Meningoencephalitis

Fever, Altered Level of Consciousness, Seizures

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J. Domachowske (ed.), *Introduction to Clinical Infectious Diseases*,
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Learning Objectives

- Describe the infectious etiologies of meningoencephalitis.
- Recognize distinguishing clinical features of meningoencephalitis by etiology.
- Identify possible etiologies for meningoencephalitis by identified risk factors.
- List the appropriate diagnostic tests that should be considered during the evaluation of a patient with meningoencephalitis.

25.1 Definitions

Meningoencephalitis - inflammation of the meninges and the brain parenchyma

Rhomboencephalitis - inflammation of the brainstem

Hypoglycorrhachia - an abnormally low glucose concentration detected in the cerebrospinal fluid

Meningoencephalitis, defined as inflammation of the brain parenchyma and the surrounding meninges, manifests as cerebral dysfunction often resulting in permanent neurologic sequelae. The underlying cause of the problem frequently goes undetected, even after thorough diagnostic evaluation. Precise etiologies, when identified, include infection, autoimmune disease, vasculitis, neoplasm, and metabolic disorders [1, 2]. The focus of this chapter is on infectious causes of meningoencephalitis [▶ Call Out Box 25.1].

25.2 Clinical Evaluation

Meningoencephalitis is an acute disease process that presents with fever and headache together with signs of both meningeal irritation, such as nuchal rigidity and cerebral inflammation manifesting as an altered mental status, abnormal behavior or speech, focal neurologic deficits, and/or new-onset seizures [3, 4] [▶ Call Out Box 25.2]. The evaluation of a patient with suspected meningoencephalitis should begin with a thorough history and physical examination. The age, past medical history, and medication list may identify patients at risk for intracranial hemorrhage, cerebral vasculitis, or central nervous system (CNS) depression, all potential mimics of meningoencephalitis that is caused by infection. Medications that by themselves, can cause symptoms consistent with meningoencephalitis, include amoxicillin, methylphenidate, rituximab, ibuprofen, and immunoglobulin intravenous (IgIV) [5–8]. A vaccination history could highlight increased risk for meningoencephalitis due to vaccine-preventable diseases, including varicella, measles, mumps, and polio. A prolonged duration of symptoms, particularly with no history of fever or systemic illness, is more suggestive of an intracranial mass, while the history of a respiratory tract infection or nonspecific febrile illness days to weeks before the development of neurologic symptoms suggests a post-infectious process, such as acute disseminated encephalomyelitis (ADEM) [9].

Call Out Box 25.1
All patients with suspected infectious meningoencephalitis should be treated empirically with intravenous acyclovir until herpes simplex virus infection has been ruled out.

Call Out Box 25.2
Clinically, meningoencephalitis includes features of both meningitis and encephalitis.

Meningoencephalitis		
Meningitis	**Encephalitis**	**Typical of all CNS infections**
Nuchal rigidity	Altered mental status	Fevers
Positive Kernig sign		Headache
Positive Brudzinski sign	Focal neurologic deficits	Photophobia
	Seizures	

Epidemiologic data and details learned by taking a thorough travel history may offer clues regarding the etiology since several of the known infectious causes are restricted to specific geographic locations or are more likely to circulate during certain times of the year (Table 25.1). For example, Powassan virus causes disease in Northeastern and Northcentral United States and the bordering areas of Canada, disease caused by Colorado tick fever is restricted to the Western United States, and cases of tick-borne encephalitis virus are seen predominately from Europe and Asia [10–13]. Furthermore, enteroviral disease peaks during summer, while arboviruses are transmitted in areas where their mosquitoes and ticks vectors thrive. Herpes simplex virus infections occur year-round [1]. A thorough exposure history may also provide clues to the etiology of disease process. For example, a history of swimming in warm freshwater lakes should raise the suspicion for the diagnosis of infection by *Naegleria fowleri*, while a history of cat scratches suggests *Bartonella henselae* infection as the trigger (Table 25.1).

Patients clinically suspected to have meningoencephalitis should undergo a complete physical examination with extra care to focus on overt or subtle neurologic findings. The clinical presentation and degree of symptom severity are determined by the anatomic component of the central nervous system that is affected. Encephalitis, or inflammation of the cerebral parenchyma, presents with a disturbance in brain function, with signs and symptoms that include altered mental status, changes in behavior or speech, and seizures. Very few pathogens are described as causing isolated

Table 25.1 Infectious etiologies of meningoencephalitis to consider based on known exposures

Exposure	Infectious etiologies to consider
Warm freshwater	*Naegleria fowleri* or other free-living amoebae
Arthropod bites	
Mosquitoes	WNV, EEE, WEE, VEE, SLE, JEV, La Crosse virus, Zika virus, *Plasmodium* spp.
Ticks	*Borrelia burgdorferi*, Powassan virus, rickettsia, Colorado tick fever virus, TBE
Animal contact	
Cats	*Bartonella henselae*, *Coxiella burnetii*, *Toxoplasma gondii*
Dogs, skunks foxes	Rabies virus
Bats	Rabies virus, Nipah virus
Macaque monkeys	Herpes B virus
Rodent excretion	Lymphocytic choriomeningitis virus
Raccoons	*Baylisascaris procyonis*, rabies virus
Geography	
United States—East	*B. burgdorferi*, Powassan, EEE, WNV, La Crosse virus, SLE, rickettsia, *Histoplasma capsulatum*
United States—West	WEE, WNV, Colorado tick fever, SLE, rickettsia, *B. burgdorferi*, *Coccidioides immitis*
Central/South America	EEE, Rabies, SLE, VEE, WEE, WNV, *Plasmodium* spp., rickettsia
Europe	TBE, WNV, *B. burgdorferi*
Australia	Hendra virus, JEV, *H. capsulatum*
Asia	Nipah virus, JEV, *Plasmodium* spp., rabies, WNV, *B. burgdorferi*, TBE, Powassan, *H. capsulatum*
Africa	Rabies virus, WNV, *Plasmodium* spp., *H. capsulatum*

WNV West Nile virus, *EEE* eastern equine encephalitis virus, *WEE* western equine encephalitis virus, *SLE* St. Louis encephalitis virus, *JEV* Japanese encephalitis virus, *VEE* Venezuelan equine encephalitis virus, *TBE* tick-borne encephalitis virus

Table 25.2 Signs and symptoms associated with meningoencephalitis that may offer clues about the underlying etiology

Associated signs/symptoms	Suggested underlying etiologies
Vesicular rash	VZV, HSV, EV, herpes B virus
Maculopapular rash	HHV-6, WNV
Parotitis	Mumps
Gastrointestinal prodrome	Shigellosis
Respiratory prodrome	*Mycoplasma pneumoniae*, influenza viruses
Lymphadenopathy	CMV, EBV, WNV, HIV, measles, *Bartonella henselae*
Urinary symptoms	SLE
Pneumonia	Adenoviruses, Nipah virus, Hendra virus, VEE, *Coxiella burnetii*, *Histoplasma capsulatum*
Flaccid paralysis	WNV, EV, JEV, TBE, poliomyelitis virus
Isolated tremors	SLE
Cerebella ataxia	EBV, VZV
Cranial nerve deficit	EBV, HSV, VZV, *Borrelia burgdorferi*, *Mycobacterium tuberculosis*, *Coccidioides immitis*
Rhomboencephalitis	EV-71, HSV, WNV
Hydrophobia, aerophobia, pharyngeal spasm	Rabies

VZV varicella zoster virus, *HSV* herpes simplex virus, *EV* enterovirus, *HHV*-6 human herpesvirus-6, *WNV* West Nile virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *SLE* St. Louis encephalitis virus, *VEE* Venezuelan equine encephalitis virus, *HSV* herpes simplex virus

encephalitis, that is, without associated meningeal inflammation. Two viruses that are known to be associated with encephalitis without necessarily causing an associated meningitis are rabies and herpes simplex virus.

Specific focal neurologic findings may provide hints as to the etiology of the central nervous system disease. For example, the findings of cranial nerve deficits, in addition to meningoencephalitis, can be seen in patients infected with *Borrelia burgdorferi*, *Mycobacterium tuberculosis*, and varicella zoster virus [14–16]. Flaccid paralysis is a classic presentation of neuroinvasive West Nile virus infection [17]. Meningoencephalitis that primarily involves the temporal lobe strongly suggests herpes simplex virus as the underlying etiology, although herpes simplex can involve any or all parts the brain. Cerebellar dysfunction can be seen in patients infected with varicella zoster virus or *Mycoplasma pneumoniae* [15, 18]. Rhomboencephalitis is most typical for infections caused by enterovirus 71, West Nile virus, and herpes simplex virus [19]. The presence of new-onset seizures can occur with meningoencephalitis from any cause, while isolated tremors are more characteristic of St. Louis encephalitis virus infection [20–23].

While the focus of the physical examination is the neurologic component, a thorough evaluation of the other organ systems should also be performed in search of additional clues (Table 25.2). The presence of a vesicular rash is typical

during infection with varicella zoster virus and some enteroviruses. The presence of parotitis suggests mumps infection, particularly in unvaccinated individuals. The finding of generalized lymphadenopathy in a patient with meningoencephalitis suggests several possible infectious causes including Epstein-Barr virus, West Nile virus, and human immunodeficiency virus. Measles virus infection can also cause meningoencephalitis in association with generalized lymphadenopathy, but in this case, the other classic findings of measles, cough, coryza, conjunctivitis, and a morbilliform rash will also be present. A respiratory prodrome followed by acute meningoencephalitis is consistent with infection by influenza virus or *M. pneumoniae*, while acute onset of meningoencephalitis following a gastrointestinal prodrome has been described with rotavirus infection [1, 18, 24]. Fever and seizures that can mimic meningoencephalitis are also seen regularly in patients with intestinal shigellosis, but the central nervous system manifestation is secondary to the effects of a bacterial toxin, not from central nervous system invasion by the organism itself. Neonates with meningoencephalitis caused by herpes simplex virus, enteroviruses, adenoviruses, or human parechoviruses can present with viral sepsis with associated hepatitis, pneumonia, and/or rash [25–27].

25.3 Diagnostic Evaluation

Cerebrospinal fluid (CSF) analysis is essential in the diagnostic evaluation of patients with suspected meningoencephalitis [28–30]. It is important to note, however, that a lumbar puncture should not be performed on patients with intracranial masses or midline shift, hemodynamic instability, respiratory failure, signs of disseminated intravascular coagulopathy, taking anticoagulation medications, or who are known to have severe thrombocytopenia [29]. Indications for obtaining neuroimaging prior to performing lumbar puncture include impaired consciousness, signs of increased intracranial pressure (such as papilledema or bradycardia with hypertension), focal neurologic deficits, new-onset seizures, immunocompromised state, or a prior history of a central nervous system leison [29].

If there are no contraindications to performing the lumbar puncture, the procedure should be performed without delay. Opening pressure should be documented, and generous amounts of CSF collected to be sure there is sufficient fluid available to allow the laboratory technicians to perform all of the desired diagnostic tests. Routine CSF analysis should include a total nucleated cell count with differential, the concentrations of glucose and protein, a Gram stain, and a bacterial culture. CSF findings typically seen in cases of viral meningoencephalitis include a CSF pleocytosis with a mononuclear cell predominance, an elevated protein concentration, and a normal or slightly depressed glucose concentration [31–35]. Less commonly, the CSF may be acellular or show a pleocytosis with a neutrophilic predominance, especially when sample is obtained very early in the course of infection. Since most patients with meningoencephalitis have normal or only slightly depressed CSF glucose concentrations, results showing the characteristic findings of CSF pleocytosis with a mononuclear cell predominance and elevated protein concentration in association with a moderate to profound hypoglycorrhachia should immediately be recognized as highly unusual and inconsistent with a viral etiology. The CSF analysis pattern described is absolutely classic for *Mycobacterium tuberculosis* infection and, less commonly, fungal meningitis [1, 31, 32]. Immediate recognition that the CSF findings are unusual and classically seen with central nervous system tuberculosis infection, and less commonly in patients with fungal disease, is essential for two reasons. First, medications are available for the treatment of both *M. tuberculosis* and fungal central nervous system infections, so an appropriate empiric antimicrobial treatment regimen can be started without further delay. Second, testing for these pathogens is not a routine or automatic procedure in microbiology, so the clinical microbiology team should be contacted to be sure that all appropriate cultures and other diagnostic studies have been included in their laboratory work-up. Of note, patients with noninfectious causes of meningoencephalitis typically have fewer cells observed in their CSF compared to those with infectious etiologies [32, 34, 35]. The presence of red blood cells in the CSF is often simply blamed on trauma to a small blood vessel in the path of the spinal needle during the lumbar puncture, but it is important to remember that their presence could also indicate the presence of blood in the subarachnoid space secondary to hemorrhagic meningoencephalitis. Infections with a hemorrhagic component due to herpes simplex virus, herpes B virus, and parasitic infections, like *Angiostrongylus cantonensis*, and primary amebic meningoencephalitis is quite typical [36–38].

A CSF analysis profile that includes pleocytosis, with the presence of eosinophils, should also be recognized as highly unusual. The observation is a clue that the patient's meningoencephalitis could be caused by a roundworm, such as such as *Baylisascaris procyonis*, and should likewise trigger a call to the microbiology team to be sure all appropriate diagnostic studies are underway. *B. procyonis* infection is seen almost exclusively in young children with pica and those who have had contact with infected raccoon feces [39].

Further diagnostic testing to determine a specific infectious etiology for meningoencephalitis is driven by the epidemiologic circumstances, known and potential exposures, and other clues discovered during the history and physical examination. Identification of the infecting organism may involve direct visualization on CSF wet mount or after staining, culture, polymerase chain reaction (PCR), serologic testing, or other methods (Table 25.3). Historically, the isolation of viruses from spinal fluid culture was the primary diagnostic method for patients with a viral CNS infection. However, the availability of PCR testing has dramatically improved diagnostic yield over traditional viral cultures. The sensitivity of CSF cultures is very low and when successful often requires days to weeks. On the other hand, PCR testing

Table 25.3 Diagnostic tests for infectious agents causing meningoencephalitis

Pathogen	Appropriate diagnostic studies
Viruses	
Herpesviruses	
Herpes simplex viruses 1 and 2	CSF PCR, surface viral cultures or PCR (neonates), DFA or PCR of skin, mouth, and/or genital lesions
Varicella zoster virus (VZV)	CSF PCR, CSF VZV IgM, IgM and IgG serologies, DFA of skin lesion
Epstein-Barr virus	CSF PCR, IgM, and IgG serologies
Cytomegalovirus	CSF PCR, IgM, and IgG serologies
Human herpes virus 6	CSF PCR
Enteroviruses	CSF PCR, PCR on respiratory sample, stool culture
Respiratory viruses	
Influenza virus	Antigen testing or PCR of respiratory sample
Measles virus	CSF PCR, CSF measles IgM, IgM and IgG serologies, culture or PCR of nasopharyngeal or urine sample
Mumps virus	CSF PCR, IgM and IgG serologies, culture of saliva or urine
Adenovirus	PCR of respiratory sample
Arboviruses[a]	CSF PCR (if available), CSF virus-specific IgM, IgM, and IgG serologies
Human immunodeficiency virus	IgG serology, quantitative RNA PCR, CSF PCR
Rabies virus	Immunofluorescent antigen test performed on skin snip taken from the nape of the neck or on corneal impressions (earliest, and most sensitive diagnostic test), salivary PCR, viral culture of saliva, CSF PCR, CSF virus-specific IgM, IgM, and IgG serologies
Bacteria	
Borrelia burgdorferi	IgM and IgG serologies using two-tier testing (EIA with Western blot confirmation)
Bartonella henselae	IgM and IgG serologies
Coxiella burnetii	IgM and IgG serologies
Mycoplasma pneumoniae	PCR of respiratory sample, IgM and IgG serologies
Rickettsial infections	IgM and IgG serologies
Mycobacterium tuberculosis	Purified protein derivative skin testing, Interferon gamma release assay using whole blood, large volume CSF culture (10 ml or more)
Fungal	
Cryptococcus neoformans	CSF antigen testing, CSF fungal culture, CSF multiplex PCR
Histoplasma capsulatum	IgM and IgG serologies for yeast and mycelial phases, urine antigen, CSF fungal culture
Coccidioides species	IgM and IgG serologies, CSF fungal culture
Amoeba	
Naegleria fowleri	Direct visualization in CSF on wet mount or stain. Culture using a lawn of *E. coli* bacteria, PCR of CSF or brain biopsy sample
Acanthamoeba species	PCR of CSF or brain biopsy sample
Balamuthia mandrillaris	PCR of CSF or brain biopsy sample

[a]Including but not limited to West Nile virus, Japanese encephalitis virus, Powassan virus, Western equine virus, Eastern equine virus, La Crosse virus, and St. Louis encephalitis virus

is now available for the more common viral etiologies of meningoencephalitis as a timely highly sensitive diagnostic assay [4, 40]. It is important to understand that while PCR testing has high sensitivity and specificity for many viruses, this does not hold true for all causative agents of meningoencephalitis [4, 41]. Viruses for which PCR testing has proven useful include herpes simplex virus, enteroviruses, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, human herpes virus-6, adenoviruses, human immunodeficiency virus, JC virus, rabies virus, and some of the arboviruses, including eastern equine encephalitis virus, St. Louis encephalitis virus, and the California serogroup viruses [28–30, 40, 42]. It is important to note, however, that detection of viral genome fragments in the spinal fluid, using PCR, should be interpreted carefully as the presence of specific nucleic acid may not actually correlate with the acute disease process. The detection of virus-specific IgM antibody in CSF is also quite useful for identifying the etiologic agent of meningoencephalitis, but generally later in the course of disease, when PCR assays may be negative. The detection of virus-specific IgM in CSF is particularly useful for the diagnosis of VZV and arboviruses infections. For example, the earliest and most sensitive assay used for the identification of neuroinvasive West Nile disease in a virus-specific IgM test performed on CSF [43].

Standard serologic testing can also be used diagnostically. Serum obtained from blood collected during the acute infection can be evaluated for the presence of pathogen-specific IgM and/or IgG antibody for Epstein-Barr virus, cytomegalovirus, parvovirus B19, human immunodeficiency virus,

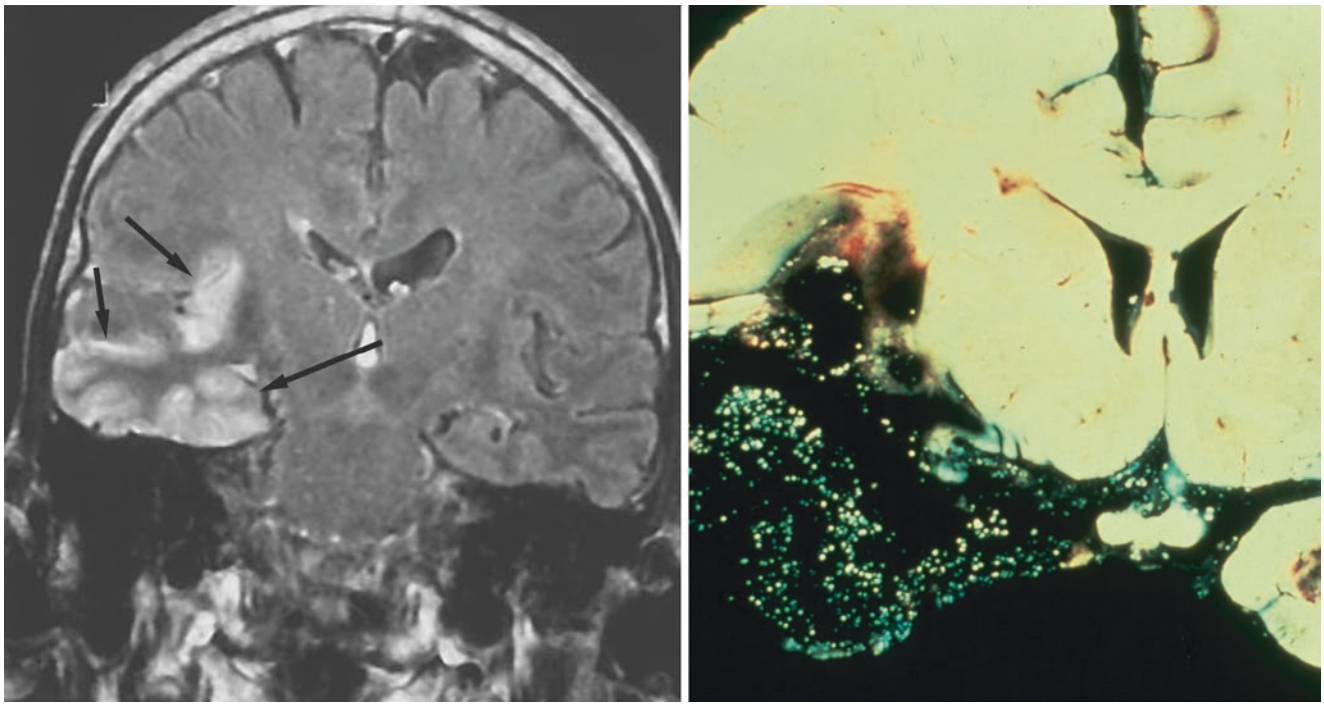

Fig. 25.1 The gadolinium contrast-enhanced magnetic resonance image of the brain on the left is a coronal view showing extensive inflammatory changes and edema (*arrows*) in the right temporal lobe of a young adult patient presenting with fever, seizures, and altered level of consciousness alternating with bizarre, combative behavior. Cerebrospinal fluid tested positive for herpes simplex virus type 1 by polymerase chain reaction. Despite treatment with intravenous acyclovir, the patient died 4 days later. Autopsy revealed extensive areas of hemorrhagic necrosis involving the entire right temporal lobe, extending superiorly to the right parietal lobe and anteriorly into the frontal lobe. The image on the right shows a coronal section of the brain, as seen at autopsy, prepared from an anatomic position at approximately the same level as the magnetic resonance image on the left from 4 days earlier. (Image provided by Dr. Joseph Domachowske)

Borrelia burgdorferi, and many of the arboviruses. In some instances, acute and convalescent titers will be necessary. Serum samples that are collected early during the illness are archived until a convalescent sample becomes available 3–6 weeks later. In general, the serologic test result is considered positive if the antibody titers detected from the paired samples differ by fourfold or more.

Diagnostic testing performed on CSF and serologic testing performed on blood are important to establish the microbiologic diagnosis, but definitive results often require somewhat lengthy turnaround times. Clues that may help to predict the underlying cause of the infection while waiting for the definitive reports can sometimes be gleaned from the patterns of results already available from routine laboratory tests. A careful review of available results from complete blood counts, serum electrolytes, blood urea nitrogen creatinine, and hepatic transaminases may show patterns that support a particular etiology. The presence of leucopenia and/or thrombocytopenia suggests rickettsial infections, particularly in those patients with hyponatremia and modest elevations in serum transaminases. The presence of a significant atypical lymphocytosis in combination with mild hepatic transaminitis is highly suggestive of EBV infection. Peripheral blood eosinophilia is characteristic of parasitic infections, including those caused by migratory roundworms. Collecting a nasopharyngeal sample for rapid turnaround, multiplex PCR testing for respiratory pathogens can be considered. The detection of *M. pneumoniae*, adenoviruses, influenza viruses, and enteroviruses from the respiratory tract is, at best, indirect evidence that the central nervous system illness is caused by the same pathogen, so care should be taken to interpret the results in the proper context. Chest radiographs may also be indicated, depending on the history and physical examination findings. Pathogens with the potential to initiate infection in the respiratory tract with subsequent spread to the central nervous system include influenza viruses, adenoviruses, *M. tuberculosis*, *Nocardia* spp., *Histoplasma capsulatum*, and other dimorphic fungi.

Neuroimaging is an important diagnostic study that should be performed in patients with meningoencephalitis to help exclude noninfectious causes of their illness and to evaluate the extent of parenchymal brain involvement. Magnetic resonance imaging (MRI) of the brain is the preferred neuroimaging modality in the evaluation of meningoencephalitis. It is more sensitive than computed tomography (CT) for the detection of parenchymal disease, including demyelination. The use of CT scans is appropriate if MRI is unavailable or cannot be performed [28]. Some etiologies of meningoencephalitis have characteristic neuroimaging findings. For example, focal lesions in the basal ganglia, thalami, and brainstem are typical of arbovirus infection, while the presence of edema and hemorrhage in the frontotemporal lobes is most characteristic of infection with herpes simplex virus [44–46] (Fig. 25.1).

25.4 Infectious Causes of Meningoencephalitis: *Viruses*

25.4.1 Human Herpesviruses

Human herpesviruses are ubiquitous, globally distributed, DNA viruses which cause infection all year-round. Initial exposure to a human herpesvirus results in primary infection, which may be subclinical or symptomatic, followed by a period of latency. Since all herpesviruses establish latency, they have the potential to reactivate at a later time. Nine members of the *Herpesviridae* family are known to cause human infection. All nine have neurotropic potential, but some are much more likely than others to cause central nervous system infection. [▶ Call Out Box 25.3].

25.4.1.1 Herpes Simplex Virus

Herpes simplex viruses (HSV) are among the leading causes of identified sporadic infectious meningoencephalitis worldwide [1, 2, 32, 47, 48]. There are two types of HSV: HSV-1 and HSV-2. Both virus types can cause primary infection and establish latency in the mucosal of the oropharynx or the genital tract. HSV-1 is the more usual cause of infection around the mouth and lips (cold sores), while HSV-2 accounts for a majority of genital HSV infections. Both HSV-1 and HSV-2 contribute to the overall burden central nervous system infection. While HSV-1 causes most cases of meningoencephalitis in immunocompetent adults, both HSV types contribute to disease seen in newborns.

HSV infection can be divided into neonatal disease and that occurring beyond the neonatal period. Neonates acquire HSV through contact with infected secretions, either during delivery or from symptomatic or asymptomatic shedding by a parent, sibling, or other caregiver during the immediate postnatal period. Infants born to mothers who experience a primary HSV infection close to the time of delivery are at the highest risk of acquiring neonatal HSV disease compared to those infants born to mothers with known recurrent genital herpes. Other factors associated with the perinatal transmission of herpes infection include maternal HSV antibody status, prolonged duration of ruptured membranes, and the use of fetal scalp monitoring electrodes [49]. Similarly, transmission of HSV to a susceptible person, beyond the neonatal period, occurs through close contact with an individual who is symptomatically or asymptomatically shedding the virus from their skin or mucosal membranes.

Individuals who are exposed to HSV become infected when the virus gains entry through injured skin or mucosal membranes. Primary infection may be subclinical, may be associated with fairly impressive signs and symptoms at the inoculation site, or may less commonly erupt as a severe systemic illness with or without involvement of the central nervous system. During the primary infection, the virus invades local sensory nerve endings, traveling retrograde along the axon to the sensory ganglion. As the host immune system controls the primary infection, virus in the sensory ganglion remains latent until reactivation. During virus reactivation, the virus migrates anterograde along the axon back to the original inoculation site on the skin or mucous membranes. HSV reactivation results in either symptomatic disease, as occurs with recurrent cold sores and recurrent genital herpes, or in asymptomatic virus shedding [49].

HSV meningoencephalitis is an uncommon complication of primary HSV infection. Presenting signs and symptoms include mental status changes, headaches, focal neurologic deficits, fever, and seizures [21, 31, 45, 46]. Complications include status epilepticus, intracranial hemorrhage, acute respiratory failure, cerebral edema, brainstem herniation, and death [21]. Neuroimaging and electroencephalogram (EEG) studies may reveal the typical temporal or frontotemporal lesions associated with HSV encephalitis (◘ Fig. 25.1), but any part of the brain can be involved [31, 45, 46].

The diagnosis of HSV meningoencephalitis is confirmed by performing an HSV-specific PCR-based assay on the patient's cerebrospinal fluid [50, 51]. HSV PCR assays are highly sensitive (~96%) and specific (~99%) for the diagnosis. Essentially all infected patients will have a positive HSV PCR test at the onset of their neurologic symptoms. PCR is so sensitive that testing remains positive even after 5 days of antiviral therapy. Before PCR-based testing became routinely available, a definitive diagnosis often depended on HSV-specific stains and cultures performed on tissue obtained from a brain biopsy [50–52]. Other antigen and antibody-based assays that were once used to aid in the diagnosis of HSV meningoencephalitis have likewise been replaced by PCR [51].

It is important to note that false negative PCR results can occur very early in disease; therefore, if clinical suspicion for HSV meningoencephalitis is high and the PCR result is negative, treatment with acyclovir should continue at least until a repeat cerebrospinal fluid sample is collected and tested 3–7 days later [43, 50, 53]. If the level of suspicion for HSV meningoencephalitis remains high despite repeat negative

Call Out Box 25.3

Cause CNS infections in both healthy and immunocompromised patients	Cause CNS infection in immunocompromised patients only	Not typically associated with CNS infections
Herpes simplex virus type 1 Herpes simplex virus type 2 Epstein-Barr virus Varicella zoster virus Human herpes virus 6 Herpes B virus	Cytomegalovirus	Human herpes virus 7 Human herpes virus 8

PCR test results, some experts recommend that the patient should receive a full 21-day treatment course with intravenous acyclovir unless or until a logical alternative diagnosis is confirmed as the results of other diagnostic tests become available.

All PCR-confirmed cases of HSV meningoencephalitis should be treated with intravenous acyclovir for at least 21 days. Cerebrospinal fluid should be collected by repeat lumbar puncture performed near the end of therapy so that a posttreatment HSV PCR can be performed. If the posttreatment PCR result is still positive, antiviral therapy should be extended beyond 21 days [28].

Without treatment, 70% of patients with HSV meningoencephalitis will die from the infection. Even with appropriate treatment, HSV meningoencephalitis can be a devastating disease. Permanent neurological sequelae should be expected. Extensive brain injury leaves some patients completely dependent on others for care. Spasticity, with motor planning problems and other developmental issues are common sequelae in children. Lifelong neurocognitive problems such as memory impairment, personality and behavioral changes, and psychiatric conditions are not uncommon [43]. Factors that are associated with worse outcomes include age more than 30 years, a Glasgow Coma Score of less than 6 during the acute phase of the illness, symptoms for more than 4 days before antiviral therapy is initiated, and a positive cerebrospinal fluid HSV PCR at the end of therapy [28]. In an effort to reduce the morbidity and mortality associated with central nervous system HSV disease, intravenous acyclovir should be administered empirically to all patients with suspected meningoencephalitis until HSV infection has been ruled out.

Intravenous acyclovir is also used to treat perinatal HSV infections in newborns. Following treatment, all newborns remain at risk for central nervous system reactivation. Suppression of reactivation is achieved by administering oral acyclovir for 6 months starting immediately after the intravenous course of therapy has been completed. Oral acyclovir suppression of HSV reactivation is associated with improved neurodevelopmental outcomes [54]. In contrast, a large clinical trial found no improvement in the neuropsychological testing results of adults who received 3 months of oral valacyclovir suppression after completing a course of intravenous acyclovir [55].

25.4.1.2 Varicella Zoster Virus

Varicella zoster virus (VZV) is a fairly common identified cause of meningoencephalitis. VZV infection results in two distinct clinical entities: varicella (chickenpox), seen with primary infection, and herpes zoster (shingles) seen with reactivation disease. Varicella epidemiology changed drastically after the introduction of varicella vaccination programs during the mid-1990s [56].

Varicella zoster virus is highly contagious. Transmission is airborne, similar to measles and smallpox. Aerosolized virus spreads from infected individuals to infect the respiratory mucosa of susceptible individuals with a very high attack rate [56]. Primary VZV infection in susceptible hosts causes varicella (chickenpox). The illness begins as a febrile respiratory infection. As the infection progresses, vesicles begin to appear on the skin. The rash is intensely itchy, typically starting on the scalp or at the hairline, moving to the trunk and then out to the extremities, sparing the palms and soles. When they first appear, the small vesicles sit on an erythematous base and contain clear fluid. Crops of vesicles turn to small pustules, eventually scabbing over as crops of new vesicles continue to appear. In 7–10 days, all vesicles have scabbed, and no new ones are formed. Varicella infection self-resolves for the majority of patients, at which time the virus remains latent in sensory ganglia. Reactivation of latent VZV results in herpes zoster (shingles) as a painful, burning, or tingling vesicular rash typically limited to a single dermatome. VZV meningoencephalitis can complicate either the primary infection or the reactivation illness.

VZV central nervous system disease can manifest as (a) acute cerebellar ataxia, a self-limiting process that occurs in children approximately 1–3 weeks after the onset of varicella infection and typically results in full recovery; (b) diffuse meningoencephalitis, a severe complication of VZV infection seen more commonly in adults that can lead to neurologic sequelae; or (c) aseptic meningitis. While initially thought to affect only immunocompromised patients, studies describing VZV central nervous system infection in immunocompetent patients have been reported [15, 16, 57].

The clinical presentation of VZV meningoencephalitis includes fever, headache, nausea, vomiting, altered mental status, and cranial nerve involvement, most commonly involving the seventh and eighth cranial nerve [15, 16, 58]. A cutaneous rash may or may not be present; thus, the absence of a rash does not exclude the possibility of central nervous system VZV infection [15, 16, 57, 58]. Neuroimaging may show diffuse encephalitis with vasculitis, ischemic stroke, demyelination, or swelling of the cerebral cortex, basal ganglia, or cerebellum [3, 28].

The diagnostic test of choice for VZV meningoencephalitis is virus-specific PCR performed on fluid from a vesicular skin lesion, saliva, or cerebrospinal fluid. This test will provide rapid and sensitive results for the detection of virus. VZV infection can also be diagnosed using antigen testing by direct immunofluorescence, detecting virus-specific antibodies in the cerebrospinal fluid, or through serologic testing, all of which have lower sensitivity and/or specificity compared to PCR-based assays [3, 28, 59, 60]. There is little utility in attempting viral culture for VZV. The virus is difficult to propagate in the laboratory even if the cell monolayers that support its growth are inoculated directly, at the bedside [59].

Currently, there are no clinical trials to guide the treatment of varicella encephalitis. However, based on the favorable safety profile of acyclovir and data suggesting that acyclovir treatment reduces symptoms and disease severity during primary varicella infection, intravenous acyclovir is recommended for the treatment patients with VZV menin-

goencephalitis [28, 60]. Ganciclovir can be used as an alternative agent. Corticosteroids can be considered as adjunctive therapy in patients with VZV CNS disease [28].

25.4.1.3 Other Human Herpesviruses

Exposure to other human herpesviruses, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6), most commonly results in asymptomatic or subclinical infection, but these viruses have also been identified as causes of meningoencephalitis in both immunocompetent and immunocompromised patients. Meningoencephalitis caused by EBV infection can be associated with the unusual symptom of metamorphopsia. Metamorphopsia is described as visual perceptions (hallucinations) of three-dimensional, overlapping, colorful geometric shapes and figures that expand and shrink in size in one visual field. It's a very rare, bizarre complaint sometimes referred to as "Alice in Wonderland" syndrome that has also been described by some patients with vascular headaches.

The clinical presentation of meningoencephalitis caused by human herpesviruses includes fever, headache, photophobia, altered level of consciousness, seizures, confusion, hallucinations, and memory changes [61–63]. Neuroimaging may reveal involvement of the temporal lobe, corpus callosum, basal ganglia, thalamus, and/or periventricular areas [63–71]. The diagnosis of meningoencephalitis due to these human herpesviruses is made primarily through the use of virus-specific PCR assays performed on CSF [28]. The diagnosis of acute EBV infection is based on serologic testing, which includes the presence of EBV antiviral capsid antigen (VCA) IgM and IgG, Epstein-Barr nuclear antigen (EBNA), and the early antigen (EA). The presence of VCA IgM is indicative of acute or recent infection. The presence of EBNA in combination with a positive VCA IgM suggests recent infection over acute infection because the EBNA takes several weeks to months to appear. The presence of both the VCA IgG and EBNA reflects a past EBV infection.

There are no clear treatment guidelines for meningoencephalitis caused by EBV, CMV, or HHV6. However, the combination of ganciclovir and foscarnet has been used to treat HIV-infected patients with CMV encephalitis, with the understanding that therapeutic concentrations of these antivirals are unlikely to be achieved in the cerebrospinal fluid [28]. Since CMV infection typically happens during severe immunosuppression, reducing immunosuppressive therapy, if possible, should be a component of the therapeutic management [28].

25.4.1.4 Herpes B Virus

Herpes B virus, a zoonotic virus endemic among macaque monkeys, is a known cause of meningoencephalitis among humans who are bitten or scratched by infected monkeys, typically in a research laboratory setting [72]. Symptoms, including fevers, lymphadenitis, and peripheral neuropathy, occur a few days to weeks after exposure, followed by the development of a destructive hemorrhagic meningoencephalitis. The diagnosis of herpes B virus infection includes serologic testing, PCR-based testing, and viral cultures from the wound. Treatment for individuals with herpes B central nervous system infection is intravenously administered ganciclovir. Prophylaxis of exposed individuals, including those who have been bitten or scratched by a macaque known to be seropositive for or shedding herpes B virus, or whose status is unknown, involves early wound cleaning and irrigating and a 14-day course of valacyclovir or acyclovir [72].

25.4.2 Picornaviruses

Enteroviruses and parechoviruses are non-enveloped, single-stranded RNA viruses in the *Picornaviridae* family [73, 74]. These viruses cause a wide spectrum of disease, from clinically asymptomatic infection to febrile illness with nonspecific rash and to aseptic meningitis (very common) and meningoencephalitis (rare). Enteroviruses, such as coxsackieviruses A and B; echoviruses 4, 5, 9, 11, 19, and 30; and enteroviruses 71, 75, 76, and 89, and human parechovirus 3 have all been implicated in sporadic and epidemic cases of meningoencephalitis, worldwide. Enterovirus 71, in particular, has been identified as an aggressive neurotropic virus causing outbreaks of life-threatening rhomboencephalitis [75]. Enterovirus and parechovirus infections are seen more commonly during the summer and fall months in temperate locations and year-round in the tropics. While these viruses infect individuals of all ages, the most common infections are seen in young children.

Transmission of enteroviruses and parechoviruses occurs through fecal-oral contamination or by contact with infected respiratory secretions. The initial viral replication occurs in the epithelial cells of the intestinal mucosa. The virus, then, crosses the intestinal cells to reach the lamina propria, where replication is more robust, eventually leading to viremia and secondary infection of the central nervous system [73]. Following primary infection, shedding of virus in upper respiratory secretions and feces can occur for weeks to months [74]. The most common manifestation of central nervous system disease is aseptic meningitis.

Patients with enterovirus or parechovirus meningoencephalitis present with the same non-specific signs and symptoms typically associated with the disease process, including fever, headache, vomiting, altered mental status, and focal neurologic deficits [16, 43, 76]. In addition, these patients may have associated symptoms of rash and diarrhea. Magnetic resonance images of patients with human parechovirus meningoencephalitis reveal inflammatory changes in the white matter, while images of those with enteroviral disease more typically show lesions in the medulla oblongata, pons, midbrain, and dentate nuclei of the cerebellum [76, 77]. These changes tend to be temporary, although long-term deficits have been described.

The preferred diagnostic test for enterovirus infection used to be isolation of virus through culture. However, with the advent of RT-PCR, with its improved sensitivity and specificity and a faster turn-around time for results, enterovirus-specific PCR assays from blood, CSF, and oropharyngeal or rectal swabs, are the new gold standard for the diagnosis of an enterovirus or parechovirus CNS infection [75].

There are currently no available antiviral treatment options for enterovirus or human parechovirus meningoencephalitis. Pleconaril, a viral capsid inhibitor with high oral bioavailability, has shown promise but remains unavailable. Immunoglobulin intravenous (IgIV) has been used anecdotally to treat patients with enteroviral or parechoviral meningoencephalitis, but evidence regarding treatment efficacy are lacking.

25.4.3 Arboviruses

Arboviruses, or viruses transmitted by arthropods (such as mosquitoes and ticks), include several small RNA viruses belonging to one of four families: *Togaviridae*, *Flaviviridae*, *Bunyaviridae*, and *Reoviridae* [78]. The arthropod vector acquires virus after feeding on an infected animal. The virus replicates in the arthropod, which then transmits infection when it bites a human. As arboviruses are dependent on their host vector's life cycle to cause human disease, these viruses vary in their geographic distribution and seasonality of infection.

25.4.3.1 West NileVirus (WNV)

WNV, a virus in the *Flaviviridae* family found across the world, is now the leading cause of mosquito-borne viral meningoencephalitis in the United States [78]. It is transmitted primarily by the female *Culex* spp. mosquito, which acquires the virus from infected birds and then passes the virus onto humans during feeding. Transmission of WNV has also been documented to occur from blood transfusions, organ transplantations, and exposure to body fluids during delivery [17]. Infection during pregnancy can result in congenital infection with neurological sequelae in the newborn. It has been estimated that while 25% of those infected with WNV develop a febrile illness, only about 1% develop central nervous system involvement [17, 79]. Risk factors for the development of neuroinvasive disease include increasing age, male gender, non-white race, organ transplant recipients, and comorbid medical conditions, such as diabetes, hypertension, and cancer [80–82].

In symptomatic WNV infection, the clinical presentation includes a non-specific febrile illness with an associated maculopapular rash that appears around time of defervescence. Those who develop central nervous system involvement tend to do so during this phase of the infection. Neuroinvasive WNV manifests as either aseptic meningitis, meningoencephalitis, or flaccid paralysis. Cranial nerve palsies and movement disorders, such as tremors, myoclonus, and parkinsonism have been described among those diagnosed with WNV infection [83, 84]. Laboratory evaluation may show a mild leukocytosis, hyponatremia, cerebrospinal fluid pleocytosis, and elevated CSF protein concentrations. Magnetic resonance imaging may reveal lesions in the pons, basal ganglia, thalamus, brainstem, and cerebellum [17, 84]. The diagnosis of WNV central nervous system infection is made through the detection of IgM antibody in cerebrospinal fluid and serum. The majority of infected patients will have detectable IgM antibodies in their CSF during the first week of symptoms [17]. On the other hand, if initial IgM testing is negative, acute- and convalescent-phase serologic testing may aid in the diagnosis [17]. Currently, there is no antiviral therapy available for the treatment of severe WNV infection. The prognosis is variable for patients with neuroinvasive WNV infection. Those who present with aseptic meningitis are most likely to fully recover, and those who present with meningoencephalitis are at a higher risk for morbidity, including persistent movement disorders and cognitive deficits. A small subset of patients do not survive the infection.

25.4.3.2 Eastern Equine Encephalitis (EEE) Virus

EEE, a virus in the *Togaviridae* family that is most commonly found in the western hemisphere, is transmitted by the *Culiseta melanura* mosquito. Interestingly, this mosquito does not usually bite humans, and people are generally infected by *Aedes* spp. or *Culex* spp. mosquitoes which act as bridging vectors between infected birds and humans [84]. Reports of EEE cases are very rare. In the United States, cases of EEE are typically seen during the summer and fall months [84].

Clinically, EEE infection may manifest as a non-specific febrile illness with headache, nausea, and vomiting, followed by either resolution or by the development of meningoencephalitis. Once neurologic symptoms develop, clinical deterioration occurs rapidly, and many cases are fatal. Laboratory evaluation may reveal leukocytosis, hyponatremia, cerebrospinal fluid pleocytosis with a neutrophil predominance, and elevated protein concentration. Magnetic resonance imaging may show lesions in the basal ganglia, thalamus, and brainstem [44]. The diagnosis of EEE meningoencephalitis can be confirmed by detecting EEE IgM in CSF, observing a fourfold rise in serum antibody titers collected during the acute and convalescent phases, or isolating EEE virus from the tissue, blood, or CSF. There is no treatment currently available for EEE infection. Mortality rates exceed 30% [85]. Patients who survive EEE meningoencephalitis are left with severe neurologic sequelae.

25.4.3.3 St. Louis Encephalitis (SLE) Virus

SLE virus, a flavivirus transmitted by *Culex* spp. mosquitoes found widely throughout the Americas, was among the leading causes of arboviral meningoencephalitis in the United States until the arrival and spread of WNV. SLE infection is most common in summer and fall months during peak mosquito activity. Uncommon modes of transmission of infection also include solid organ transplantation and blood transfusions.

The clinical spectrum of SLE virus infection varies from asymptomatic infection, to a non-specific febrile illness, to

severe meningoencephalitis. Advancing age is associated with an increased risk of central nervous system involvement and is associated with higher mortality [86, 87]. SLE virus meningoencephalitis presents with high fevers, headache, and altered mental status. Tremors of the eyelids, lips, and extremities, cranial nerve palsy, cerebellar ataxia, and seizures can also be seen [84]. Associated clues typical of SLE infection include urinary frequency, urgency, and retention. Respiratory symptoms and acute flaccid paralysis may also accompany the illness [87]. Laboratory evaluation typically shows a mild leukocytosis, hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion, sterile pyuria, and/or elevated hepatic transaminases and creatinine kinase. CSF pleocytosis with a lymphocytic predominance and elevated protein concentration are likely to be present. Neuroimaging is often normal.

The diagnosis of SLE virus meningoencephalitis is presumed by the presence of virus-specific IgM in the serum or CSF, although these antibodies may cross-react with West Nile virus antibodies. Paired acute and convalescent SLE virus antibody titers that demonstrate a fourfold rise or more is diagnostic of infection. Isolation of virus from the blood or cerebrospinal fluid is very difficult and associated with a low yield. There is currently no available treatment for SLE meningoencephalitis; however, a small pilot study suggested that early use of interferon-alpha2b may reduce the severity and complications of SLE meningoencephalitis [88]. While recovery from acute SLE virus infection can occur in the first 2 weeks, neurocognitive deficits, including gait imbalances, neuropsychiatric symptoms, and tremors, may persist.

25.4.3.4 La Crosse Virus

La Crosse virus, a member of the *Bunyaviridae* family transmitted by the *Aedes triseriatus* mosquito, is the most common and most pathogenic of the California encephalitis group viruses. Infection is most commonly seen in school-aged children during the summer months, when the mosquito activity peaks.

The clinical presentation of La Crosse virus CNS infection includes fevers, headache, vomiting, seizures, alerted mental status, or focal neurologic deficits. Increased intracranial pressure leading to herniation and death has been described [89, 90]. The laboratory evaluation may reveal hyponatremia, leukocytosis, and CSF pleocytosis, while neuroimaging will likely show generalized cerebral edema with focal areas of gadolinium enhancement [89]. There are no currently available treatment options for La Crosse virus infections.

25.4.3.5 Rabies

Rabies virus, a Lyssavirus in the *Rhabdoviridae* family, is a zoonotic infection found worldwide that is responsible for the deaths of 55,000 people annually. Most deaths occur in developing countries where there is a lack of rabies control among domesticated animals. Transmission of infection occurs through the bite of an infected animal, particularly dogs, raccoons, skunks, bats, or foxes. Virus transmission can also occur from inhaling contaminated aerosols while exploring caves or from accidental occupational exposure in the laboratory. Rabies virus has also been transmitted from an infected donor during organ transplantation [91, 92].

The incubation period for rabies averages between 1 and 3 months but can be several years. Clinical symptoms of rabies infection start with a non-specific prodrome, including low-grade fevers, malaise, and anorexia. The prodrome is then followed by either an encephalopathic phase, which includes progressively worsening altered mental status, autonomic instability, dysphagia, hydrophobia, and agitation, or a paralysis phase, evident by an ascending paralysis similar to Guillain-Barre syndrome [91, 93]. The progression of disease almost always results in death within a few weeks of symptom onset.

Diagnostic testing for rabies infection must come from multiple sources: a saliva sample for virus isolation and/or reverse-transcription PCR, serum and CSF for rabies antibodies, a skin biopsy including hair follicles from the nape of the neck for rabies antigen detection by direct fluorescent antibody testing, and corneal impressions for rabies antigen detection by direct fluorescent antibody testing. There is currently no known effective therapy for rabies infection once symptoms develop; however rabies treatment protocols continue to explored systematically using variations of the Milwaukee protocol.

The best strategies for preventing the development of rabies infection include both pre- and postexposure prophylaxis. Pre-exposure rabies prophylaxis is indicated for those individuals who are at high risk for exposure, including veterinarians and lab workers, those who work with rabies virus or rabid animals, and international travelers who may come into contact with rabid animals. Active vaccination of these at-risk groups, with regular booster doses for those who continue to be at risk, is recommended. Postexposure rabies prophylaxis, including rabies vaccine and rabies immunoglobulin (RIG), is indicated for those individuals who have been exposed to an animal known or possibly infected with rabies virus.

25.5 Infectious Causes of Meningoencephalitis: Bacteria

25.5.1 *Bartonella henselae*

This fastidious Gram-negative bacillus is responsible for most cases of cat-scratch fever, an illness that is occasionally associated with central nervous system involvement and does not always cause fever. Despite the occasional nature of the complication, *Bartonella henselae* is the most common cause of *bacterial* meningoencephalitis [35]. *B. henselae* infect the cat flea, *Ctenocephalides felis*, which transmits infection from cat to cat when it feeds. Humans most commonly acquire infection after being scratched by an infected, asymptomatic kitten. Perhaps a better name for the illness would be "kitten scratch disease." Infection is sometimes transmitted through bites or via mucosal contact with contaminated flea feces. Puppies and adult cats and dogs can also be sources of infection.

Cat-scratch disease (the most widely accepted medical term for this illness) begins with the appearance of a papule at the site of inoculation. Lymphadenopathy develops in the local or regional draining lymph nodes, often persisting for several weeks. On physical examination, the inflamed lymph node can feel unusually hard raising concern for possible malignancy. Fevers are not always present, but ironically, cat-scratch disease is one of the most common causes of prolonged, unexplained fevers in children.

Atypical manifestations of cat-scratch disease include hepatosplenic involvement, retinitis, endocarditis, and meningoencephalitis. Meningoencephalitis presents abruptly with fevers and seizures between 1 and 6 weeks after the onset of lymphadenopathy [35]. Neuroimaging study results are often normal but may show subtle non-specific abnormalities. Acute and convalescent antibody titers are used to make the diagnosis of cat-scratch disease. If the acute titer is already markedly elevated in a patient with illness manifestations that are consistent with cat-scratch disease, a convalescent sample is unnecessary. Treatment of cat-scratch disease meningoencephalitis is supportive. Treatment with antibiotics, including doxycycline or azithromycin, with or without the addition of rifampin, may speed recovery [28]. The prognosis is excellent. The vast majority of patients recover without sequelae within 2 weeks or less.

25.5.2 *Mycoplasma pneumoniae*

M. pneumoniae, a fastidious bacterium lacking a cell wall, is ubiquitous, causing infection year-round, worldwide. The organism is a leading cause of pneumonia among school-aged children and young adults. Respiratory infection can be associated with various immunological phenomenon including the production of cold agglutinin antibodies, sometimes with evidence for an associated autoimmune hemolytic anemia. Infection with *M. pneumoniae* is also one of the most common known infectious triggers for the development of Stevens-Johnsons syndrome. Meningoencephalitis has been described as another, much less common complication of *M. pneumoniae* infection. Transmission of *M. pneumoniae* occurs through contact with the respiratory droplets of an infected individual.

Patients with *M. pneumoniae* meningoencephalitis present with fevers, altered mental status, seizures, and/or focal neurologic deficits [94]. Results of neuroimaging studies are usually normal. In contrast, electroencephalogram (EEG) studies are usually abnormal showing either diffuse slowing or identifying focal abnormalities [94]. The failure to reliably and convincingly demonstrate the presence of *M. pneumoniae* in cerebrospinal fluid via culture or PCR under these circumstances and the proclivity of the organism to trigger unusual immunologic events have led to the suggestion that meningoencephalitis may be a noninfectious, immune-mediated complication of the pulmonary infection. Treatment options for *M. pneumoniae* infection include azithromycin, doxycycline, or fluoroquinolones [28].

25.5.3 *Borrelia burgdorferi*

Borrelia burgdorferi is the bacterium that causes Lyme disease. The most common central nervous system manifestations of Lyme disease occur during the early disseminated phase of infection and include aseptic meningitis and seventh cranial nerve palsy, among others. Meningoencephalitis is a rare but very serious manifestation of late Lyme disease. Comprehensive discussions on all aspects of Lyme disease are included in ▶ Chap. 32. Additional information about central nervous system manifestations can be found in ▶ Chap. 22.

25.6 Amoebic Meningoencephalitis

Primary amoebic meningoencephalitis (PAM) is caused by the free-living amoeba, *Naegleria fowleri*. This parasitic disease causes a devastating, rapidly fatal central nervous system infection. *N. fowler* is most commonly found in warm bodies of freshwater, including lakes, rivers, and hot springs. Infections are most commonly reported from the southern United States. Transmission occurs when water contaminated with the parasite enters the nasal passages while the head is partially or completely submerged, as with swimming [95]. Amoebae migrate in retrograde fashion along the olfactory nerves to the olfactory bulb directly into the brain.

Patients with PAM present similarly to those with bacterial meningitis, with fevers, bifrontal or temporal headaches, nausea, vomiting, and nuchal rigidity. These early signs and symptoms are followed by progressive neurologic dysfunction with altered mental status, seizures, behavioral changes, and cranial nerve palsies [95, 96]. Results from neuroimaging and routing laboratory testing are non-specific. The diagnosis of PAM is made primarily through real-time PCR assays of performed on cerebrospinal fluid. Direct visualization on wet mount, or with staining techniques, is also possible. Cultures can also be requested. CSF is incubated on a lawn of *E. coli* bacteria. As the amoebae reproduce, they consume the bacteria leaving behind trails that can be visualized microscopically.

The mortality rate for PAM exceeds 95%. Optimal treatment is unknown; however liposomal amphotericin B is a recommended therapy when this disease process is suspected [28].

Granulomatous amebic meningoencephalitis, caused by either *Acanthamoeba* species or *Balamuthia mandrillaris*, is a chronic infection that progresses much more slowly than PAM, leading to death in weeks to months following the first signs of infection. These free-living amoebae are found worldwide in freshwater, soil, and dust. Infection occurs after inhalation of amebic cysts that are present in the water or following contact with contaminated soil [96].

Patients with granulomatous amebic meningoencephalitis present with gradual onset of behavioral changes, vision loss, ataxia, headaches, and seizures over the course of weeks to months [96]. Findings on neuroimaging are non-specific and of limited value in making diagnosis. The diagnostic tests

of choice are organism-specific real-time PCR assays performed on cerebrospinal fluid. Treatment options for *Acanthamoeba* spp. infection include various combinations of trimethoprim-sulfamethoxazole, miltefosine rifampin, fluconazole, pentamidine, and sulfadiazine [28].

25.7 Special Populations

Immunodeficient patients are susceptible to the development of central nervous system infections from a variety of causes. For example, patients with underlying agammaglobulinemia and CD40 ligand deficiency are at risk for developing chronic enteroviral meningoencephalitis. The chronic nature of the infection results in a gradual loss of developmental milestones with progressive neurologic dysfunction over the course of several months to years before causing the patient's death. A second example includes patients with primary immune deficiencies involving the toll-like receptor (TLR) 3 signaling pathway. Patients with these TLR3-associated signaling deficiencies are at an increased risk for the development of recurrent HSV meningoencephalitis [97].

Case Study

Practical Example

A previously healthy 5-year-old male presents to the Emergency Department with a 2-day history of fevers and headaches when he developed seizures and altered mental status. After securing the airway, a diagnostic evaluation was initiated including a complete blood count, electrolytes, creatinine, hepatic transaminases, blood cultures, a nasopharyngeal swap for respiratory virus studies, and complete cerebrospinal fluid analysis. Which of the following is the next appropriate step in the management of this patient?

A. Magnetic resonance imaging (MRI) of the brain
B. Electroencephalogram (EEG)
C. Intravenous administration of acyclovir
D. Computed tomography (CT) scan of the brain and spine

(C) In the management of patients with meningoencephalitis, it is important to treat for herpes simplex virus infection as soon as the diagnosis is suspected to improve outcomes associated with disease process. Following the administration of intravenous acyclovir, MR imaging of the brain will aid in determining the severity of disease, and EEG studies will assist in the evaluation of the persistent seizure activity.

25.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. Which of the following causes of meningoencephalitis is not an arbovirus?
   a. West Nile virus
   b. Powassan virus
   c. Rabies virus
   d. La Crosse virus

2. List the vaccine-preventable causes of meningoencephalitis.

3. Match the clinical symptom or exposure with associated etiology of meningoencephalitis.

Pathogen	Characteristic finding
1. Warm freshwater swimming	A. St Louis encephalitis virus
2. Hydrophobia	B. Varicella zoster virus
3. Urinary symptoms	C. Herpes B virus
4. Cranial nerve involvement	D. *Naegleria fowleri*
5. Macaques	E. Rabies virus

References

1. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, Schuster FL, Christie LJ, Tureen JH. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006;43:1565–77.
2. Calleri G, Libanore V, Corcione S, DeRosa FG, Caramello P. A retrospective study of viral central nervous system infections: relationship amongst aetiology, clinical course, and outcome. Infection. 2017;45:227–31.
3. Bookstaver PB, Mohorn PL, Shah A, Tesh LD, Quidley AM, Kothari R, Bland CM, Weissman S. Management of viral central nervous system infections: a primer for clinicians. J Cent Nerv Syst Dis. 2017;9:1179573517703342.
4. Kennedy PG, Quan PL, Lipkin WI. Viral encephalitis of unknown cause: current perspective and recent advances. Viruses. 2017; 9:138.
5. Shahien R, Vieksler V, Bowirrat A. Amoxicillin-induced aseptic meningoencephalitis. Int J Gen Med. 2010;21:157–62.
6. Snell LB, Bakshi D. Neurological adverse effects of methylphenidate may be misdiagnosed as meningoencephalitis. BMJ Case Rep. 2015; https://doi.org/10.1136/bcr-2014-207796.
7. Hadley I, Jain R, Sreih A. Nonvasculitic autoimmune meningoencephalitis after rituximab: the potential downside of depleting regulatory B cells in the brain. J Clin Rheumatol. 2014;20:163–6.
8. Moreno-Ancillo A, Gil-Adrados AC, Jurado-Palomo J. Ibuprofen-induced aseptic meningoencephalitis confirmed by drug challenge. J Investig Allergol Clin Immunol. 2011;21:484–7.
9. Sonneville R, Klein I, de Broucker T, Wolff M. Post-infectious encephalitis in adults: diagnosis and management. J Infect. 2009;58: 321–8.
10. Piantadosi A, Rubin DB, McQuillen DP, Hsu L, Lederer PA, Ashbaugh CD, Duffalo C, Duncan R, Thon J, Bhattacharyya S, Basgoz N, Feske SK, Lyons JL. Emerging cases of Powassan virus encephalitis in New

England: clinical presentation, imaging, and review of the literature. Clin Infect Dis. 2016;62:707–13.
11. Yendell SJ, Fischer M, Staples JE. Colorado tick fever in the United States, 2002-2012. Vector Borne Zoonotic Dis. 2015;15:311–6.
12. Steffen R. Epidemiology of tick-borne encephalitis (TBE) in international travelers to Western/Central Europe and conclusions on vaccination recommendations. J Travel Med. 2016;23 https://doi.org/10.1093/jtm/taw018.
13. Bogovic P, Strle F. Tick-borne encephalitis: a review of epidemiology, clinical characteristics, and management. World J Clin Cases. 2015;3:430–41.
14. Halperin JJ. Neuroborreliosis. J Neurol. 2017;264:1292–7.
15. Chamizo FJ, Gilarranz R, Hernandez M, Ramos D, Pena MJ. Central nervous system infections caused by varicella-zoster virus. J Neurovirol. 2016;22:529–32.
16. Hong HL, Lee EM, Sung H, Kang JK, Lee SA, Choi SH. Clinical features, outcomes, and cerebrospinal fluid findings in adult patients with central nervous system (CNS) infections caused by varicella-zoster virus: comparison with enterovirus CNS infections. J Med Virol. 2014;86:2049–54.
17. Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. JAMA. 2013;310:308–15.
18. Kammer J, Ziesing S, Davila LA, Bultmann E, Illsinger S, Das AM, Haffner D, Hartmann H. Neurological manifestations of *Mycoplasma pneumonia*e infection in hospitalized children and their long-term follow-up. Neuropediatrics. 2016;47:308–17.
19. Jubelt B, Mihair C, Li TM, Verrapaneni P. Rhomboencephalitis/brainstem encephalitis. Curr Neurol Neurosci Rep. 2011;11:543–52.
20. Mazur-Melewska K, Brenska I, Jonczyk-Potoczna K, Kemnitz P, Pieczonka-Ruszkowska I, Mania A, Sluzewski W, Figlerowicz M. Neurologic complications caused by Epstein-Barr virus in pediatric patients. J Child Neurol. 2016;31:7010–8.
21. Modi S, Mahajan A, Dharaiya D, Varelas P, Mitsias P. Burden of herpes simplex virus encephalitis in the United States. J Neurol. 2017;264:1204–8.
22. Jones SC, Morris J, Hill G, Alderman M, St RRC. Lousi encephalitis outbreak in Louisiana in 2001. J La State Med Soc. 2002;154:303–6.
23. McJunkin JE, Khan RR, Tsai TF. California-La Crosse encephalitis. Infect Dis Clin N Am. 1998;12:83–93.
24. Yis U, Kurul SH, Cakmakci H, Dirik E. *Mycoplasma pneumoniae:* nervous system complications in childhood and review of the literature. Eur J Pediatr. 2008;167:973–8.
25. Pinninti SG, Kimberlin DW. Maternal and neonatal herpes simplex virus infections. Am J Perinatol. 2013;30:113–9.
26. Lin TY, Kao HT, Hsieh SH, Huang YC, Chiu CH, Chou YH, Yang PH, Lin RI, Tsao KC, Hsu KH, Chang LY. Neonatal enterovirus infections: emphasis on risk factors of severe and fatal infections. Pediatr Infect Dis J. 2003;22:889–94.
27. Davis J, Fairley D, Christie S, Coyle P, Tubman R, Shields MD. Human parechovirus infection in neonatal intensive care. Pediatr Infect Dis J. 2015;34:121–4.
28. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan SL, Scheld WM, Whitley RJ. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47:303–27.
29. Britton PN, Eastwood K, Paterson B, Durrheim DN, Dale RC, Cheng AC, Kenedi C, Brew BJ, Burrow J, Nagree Y, Leman P, Smith DW, Read K, Booy R, Jones CA. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Intern Med J. 2015;45:563–76.
30. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PGE. Viral meningoencephalitis: a review of diagnostics methods and guidelines for management. Eur J Neurol. 2010;17:999–e57.
31. Sili U, Kaya A, Mert A, HSV Encephalitis Study Group. Herpes simplex virus encephalitis: clinical manifestations, diagnosis, and outcome in 106 adult patients. J Clin Virol. 2014;60:112–8.
32. Granerod J, Ambrose HE, Davies NWS, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, Ward KN, Lunn MPT, Irani SR, Vincent A, Brown DWG, Crowcroft NS. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10:835–44.
33. Kupila L, Vuorinen T, Vainionpaa R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology. 2006;66:75–80.
34. Singh TD, Fugate JE, Rabinstein AA. The spectrum of acute encephalitis. Neurology. 2015;84:359–66.
35. Glaser CA, Gilliam S, Schnurr D, Forghani B, Honarmand S, Khetsuriani N, Fischer M, Cossen CK, Anderson LJ. In search of encephalitis etiologies: diagnostic challenges in the California encephalitis project: 1998-2000. Clin Infect Dis. 2003;36:731–42.
36. Ascencao BB, Goncalves AC, Luis N, Sa J, Brito AP, Pocas JM. Epstein-Barr virus hemorrhagic meningoencephalitis: case report and review of the literature. J Neurovirol. 2016;22:695–8.
37. Morton NJ, Britton P, Palasanthiran P, Bye A, Sugo E, Kesson A, Ardern-Holmes S, Snelling TL. Severe hemorrhagic meningoencephalitis due to *Angiostrongylus cantonensis* among young children in Sydney, Australia. Clin Infect Dis. 2013;57:1158–61.
38. Martinez AJ, Visvesvara GS. Free-living amphizoic and opportunistic amebas. Brain Pathol. 1997;7:583–98.
39. Gavin PJ, Kazacos KR, Shulman ST. Baylisascariasis. Clin Microbiol Rev. 2005;18:703–18.
40. DeBiasi RL, Tyler KL. Molecular methods for diagnosis of viral encephalitis. Clin Microbiol Rev. 2004;17:903–25.
41. Steiner I, Schmutzhard E, Sellner J, Chaudhuri A, Kennedy PGE. EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system. Eur J Neurol. 2012;19:1278–97.
42. Huang C, Morse D, Slater B, Anand M, Tobin E, Smith P, Dupuis M, Hull R, Ferrera R, Rosen B, Grady L. Multiple-year experience in the diagnosis of viral central nervous system infections with a panel of polymerase chain reaction assays for detection of 11 viruses. Clin Infect Dis. 2004;39:630–5.
43. Studahl M, Bergstrom T, Hagberg L. Acute viral encephalitis in adults – a prospective study. Scand J Infect Dis. 1998;30:215–20.
44. Deresiewicz RL, Thaler SJ, Hsu L, Zamani AA. Clinical and neuroradiographic manifestations of eastern equine encephalitis. N Engl J Med. 1997;336:1867–74.
45. Riancho J, Delgado-Alvarado M, Sedano MJ, Polo JM, Berciano J. Herpes simplex encephalitis: clinical presentation, neurological sequelae, and new prognostics factors. Ten years of experience. Neurol Sci. 2013;34:1879–81.
46. Kaewpoowat Q, Salazar L, Aguilera E, Wootton SH, Hasbun R. Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments, and outcomes. Infection. 2016;44:337–45.
47. George BP, Schneider EB, Venkatesan A. Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010. PLoS One. 2014;9:e104169.
48. De Ory F, Avellon A, Echevarria JE, Sanchez-Seco MP, Trallero G, Cabrerizo M, Casas I, Pozo F, Fedele G, Vicente D, et al. Viral infections of the central nervous system in Spain: a prospective study. J Med Virol. 2013;85:554–62.
49. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev. 2004;17:1–13.
50. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. Neurotherapeutics. 2016;13:493–508.
51. Cinque P, Cleator GM, Weber T, Monteyne P, Sindic CJ, van Loon AM. The role of laboratory investigation in the diagnosis and management of patients with suspected herpes simplex encephalitis: a consensus report. J Neurol Neurosurg Psychiatry. 1996;61:339–45.

52. Guffond T, Dewilde A, Lobert PE, Caparros-Lefebvre D, Hober D, Wattre P. Significance and clinical relevance of the detection of herpes simplex virus DNA by the polymerase chain reaction in cerebrospinal fluid from patients with presumed encephalitis. Clin Infect Dis. 1994;18:744–9.
53. Weil AA, Glaster CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. Clin Infect Dis. 2002;34:1154–7.
54. Kimberlin DW, Whitley RJ, Wan W, Powell DA, Storch G, Ahmed A, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med. 2011;365:1284–92.
55. Gnann JW, Skolenberg B, Hart J, Aurelius E, Schliamser S, Studahl M, Eriksson BM, Hanley D, et al. Herpes simplex encephalitis: lack of clinical benefit of long-term valacylovir therapy. Clin Infect Dis. 2015;61:683–91.
56. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, Grose C, Hambleton S, Kennedy PG, Oxman MN, Seward JF, Yamanishi K. Varicella zoster virus infection. Nat Rev Dis Primers. 2015;1:15016.
57. De Broucker T, Mailles A, Chabrier S, Morand P, Stahl JP. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. Clin Microbiol Infect. 2012;18:808–19.
58. Becerra JC, Sieber R, Martinetti G, Costa ST, Meylan P, Bernasconi E. Infection of the central nervous system caused by varicella zoster reactivation: a retrospective case series study. Int J Infect Dis. 2013;17:e529–34.
59. Wilson DA, Yen-Lieberman B, Schindler S, Asamoto K, Schold JD, Procop GW. Should varicella-zoster virus culture eliminated? A comparison of direct immunofluorescence antigen detection, culture, and PCR, with a historical review. J Clin Microbiol. 2012;50:4120–2.
60. Studahl M, Lindquist L, Eriksson BM, Gunther G, Bengner M, Franzen-Rohl E, Fohlman J, Bergstrom T, Aurelius E. Acute viral infections of the central nervous system in immunocompetent adults: diagnosis and management. Drugs. 2013;73:131–58.
61. Bathoorn E, Vlaminckx BJ, Schoondermark-Stolk S, Donders R, van der Meulen M, Thijsen SF. Primary Epstein-Barr virus infection with neurological complications. Scand J Infect Dis. 2011;43:136–44.
62. Belo F, Mendes I, Calha M, Mendonca C. Cytomegalovirus encephalitis in an immunocompetent child: a sceptic diagnosis. BMJ Case Rep. 2012; https://doi.org/10.1136/bcr-2012-006796.
63. Sadighi Z, Sabin ND, Hayden R, Stewart E, Pillai A. Diagnostic clues to human herpesvirus 6 encephalitis and Wernickie encephalopathy after pediatric hematopoietic cell transplantation. J Child Neurol. 2015;30:1307–14.
64. Yamamoto S, Takahashi S, Tanaka R, Okayama A, Araki A, Katano H, Tanaka-Taya K, Azuma H. Human herpesvirus-6 infection-associated acute encephalopathy without skin rash. Brain and Development. 2015;37:829–32.
65. Shahani L. HHV-6 encephalitis presenting as status epilepticus in an immunocompetent patient. BMJ Case Rep. 2014; https://doi.org/10.1136//bcr-20140295880.
66. Noguchi T, Yoshiura T, Hiwatashi A, Togao O, Yamashita K, Nagao E, Uchino A, Hasuo K, Atsumi K, Matsuura T, Kurolwa T, Mihara F, Honda H, Kudo S. CT and MRI findings of human herpesvirus 6-associated encephalopathy: comparison with findings of herpes simplex virus encephalitis. AJR Am J Roentoenol. 2010;194:754–60.
67. Provenzale JM, van Landingham K, White LE. Clinical and imaging findings suggesting human herpesvirus 6 encephalitis. Pediatr Neurol. 2010;42:32–9.
68. Guo Y, Wang S, Jiang B, Li J, Liu L, wang J, Zhao W, Jia J. Encephalitis with reversible splenial and deep cerebral white matter lesions associated with Epstein-Barr virus infection in adults. Neuropsychiatr Dis Treat. 2017;13:2085–92.
69. Zhang S, Feng J, Shi Y. Transient widespread cortical and splenial lesions in acute encephalitis/encephalopathy associated with primary Epstein-Barr virus infection. Int J Infect Dis. 2016;42:7–10.
70. Renard T, Daumas-Duport B, Auffray-Calvier E, Bourcier R, Desai H. Cytomegalovirus encephalitis: undescribed diffusion-weighted imaging characteristics. Original aspects of cases extracted from a retrospective study and from literature review. J Neuroradiol. 2016;43:371–7.
71. Maschke M, Kastrup O, Diener HC. CNS manifestations of cytomegalovirus infections: diagnosis and treatment. CNS Drugs. 2002;16:303–15.
72. Johnston WF, Yeh J, Nierenberg R, Procopio G. Exposure to macaque monkey bite. J Emerg Med. 2015;49:634–7.
73. De Crom SCM, Rossen JWA, van Furth AM, Obihara CC. Enterovirus and parechovirus infection in children: a brief overview. Eur J Pediatr. 2016;175:1023–9.
74. Dunn JJ. Enterovirus and parechovirus. Microbiol Spectr. 2016;4 https://doi.org/10.1128/microbiolspec.DMIH2-00006-2015.
75. Jain S, Patel B, Bhatt GC. Enteroviral encephalitis in children: clinical features, pathophysiology, and treatment advances. Pathog Glob Health. 2014;108:216–22.
76. Renaud C, Harrison CJ. Human parechovirus 3: the most common viral cause of meningoencephalitis in young infants. Infect Dis Clin N Am. 2015;29:415–28.
77. Shen WC, Chiu HH, Chow KC, Tsai CH. MR imaging findings of enteroviral encephalomyelitis: an outbreak in Taiwan. AJNR Am J Neuroradiol. 1999;20:1889–95.
78. Suthar MS. West Nile virus infection and immunity. Nat Rev Microbiol. 2013;11:115–28.
79. Montgomery RR, Murray KO. Risk factors for West Nile infection and disease in populations and individuals. Expert Rev Anti-Infect Ther. 2015;13:317–25.
80. Yeung MW, Shing E, Nelder M, Sander B. Epidemiologic and clinical parameters of West Nile virus infections in humans: a scoping review. BMC Infect Dis. 2017;17:609.
81. Nett RJ, Kuehnert MJ, Ison MG, Orlowski JP, Fischer M, Staples JE. Current practices and evaluation of screening solid organ donors for West Nile virus. Transpl Infect Dis. 2012;14:268–77.
82. Mezochow AK, Henry R, Blumberg EA, Kotton CN. Transfusion transmitted infections in solid organ transplantation. Am J Transplant. 2015;15:547–54.
83. Seivar JJ, Haddad MB, Tierney BC, Campbell GL, Marfin AA, Van Gerpen JA, Fleischauer A, Leis AA, Stokic DS, Petersen LR. Neurologic manifestations and outcome of West Nile virus infection. JAMA. 2003;290:511–5.
84. Davis LE, Beckham JD, Tyler KL. North American encephalitic arboviruses. Neurol Clin. 2008;26:727.
85. Gaensbauer JT, Lindsey NP, Messacar K, Staples JE, Fischer M. Neuroinvasive arboviral disease in the United States: 2003 to 2012. Pediatrics. 2014;134:e642.
86. Marfin AA, Bleed DM, Lofgren JP, Olin AC, Savage HM, Smith GC, Moore PS, Karabatsos N, Tsai TF. Epidemiologic aspects of a St. Louis encephalitis epidemic in Jefferson County Arkansas, 1991. Am J Trop Med Hyg. 1993;49:30–7.
87. Calisher CH. Medically important arboviruses of the United States and Canada. Clin Microbiol Rev. 1994;7:89–116.
88. Rahal JJ, Anderson J, Rosenberg C, Reagan T, Thompson LL. Effect of interferon-alpha2b therapy on St. Louis viral meningoencephalitis: clinical and laboratory results of a pilot study. J Infect Dis. 2004;190:1084–7.
89. McJunkin JE, de los Reyes EC, Irazuzta JE, Caceres MJ, Khan RR, Minnich LL, Fu KD, Lovett GD, Tsai T, Thompson A. La Crosse encephalitis in children. N Engl J Med. 2001;344:801–7.
90. Miller A, Carchman R, Long R, Denslow SA. La Crosse viral infection in hospitalized pediatric patients in Western North Carolina. Hosp Pediatr. 2012;2:235–42.

91. Yousaf MZ, Qasim M, Zia S, Khan MR, Ashfaq UA, Khan S. Rabies molecular virology, diagnosis, prevention and treatment. Virol J. 2012;9:50.
92. Maier T, Schwarting A, Mauer D, Ros RS, Martens A, Kliem V, Wahl J, Panning M, Baumgarte S, Muller T, Pfefferle S, Ebel H, Schmidt J, Tenner-Racz K, Racz P, et al. Management and outcomes after multiple corneal and solid organ transplantations from a donor infected with rabies virus. Clin Infect Dis. 2010;50:1112.
93. Dimaano EM, Scholand SJ, Alera MP, Belandres DB. Clinical and epidemiological features of human rabies cases in the Philippines: a review from 1987 to 2006. Int J Infect Dis. 2011;15:e495–9.
94. Christie LJ, Honarmand S, Talkington DF, Gavali SS, Preas C, Pan CY, Yagi S, Glaser CA. Pediatric encephalitis: what is the role of *Mycoplasma pneumoniae*? Pediatrics. 2007;120:305–13.
95. Cope JR, Ali IK. Primary amebic meningoencephalitis: what have we learned in the last five years? Curr Infect Dis Rep. 2016;18:31.
96. Krol-Turminska K, Olender A. Human infections caused by free-living amoebae. Ann Agric Environ Med. 2017;24:254–60.
97. Gnann JW, Whitley RJ. Herpes simplex encephalitis: an update. Curr Infect Dis Rep. 2017;19:13.