



TEAM443  
MICROBIOLOGY

# Viral infections of the CNS

LECTURE 4



# Objectives



Understand the different acute viral infections of the CNS (Meningitis, paralysis and encephalitis).



Differentiate between the clinical presentation and cerebrospinal fluid finding in the viral meningitis (aseptic meningitis) and bacterial meningitis (septic meningitis).



Understand the common viruses causing aseptic meningitis and encephalitis with regard to classification, structure, epidemiology pathogenesis, infections, clinical presentation, lab diagnosis and prevention.



Understand general information of arboviruses and giving some example of arboviruses causing CNS infection.

## Color Index:

Main text

Important

Notes

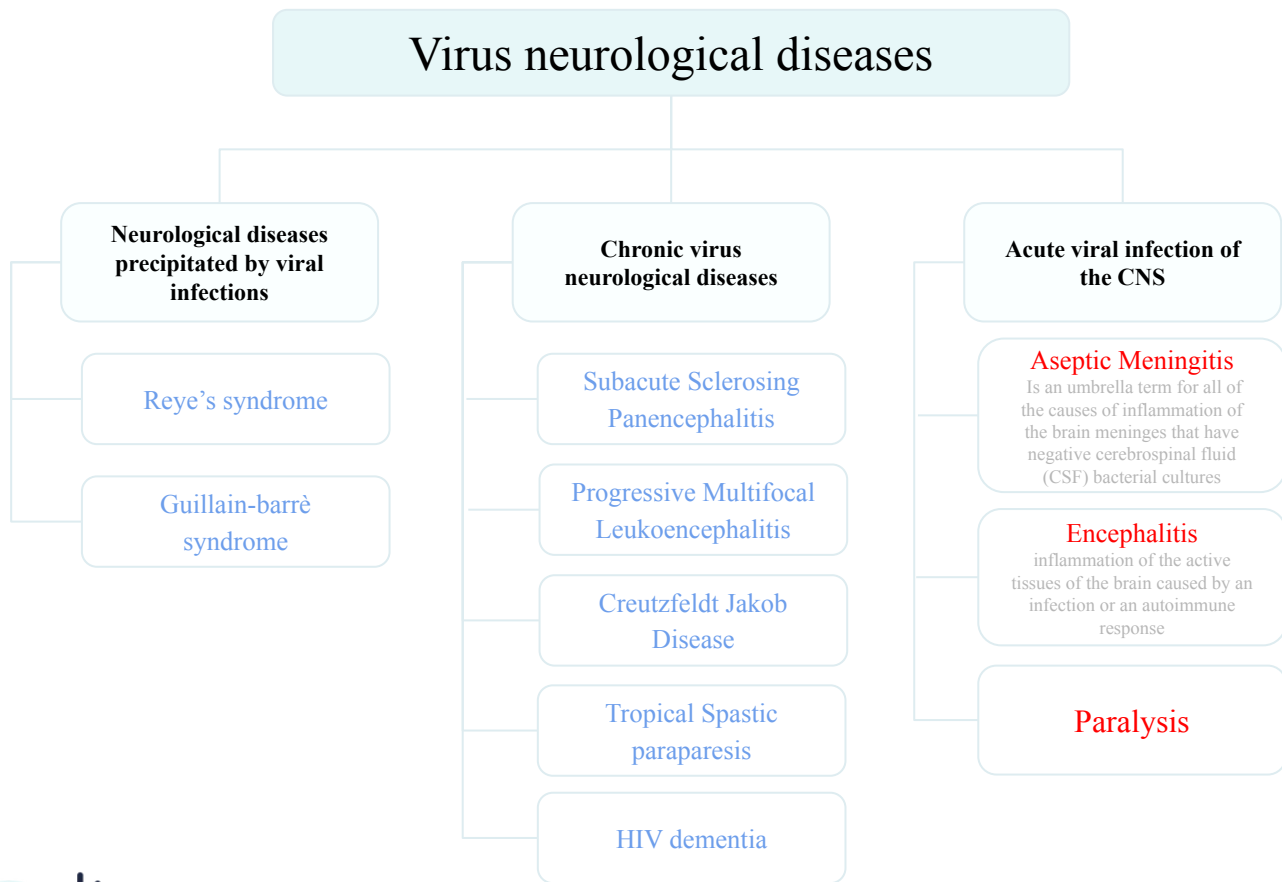
Boys slides

Girls slides

Extra



# Virus neurological diseases



## Acute viral infections of the CNS

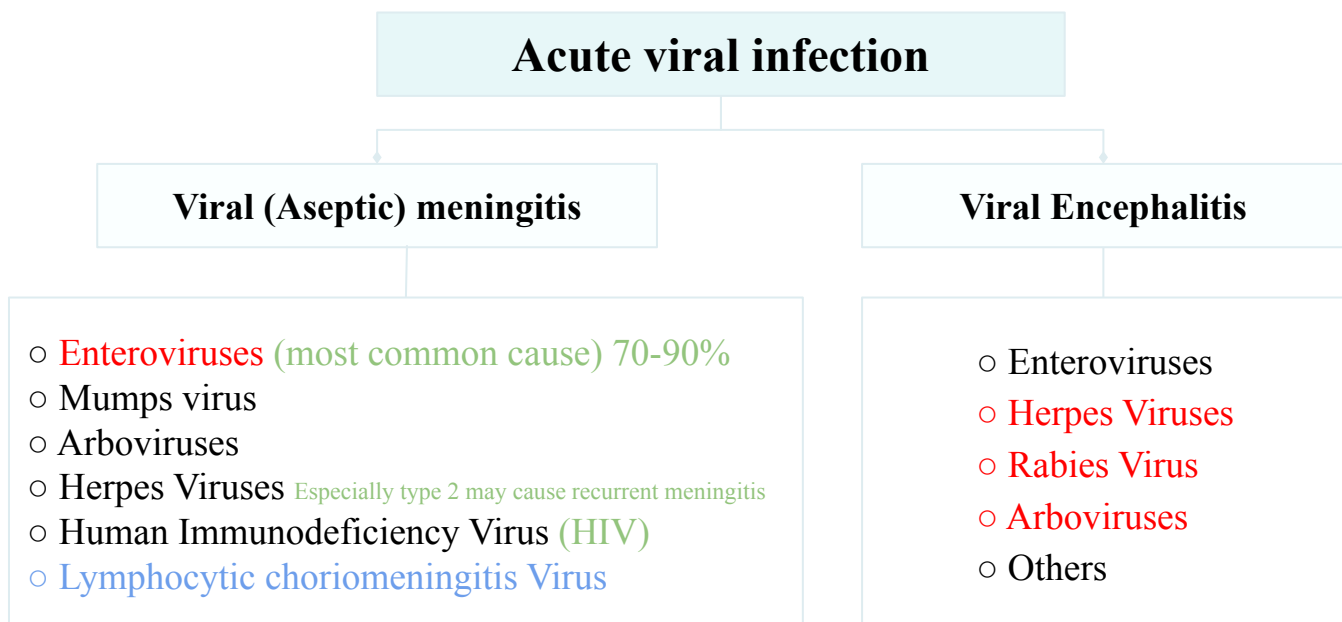
### Meningitis

Definition	It's Inflammation of leptomeninges (affect Pia, Arachnoid, and Subarachnoid space)	
Causes	<ul style="list-style-type: none"> <li>○ <b>Infectious agents:</b> Bacteria , Fungi , Protozoa, viruses [1]</li> <li>○ <b>Non- infectious agents:</b> autoimmune disease SLE, subarachnoid haemorrhage, tumours</li> </ul>	
Classification	Viral meningitis	Bacterial meningitis [2]
Type [3]	<b>Aseptic meningitis</b> caused by virus	<b>Septic meningitis</b> caused by bacteria Meningitis due to an infection can cause sepsis
Severity	Less severe	Quite severe and may result in: <ul style="list-style-type: none"> <li>- Brain damage</li> <li>- Hearing loss</li> <li>- Learning disability</li> </ul>
Prognosis	resolves without specific treatment within a week or two	Medical emergency and would also cause death !!



# Cerebrospinal fluid CSF analysis

Cerebrospinal fluid (CSF) analysis			
	Normal	Aseptic meningitis	Septic meningitis
Colour [4]	Clear	Clear	Cloudy[4]
Cells/mm <sup>3</sup>	<5	↑Lymphocytes 100-1000	High/very high Neutrophils 200-20,000
Glucose mg/dl	45-85	Within the normal range	Low < 45
Protein mg/dl	15-45	Normal or slightly high (50-100)	High > 100 [5]
Causes	-	Viruses, others	Bacteria



Sign and symptoms of meningitis [6]



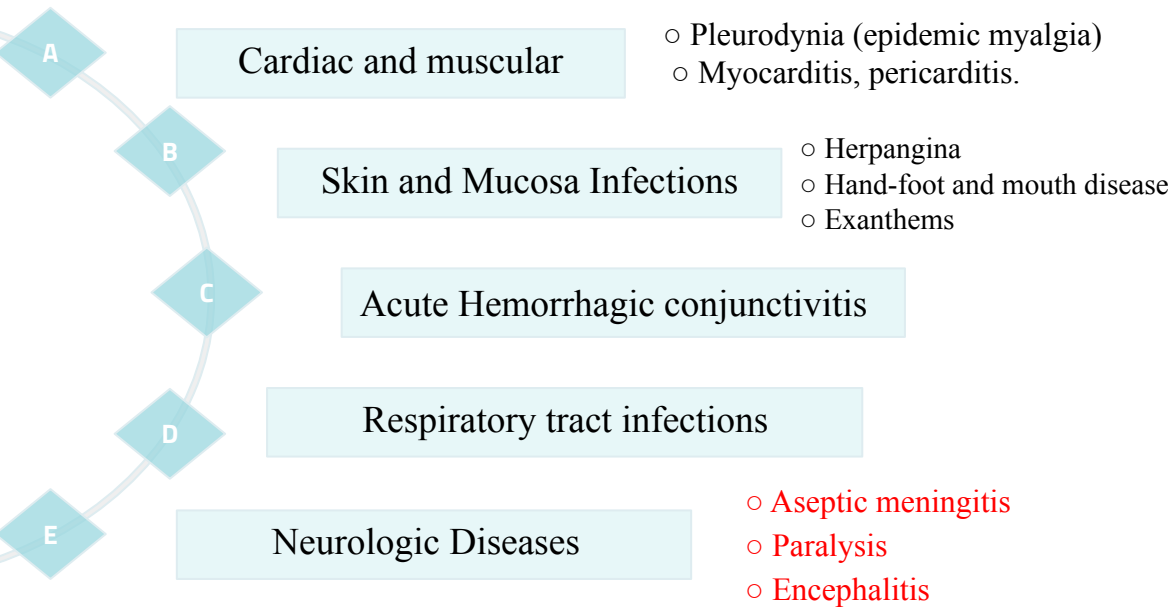


# Viral meningitis (Aseptic meningitis)

Enteroviruses		
Family	Picornaviridae. <b>pico = small</b>	
Structural features	<ul style="list-style-type: none"> <li>- <b>Non-enveloped</b> - <b>Icosahedral capsule</b></li> <li>- +ve Single Stranded RNA genome (+ <b>ssRNA</b>) [7]</li> </ul>	
Enterovirus include:	<ul style="list-style-type: none"> <li>○ <b>Poliovirus</b> (1, 2&amp;3 types)</li> <li>○ <b>Coxsackieviruses</b> (A&amp;B)</li> <li>○ <b>Echoviruses</b></li> <li>○ <b>Enteroviruses</b> (68-71)</li> </ul>	
Epidemiology	Reservoir	Humans
	Spread	<ul style="list-style-type: none"> <li>○ <b>Mainly fecal - oral route</b> [8]</li> <li>○ Inhalation of infectious aerosols (crowded, poor hygiene &amp; sanitation).</li> </ul>
	Age	Affect Children more than Adults. <b>can affect all ages but children more susceptible</b>
	Seasonal distribution	<b>Mainly summer &amp; fall however in tropical area enteroviruses can be seen all the year</b>
Diagnosis	Samples: Stool (best), rectal, throat swabs & CSF	
	<b>Virus isolation</b> <b>gold standard</b>	<ul style="list-style-type: none"> <li>- Inoculate in <b>cell culture MKC &amp; HDF</b></li> <li>- All EVs grown except some strains of Cox A viruses</li> <li>- <b>Observe for CPE</b></li> <li>- <b>Identify the type by Neutralization Test</b></li> </ul>
	CSF	in aseptic meningitis; <ul style="list-style-type: none"> <li>- Glucose: Normal to slightly decreased</li> <li>- Protein: Normal or slightly high.</li> <li>- <b>Isolation rate is variable</b></li> <li>- lymphocytosis</li> </ul> <b>EV RNA detected in CSF by RT-PCR [9]</b>
	Serology	limited value [10]
Enteroviral infections	<ul style="list-style-type: none"> <li>- <b>Major asymptomatic Infections to severe diseases affected many organ</b></li> <li>- Diseases; Next slide</li> </ul>	



# Enteroviral infections



Neurologic Diseases:					
Virus / disease	Polio types 1-3	GPA COX. types 1-24	GPB COX. types 1-6	Echo types 1-34	Entero types 68-71
Aseptic meningitis	1-3	Many	1-6	Many	71
Paralysis	1-3	7,9	2-5	2,4,6,9,11,30	70,71
Encephalitis	-	2,5-7,9	1-5	2,6,9,19	70,71

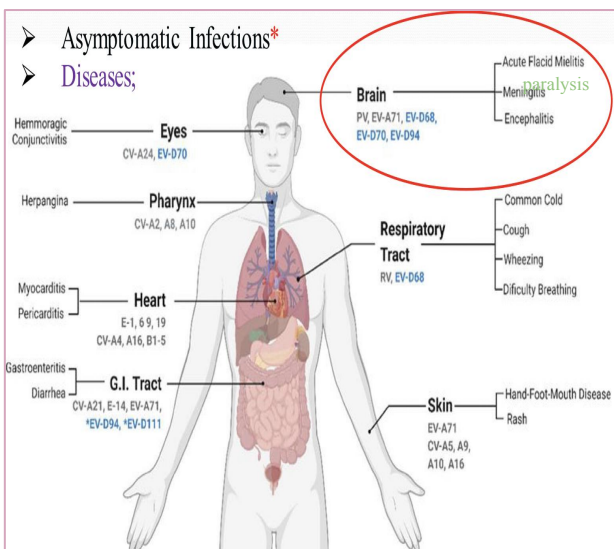


TABLE 1. Traditional Versus Newer Enterovirus Classification

	TRADITIONAL CLASSIFICATION Host disease pattern and tissue culture effects in infected animal models	NEWER CLASSIFICATION Molecular serotyping (RNA sequence)
Groups & Serotype	<b>Coxsackieviruses A</b> 1-22, 24*	<b>Group A</b> Coxsackievirus A serotypes 2-8, 10, 12, 14, 16; Enterovirus serotypes 71, 76, 89-92
	<b>Coxsackieviruses B</b> 1-6	<b>Group B</b> Coxsackievirus A serotype 9; B serotypes 1-6
	<b>Echoviruses</b> 1-9, 11-27, 29-33	Echovirus serotypes 1-7, 9, 11-21, 24-27, 29-33; Enterovirus serotypes 69, 73-75, 77-88, 93, 97, 98, 100, 101, 106, 107
	<b>Polioviruses</b> 1-3	<b>Group C</b> Poliovirus serotypes 1-3; Coxsackievirus A serotypes 1, 11, 13, 17, 19-22, 24
	<b>Enterovirus</b> 68-72	<b>Group D</b> Enterovirus D68, D70, D94, D111

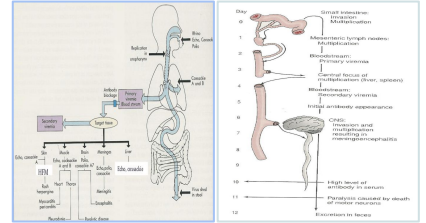
\*Coxsackievirus A23 was reclassified as echovirus 9.  
Adapted from <http://www.picornastudygroup.com/taxa/taxa.htm>.



# Poliovirus

## Poliovirus [16]

<p>Pathogenesis [12]</p>	<ul style="list-style-type: none"> <li>○ Pathway to CNS by:           <ul style="list-style-type: none"> <li>- <b>Blood (viraemia).</b></li> <li>- <b>Peripheral nerves.</b> How? by affecting skeletal muscle</li> </ul> </li> <li>○ Causing destruction of <b>motor neurons AHCs</b> [13]</li> <li>○ Rarely affects brain stem (bulbar Poliomyelitis) with respiratory failure</li> <li>○ Immunity:- IgA &amp; IgG = Lifelong type-specific immunity [14]</li> </ul>		
<p>Infections ★</p>	<p><b>No illness (90-95%):</b></p> <ul style="list-style-type: none"> <li>- Asymptomatic but still secrete and release poliovirus in stool</li> </ul>	<p><b>Minor illness (4-8%):</b></p> <ul style="list-style-type: none"> <li>- Abortive poliomyelitis (<b>No CNS involvement</b>). recover usually within 1 weeks</li> </ul>	<p><b>Major illness (1-2%) [15]</b></p> <ol style="list-style-type: none"> <li>1- Non-paralytic poliomyelitis (Aseptic meningitis)</li> <li>2- Paralytic poliomyelitis (Flaccid paralysis)</li> </ol>
<p>Treatment</p>	<p>No antiviral therapy “there is no specific treatment but only supportive”</p>		
<p>Prevention</p>	<ol style="list-style-type: none"> <li>1- Sanitation &amp; Hygienic measures</li> <li>2- Poliovirus vaccines (IPV and OPV)</li> </ol>		



## Poliovirus vaccines

Inactivated polio vaccine (IPV)

Live-attenuated polio vaccine

- For adults & immunocompromised
- known as the Salk or killed vaccine
- can be injected SC, or IM.
- Adverse reactions: **Local reactions.**
- Indications **not recommend for adult except:** Travelers to polio-endemic countries, Health care workers.
- **Pediarix contains / combination vaccine:** IPV, DTaP, Hib & HB vaccines

- For children
- known as Sabin's oral polio vaccine
- Only oral
- Adverse reactions: **Vaccine Associated Paralytic Poliomyelitis in adult and low immuned** [17]
- 4 doses of Polivitus: 2, 4, 6-18 ms, then 4-6 yrs.



# Important features of Polio vaccines

Attribute	Killed (IPV)	Live (OPV)
3 types (trivalent)	Yes	Yes
Prevents disease	Yes	Yes
Induces humoral IgG	Yes	Yes
Route of administration	Injection	Oral
Induces intestinal IgA	No	Yes
Affords secondary protection by spread to others	No	Yes
Reverts to virulence	No	Yes (Rarely)
Causes disease in low immuned	No	Yes
Duration of immunity	Shorter	Longer
Transmission to others	No	Yes





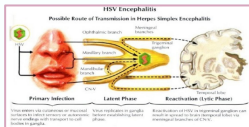
# Viral Encephalitis

Definition	Encephalitis is severe disease, non self limiting, it's inflammation of brain parenchyma, associated with high mortality, usually present with non-specific illnesses, in addition of loss of consciousness, seizures, neurological signs.
Caused by	Enteroviruses, Herpes viruses, Rabies virus, Arboviruses & Others.



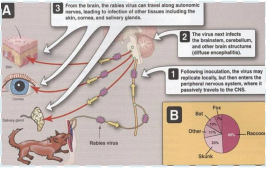
# Herpes Simplex Encephalitis

Herpes simplex Encephalitis (HSV) ★	
Family	Herpesviridae family
Caused by	<ul style="list-style-type: none"> <li>○ Herpes simplex virus -1 (HSV-1) [18]</li> <li>○ Double Stranded DNA genome (<b>dsDNA</b>)</li> <li>○ <b>Enveloped</b> notice that all the viruses that will cause encephalitis are enveloped</li> <li>○ <b>Icosahedral virus</b></li> </ul>
Clinical presentation/features	<ul style="list-style-type: none"> <li>○ Fever, headache, vomiting, seizures &amp; altered mental status</li> <li>○ High mortality rate [20]</li> </ul>
Pathogenesis [19]	<ol style="list-style-type: none"> <li>1. 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</li> <li>2. Latent phase</li> <li>3. Reactivation (lytic phase): reactivation of HSV in trigeminal ganglion can result in spread to temporal lobe via meningeal branch of CN-V (trigeminal nerve)</li> </ol>
Treatment	<b>Acyclovir</b> [22]
Diagnosis	<b>Magnetic resonance imaging (MRI)</b> <ul style="list-style-type: none"> <li>- suspected diagnosis</li> <li>- Diagnosis For temporal lobe lesion of HSV</li> </ul>
	<b>CSF</b> <ul style="list-style-type: none"> <li>- Definitive diagnosis</li> <li>- ↑ in Lymphocytes, glucose is normal, and protein is↑</li> <li>- Detection of HSV-1 DNA by PCR [21]</li> </ul>



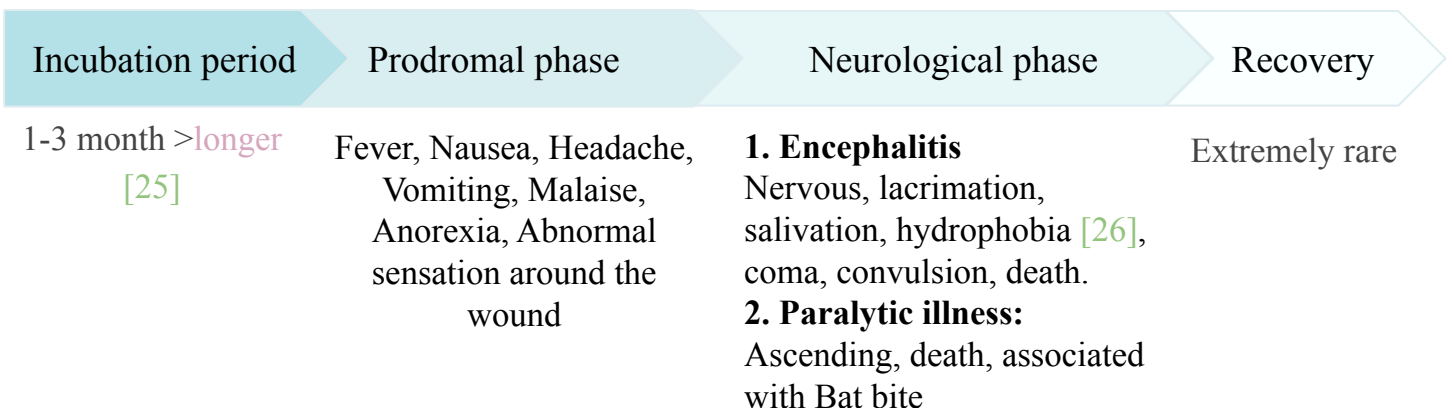


# Rabies Encephalitis

Rabies Encephalitis: A <b>fatal</b> acute encephalitis [24]	
Caused by	<ul style="list-style-type: none"> <li>○ Rabies virus</li> <li><b>It's zoonotic disease</b></li> </ul>
Family	Rhabdoviridae
Epidemiology	<b>Reservoir</b> <ul style="list-style-type: none"> <li>○ Major: Raccoons, Foxes, Wolves, Bats</li> <li>○ <b>Important : Cats &amp; Dogs</b> due to their close contact with human</li> </ul>
	<b>Transmission</b> <ul style="list-style-type: none"> <li>○ Common route: <b>bite of rabid animal</b></li> <li>○ Uncommon route (non-bite exposure):</li> <li>1- Inhalation while in a bat infested cave</li> <li>2- Corneal transplant [23]</li> </ul>
Pathogenesis	<p>After getting a bite from a rabid animal that is infected rabies → the virus will enter the PNS → reaches spinal cord, medulla &amp; brain → from the brain it travel down to infect other tissues like the cornea, skin &amp; salivary glands</p> 
Structural Features	<ul style="list-style-type: none"> <li>- <b>Helical nucleocapsid</b></li> <li>- <b>Enveloped virus</b></li> <li>- <b>-ve Single Stranded RNA genome (-ssRNA)</b></li> <li>- <b>Bullet shaped virus</b></li> </ul>

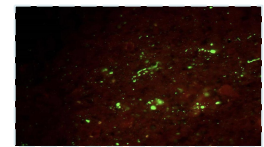
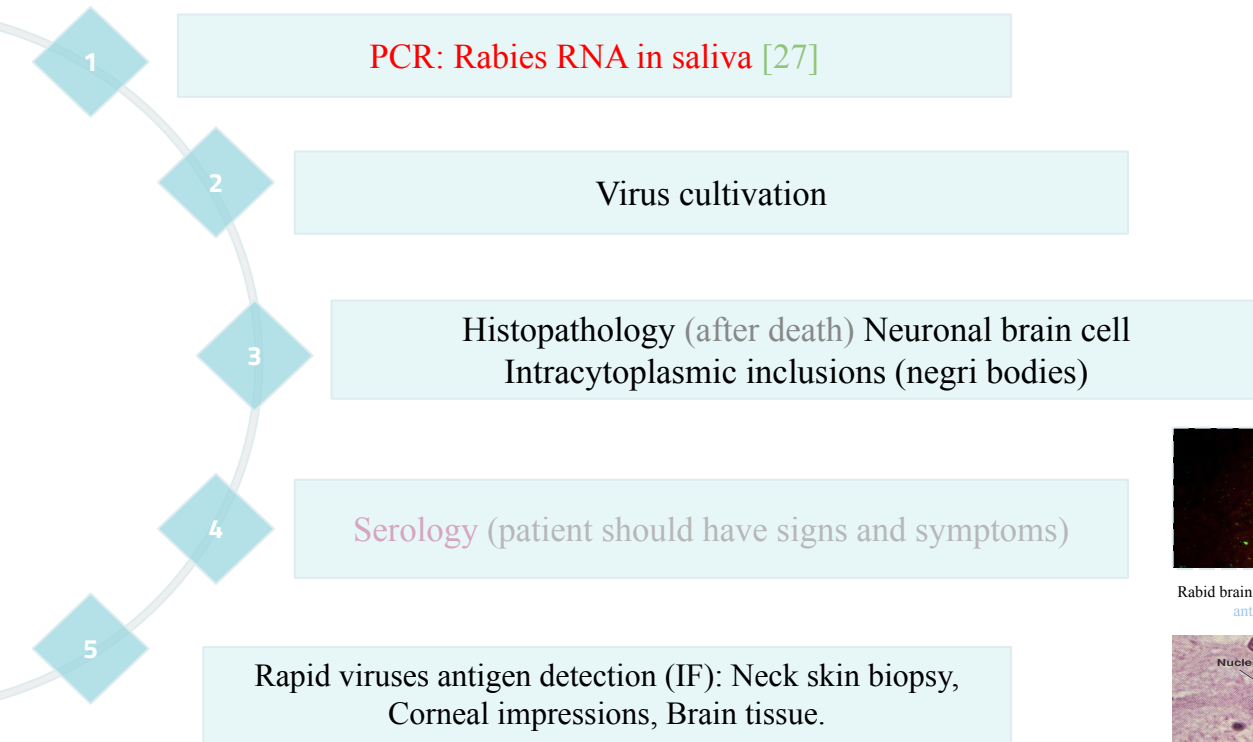


## Phases of Rabies Encephalitis

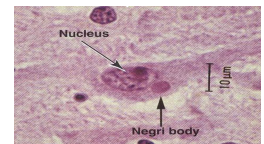




# Lab diagnosis of Rabies Encephalitis



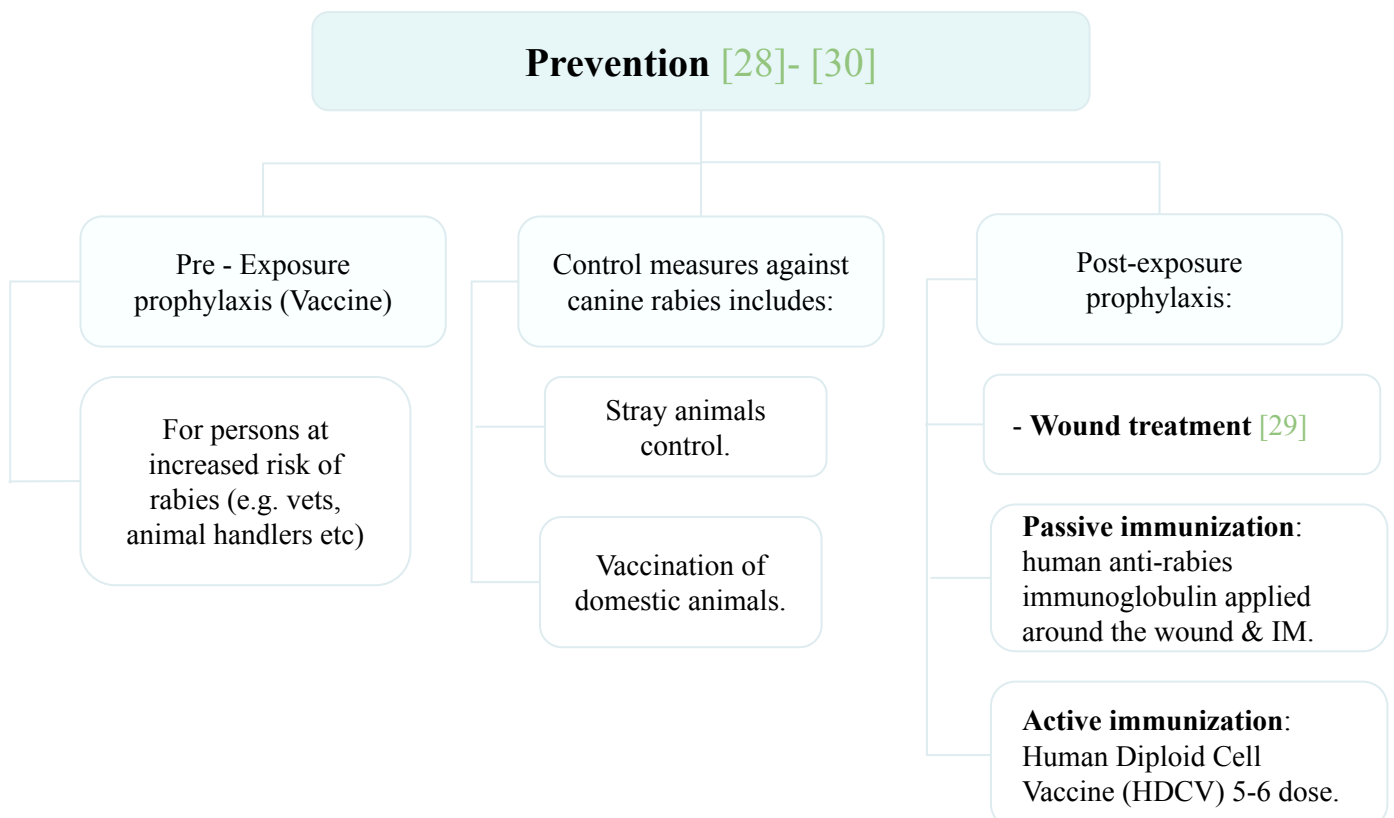
Rabid brain stained with Fluorescent anti-rabies antibody



Negri bodies are diagnostic of rabies.



# Prevention of Rabies Encephalitis





# Arthropod-borne Viruses

Arthropod-borne Viruses		
Include	Arboviruses > 500 viruses.	
Epidemiology	Reservoir	Wild birds & Mammals الثدييات
	Vector	Mosquito, Tick, & Sandfly
	Transmission	Bite of infected vector
Infections	Asymptomatic infections	
	Diseases: - Fever, Rash, & Arthralgia - Hemorrhagic fever ± hepatitis - CNS diseases in the next table (meningitis & encephalitis)	



## ArboVirus associated with CNS disease:

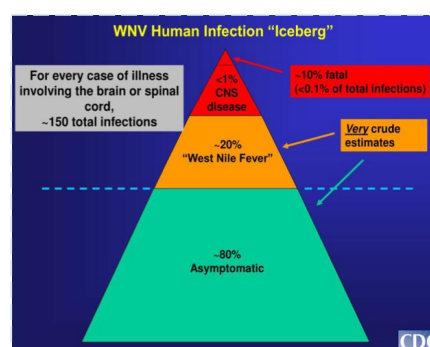
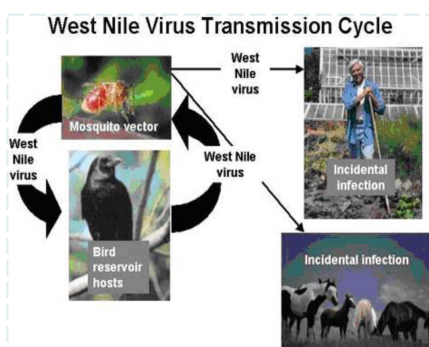
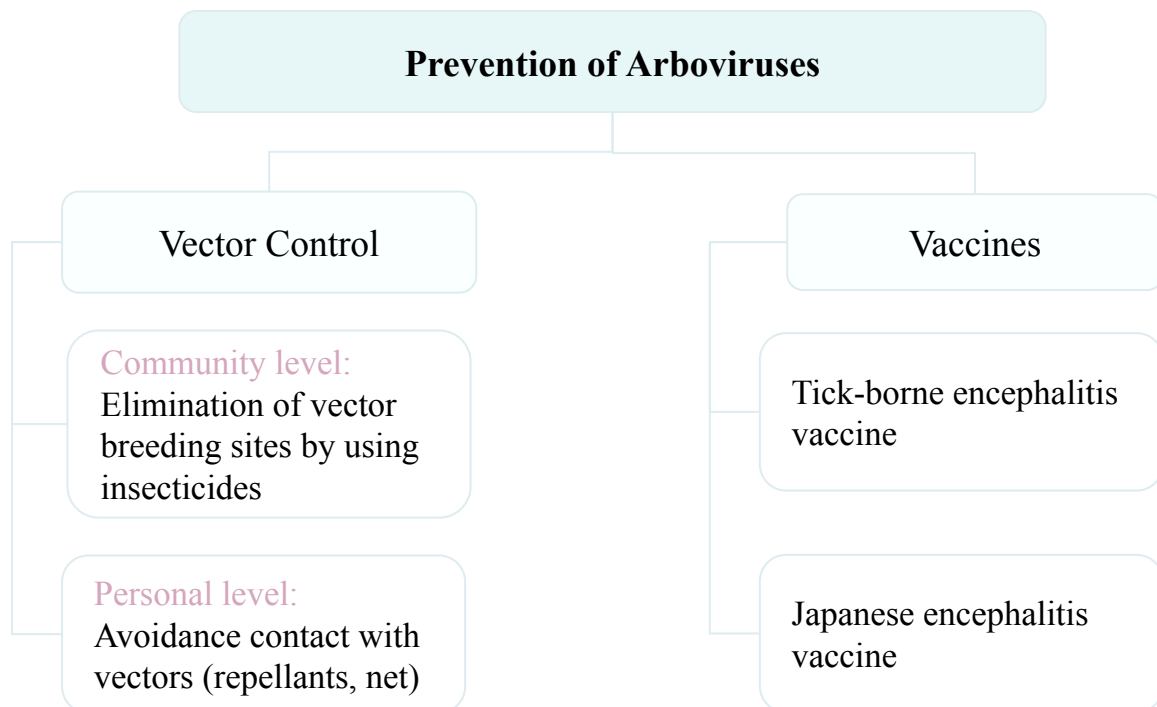
Just focus on what is in red

Virus	Vector	Reservoir	Distribution
Eastern equine encephalitis (EEEV)	Mosquito	Birds	America
Western equine encephalitis (WEEV)	Mosquito	Birds	America
Venezuelan equine encephalitis (VEEV)	Mosquito	Rodent	America
Japanese encephalitis V	Mosquito	Birds, Pigs	Orient
Murray Valley encephalitis V	Mosquito	Birds	Australia
<b>West Nile Virus</b>	<b>Mosquito</b>	<b>Birds</b>	<b>Middle East, Europe, Africa, Asia, America</b>



# West Nile Virus

West Nile Virus	
Family	Flaviviridae ( <b>Zoonotic virus</b> )
Structural Features	<ul style="list-style-type: none"> <li>○ Enveloped virus</li> <li>○ Febrile illness → meningitis, encephalitis, AFP</li> <li>○ +ve Single Stranded RNA genome (+ssRNA)</li> </ul>
Diagnosis of Arboviruses	<ul style="list-style-type: none"> <li>○ Reference lab</li> <li>○ Lab Methods :               <ol style="list-style-type: none"> <li>1. Isolation (Gold standard) Samples: blood, CSF, Viscera Cell culture: CPE (cellular pathological effect) → Identify by IF</li> <li>2- IgM -AB, ELISA, IF (most used)</li> <li>3- west Nile virus RNA (WNV-RNA) by RT-PCR</li> </ol> </li> </ul>





# Dr malak Notes

[1] **viral is most common cause of Aseptic meningitis** but bacterial meningitis is medical emergency so patient will visit emergency room and need immediate empirical therapy after collection of CSF cuz if it's not treated early will lead to complication

however patient with Aseptic meningitis usually will not visit emergency room why? cause it's **usually mild & self limited** & rapid within 1-2 weeks in contrast to bacterial meningitis .

[2] The majority of meningitis that present in emergency room or hospital are due to bacteria

[3] Different between septic and Aseptic?

Septic: organism usually seen in gram stain of CSF & the routine bacteria culture or routine culture of CSF

Aseptic: gram stain usually normal and no organism seen and normal culture is -ve so it's not identified by gram stain and the routine culture of CSF.

[4] usually turbid & sometimes may be clear and this depended on the number of leukocyte and protein.

[5] why? because of inflammation in meninges will lead to increased permeability of BBB.

[6] you have to think about the age of patient ,so usually infants & very old people present with non specific symptoms & sign however the older children & adult usually present with specific symptoms like: fever , vomiting , nausea in addition severe headache (usually depending on organism), neck stiffness & photophobia.

[7]:ss(+) RNA means +ve polarity when the virus enter the cell directly act as messenger RNA for the replication.

[8] enterovirus replicate in enteric tract (GIT) so they transmitted by fecal -oral route through contamination of food & water and infected hand

[9] highly sensitive, specific and rapid test for diagnosis of enteroviral.

[10] not useful against enterovirus infection cuz many enteroviruses may cross reaction with other and there is lack of common antigen

[11] polioviruses is most important of enteroviruses and have 3 serotype and reclassified in group C

[12]

1. polioviruses which it's type of enteroviruses is transmitted by fecal - oral route

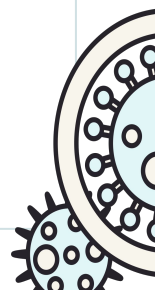
2. replicate in GIT & lymph nodes

3. enter the bloodstream and cause primary viremia

4. infect the reticuloendothelial system such as liver and spleen & other multiplication take place

5. enter the bloodstream causing secondary viremia

6. from the blood will go and infect CNS which part? mainly AHC (motor cell)





# Dr malak Notes

[13] LMNL lead to flaccid paralysis & UMNL lead to rigid (spastic) paralysis

[14] once the patient recover will have immunity composed of IgA & IgG with specific serotype

ex: if the patient infect with serotype 1 will develop immunity against poliovirus serotype 1 so it will not protect him from other serotype

[15]

- Non-paralytic poliomyelitis → recover within 1 weeks to 10 days

- Paralytic poliomyelitis → recover within few months and some patient will have residual paralysis and weakness of affected muscle and usually asymmetrical & there is no sensory loss

[16] polioviruses usually in children & adult if it was infected it will more likely to have severe disease and major illness with paralysis and the risk of paralysis increase with age

[17] cuz it's contain live virus that may revert to virulent form, and the adult and immunocompromised should avoid it and receive killed vaccine

[18] Remember herpesvirus type 2 → cause Recurrent meningitis

[19] it will be in Trigeminal ganglion as a latent phase, but when herpesvirus activate it will spread to the temporal region via meningeal branches of CN 5

[20] High mortality rate If not treated early,, even if the patient survive he will suffer from neurological sequelae

[21] The definitive diagnosis is PCR looking for HSV DNA

[22] IV for 21 day

[23] cornea was taken from patient died from undiagnosed rabies

[24] only very few cases have been survived, but once the signs and symptoms appear → fatal disease

[25] the incubation period about 1-3 months or maybe longer depends on the site of bite and how many bites , for example, bite in the neck has a shorter incubation period than the bite in leg due to the the short distance for the virus to travel to the brain

[26] - hydrophobia is the characteristic sign for rabies encephalitis.

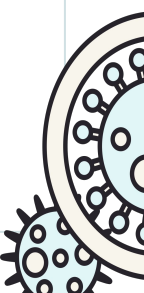
- what is hydrophobia ? when patient drink he will have painful spasms of pharyngeal muscle

[27] PCR is the definitive diagnosis and its highly sensitive rapid test

[28] there's no specific antiviral therapy for patients with rabies , only supportive treatment

[29] running water for at least 15 min, then clean with antiseptic solution

[30] what is more severe herpetic encephalitis or rabies encephalitis? rabies encephalitis because herpetic encephalitis it's treatable, so herpetic encephalitis is treatable but not preventable , rabies encephalitis is preventable but not treatable





# MCQs - SAQ

Q1 - Common route for transmission of rabies virus?

- |  |             |                       |                         |
|--|-------------|-----------------------|-------------------------|
| A) Inhalation while in a bat-infested cave | B) Sexually | C) Corneal transplant | D) Bite of rabid animal |
|--|-------------|-----------------------|-------------------------|

Q2 - What is the most common etiology for **Aseptic** meningitis?

- |                    |                        |                     |          |
|--------------------|------------------------|---------------------|----------|
| A) Viral infection | B) Bacterial infection | C) Fungal infection | D) A & B |
|--------------------|------------------------|---------------------|----------|

Q3 - Which of the following viral CNS infection is treatable?

- |                |                        |                                |                |
|----------------|------------------------|--------------------------------|----------------|
| A) Brucellosis | B) Rabies Encephalitis | C) Herpes Simplex Encephalitis | D) Enterovirus |
|----------------|------------------------|--------------------------------|----------------|

Q4 - Which one of the following should be avoided in cases of immunocompromised patients?

- |                 |                  |                   |                               |
|-----------------|------------------|-------------------|-------------------------------|
| A) Salk Vaccine | B) Sabin Vaccine | C) Killed Vaccine | D) Human Diploid Cell Vaccine |
|-----------------|------------------|-------------------|-------------------------------|

Q5 - What will you find in a CSF analysis of an aseptic meningitis?

- |                      |                |                        |                     |
|----------------------|----------------|------------------------|---------------------|
| A) Cloudy appearance | B) low glucose | C) normal glucose rate | D) high neutrophils |
|----------------------|----------------|------------------------|---------------------|

5-5  
4-8  
3-3  
2-2  
1-D



## Case

A 73-year-old man had pain in his left shoulder and severe dehydration because he was phobic to water. He looked very sick. Initial evaluation showed irritability and lethargy. After 48 hours, the patient exhibited multifocal myoclonus and decorticate posturing. Intubation, and mechanical ventilation were performed. He was given vasopressors, corticosteroids and broad-spectrum antibiotics. His family confirmed that he had sustained a bat bite on his left shoulder 6 months previously but had not sought treatment.

Q1: What is the most likely diagnosis?

A: Rabies Encephalitis

Q2: What is the most likely causative agent?

A: Rabies virus

Q3: What are the best diagnostic methods for this case?

A: RT-PCR and Immunofluorescence

Q4: What is the prognosis and treatment in this case?

A: Prognosis is poor, no treatment (exposed individuals must seek medical care right after after exposure, to be given post-exposure prophylaxis vaccine before the





TEAM 443  
MICROBIOLOGY

## 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)