

Aseptic meningitis

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General Definition

- **Asepsis- Pronunciation: (a-sep'sis, a-)**
A condition in which living pathogenic organisms are absent; a state of sterility (2). Etymology: G. [a-] priv. + [sepsis,] putrefaction
- **meningitis - Pronunciation: (men-in-ji'tis)**
Inflammation of the membranes of the brain or spinal cord.
- **Aseptic meningitis** – refers to patients who have clinical signs and laboratory evidence for meningeal inflammation with negative routine bacterial cultures

Differential Diagnosis

Differential diagnosis of Aseptic Meningitis†

| | Common | Uncommon | Rare |
|-------------------|---|--|---|
| Viral | Echoviruses Coxsackieviruses types A and B Herpes simplex type 2 Human immunodeficiency virus Lymphocytic choriomeningitis virus Arboviruses Mumps Poliovirus | Cytomegalovirus Epstein Barr virus Varicella zoster virus Herpes simplex type 1 Adenovirus Measles Rubella | Rotavirus Encephalomyocarditis virus Vaccinia Influenza A and B Parainfluenza |
| Bacterial | Parameningeal bacterial infection (epidural, subdural abscess) Partially treated bacterial meningitis Leptospira sp. Borrelia burgdorferi (Lyme disease) Mycobacterium tuberculosis Bacterial endocarditis | Treponema pallidum (syphilis) Mycoplasma pneumoniae Rickettsia sp. Ehrlichia sp. Brucella sp. Chlamydia sp. | Borrelia recurrentis (relapsing fever) Spirillum minor (rat bite fever) Listeria monocytogenes Mycoplasma hominis Nocardia sp. Actinomyces sp. |
| Fungal | | Cryptococcus neoformans Coccidioides immitis Histoplasma capsulatum | Candida sp. Aspergillus sp. Blastomyces dermatitidis Sporothrix schenckii |
| Parasitic | | Angiostrongylus cantonensis Toxoplasma gondii | Taenia solium (cysticercosis) Trichinella spiralis |
| Drug | Ibuprofen | Trimethoprim-sulfamethoxazole Other NSAIDs Pyridium (phenazopyridine) anti-CD3 monoclonal antibody Azathioprine | |
| Malignancy | Lymphoma Leukemia Metastatic carcinomas and adenocarcinomas | | |
| Autoimmune | | Sarcoid Behcet's disease Systemic lupus erythematosus | Vogt-Koyanagi-Harada syndrome |

Viral Meningitis

Etiological Agents:

Enteroviruses (Coxsackie's and echovirus): most common.

- Arbovirus
- Measles virus
- Herpes Simplex Virus
- Varicella
- Lymphocytic Choriomeningitis virus (LCM)
- Mumps
- Other less common causes include West Nile, St Louis Encephalitis, and California Encephalitis (although most commonly assoc. with encephalitis). May also accompany primary VZV, outbreaks of herpes zoster, EBV, CMV, and adenoviruses.

Reservoirs:

- Humans for Enteroviruses, Adenovirus, Measles, Herpes Simplex, and Varicella
- Natural reservoir for arbovirus birds, rodents etc.

Modes of transmission:

- Primarily person to person and arthropod vectors for Arboviruses

Incubation Period:

- Variable. For enteroviruses 3-6 days, for arboviruses 2-15 days

Treatment: *No specific treatment available.*

Most patients recover completely on their own.

Non Polio Enteroviruses

Types: 62 different types known

- 23 Coxsackie A viruses
- 6 Coxsackie B viruses
- 28 echoviruses
- 4 Enteroviruses 68-71

How common?

-90% of all viral meningitis is caused by Enteroviruses

Who is at risk? Everyone, children <10yrs 2/3 of cases.

How does infection spread?

Virus present in the respiratory secretions & stool of a patient.

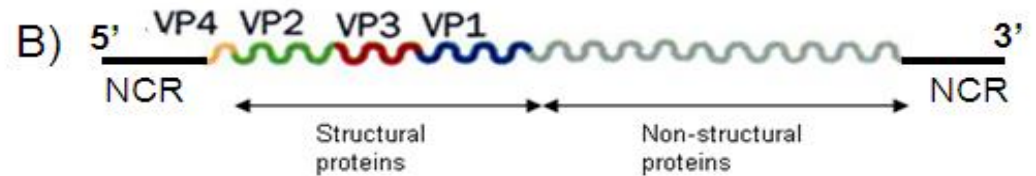
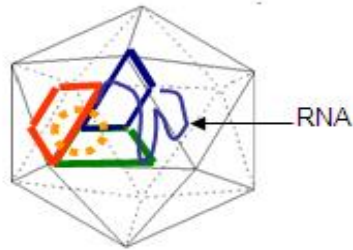
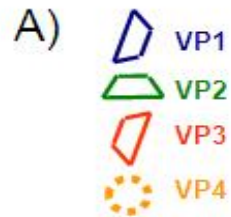
Direct contact with secretions from an infected person.

Parents, teachers, and child care center workers may also become infected by contamination of the hands with stool.

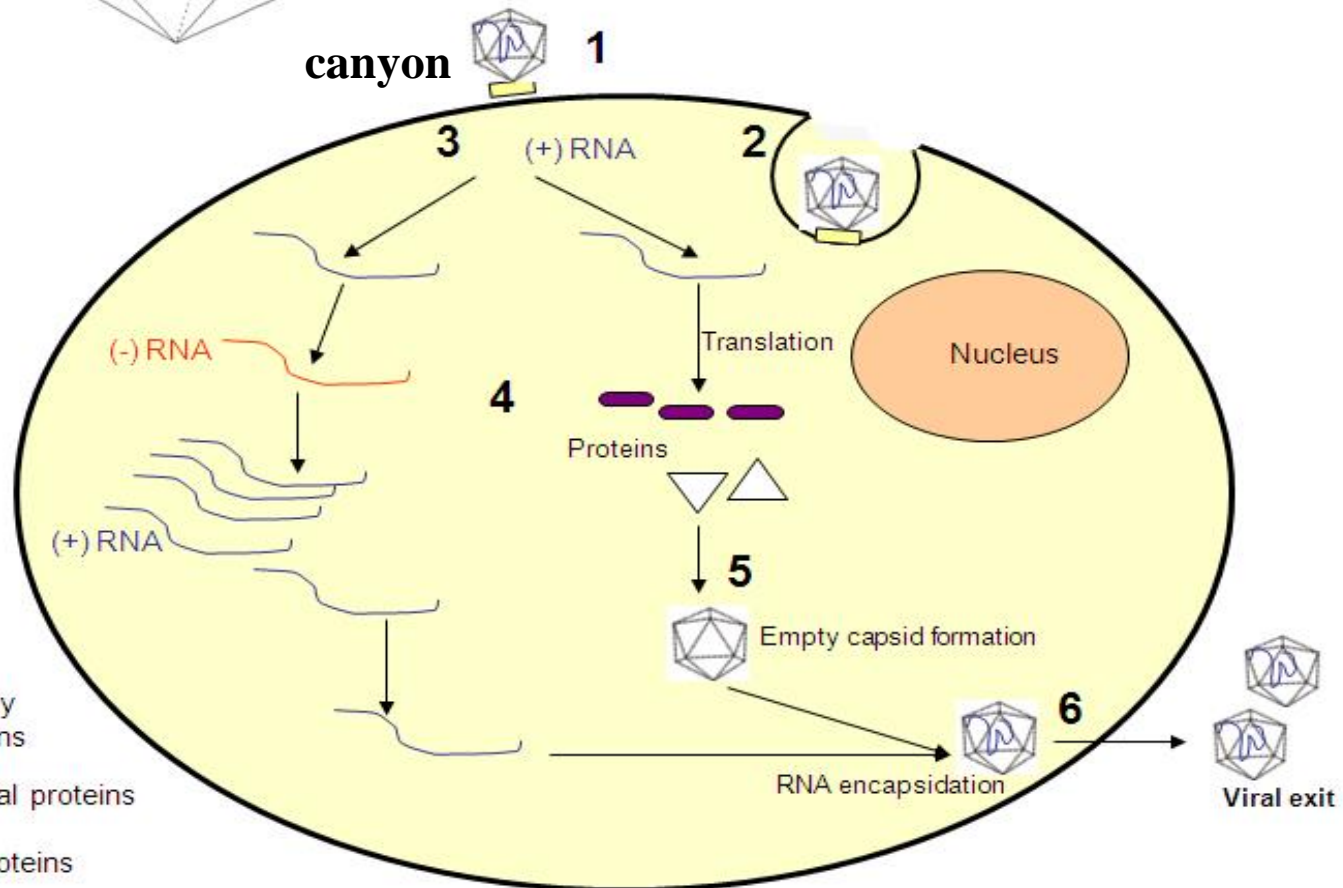
Enteroviruses

- Positive sense, naked, single stranded RNA virus
- Small (22-30nm in diameter) with icosahedral capsid composed of four proteins (VP1, VP2, VP3 and VP4).
- Replicates in the cytoplasm leading to host cell protein synthesis cessation and cell lysis.
- Resistant to acidic pH, 70% ethanol and ether.
- Genetic variation as a result of mutation and antigenic drift occurs in some strains, altering cellular tropism some times.


Enterovirus replication



C)



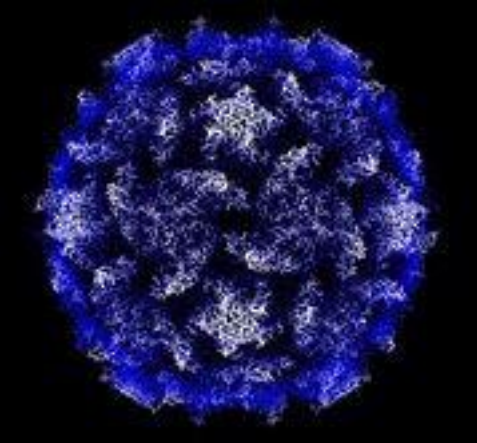
- 1 - Attachment
- 2 - Penetration
- 3 - Uncoating
- 4 - Replication
- 5 - Capsid assembly
- 6 - Release of virions

 Non-structural proteins

 Structural proteins

Pathogenesis

- Primary replication occur in epithelial cells and lymphoid tissue of RS and GI, 1ry Viremia
- Spread to CNS, heart, liver, vascular endothelium, lungs, gonads, pancreas, skeletal muscles, synovial tissues, skin and mucous membrane. 2ry viremia may occur.
- Initial tissue damage result from lytic cycle of virus replication.
- Viremia undetectable by the time that symptoms appear
- Termination of virus replication associated with appearance of Abs, interferon and PMNs in infected tissue.
- IgM followed 6-12wks by IgG
- Secondary tissue damage may be immunologically mediated. (pericarditis, nephritis, and myositis) Serology +ve, virus rarely isolated. Tissue damage due to host immune response against the virus or viral antigens that persist in affected tissues.
- Molecular mimicry: viral epitope peptide sequence shared with host tissue/s.



Enteroviral Meningitis

- Enteroviruses are thought to be the most common cause of viral meningitis
- Are a diverse group of RNA viruses including Coxsackie A & B, Echoviruses, and polioviruses.
- Account for >50% of cases and approximately 90% of cases in which no specific etiologic agent is identified. Majority of cases are in children or adolescents, but patients of any age can be affected.
- As many as 75000 cases occur in US yearly
- Transmitted primarily by fecal-oral route, but can also be spread by contact with infected respiratory secretions.
- The incidence is increased in the summer months, but cases occur throughout the year.

Coxsackieviruses

- Coxsackieviruses are distinguished from other enteroviruses by their pathogenicity for suckling rather than adult mice. They are divided into 2 groups on the basis of the lesions observed in suckling mice.
 - Group A viruses produce a diffuse myositis with acute inflammation and necrosis of fibers of voluntary muscles.
 - Group B viruses produce focal areas of degeneration in the brain, necrosis in the skeletal muscles, and inflammatory changes in the dorsal fat pads, the pancreas and occasionally the myocardium.
- Each of the 23 group A and 6 group B coxsackieviruses have a type specific antigen.
- Cross-reactivities have also been demonstrated between several group A viruses but no common group antigen has been found.

Echoviruses

- The first echoviruses were accidentally discovered in human faeces, unassociated with human disease during epidemiological studies of polioviruses. The viruses were named echoviruses (enteric, cytopathic, human, orphan viruses).
- These viruses produced CPE in cell cultures, but did not induce detectable pathological lesions in suckling mice.
- Altogether, There are 32 echoviruses (types 1-34; echovirus 10 and 28 were found to be other viruses and thus the numbers are unused)
- There is no group echovirus Ag but heterotypic cross-reactions occur between a few pairs.

New Enteroviruses

- 4 new enteroviruses have been identified (68 - 71). Enterovirus 68 is associated with respiratory illness and share Enteroviral and Rhinoviral structures. Enterovirus 70 is the causative agent epidemics of acute haemorrhagic conjunctivitis that swept through Africa, Asia, India and Europe from 1969 to 1974. The virus is occasionally neurovirulent.
- Enterovirus 71 appears to be highly pathogenic and has been associated with epidemics of a variety of acute diseases, including aseptic meningitis, encephalitis, paralytic poliomyelitis-like disease and hand-foot-mouth disease.
- Enterovirus 72 was originally assigned to hepatitis A virus, but it had now been assigned to the genus hepatoviruses of the Picornaviridae family.

Diseases associated with Enteroviruses

| Syndrome | Polio | Cox A | Cox B | Echo |
|-------------------------|--------------|--------------|--------------|-------------|
| Paralytic disease | + | + | + | + |
| Meningitis-encephalitis | + | + | + | + |
| Carditis | + | + | + | + |
| Neonatal disease | - | - | + | + |
| Pleurodynia | - | - | + | - |
| Herpangina | - | + | - | - |
| Rash disease | - | + | + | + |
| Haemorr. conjunctivitis | - | + | - | - |
| Respiratory infections | + | + | + | + |
| Undifferentiated fever | + | + | + | + |
| Diabetes/pancreatitis | - | - | + | - |

Disease Associations (1)

- **Paralytic Disease** - most commonly associated with polioviruses but other enteroviruses may also be responsible, notably enterovirus 71
- **Meningitis** - caused by all groups of enteroviruses, most commonly seen in children under 5 years of age.
- **Encephalitis** - focal or generalized encephalitis may accompany meningitis. Most patients recover completely with no neurological deficit.
- **Undifferentiated febrile illness** - may be seen with all groups of enteroviruses.
- **Hand foot mouth disease** - usually caused by group A coxsackieviruses although group B coxsackieviruses and enterovirus 71.
- **Herpangina** - caused by group A coxsackieviruses.
- **Epidemic Pleurodynia (Bornholm disease)** - normally caused by group B coxsackieviruses. Fever, sudden pain in lower abd or thoracic region. Last 14 days



Hand-foot-mouth
Fever, sore throat, loss of
appetite, diarrhea
Resolve in 7-10 days



HERPANGINA
Fever, sore throat
Heel in a week

Disease Associations (2)

- **Myocarditis** - group B coxsackieviruses are the major cause of myocarditis, although it may be caused by other enteroviruses. It may present in neonates as part of neonatal infection and is often fatal. In adults, the disease is rarely fatal.
- **Respiratory Infections** - several enteroviruses are associated with the common cold.
- **Rubelliform rashes** - a rash disease resembling rubella may be seen with several coxsackie A, B, and echoviruses.
- **Neonatal Infection** - some coxsackie B viruses and echoviruses may cause infection in newborn infants. The virus is usually transmitted perinatally during the birth process and symptoms vary from a mild febrile illness to a severe fulminating multisystem disease and death.
- **Conjunctivitis** - associated with several types of enteroviruses, notably Coxsackie A24 and Enterovirus 70 (haemorrhagic conjunctivitis)
- **Pancreatitis/Diabetes** - associated with Coxsackie B virus infection. The extent of the role of the virus in diabetes is unknown.

Common Symptoms

- Fever
- Headache
- Stiff neck
- Photophobia
- Nausea/vomiting
- Can also include rash, URI symptoms, abdominal pain, and diarrhea

Physical Exam

- Can vary depending on the etiology
- +/- Fever
- +/- Lethargy
- +/- Kernig's sign
- +/- Brudzinski's signs

Kernig's sign

- Vladimir Kernig was a Russian physician who first described his sign in 1882. This is Kernig's original description:

"I have observed for a number of years in cases of Meningitis a symptom which is apparently rarely recognized although, in my opinion, it is of significant practical value. I am referring to the occurrence of flexion contracture in the legs or occasionally also in the arms which becomes evident only after the patient sits up....the stiffness of neck and back will ordinarily become much more severe and only now will a flexion contracture occur in the knee and occasionally also in the elbow joints. If one attempts to extend the patient's knees one will succeed only to an angle of approximately 135° . In cases in which the phenomenon is very pronounced the angle may even remain 90° ."

Kernig's Sign



Brudzinski's signs

- Jozef Brudzinski was a Polish physician who described many meningeal signs in children in the early 1900's. These include :
- Symphyseal sign- pressure on the symphysis elicits a reflexive hip and knee flexion and abduction of the leg.
- Cheek phenomenon- pressure on the cheek below the cheekbone elicits a reflexive rising and a simultaneous flexion of the lower arm. The phenomenon is somewhat analogous to the symphyseal sign for the lower extremity.
- Contralateral reflex- With the patient supine, passive flexion of one knee into the abdomen results in flexion of opposite hip and knee. Reversely, a forced stretching of a previously flexed limb caused the other to stretch out.
- Neck sign- With the patient lying on the back: if the neck is forcibly bended forward, there occurs a reflexive flexion of the knees. (the one we are most familiar with)

Brudzinski's Neck Sign



Laboratory findings (CSF)

| | Leukocyte /mm³ | % PMN | Glucose % of blood | Protein (mg/dl) |
|------------------|--------------------------------------|--------------|-----------------------------------|----------------------------|
| Normal | 0-5 | 0 | ≥ 60 | ≤ 30 |
| Viral | 2-2000 (80) | ≤ 50 | ≥ 60 | 30-80 |
| Bacterial | 5-5000 (800) | ≥ 60 | ≤ 45 | >60 |
| TB and fungal | 5-2000 (100) | ≤ 50 | ≤ 45 | >60 |
| N neonate | 0-32 (8) | ≤ 60 | ≥ 60 | 20-170 (90) |

Laboratory Diagnosis

● Virus Isolation

- Mainstay of diagnosis of enterovirus infection
- Coxsackie B and Echoviruses can be readily grown in cell culture from throat swabs, faeces, and rectal swabs. They can also be isolated from the CSF
- Coxsackie A viruses cannot be easily isolated in cell culture. They can be isolated readily in suckling mice but this is not offered by most diagnostic laboratories because of practical considerations. Molecular techniques may provide a better alternative.

● PCR

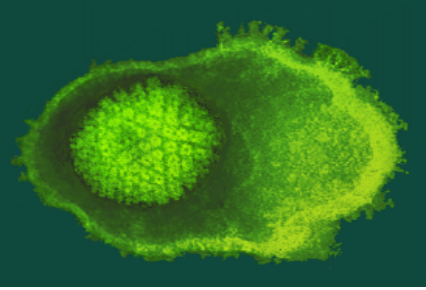
- is the **most specific** (close to 100%) and sensitive (97-100%) test and is positive in more than 2/3 of culture negative CSF in patients with aseptic meningitis

● Serology

- **Very rarely used for diagnosis** since cell culture is efficient.
- Neutralization tests or EIAs are used but are very cumbersome and thus not offered by most diagnostic laboratories

Management and Prevention

- There is no specific antiviral therapy available against enteroviruses other than polio.
- Some authorities use IVIG in the treatment of neonatal infections or severe infections in immunocompromised individuals. However, the efficacy is uncertain.
- IG has been used to prevent outbreaks of neonatal infection with good results.
- For severe enteroviral infections a new investigational drug named Pleconaril, which works by integrating into the capsid of picornaviruses, including enteroviruses and rhinoviruses, preventing the virus from attaching to cellular receptors and uncoating to release RNA into the cell, has been shown in limited use to be effective but is not currently FDA approved



Herpes Simplex Meningitis

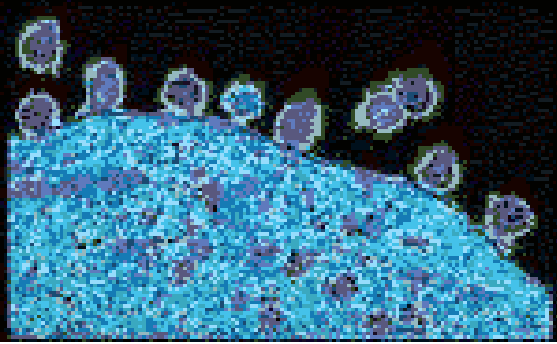
- Generally caused by HSV-2 (as opposed to encephalitis which is caused by HSV-1)
- dsDNA virus
- Increasingly recognized as a cause of aseptic meningitis, with improving diagnostic techniques and a continued increase in the transmission of HSV-2
- Can be due to primary or recurrent HSV infection
- Between 13 and 36% of patients presenting with primary genital herpes have clinical findings consistent with meningeal involvement including HA, photophobia, and meningismus. The genital lesions are typically present (85% of the time), and usually precede the CNS symptoms by seven days.
- HSV meningitis can be recurrent, these patients may not have clinically evident genital lesions. For patients with benign recurrent lymphocytic meningitis, careful analysis has revealed that over 80% are due to HSV meningitis.

HSV Diagnosis

- CSF- typical of a viral meningitis, with lymphocytic pleocytosis, modest elevation in protein, and normal glucose. Viral cultures are + in approx. 80% of patients with primary HSV meningitis, but less frequently positive in patients with recurrent HSV meningitis.
- HSV PCR of the CSF is the single most useful test for the evaluation of a patient with suspected HSV meningitis.

HSV Meningitis treatment

- Most cases are self limited and will require only symptomatic treatment.
- Antiviral therapy is recommended in patients with primary HSV infection or with severe neurological symptoms.
(inpatient-IV acyclovir 10mg/kg Q8^o, outpatient with high dose oral acyclovir/valacyclovir/or famciclovir)



HIV meningitis

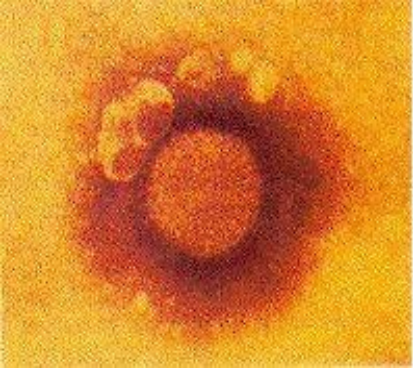
- A subset of patients with primary HIV infection will present with meningitis or meningoencephalitis, manifested by HA, confusion, seizures or cranial nerve abnormalities.
- ssRNA retrovirus

HIV Meningitis Diagnosis

- Serum might reveal an atypical lymphocytosis, leukopenia, and elevated serum aminotransferases. Documentation of seroconversion or detection of HIV plasma viremia by nucleic acid techniques can be used for diagnosis.
- CSF- might show a lymphocytic pleocytosis, elevated protein, and normal glucose. CSF cultures are often positive, but are not available in most centers.

HIV Meningitis Treatment

- The meningitis associated with primary infection resolves in most patients without treatment, and patients are typically assumed to have a benign viral meningitis. This occasionally leads to missing the diagnosis of HIV.



Lymphocytic Choriomeningitis Virus

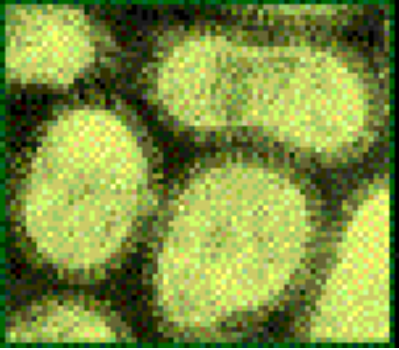
- LCM is thought to be an underdiagnosed cause of viral meningitis, in one review it was noted to be responsible for 10-15% of cases.
- ssRNA virus of the arenavirus group
- LCM is excreted in the urine and feces of rodents, including mice, rats, and hamsters (that probably includes Jorge's hamster Houdini). It is transmitted to humans by either direct contact with infected animals or environmental surfaces. Infection occurs more commonly in the winter months.
- Symptoms generally include a influenza like illness accompanied by HA and meningismus. A minority of patients develop orchitis, parotitis, myopericarditis, or arthritis.

LCM Diagnosis

- CSF- typical of other viral meningitis causes except that 20-30% of the time low glucose levels are present, and cell counts of $> 1000/\text{mm}^3$ are not unusual
- Diagnosis is made by documentation of seroconversion to the virus in paired serum samples.

LCM Therapy

- Most patients will recover spontaneously
- There is no specific anti-viral therapy available presently



Mumps Meningitis

- Caused by paramyxovirus which is a ssRNA virus
- Prior to the creation of the mumps vaccine in 1967, it accounted for 10-20% of all cases of viral meningitis.
- Even now this virus causes a significant minority of cases in unvaccinated adolescents and adults.
- In patients who do acquire mumps, CNS infection occurs rather frequently, with CSF pleocytosis detected in 40-60% of patients, and 10-30% of those have clinical signs and symptoms of meningitis.

Mumps Diagnosis

- CSF- similar to other viral causes, but like LCM it can induce a lymphocytic pleocytosis with cell counts $>1000/\text{mm}^3$ or a decreased glucose $<50\text{mg/dl}$, can isolate the virus from the CSF
- Can document seroconversion
- Clinical correlation is very helpful, ex. If the patient has parotitis or orchitis.

Mumps Treatment

- Most cases resolve without serious sequelae, and there is no specific therapy available

Miscellaneous viruses

- West Nile Virus, St Louis Encephalitis, California Encephalitis, primary VZV, outbreaks of herpes zoster,EBV,CMV, and adenoviruses.
- Less common causes of meningitis, but they do occur. In most cases the course is self-limited, and the treatment is supportive in nature.