

# Viral Encephalitis

# Terminology

- Encephalopathy
  - Clinical syndrome of reduced consciousness
  - Many causes, incl. viral encephalitis
- Encephalitis
  - Acute, diffuse, inflammatory process affecting brain parenchyma
  - Most commonly viral

# Encephalopathy vs encephalitis?

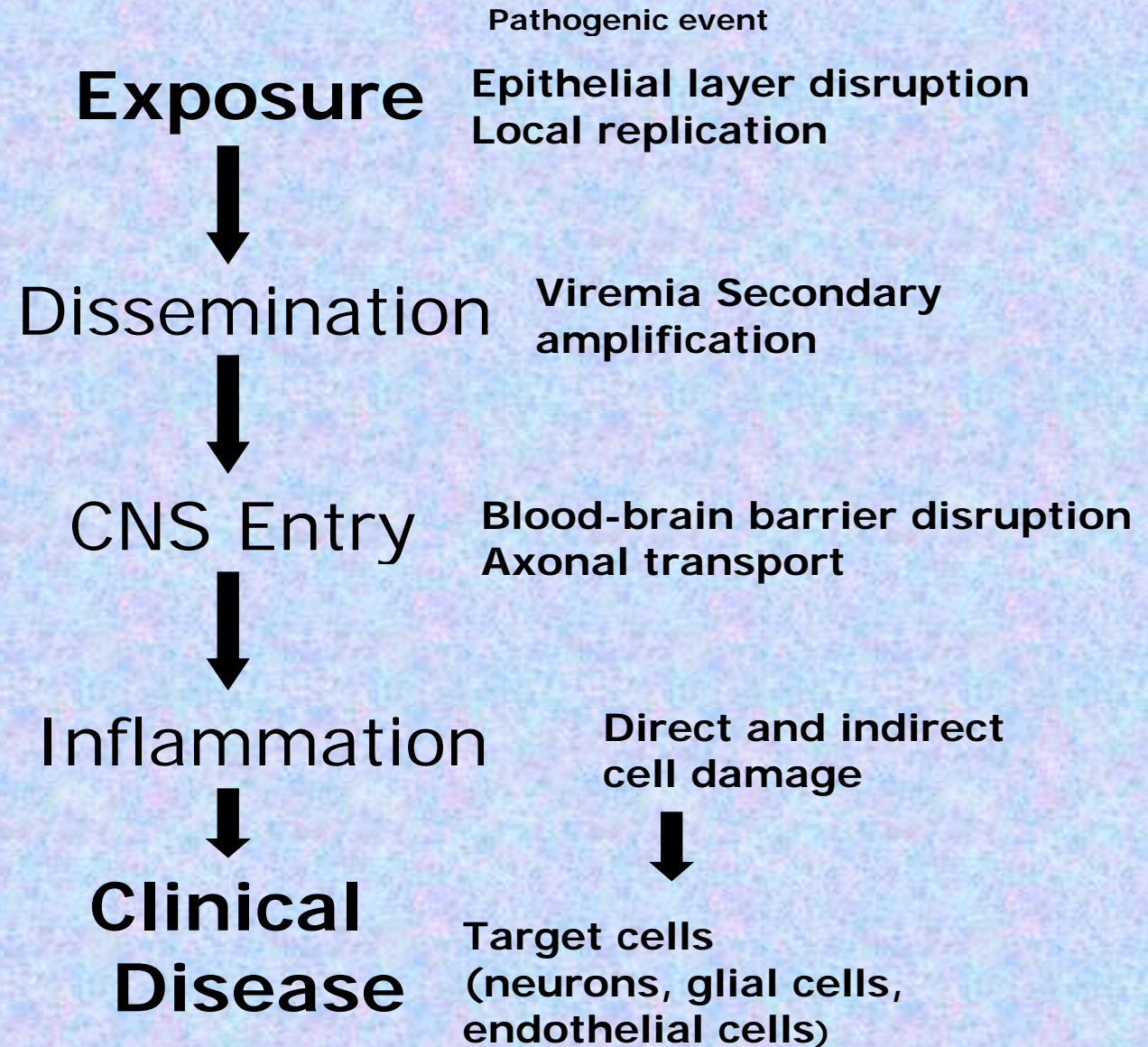
	Encephalopathy	Encephalitis
<b><i>Clinical features</i></b>		
Fever	Uncommon	Common
Headache	Uncommon	Common
Depressed mental status	Steady deterioration	May fluctuate
Focal neurological signs	Uncommon	Common
Type of seizure	Generalised	Generalised or focal
<b><i>Laboratory findings</i></b>		
Blood	Leucocytosis uncommon	Leucocytosis common
CSF	Pleocytosis uncommon	Pleocytosis common
EEG	Diffuse slowing	Diffuse slowing and focal abnormalities
MRI	Often normal	Focal abnormalities

# Primary and Secondary Encephalitis

- There are **two ways** that viruses can infect brain cells and cause encephalitis:
- **Primary encephalitis**, also called Acute viral encephalitis is when the virus directly affects the brain or spinal cord. The resulting inflammation can occur in one area (focal) or can occur throughout the brain (diffuse).
- **Secondary encephalitis**, also called post-infectious encephalitis, is when the virus first attacks another part of the body and the infection then spreads to the brain



# CNS virus pathogenesis



# Causes of acute viral encephalitis

## Geographically restricted causes

- **Arboviruses** — Japanese B, St Louis, West Nile, Eastern equine, Western equine, Venezuelan equine, tick borne encephalitis viruses
- **Bunyaviruses** — La Crosse strain of California virus
- **Reoviruses** — Colorado tick fever virus

## Sporadic causes (not geographically restricted)

- **Herpes viruses**
  - HSV-1, HSV-2, VZV, CMV, EBV, HHV6, HHV7
- **Enteroviruses**
  - Coxsackie, echoviruses, enteroviruses 70/71, parechovirus, poliovirus
- **Paramyxoviruses**
  - Measles, mumps
- **Others (rarer causes)**
  - Influenza viruses, Adenovirus, JC virus (PML) , rabies ,parvovirus, lymphocytic choriomeningitis virus, rubella virus,,

# Primary Cause

- Arboviruses are the most common causes of viral encephalitis
- Arbovirus stands for arthropod-borne viruses
- There are 3 virus families associated with encephalitis
  - *Togaviridae* (Alphavirus) – most common
  - *Flaviviridae* (Flavivirus)
  - *Bunyaviridae* (Bunyavirus)



# Arboviruses

- Arthropod-borne viruses
- 534 registered arboviruses
  - 134 documented human pathogens
- Major vectors





# Arbovirus Families

- **Flaviviruses** (single-stranded positive-sense RNA viruses)
  - *West Nile virus*
  - *St. Louis encephalitis virus*
  - *Japanese encephalitis virus*
  - Yellow fever virus
  - Dengue virus
- **Togaviruses** (single-stranded positive sense RNA viruses)
  - *Eastern, western, and Venezuelan equine encephalitis viruses*
- **Bunyaviruses** (segmented single-stranded negative sense RNA viruses)
  - *La Crosse virus*
  - Rift Valley fever virus

<b>Disease</b>	<b>Mosquito Vector</b>
<b>EEE</b>	<i>Culiseta melanura</i> , <i>Aedes spp.</i> , <i>Culex (Cx.) nigrapalpus</i> , <i>Coquilletidia spp.</i>
<b>WEE</b>	<i>Culex tarsalis</i> , <i>Aedes melanimon</i> , <i>Aedes dorsalis</i> , <i>Aedes campestris</i>
<b>VEE</b>	<i>Culex (Melanoconion) spp.</i>
<b>LAC</b>	<i>Ochleratatus triseriatus</i>
<b>SLE</b>	<i>Culex pipiens</i> , <i>Cx. quinquefasciatus</i> , <i>Cx. nigrapalpus</i> , <i>Cx. tarsalis</i>



# Arboviral Diseases in Humans

## Systemic febrile illness

West Nile virus

Dengue virus

Rift Valley fever virus

Chikungunya virus



## Hemorrhagic fever

*Yellow fever virus*

Dengue virus

Rift Valley fever virus



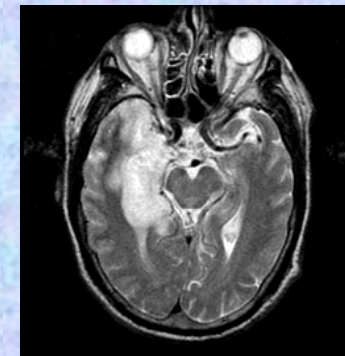
## Encephalitis

West Nile virus

Japanese encephalitis virus

Eastern equine encephalitis virus

La Crosse virus





# Arbovirus Meningoencephalitis Pathogenesis

- **Exposure route/dissemination**
  - Replication within insect vector required
  - Primary exposure is cutaneous
  - Respiratory transmission demonstrated experimentally
  - Local replication followed by viremia
- **CNS entry**
  - Hematogenous
    - Traverse blood brain barrier (BBB) endothelium through unknown mechanism
  - Direct neuronal spread for respiratory exposure (olfactory bulb)
- **Cell damage**
  - Neurons are primary targets for many viruses
  - Direct cell death and inflammatory responses

# Arbovirus Epidemiology

- Seasonal (summer/fall)
- Incidence varies with virus and *time*
- Extremes of age more susceptible to severe disease
- Mortality rate varied with virus
  - Eastern equine encephalitis virus (EEEV) ~50%
  - West Nile virus (WNV) ~10%
  - La Crosse virus (LACV) <1%

## Arbovirus Meningoencephalitis Clinical Manifestations

- **Primary symptoms**
  - Most infections asymptomatic or produce non-specific “viral syndrome”
  - Fever, headache, seizures
  - Neuronal targets dictate clinical symptoms
    - Anterior motor neurons (WNV) – poliomyelitis
    - Basal ganglia neurons (JEV) – Parkinsonian
- **Long-term neurological sequelae possible**



# Arbovirus Meningoencephalitis Diagnosis, Treatment, and Prevention

- **Diagnosis**
  - Clinical suspicion
  - Social history/exposure/travel provide important clues
  - CSF profile
    - Lymphocytic pleocytosis, high protein
  - CSF PCR, intrathecal IgM
  - Acute and convalescent serologies useful for epidemiology
- **Treatment**
  - Supportive
- **Prevention**
  - Inactivated vaccine available for JEV
  - Live attenuated YFV vaccine also available
  - Vector control efforts

# Other CNS viruses

- Herpes simplex, type 1 and type 2
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- Varicella zoster virus (VZV)
- Human herpes virus 6 (HHV-6)
- Herpes B virus (simian herpesvirus)
- Rabies
- Influenza A and B
- JC virus (PML)
- Measles
- Mumps
- Rubella
- Human immunodeficiency virus (HIV)

# Herpesviridae

Subfamily	Growth & Cytopathology	Latent infections	Genus	Official name (herpes virus)	Common name
Alphaherpesvirinae	Short, cytolytic	Neurons	Simplexvirus	1	HSV-1
				2	HSV-2
			Varicellvirus	3	VZV
Betaherpesvirinae	Long, cytomegalic	Glands, kidneys	Cytomegalovirus	5	CMV
	Long, lymphoproliferative	Lymphoid tissue	Roseolovirus	6	HHV-6
				7	HHV-7
Gammaherpesvirinae	Long, lymphoproliferative	Lymphoid tissue	Lymphocryptovirus	4	EBV
			Rhadinovirus	8	Kaposi' sarcoma virus



# Herpes simplex encephalitis

- HSV encephalitis (HSE) most common cause of viral encephalitis in industrialised nations
- Annual incidence 1 in 250,000-500,000
- 90% HSV-1
- HSV-2 more common in immuno-compromised, neonates

# HSV-1

- Primary infection occurs in oral mucosa
  - 30% people get clinically apparent cold sores
  - 90% healthy people have been infected with HSV-1
- Virus then travels along trigeminal nerve to ganglion in most those infected
- 70% cases of HSV-1 encephalitis **already have antibody present** suggesting reactivation of virus most common mechanism
- Why HSV-1 reactivates not known
- In children, HSV-1 encephalitis occurs during primary infection

# HSV-2

- Transmitted via genital mucosa
  - Genital herpes in adults
  - USA, 20% of adults sero-positive for HSV-2
- HSV-2 may cause
  - Meningitis (esp. recurrent meningitis)
  - Encephalitis (esp in neonates)
- Neonates can be infected during delivery: neonatal herpes (disseminated infection often with CNS involvement)



# HSV Encephalitis Pathogenesis

- **Exposure route/dissemination**
  - Primary exposure (cutaneous)
  - Reactivation from latency (sensory ganglion)
- **CNS entry**
  - Direct neuronal spread
- **Cell damage**
  - Direct cell lysis and inflammatory responses

# HSV Encephalitis Clinical Manifestations

- **Primary symptoms**
  - Fever, headache
  - Progressive neurological symptoms
  - Focal symptoms represent region of brain involvement (temporal lobe common)
  - Mental status changes frequent
  - Seizures
- **Meningitis and myelitis also seen**
  - Primary genital HSV
  - Recurrences possible (Mollaret's meningitis)
- **Long-term neurological sequelae possible**
  - Especially without prompt therapy

# HSV Encephalitis Diagnosis, Treatment, and Prevention

- **Diagnosis**

- Clinical suspicion

- **CSF profile:**

- Lymphocytic pleocytosis, increased RBCs common, high protein

- WBC: 20-300 cells/mm<sup>3</sup>

- Protein: median 80 (normal <60)

- Glucose usually normal

- **CSF PCR is gold-standard diagnostic test**

- MRI and EEG also helpful but not specific

- **Treatment**

- Acyclovir

- **Prevention**

- No vaccine available



# Varicella Encephalitis - 1

- Incidence

- 1-2/10,000 cases of varicella
- Incidence is highest in adults and infants

- Presentation

- Symptoms usually appear about one week after rash (though may be earlier or later).
- Acute or gradual onset.
- Fever, headache, vomiting, altered mental status
- Focal neurologic findings, hyper/ hyporeflexia, hemiparesis, and sensory changes
- Seizures 29-52% of cases

# Varicella Encephalitis - 2

- **Pathogenesis**

- Role of active viral replication in CNS?
- Pathologic findings are more consistent with a post-infectious demyelinating process. Inclusion bodies are rarely seen.

- **Prognosis**

- Mortality of about 5-10% (higher mortality in older literature probably due to Reye's syndrome)
- 10-20% of survivors will have neurologic sequelae

- **Therapy**

- IV acyclovir recommended

## Varicella in the Immunocompetent Host

- Serious neurologic complications occur in <1% of cases:
  - Aseptic meningitis
  - Cerebellar ataxia
  - Transverse myelitis
  - **Encephalitis**
  - Guillain-Barré syndrome
  - Arterial ischemic strokes
  - Optic neuritis



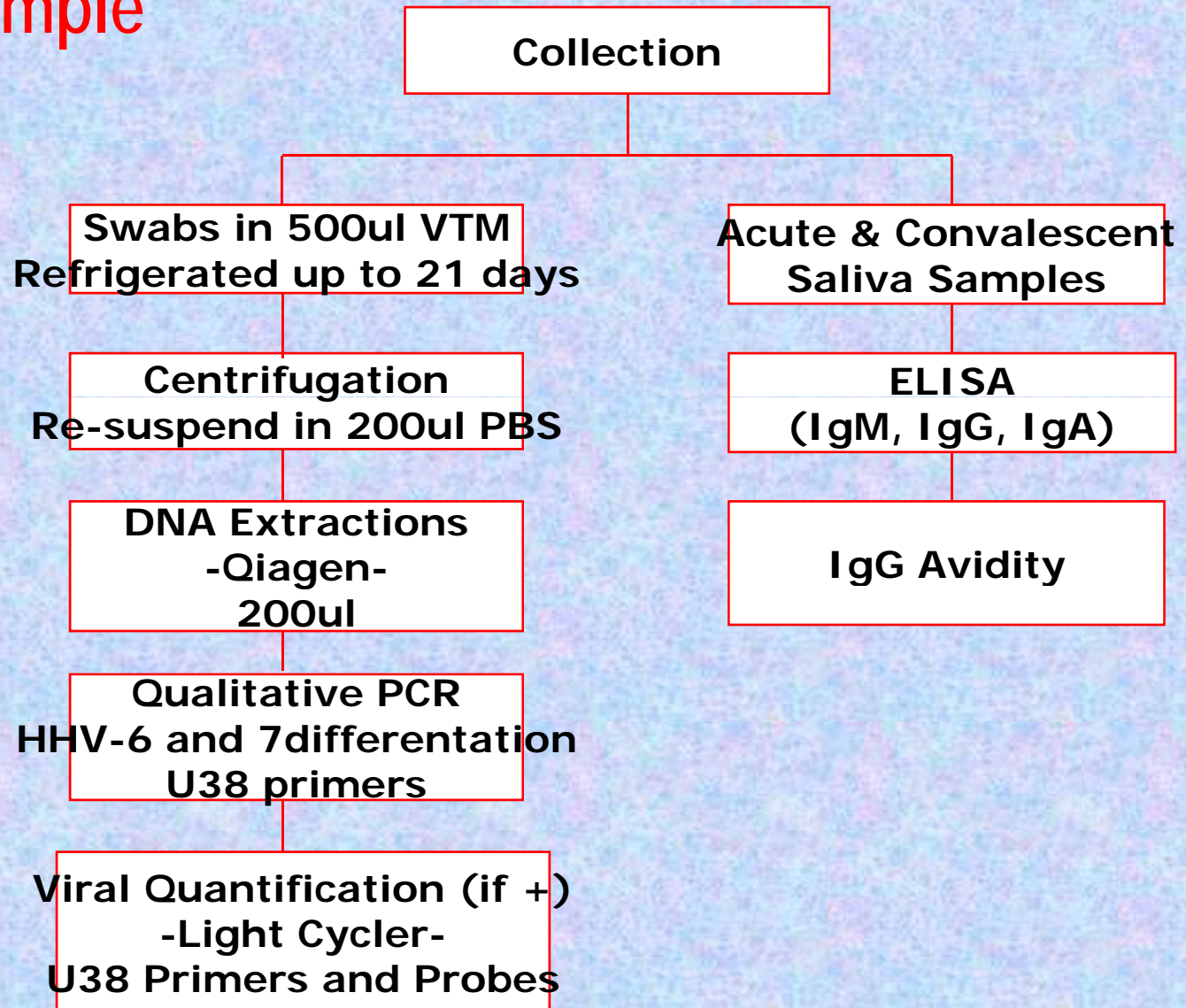
# Diagnosis of VZV Encephalitis

- Both **PCR on CSF** and **antibody testing** for VZV IgG and IgM (EIA) on both serum and CSF
- Diagnosis of VZV infection of the CNS is supported by detection of **VZV antibody in the CSF**, even in the absence of PCR- amplifiable VZV DNA. Therefore, Clinicians should request both PCR and antibody analysis

# Human herpesvirus 6 encephalitis

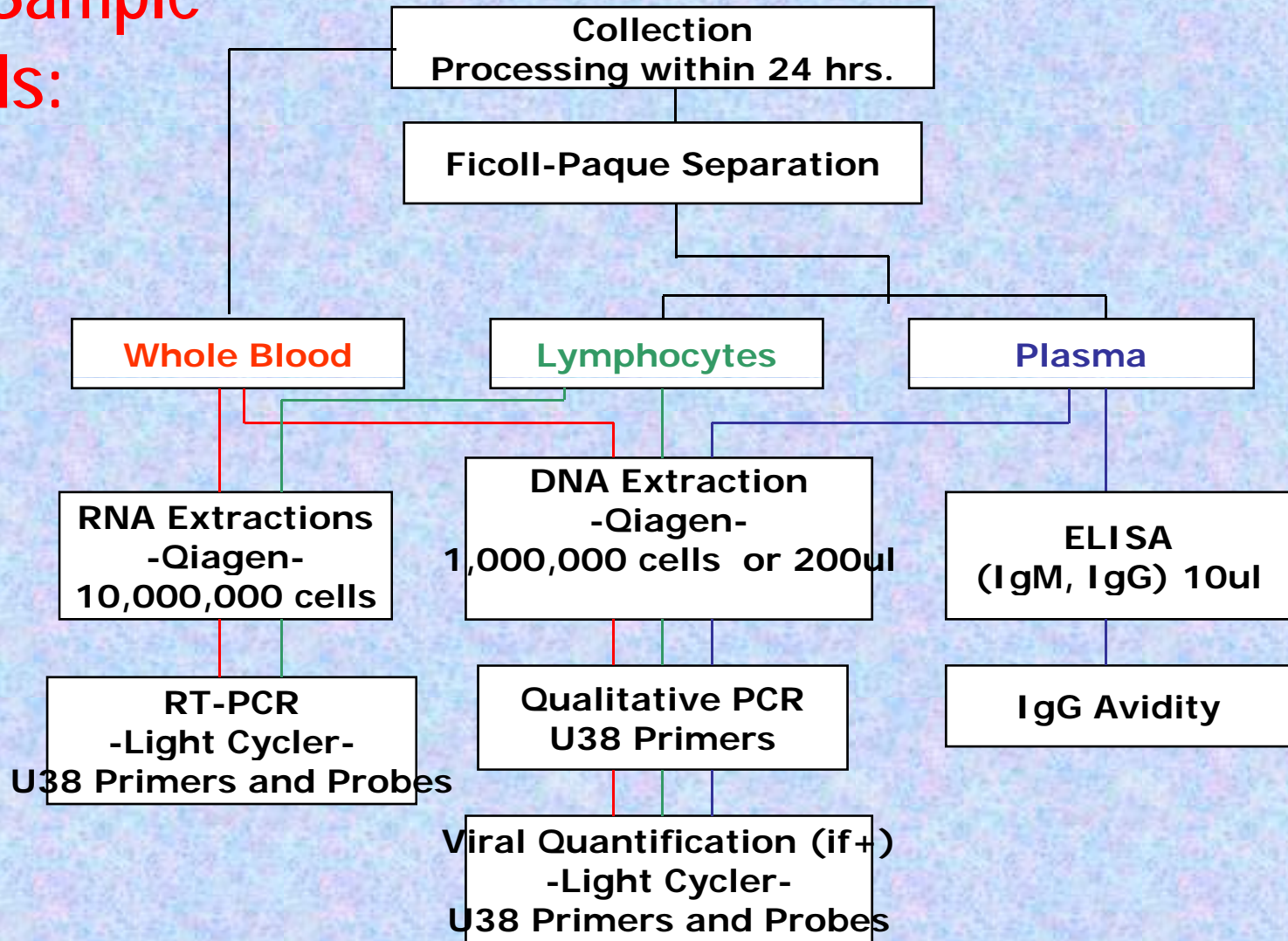
- Human herpesvirus (HHV) 6, the etiologic agent of roseola, is nearly universally acquired during childhood.
- The virus establishes lifelong infection, including within the central nervous system (CNS), and replicates within several CNS cell types
- HHV-6 encephalitis is a significant consequence of [transplant immunosuppression](#), although it is seen in immunocompetent patients as well.

# Saliva Sample Methods:





# Blood Sample Methods:



# Adenoviruses

- First isolated in 1953 in a human adenoid cell culture.
- Approximately 100 serotypes have been recognized, at least 47 of which infect humans.
- Have been classified into seven subgroups (A through G).

**TABLE 55.1****Classification Schemes for Human Adenoviruses (HAdVs, Genus *Mastadenovirus*)**

Species	Hemagglutination Groups	Types	Oncogenic potential		% GC	Associated disease
			Tumors in animals	Transformation in cell culture		
HAdV-A	IV (little or none)	12, 18, 31	High	Positive	46–47	Cryptic enteric infection
HAdV-B	I (complete for monkey erythrocytes)	3, 7, 11, 14, 16, 21, 34, 35, 50	Moderate	Positive	49–51	Conjunctivitis Acute respiratory disease Hemorrhagic cystitis Central nervous system
HAdV-C	II (partial for rat erythrocytes)	1, 2, 5, 6	Low or none	Positive	55	Endemic infection Respiratory symptoms
HAdV-D	III (complete for rat erythrocytes)	8, 9, 10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51, 53, 54	Low or none (mammary tumors)	Positive	55–57	Keratoconjunctivitis in immunocompromised and AIDS patients
HAdV-E	III	4	Low or none	Positive	58	Conjunctivitis Acute respiratory disease
HAdV-F	III	40, 41	Unknown	Negative	51	Infantile diarrhea
HAdV-G	Unknown	52	Unknown	Unknown	55	Gastroenteritis

Adapted from Benko M. Adenoviruses: Pathogenesis. In: Mahy BWJ, Van Regenmortel MHV, eds. *Encyclopedia of Virology*. 3<sup>rd</sup> ed. Oxford, UK: Elsevier, 2008: 24–29.



# Clinical Syndromes

1. Pharyngitis 1, 2, 3, 5, 7
2. Pharyngoconjunctival fever 3, 7
3. Acute respiratory disease of recruits 4, 7, 14, 21
4. Pneumonia 1, 2, 3, 7
5. Follicular conjunctivitis 3, 4, 11
6. Epidemic keratoconjunctivitis 8, 19, 37
7. Pertussis-like syndrome 5
8. Acute haemorrhagic cystitis 11, 21
9. Acute infantile gastroenteritis 40, 41
10. Intussusception 1, 2, 5
- 11. Severe disease in AIDS and other immunocompromized patients 5, 34, 35
- 12. Meningitis 3, 7

# Adenovirus Virus Meningoencephalitis

Adenovirus is a common pathogen in the pediatric population

Several neurologic syndromes have been attributed to adenovirus, such as adenovirus:

aseptic meningitis, myelitis, subacute focal encephalitis, and Reye-like syndrome

It is rare to isolate any of the **adenoviruses** from either the cerebrospinal fluid (CSF) or the brain.

In immunosuppress and transplantation

Several reports, however, have directly demonstrated adenoviruses in CSF (Ad3, 5, 6, 7, 7A, and 12).

# Laboratory Diagnosis

- Should be obtained from a site or secretion relevant to the disease symptoms.
- Fluorescent antibody assays and the polymerase chain reaction can be used to detect, type, and group the virus.
- Serologic testing is rarely used except for epidemiologic purposes.



# Rhabdoviridae

## Classification

Four genera: *Lyssavirus*, *Vesiculovirus*, *Ephemerovirus*, and *Novirhabdovirus*

Genus: *Lyssavirus* – 6 serotypes

Rabies virus - distributed worldwide

Mokola virus – Central Africa

Lagos bat virus – Central and southern Africa

Duvenhage virus – South Africa

European bat lyssavirus 1 and 2 – Europe

Australian bat lyssavirus – Australia

# Rabies Virus Encephalitis Pathogenesis

- Rabies virus multiplies in muscle or connective tissue at the site of inoculation
- Rabies enters peripheral nerves through sensory and motor nerve endings – primarily through neurotransmitter acetylcholine as receptor. Also uses gangliosides and phospholipids.
- Virus enters the brain through the **limbic system**
- Multiplies in CNS and progressive encephalitis develops
- The virus then spreads through peripheral nerves to the **salivary glands and other tissues**
- Susceptibility to infection and incubation period may depend on the host's age, genetic, immune status, viral strain, amount of inoculation, the severity of laceration



# Rabies Virus Encephalitis Clinical Manifestations

- **Epidemiology**
  - Disease recognized for thousands of years (2300 B.C.)
  - Only handful of cases in U.S. per year
  - More common in underdeveloped countries
  - Only 10-20% of “true” exposures will result in disease
- **Reservoir (U.S.)**
  - Bats, skunks, raccoons, and foxes
  - Rodents, lagomorphs, and domestic dogs/cats almost never infected
- **Primary symptoms**
  - Fever, dysphagia, hydrophobia, increased muscle tone
  - Progression to coma and death



# Rabies Virus Encephalitis Clinical Manifestations

- Rabies is an **acute, fulminant, fatal encephalitis**, Incubation period 1-2 months
- **Short prodromal phase**: 2-10 days, malaise, anorexia, headache, **photophobia**, nausea and ting, sore throat and fever
- **Acute neurologic phase**: 2-7 days, nervousness, apprehension, hallucinations and bizarre behavior; lacrimation, pupillary dilation, salivation, perspiration, **hydrophobia**
- **Coma**: death by respiratory paralysis

# Rabies Virus Encephalitis Diagnosis, Treatment, and Prevention

- **Diagnosis**
  - Clinical suspicion with exposure history
  - CSF profile (cell count, glucose, protein) often unhelpful
  - CSF/tissue RT-PCR
  - DFA of neck skin biopsies
  - Serologies can be helpful
- **Treatment**
  - None (universally fatal once symptoms develop)
- **Prevention**
  - **Preexposure** vaccination for all persons at high risk of contact with rabid animals
  - **Postexposure** prophylaxis

# *Polyomaviridae*

- **Species**

BK polyomavirus

Bovine polyomavirus

Canary polyomavirus

Chimpanzee polyomavirus

Goose hemorrhagic polyomavirus

Hamster polyomavirus

Human Polyomavirus

**JC polyomavirus**

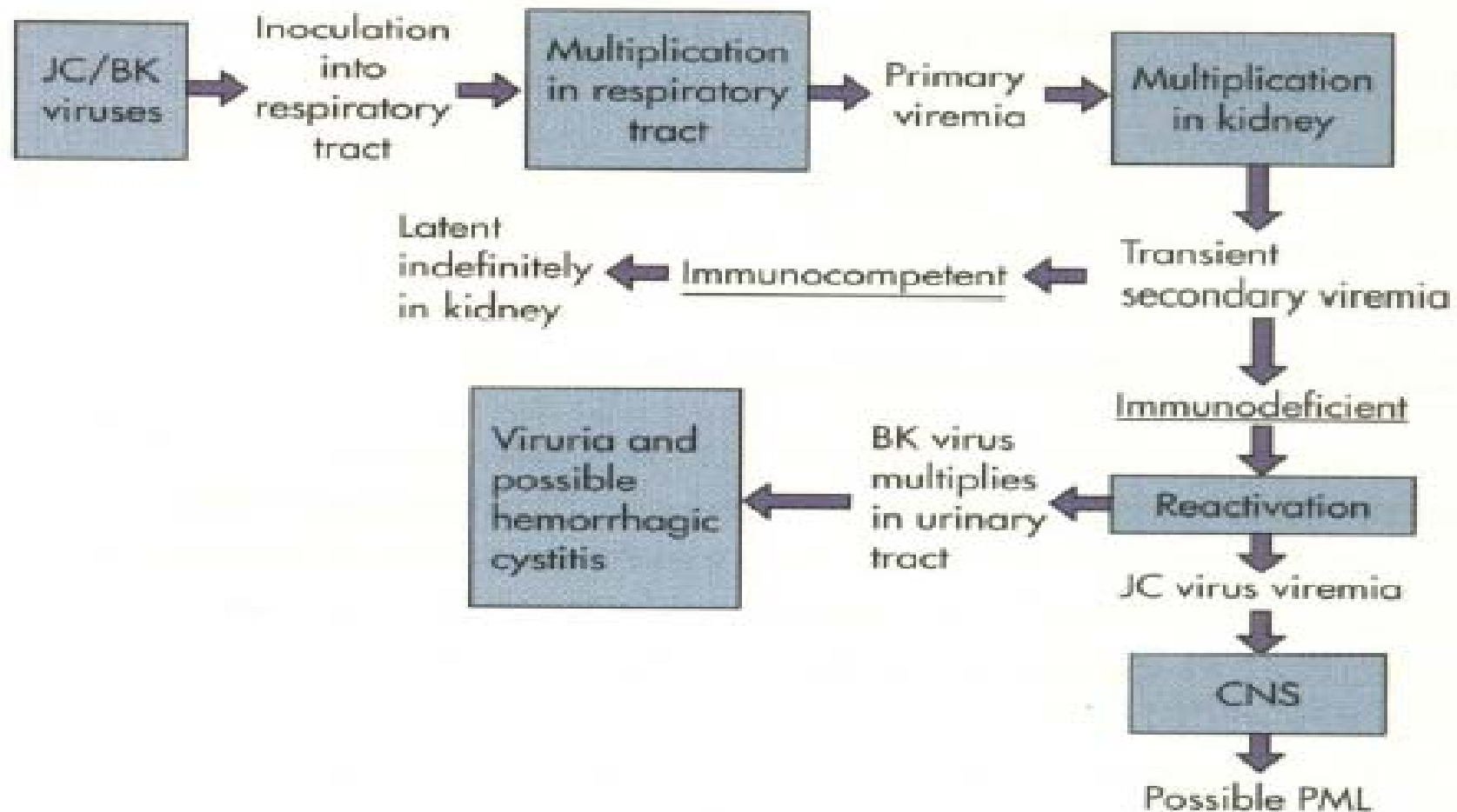
Merkel cell polyomavirus

Murine polyomavirus

Rabbit kidney vacuolating virus

Simian virus 40





**FIGURE 52–8.** Mechanisms of spread of polyomaviruses within the body. PML, Progressive multifocal leukoencephalopathy.

# JC virus

- **JC virus (JCV) is a polyomavirus** infecting greater than 80% of the human population early in life.
- Replication of this virus in oligodendrocytes and astrocytes results in the fatal demyelinating disease **progressive multifocal leukoencephalopathy (PML)** in immunocompromised individuals, most notably acquired immunodeficiency syndrome (AIDS) patient.

JCV can cross the **blood–brain barrier** into the central nervous system, where it infects oligodendrocytes and astrocytes, possibly through the **serotonin receptor**.

## Diagnosis *Clinical Samples and Biopsies* JCV and PML

- viral protein was detected in biopsy tissue using antibody to the capsid protein, VP1.
- *in situ* DNA hybridization → Use of biotin-labelled DNA probes helped identify in biopsy and autopsy brain tissue
- PCR for JCV DNA was then applied to CSF samples of patients with PML → a high degree of correlation with biopsy results



# Orthomyxoviridae

- Three types of flu virus
  - Genus *Influenzavirus A* – 8 genome segments
  - Genus *Influenzavirus B* - 8 genome segments
  - Genus *Influenzavirus C* - 7 genome segments, no NA
- *On the basis of antigenic differences between NP and M: **A, B and C***
- *type **A, B, C** : NP, M1 protein sub-types: HA or NA protein*

# INFLUENZA

## Encephalopathy -Mechanisms

- Direct virus infection of ependymal cells, vascular endothelium, neurons (rarely found in CSF)
- Cytokine-mediated destruction of blood-brain barrier
- Autoantibody production

# INFLUENZA

## Encephalopathic Syndromes

- encephalopathy
- liver and CNS
  - Reye's syndrome
- peripheral nervous system
  - Guillian-Barré syndrome
- **Post-encephalitic Parkinson's**
  
- **MERS: mild encephalopathy with promptly reversible splenial lesions**



# Typical CSF findings in CNS infections

	<b>Viral</b>	<b>Bacterial</b>	<b>TB</b>	<b>Fungal</b>	<b>Normal</b>
<b>Opening pressure</b>	Normal/high	High	High	High/v. high	10-20 cm
<b>Colour</b>	Clear	Cloudy	Cloudy/yellow	Clear/cloudy	Clear
<b>Cells/mm<sup>3</sup></b>	Sl. increase 5-1000	High/v. high 100-50,000	Sl. increase 25-500	Normal/high 0-1000	< 5
<b>Differential</b>	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
<b>CSF/plasma glc ratio</b>	Normal	Low	Low/v. low (<30%)	Normal/low	66%
<b>Protein (g/l)</b>	Normal/high 0.5-1	High >1	High/v. high 1-5	Normal/high 0.2-5	<0.45

