



## *Viral Meningitis*

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**V**iral meningitis is a central nervous system (CNS) infection characterized by signs and symptoms of meningeal inflammation in the absence of positive bacterial cultures. The incidence varies with season, and the clinical presentation often includes fever, headache, and nuchal rigidity (stiffness of the neck) accompanied by symptoms typical of the specific causal virus. Viral meningitis is usually self-limited and resolves without treatment, although case reports suggest that treatment is indicated and beneficial in certain clinical scenarios.

Viral meningitis should be differentiated from the broader category of aseptic meningitis. Although patients with aseptic meningitis by definition have negative bacterial cultures, the clinical picture of meningitis is not always caused by a virus and is not always infectious.

Diagnosing viral meningitis is complex for two reasons. First, a multitude of viruses can cause meningitis, each with its own characteristic mode of transmission, presentation, and work-up. Second, and more importantly, the presentation of viral meningitis may only differ slightly from that of bacterial meningitis, a life-threatening and highly contagious disorder that requires immediate recognition and treatment.

### **Prevalence and Distribution**

Viral meningitis occurs with a peak monthly incidence of 1 per 100,000 persons in temperate climates. Reported cases are highest during the summer and early fall. The exact incidence is difficult to determine since many cases of viral meningitis are not reported to public health authorities. Many cases are probably undiagnosed because this self-limited disorder often resolves without progression of symptoms.

Enteroviruses are the most common cause of viral meningitis, accounting for 75-90% of cases. The enterovirus genus includes coxsackievirus, echovirus, poliovirus, and human enteroviruses 68 to 71. Other common causes of viral meningitis include herpes simplex virus-2 (HSV-2), human

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*Mother comforts her child despite the hardships of living in a sparse motel room. Photo by David Comb*

**Table 1: Causes of Viral Meningitis**

Common	Less common	Rare
Enteroviruses	HSV-1	Influenza
HSV-2	CMV	Parainfluenza
HIV	EBV	Rotavirus
LCMV	VZV	Vaccinia
Arbovirus	Adenovirus	Encephalomyocarditis
Mumps	Measles	virus
	Rubella	

*Note: HSV=herpes simplex virus;  
HIV=human immunodeficiency virus;  
LCMV= lymphocytic choriomeningitis virus;  
CMV=cytomegalovirus; EBV=Epstein Barr virus;  
VZV=varicella zoster virus*

immunodeficiency virus (HIV), lymphocytic choriomeningitis virus (LCMV), arbovirus, and mumps virus. Less commonly, HSV-1, cytomegalovirus (CMV), Epstein Barr virus (EBV), varicella zoster virus (VZV), adenovirus, measles, and rubella cause viral meningitis. Rare causes of viral meningitis include influenza, parainfluenza, rotavirus, vaccinia, and encephalomyocarditis virus. Most cases of recurrent viral meningitis are caused by HSV-2. HSV-1 typically causes encephalitis rather than meningitis. Table 1 lists the causes of viral meningitis by frequency.

Enteroviruses are estimated to cause approximately 75,000 cases of viral meningitis in the USA annually. The rising prevalence of HSV-2 in the USA has led to recognition of this virus as a common cause of meningitis, with some estimates ranking it the second leading cause. LCMV is thought to account for 10-15% of cases of viral meningitis. The incidence of mumps meningitis has fallen by more than 95% since initiation of widespread vaccination measures. In the past, as many as half of the cases of aseptic meningitis were of unknown etiology, but better laboratory techniques have resulted in improved identification of a causal agent.

Some forms of viral meningitis occur with seasonal variation. Cases in the summer or early fall are most likely to be caused by enteroviruses or arboviruses. LCMV or mumps are the most probable causes during the winter months. Cases of HIV- and HSV-associated meningitis are not seasonal.

Depending on risk factors, certain groups are more likely to develop a particular form of

meningitis or experience a more severe illness. For example, sexually active populations are more likely to develop HSV-2 or HIV meningitis. Unvaccinated individuals are at risk for meningitis caused by mumps, measles, or rubella. Finally, neonates (especially those less than 2 weeks of age) and adults with agammaglobulinemia who contract enteroviral meningitis tend to develop more severe cases.

### Mode of Transmission

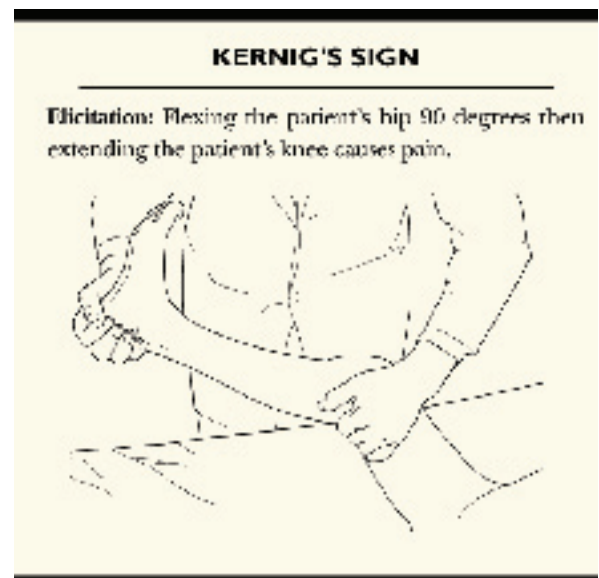
The mechanism of transmission of viral meningitis depends upon the specific viral etiology. Ninety percent of cases in which a specific virus is identified are caused by enteroviruses, which are transmitted via the fecal-oral route or through infected respiratory secretions.

HSV-2 is transmitted through contact with an active ulcerative lesion or contact with an infected host shedding HSV from a mucosal surface. HIV is transmitted via sexual contact or contact with infected blood. LCMV is contracted through contact with infected rodents or through contaminated environmental surfaces. Arboviruses are transmitted in the setting of tick bites, and mumps virus is spread via respiratory droplets.

### Symptoms and Diagnosis

Classic symptoms of meningitis include fever, headache, and nuchal rigidity. Viral meningitis can present more sub-acutely than bacterial, with malaise, lethargy, myalgias, anorexia, nausea, vomiting, abdominal pain, or diarrhea. The headache in viral meningitis is often frontal or retro-orbital and can be associated with photophobia or

**Figure 1:**



pain on eye movement. While nuchal rigidity is usually present, it is frequently mild, occurring only near the limit of neck antelexion (bending the neck forward so that the chin touches the upper chest).

Diagnosis can be confirmed by lumbar puncture and analysis of cerebrospinal fluid (CSF). CSF findings in viral and bacterial meningitis both reflect the presence of meningeal irritation but are otherwise quite distinct. Viral meningitis is characterized by an increased WBC count with a lymphocyte predominance, slightly elevated protein, and normal glucose. Early viral meningitis can show a neutrophil predominance, but the differential shifts towards lymphocytes within eight to 24 hours. Glucose is usually normal (greater than 50 percent of serum value) but can be moderately decreased in some cases of enterovirus, mumps, HSV, and LCMV. Assuming a non-traumatic tap, red blood cells are typically absent; however, they can be present in HSV-1 meningitis. In contrast, CSF findings in bacterial meningitis typically include a very high WBC count with neutrophil predominance, higher protein, and low glucose.

Polymerase chain reaction (PCR) is increasingly used to diagnose viral meningitis when routine viral cultures are negative. On average, CSF cultures are positive in only half of aseptic meningitis cases. In two-thirds of culture-negative cases, the specific viral etiology can be identified by PCR. With the present technology, PCR is routinely used to diagnose enterovirus, HSV, CMV, EBV, and VZV meningitis.

A brief discussion of the clinical presentations of some of the common viral causes of meningitis is merited, as identification of a specific viral etiology can direct treatment.

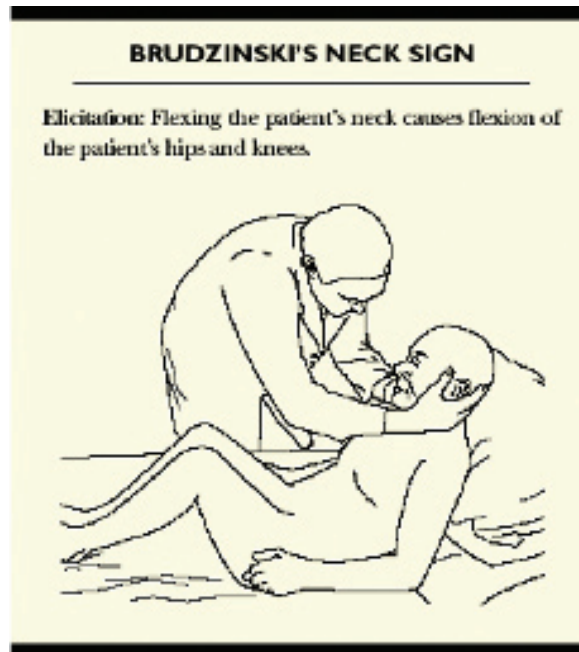
#### *Enterovirus*

In addition to an abrupt onset of headache, fever, nausea, vomiting, malaise, photophobia, and nuchal rigidity, enteroviral meningitis may present with herpangina, pleuritic chest pain, conjunctivitis, or abdominal pain. Enterovirus CSF cultures are positive in 40-80% of patients who undergo lumbar puncture, but incubation time ranges from 4-12 days. Enteroviruses can also be isolated from throat or stool specimens but can yield false positive results. CSF PCR for enterovirus, with a sensitivity of over 97% and a specificity of close to 100%, is the diagnostic test of choice.

#### *HSV-2*

Primary HSV-2 infection results in meningeal

**Figure 2:**



involvement in 13-36% of patients. Some studies have indicated that 25% of women and 11% of men with initial HSV-2 infection develop meningitis. On rare occasions, HSV-2 meningitis can present with severe but atypical symptoms of meningitis, such as urinary retention, paresthesias, focal weakness, or signs of ascending myelitis. The majority (85%) of patients with HSV-2 meningitis also have genital lesions that typically precede CNS symptoms by 7 days. While viral cultures are positive in 80% of cases of HSV-2 meningitis, HSV PCR is the diagnostic test of choice.

#### *HIV*

In 5-10% of new HIV diagnoses, meningitis is a component of the initial viral illness. This mononucleosis-like syndrome is characterized by fever, malaise, lymphadenopathy, rash, and pharyngitis. In contrast to other types of viral meningitis, HIV meningitis can present with seizures or cranial nerve palsies. Cranial nerves V, VII, and VIII are most commonly affected. While CSF cultures for HIV are often positive, diagnosis is more typically made by standard HIV testing. HIV meningitis tends to be self-limited.

#### *LCMV*

In LCMV meningitis, flu-like symptoms can accompany headache and meningeal signs. Rarely, patients can present with a rash, pulmonary infiltrates, alopecia, orchitis, parotitis, myopericarditis, or arthritis. CSF findings are typical of viral

**Table 2: Differential Diagnosis of Viral Meningitis**

Broad Category	Example
Bacterial meningitis	<i>Leptospira</i> sp. <i>Borrelia burgdorferi</i> <i>Treponema pallidum</i> <i>Mycoplasma pneumoniae</i> Rickettsia sp. Ehrlichia sp. Brucella sp. Chlamydia sp.
Fungal meningitis	<i>Cryptococcus neoformans</i> <i>Coccidioides immitis</i> <i>Histoplasma capsulatum</i>
Parasitic meningitis	<i>Toxoplasma gondii</i> Angiostrongylus
Mycobacterial meningitis	
Bacterial endocarditis	
Parameningeal infections	Epidural or subdural abscess
Neoplastic	Carcinomatous meningitis Leukemias Lymphomas
Autoimmune	Sarcoid Behcet's disease SLE
Drug-induced	Nonsteroidal anti-inflammatory drugs (ibuprofen most common) Sulfa drugs Phenazopyridine Azathioprine Anti-CD3 monoclonal antibody Intravenous immune globulin

meningitis, with the exception of occasionally lower glucose and higher cell counts.

### Mumps

Common features of mumps infection include orchitis, parotitis, and laboratory evidence of pancreatitis. However, the characteristic parotitis is present in only half of patients with mumps meningitis. Infection is more common in males, and documented prior infection excludes the possibility of current infection. In contrast to other viral meningitides, the CSF can show a neutrophilic pleocytosis and a decreased glucose.

### Arbovirus

Arbovirus infections typically occur in clusters in a localized geographic region during the summer or fall. In addition to typical symptoms of viral meningitis, a history of tick exposure is often present.

The differential diagnosis of viral meningitis is critical because the signs and symptoms can be very similar to other forms of meningitis that are life-threatening if not treated promptly. It is critical for the clinician to distinguish bacterial and non-bacterial causes of meningitis. The severity of the clinical

presentation and the analysis of the CSF findings are helpful in making this distinction. The presence of either or both of two classical signs, called the Kernig and Brudzinski signs, suggests a non-viral etiology of the meningitis. When a patient is supine or seated, a positive Kernig sign is the inability or reluctance to fully extend the knee when the hip is flexed 90 degrees as illustrated in Figure 1. Patients who spontaneously flex the hip during passive flexion of the neck have a positive Brudzinski sign as illustrated in Figure 2. Both tests were initially developed as diagnostic tools in chronic (e.g. tuberculous) meningitis but are now used to demonstrate the nuchal rigidity that is characteristic of acute bacterial meningitis. Profound alterations in consciousness, seizures, or focal neurological deficits are suggestive of a parenchymal rather than meningeal process.

Viral meningitis should also be differentiated from West Nile meningoencephalitis. From an epidemiological perspective, the risk of contracting West Nile virus increases more than twenty-fold in those over 50 years of age. In contrast, viral meningitis is common in the young as well as the elderly. While West Nile virus in its mild form can present with symptoms that resemble viral meningitis – malaise, headache, and gastrointestinal symptoms – it has several distinct clinical features. Unlike viral meningitis, meningoencephalitis caused by West Nile virus is characterized by severe muscle weakness, a diffuse flaccid paralysis, and diminished reflexes. In some cases it can resemble Guillain-Barre syndrome. In addition, nearly 20% of patients with West Nile virus have an erythematous rash. The differential diagnosis of viral meningitis is outlined in Table 2.

### Treatment and Complications

Most cases of viral meningitis are self-limited and require only symptomatic treatment. Hospitalization is not usually necessary. Treatment with intravenous immunoglobulin is indicated in persons with humoral immunity deficiency and neonates with severe infection. Patients whose CSF or other clinical findings are ambiguous or suggest the possibility of non-viral meningitis should be treated promptly with antibiotics.

Anecdotal evidence supports the use of acyclovir (Zovirax™) to treat HSV meningitis and severe EBV or VZV meningeal infection. Controlled trial data are unavailable, and whether treatment decreases the severity or duration of symptoms or reduces complications remains unknown. Antiviral

therapy is considered to be appropriate in the setting of primary HSV meningitis (versus recurrent) or for patients with severe neurological symptoms and signs. Therapy consists of IV acyclovir or oral acyclovir (Zovirax™), famciclovir (Famvir™), or valacyclovir (Valtrex™). Prophylaxis with acyclovir is indicated in patients who have frequent recurrences of HSV meningitis.

A new antiviral agent, pleconaril, is currently being investigated for the treatment of enteroviral meningitis. Previous trials have suggested that pleconaril shortens the duration of symptoms. Although a randomized placebo-controlled trial has shown the agent to be effective and safe for enteroviral meningitis, indications for its use are still being defined.

### Prevention and Control

Prevention of viral meningitis can be achieved by reduction of risk factors and by vaccination strategies. The spread of HSV-2 and HIV can be reduced through education on how the viruses are transmitted and the promotion of strategies for preventing transmission, such as barrier protection during sexual contact and needle exchange programs. Meningitis from mumps, measles, and rubella, as well as VZV, can be prevented by vaccination.

Control of the spread of viral meningitis depends on the specific viral agent. Transmission of enterovirus meningitis, for example, can be decreased through basic hygiene techniques such as hand washing.

### Special Consideration for Homeless Populations

Homeless populations living in shelters are at an increased risk of developing communicable diseases because of the large number of individuals with diverse exposures living in close quarters. Given the easy transmissibility of infectious diseases in shelter settings, it is imperative to identify serious and treatable infections early to prevent spread to co-habitants. Any individual with symptoms of meningitis should be emergently directed to medical

attention so that bacterial meningitis can be ruled out by lumbar puncture. Despite signs of systemic viral infection, symptoms of meningitis should not be automatically ascribed to a viral etiology, as a concurrent bacterial infection may still be present.

Shelters are unique settings that can facilitate the screening of risk factors for preventable infections. Upon intake to a shelter, guests can be screened for a vaccination history and current medical conditions. Depending on the risk factor or medical history, guests can be offered education, counseling, or access to vaccinations.

### Summary

- The differential diagnosis of viral meningitis is broad: always rule out non-viral causes first, as the untreated mortality rate of bacterial meningitis is very high.
- If there is any question about the etiology of meningitis, start antibiotics.
- Viral meningitis is usually self-limited.
- Cases vary seasonally, with enterovirus being the most common cause.
- A detailed history and physical exam help to hone the diagnosis.
- Hallmark symptoms include fever, headache, and stiff neck.
- Diagnosis is by lumbar puncture and CSF analysis.
- Viral PCR studies of the CSF are more sensitive and specific than routine cultures.
- Treatment is usually not indicated.
- Acyclovir (Zovirax™) is used for treatment and prophylaxis of HSV meningitis.
- New antiviral therapies are under investigation.
- Shelter settings can increase transmission of meningitis but facilitate risk factor assessment and prevention strategies. ■

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Viral Meningitis Medication List		
Generic	Brand Name	Cost
acyclovir	Zovirax	\$
famciclovir	Famvir	\$\$\$
valacyclovir	Valtrex	\$\$\$\$

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