due to presence of inflammatory substance, dead organism, protein and WBC. •Reduced glucose level (Normally it is 2/3 of serum glucose level). •Increased local white cell count (polymorphonuclear leukocytes.)

•Management

•Urgent , A MEDICAL EMERGENCY
•Antibiotics after taking specimens for lab diagnosis
•Parenteral administration of Ceftriaxone (or Cefotaxime) + Vancomycin (cover the main 3 pathogens) or ,
Amplicillin + Gentamicin or Cefotaxime (neonates)
•Duration : 10-14 days according to the medical condition
•Prevention: vaccination , prophylaxis of contacts (Hib& N.meningitidis)
•Prophylaxis antibiotic (rifampin)

LECTURE: Fungal Infections of Central Nervous System

Risk factors: HIV , diabetes mellitus, surgery , trauma, immunosuppressive medication Fungi reach the CNS by : Hematogenous spread / Local extension from the paranasal sinuses, the ear, or the orbits / Traumatic introduction	
Cryptococcal meningitis	- AIDS (HIV) is the leading predisposing factor. - Acquired by inhalation. - clinical syndrome: Meningitis. - Etiology: Cryptococcus neoformans : found naturally in pigeon habitats – capsulated yeast cells .
Candidiasis	-Reach CNS by: Hematogenous spread, surgery, catheters. -clinical syndrome: Cerebral abscess and meningitis. -Etiology: is mainly C.albicans.
CNS Aspergillosis	clinical syndrome: usually Brain abscesses. - Risk factors: Malignancy, transplantation, chemotherapy. Spread Hematogenously, or direct spread from adjacent sinuses. - - Mortality rate is high. - Etiology: Aspergillus fumigatus, A.flavus and A.terrus
CNS Zygomycosis (Mucoromycosis)	-The rhinocerebral form is the most frequent presenting clinical syndrome in CNS zygomycosis. -Mortality rate is high. - etiology: Zygomycetes e.g. Rhizopus, Absidia. - Risk factor: Diabetic with ketoacidosis + other risk factors - Clinical manifestations: Start as Sinusitis → rapidly progress → involve the orbit → eye → optic nerve → brain. - Symptoms: Facial edema, necrosis, loss of vision, black discharge, angiotropism.
Pheohyphomycosis	-Etiology: Rhinocladiella mackenziei→ most common in middle east. -Caused by dematiaceous fungi (neurotropic fungi) darkly colored due to melanin pigment -Affects **immunecompetent** hosts. - Clinical syndrome: Chronic brain abscess.

Diagnosis: Clinical features (history, risk factors, etc but they are not specific),Neuro-imaging, Lab Investigations

Lab Investigations

(CSF examination (cell count, chemistry), Histopathology, Microbiology)

CSF abnormalities	Direct microscopy	Culture	Serology	PCR
Not specific for fungal infection.	Fungal stains: Giemsa, GMS, PAS, India ink (Cryptococcus neoformans)	Fungal media: SDA, BHI	To detect the antigens or antibody	

CNS infection	Direct microscopy	Culture	Serology*
Aspergillosis	Septate branching hyphae	Hyaline mould	Galactomannan Ag
Zygomycosis	Broad non-septate hyphae	Hyaline mould Fast growing	No serology available
Pheohyphomycosis	Brown septate hyphae	Dematiaceous mould	β-D- Glucan For diagnosis of invasive fungal infections except cryptococcosis and zygomycosis

CNS fungal infection	Treatment
Cryptoccocal meningitis	Amphotericin B (combination with Flucytosine)
CNS Candidiasis	Caspofungin, Fluconazole, Voriconazole, Amphotericin B
CNS Aspergillosis	Voriconazole
CNS Zygomycosis	Amphotericin B

THANK YOU FOR CHECKING OUR WORK, BEST OF LUCK!

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Doctors slides