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CHAPTER

88

Life-Threatening Viral Disease and Its Treatment

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PEARLS

- Obtain serum to store for future serological testing when viral pathogens are considered as the potential cause of a critical illness.
- Diagnostic sensitivity is generally enhanced when samples for viral culture and staining are sent as early as possible in the course of illness.
- Samples that are obtained for fluorescent antibody, whether for a herpes virus or a respiratory pathogen, should contain adequate cells.
- Initiate empiric treatment with acyclovir rapidly when herpes simplex virus encephalitis or neonatal disease is suspected.
- Initiate appropriate infection control precautions early to prevent spread of infection to staff and other patients when viral pathogens are suspected.

Viral infections are a frequent cause of disease in individuals of all ages. In general, the spectrum of illness is varied; however, young children and those with suppressed or deficient immune systems are at higher risk of having severe disease. This chapter covers viral causes of entities commonly seen in the intensive care unit: myocarditis, hepatitis, pneumonitis, and meningitis/encephalitis. The content is focused on cause, diagnosis, and treatment, in an attempt to provide the reader with guidance on the initial management of patients with serious viral diseases in terms of diagnosis and specific antiviral therapy.

Myocarditis

Background

Although many infectious and noninfectious causes have been identified, viruses account for most cases of myocarditis.[1] The spectrum of disease ranges from asymptomatic, with only minimal changes on the electrocardiogram (ECG), to fulminant, with rapid onset of severe disease. Most patients have an indolent illness, which may progress to dilated cardiomyopathy. Because of the varied presentations and the difficulty in the establishment of a definitive diagnosis, the true incidence of myocarditis is unknown. In a large series from Sweden, 1% of myocardial biopsies from autopsies conducted over a 10-year period fulfilled the Dallas criteria for myocarditis.[2]

Pathogenesis

Although the pathogenesis of viral myocarditis is not well understood, myocardial damage is thought to occur at least in part as a direct result of viral infection, with active viral replication leading to myocardial necrosis.[3] Coxsackie virus protease 2A cleaves dystrophin in cultured myocytes and in infected mouse hearts. The results are impaired dystrophin function and poor myocyte contractility.[4] In addition, both humoral and cellular immune responses contribute to the pathogenesis of myocarditis,[5,6] through postinfectious autoimmune processes,[6] cytotoxic T lymphocytes, and

antibody-dependent cell-mediated cytotoxicity.[7] Cytokines may also cause direct myocardial injury and affect cardiac function.

Cause

The viruses most frequently associated with myocarditis are enteroviruses, particularly Coxsackie virus B, and adenoviruses (serotypes 2 and 5). Many other viruses have caused myocarditis in children, including influenza A, herpes simplex virus (HSV); human immunodeficiency virus (HIV); cytomegalovirus (CMV); respiratory syncytial virus (RSV); and the mumps and measles viruses, before the widespread use of the measles-mumps-rubella (MMR) vaccine (Table 88–1). Polymerase chain reaction (PCR) of cardiac tissue from endomyocardial biopsy specimens in 34 children with a clinical diagnosis of myocarditis identified adenovirus in 44%, enterovirus in 24%, and HSV in 6%.[8] In addition to enteroviruses, adenovirus and CMV are increasingly recognized as important causes of myocarditis in adolescents and adults. Adenoviruses and enteroviruses are the viruses most frequently identified in patients with dilated cardiomyopathy.

Clinical Presentation

Infants with myocarditis usually have symptoms that include poor feeding, fever, irritability, and listlessness. Physical findings are consistent with congestive heart failure. Enteroviral myocarditis in infancy frequently occurs in conjunction with severe hepatitis, pneumonitis, or both and can be difficult to distinguish from bacterial sepsis.[9] The death rate may be as high as 75%. Severe dysrhythmias have been described in infants with myocardial involvement from RSV,[10] and viral myocarditis has been implicated in some cases of sudden infant death.[11]

Older children and adolescents are more likely to appear for examination after a prodromal viral illness. Early symptoms include lethargy, low-grade temperature, and decreased appetite. They may have diaphoresis, dyspnea on exertion, malaise, and palpitations. Chest pain was a frequent symptom in series of adult patients.[12] Resting tachycardia disproportionate to the amount of fever is common, and an apical systolic murmur may be heard. A subset of children and adults have fulminant myocarditis, characterized by rapid onset of symptoms, severe hemodynamic compromise, and fever.[13]

Laboratory abnormalities may include elevated white blood cell count and erythrocyte sedimentation rate.[14] Serum aspartate aminotransferase levels are often elevated,[15] as are creatinine kinase—MB levels. Cardiac troponin I (cTnI) may be a more sensitive measure of cardiac muscle injury in myocarditis.[16]

Electrocardiographic abnormalities are almost always present in acute myocarditis, with findings of low-voltage QRS complexes and nonspecific ST and T wave changes. Both atrial and ventricular arrhythmias may be present, including supraventricular and ventricular tachycardia, as well as conduction abnormalities. Echocardiography reveals left ventricular dysfunction either with segmental wall motion abnormalities or global hypokinesis in most cases. Pericardial effusions are common. In one series, nondilated, thickened, and hypocontractile left ventricles (LVs) were seen in subjects with fulminant myocarditis compared with significant LV dilatation and normal LV thickness in subjects with a more insidious onset. The subjects with fulminant myocarditis had more evidence of inflammation on endomyocardial biopsy and were more likely to recover ventricular function.[17] Pulmonary edema, enlarged cardiac silhouette, and prominent pulmonary vasculature may be seen on a chest radiograph.

Fulminant Hepatitis

Background:

Fulminant hepatic failure (FHF) is a rare condition, which, before the availability of orthotopic liver transplant, carried a death rate of more than 80%. FHF is defined as the rapid development of jaundice and hepatic encephalopathy in a person without a history of liver disease. Because there is a relationship between the time course of symptoms and prognosis, a classification scheme has been suggested (hyperacute, acute, and subacute liver failure) with an interval of 1 week, 1 to 4 weeks, and 5 to 12 weeks between the appearance of jaundice and encephalopathy.[18] There is significant overlap between causes and prognoses of the different classes. Approximately 30% to 50% of cases of hepatic failure are caused by viral infections.

Cause

Although less than 1% of infections with these viruses results in FHF, the hepatotropic viruses, hepatitis A and B, cause most cases of FHF with a definitive viral diagnosis. Studies in adults with FHF have found hepatitis A to be the cause in 4% to 10% and hepatitis B in 10% to 45% of the reported cases.[19] A greater percentage of cases of FHF in children may be due to hepatitis A.[20] Many other viruses have been implicated in fulminant hepatitis including hepatitis C, D, E, and G, as well as HSV. Infants with perinatally acquired hepatitis B and C rarely have symptoms, and fulminant hepatitis in infants is more likely to be associated with systemic illness due to enteroviruses, HSV, human herpesvirus 6 (HHV-6), or CMV.[21] Infants born to women with both HBsAg (hepatitis B surface antigen) and anti-HBeAb (hepatitis B e-antibody) appear to be at greater risk for fulminant hepatitis due to perinatally acquired hepatitis B.[22]

Infection with hepatitis C rarely causes FHF; however, there are case reports of fulminant hepatitis both with postnatally and perinatally acquired hepatitis C in children.[23,24] The prevalence of hepatitis C virus (HCV) infection as a cause of FHF appears to have geographic variability. Most studies from the United States and Europe have failed to show the presence of HCV-RNA in patients with non-A, non-B FHF[25]; however, in several Japanese series, HCV-RNA has been shown in a significant number of patients with non-A, non-B FHF.[26] Coinfection with hepatitis B virus (HBV) and HCV has been associated with a worse prognosis.[19] HSV should be considered as a cause of FHF, particularly in patients with minimally elevated bilirubin levels. Risk factors for HSV hepatitis include pregnancy

TABLE 88–1

Viral Causes of Myocarditis, Fulminant Hepatitis, Pneumonia, Meningitis, Encephalitis, and Myelitis

	Myocarditis	Hepatitis	Pneumonia	Meningitis	Encephalitis	Myelitis
Adenovirus	XXX	X	XX	X	X	X
Arboviruses (arthropod-borne viruses):				XX	XX	
• Western equine encephalitis virus				X	X	
• Eastern equine encephalitis virus					X	
• St Louis encephalitis virus				X	X	
• California encephalitis virus (La Crosse)				X	X	
• Colorado tick fever				X	X	
• West Nile encephalitis virus					X	
Enteroviruses	XXX	X	X	XXX	XX	XX
Hantavirus			X			
Hepatitis A		XXX				X
Hepatitis B		XXX				
Hepatitis C		X				
Hepatitis D		X				
Hepatitis E		X				
Hepatitis G		X				
Herpesviruses:						
• HSV 1 and 2	X	X		XX	XX	X
• VZV			XX*	X	X	X
• EBV				X	X	XX
• CMV	X	X	XXX*		X	XX
• HHV-6		X			X	
HIV	X				X	
HTLV					X	
Influenza A	X		XXX		X	X
Influenza B			X			
JC virus					X*	
Lymphocytic choriomeningitis virus				X	X	X
Mumps	X			X	X	X
Measles	X			X	X	X
Parainfluenza virus types 1, 2, 3			XXX			
Rabies					X	
Respiratory syncytial virus	X		XXX			
Rhinovirus			X			
Rubella					X	X

*Primarily in immunocompromised hosts.
XXX = most frequent, XX = frequent, and X = less common or rare.
CMV, cytomegalovirus; *EBV,* Epstein-Barr virus; *HHV-6,* human herpes virus 6; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *HTLV,* human T-lymphotropic virus; *VZV,* varicella-zoster virus.

and immune suppression.[27] Hepatitis E virus (HEV) is an enterically transmitted virus that causes epidemic hepatitis in many areas of the world, particularly the Indian subcontinent and Southeast Asia. It is not endemic in Western countries.

Clinical Presentation

Symptoms of acute hepatitis include jaundice, anorexia, fatigue, nausea, and vomiting.[28] In fulminant disease there is rapid progression to hepatic failure and encephalopathy. Physical examination may reveal fever, hepatosplenomegaly

with liver tenderness, scleral or cutaneous icterus, and mucosal bleeding. Patients with severe vomiting may have significant dehydration. Laboratory studies include elevated hepatic enzymes (tenfold to 100-fold increases in serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), hyperbilirubinemia, prolonged prothrombin time, and elevated ammonia levels. As hepatocyte necrosis progresses, hepatic enzyme levels and liver size may decrease. Cerebral edema is common in patients with severe encephalopathy, and renal failure occurs in more than 50% of patients with FHF.[28]

Viral Pneumonia/Pneumonitis

Background

Influenza and pneumonia combined are a leading cause of death of children in developing countries and the seventh leading cause of death in the United States for patients of all ages. A greater burden of disease is present in infants, young children, and older individuals.[29] Although only 10% of pneumonias in adults are attributed to viral pathogens, viral pathogens account for most of the 200,000 pneumonia hospitalizations each year for children younger than 15 years. Peak seasons are from midwinter to early spring.

Cause

The etiological agents of viral pneumonia are varied (Table 88–1) and are identified in approximately 50% of cases. RSV is responsible for most severe viral respiratory illness, accounting for approximately 90,000 to 100,000 hospitalizations and 4500 deaths each year in both infants and young children.[30] Usually primary RSV infection is more symptomatic than repeat infection, involving the lower respiratory tract approximately 90% of the time. Repeat infections are common, and in the healthy host, they are localized in the upper respiratory tract. Infection of infants may be more severe when coinfected with a newly discovered virus, human metapneumovirus.[31]

Influenza epidemics occur annually with significant morbidity and death in young children and older individuals. Infected infants younger than 2 months may have symptoms mimicking bacterial sepsis, commonly including apnea. In children younger than 5 years, influenza can cause symptoms of laryngotracheobronchitis, whereas pneumonia occurs in 10% to 15% of those younger than 3 years. Finally, older children generally have the classic flulike symptoms of fever, headache, myalgia, and malaise with upper respiratory tract symptoms. Bacterial superinfection is a common and potentially severe complication of influenza.

Parainfluenza 1, 2, and 3 are the most common agents of acute laryngotracheitis in children aged 6 months to 3 years and are also a common cause of upper respiratory tract infection. In infants and immunocompromised hosts, however, parainfluenza can cause bronchiolitis and pneumonia. In immunocompromised hosts, parainfluenza pneumonia (proven lower tract disease) has a death rate of 30% to 35%.[32,33] Unlike RSV lower tract disease, in which RSV is usually the single pathogen, copathogens are identified with parainfluenza pneumonia more than 50% of the time,[34] and treatment for parainfluenza pneumonia should include coverage for copathogens. Additional information about RSV, parainfluenza, influenza, measles, and adenovirus is available in Chapter 42.

Although CMV usually causes relatively benign disease in immunocompetent hosts, it is frequently severe and often fatal in immunocompromised hosts. The large DNA virus infects epithelial cells and leukocytes. Cellular damage is caused directly by the viral lytic infection or indirectly by the immune response of the host. Risk factors for CMV disease include seropositivity of donor, allogeneic transplant, human leukocyte antigen (HLA) mismatch, age older than 10 years, and development of graft-versus-host disease. CMV occurs at a median time of 40 to 50 days after transplant and is rare before engraftment. The pneumonitis is severe with diffuse interstitial infiltrates. Death rates from CMV pneumonitis are greater than 50%, even when ganciclovir and CMV immunoglobulin are administered.[35]

Hantaviruses are known for causing hemorrhagic fevers and acute severe respiratory infection in young adults. Hantaviruses can spread from mammal to mammal, including humans, by exposure to aerosolized feces, infected urine, or other secretions. In the United States, the Sin Nombre virus, which causes the pulmonary syndrome, is found in 10% to 80% of deer mice in rural areas of North America. Hantaviruses cause disease by creating leakage of plasma and erythrocytes through the vascular endothelium in the lung (hantavirus pulmonary syndrome [HPS]) or the kidneys (hemorrhagic fever syndrome). The differential diagnosis includes influenza A, *Legionella, Chlamydia pneumoniae,* and *Pneumocystis carinii.* Despite current therapy, HPS is fatal in 40% to 70% of clinical cases.[36,37] Hantavirus pulmonary syndrome is also discussed in Chapter 89.

Severe acute respiratory syndrome (SARS) results in a life-threatening, atypical pneumonia caused by a novel coronavirus, now named the SARS virus.[38-40] The virus, thought to be derived from animal reservoirs, potentially palm civets, or raccoon dogs,[41] crossed into humans in the Guangdong Province in China in fall 2002. SARS is spread by close contact with infected humans, mostly to household contacts and health care workers. The incubation period is 2 to 7 days. The case definition of SARS is continuously evolving (see www.cdc.gov/SARS for update) but should be suspected in individuals who meet the clinical criteria for moderate or severe respiratory illness of unknown cause and epidemiologic criteria for exposure. *Moderate respiratory illness* is defined as a temperature greater than 100.4° F (>38 °C) and one or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), and *severe respiratory illness* is defined as moderate respiratory illness plus radiographic evidence of pneumonia, or respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome. Epidemiologic criteria include travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or previously documented or suspected community

transmission of SARS or close contact within 10 days of onset of symptoms with a person known or suspected to have SARS. Death from progressive respiratory failure occurs in approximately 3% to 10% of adult patients; in children, morbidity is less and death rarely occurs.[42,43]

Clinical Presentation

The clinical presentation of viral pneumonia/pneumonitis usually consists of fever; increased respiratory rate; cough; and increased work of breathing with grunting, flaring, retracting, and use of accessory muscles in infants and young children. Decreased oral intake with increased insensible loss due to the increased respiratory rate is often present and may lead to dehydration. Some patients have centrally mediated apnea, and other patients have an overwhelming sepsislike syndrome with increased peripheral pulses, decreased central blood pressure, and lethargy. A history or examination findings of certain symptoms, including rhinorrhea, conjunctivitis, otitis media, and previous exposure to an ill child or adult, should immediately raise suspicion of a viral cause. Radiographic findings generally include evidence of hyperinflation and peribronchial cuffing, and a focal or diffuse infiltrate may or may not be present.

Clinical features of HPS, a noncardiogenic pulmonary edema, include a prodrome of fever, headache, and myalgia usually with nausea and diarrhea for 4 to 5 days before the onset of cough and dyspnea. Tachycardia and tachypnea with hypotension then develop and rapidly progress to acute respiratory distress syndrome (ARDS). Laboratory findings include leukocytosis, abnormal or increased lymphocytes, thrombocytopenia, and prolonged partial thromboplastin time (PTT) in severe cases. Rapidly evolving diffuse, bilateral, interstitial infiltrates are seen on chest radiograph.

SARS in adolescents and adults has a similar presentation to HPS with initial infection characterized by fever (99% of patients), chills or rigor (78%), and development of a dry, nonproductive cough (60%) and dyspnea (30%) a few days later. Other associated symptoms include malaise, headache, dizziness chest pain, sore throat, vomiting, and diarrhea. Oxygen saturation is less than 95% in only 10% of patients at presentation, with severe hypoxemia developing as the disease progresses.[38,44-47] Children are more frequently seen with cough and rhinorrhea rather than chills and rigor.[42] Laboratory findings in children include lymphopenia (68%) rather than lymphocytosis, thrombocytopenia (33% to 44%), anemia (78%), and leukopenia (26%). Elevations in lactate dehydrogenase creatine kinase and ALT may also be seen. Early in the disease, chest radiographs are often normal or have a peripheral/pleural-based opacity as the only abnormality.

Central Nervous System Infections

Background

Aseptic meningitis, encephalitis, and myelitis are inflammatory conditions of the central nervous system (CNS) (meninges, brain, and spinal cord, respectively). Disease is caused by a variety of infectious pathogens, but viruses cause most disease. Viruses gain entry to the CNS via the bloodstream (enteroviruses and arboviruses) or by direct neuronal spread (HSV and rabies). Pathogenesis may involve direct viral invasion or a vigorous virus-specific immune response resulting in damage to the neurons and supporting cells. Alternatively, infection may trigger activation of an immune response specific for the oligodendroglia or the myelin components themselves. In the latter case, disease may follow an upper respiratory tract or other infection and primarily take the form of a demyelinating process. This disease is commonly termed *postinfectious encephalomyelitis* or *acute disseminated encephalomyelitis*.

Individuals of all ages are at risk for CNS viral infections. Neonates, older individuals, and those with immune deficiencies are prone to more frequent and more serious CNS viral infections, though.

Cause

The potential viral causes are multiple; however, enteroviruses, herpesviruses, and arboviruses are responsible for most disease (Table 88–1). Enteroviruses account for up to 99% of cases of aseptic meningitis when a cause is identified.[48] Enterovirus meningitis in older children and adults is typically self-limited and associated with few complications. In contrast, enteroviral infections in neonates may mimic bacterial sepsis, and CNS involvement is often manifested as encephalitis.

HSV is a common cause of CNS infection in individuals of all ages. During the neonatal period, type 2, and to a lesser extent type 1 causes encephalitis because of the vertical transmission of the virus.[49] In contrast, in older children and adults, most HSV encephalitis is caused by type 1. HSV 2, however, can cause benign aseptic meningitis in association with primary and recurrent genital infections.[50] Other members of the herpesvirus family (CMV, Epstein-Barr virus [EBV], varicella-zoster virus [VZV], and HHV-6) can also cause aseptic meningitis and encephalitis, though they are less common. CMV encephalitis occurs mostly in immunosuppressed individuals but may occasionally appear in otherwise healthy individuals.[51,52] EBV aseptic meningitis and encephalitis presents with or without the classic findings of infectious mononucleosis.[53] Acute cerebellar ataxia is a common and usually benign complication of chickenpox. VZV encephalitis can sometimes occur in immunocompetent individuals,[54,55] but more frequently occurs in immunocompromised individuals following days, weeks, or months after varicella or zoster. Zoster encephalitis can be complicated by small or large vessel vasculitis (granulomatous arteritis), which carries the potentially serious consequences of infarction.[54,56] HHV-6 has only rarely been reported to cause encephalitis in healthy children during primary infection,[57] whereas it appears to be a more common problem for immunosuppressed patients, such as those receiving stem cell transplants.[58,126]

Arboviruses (arthropod-spread viruses) are important causes of aseptic meningitis and encephalitis. The specific arbovirus determines the epidemiology, morbidity, and risk of death of associated disease. The La Crosse and St. Louis encephalitis viruses account for most arboviral CNS infections in the United States. The La Crosse virus is found

mainly in the Midwest, typically occurs in the summer and early fall, and is associated with a relatively low death rate. The St. Louis encephalitis virus occurs in every state but is more common in the Midwest, Florida, and Texas and has been responsible for large urban outbreaks.[59,60] Eastern equine virus occurs less frequently, mainly in the Northeast and Southeast, but carries a high rate of morbidity (70% to 80%) and death (20% to 80%).[61,62] West Nile virus encephalitis first appeared in the United States in the summer of 1999 in New York State.[63] Over the following summers, the West Nile virus moved southward and westward across the United States, infecting both animals and humans. Most individuals infected with the West Nile virus are symptom free or experience flulike illness; however, older individuals and those with underlying immune deficiency can experience encephalitis that may result in death. In addition to the more typical presentation of encephalitis, an acute flaccid paralysis has also been associated with West Nile virus infection.[64]

A number of viruses are infrequent causes of encephalitis, including mumps, influenza, and lymphocytic choriomeningitis viruses (LCMVs). Historically, mumps virus accounted for a large proportion of aseptic meningitis and encephalitis cases in the United States.[65] Currently, because of the widespread use of the trivalent MMR vaccine, meningitis and encephalitis due to mumps are extremely rare.[66] Influenza has been associated with encephalitis/encephalopathy, especially in Japan. In a national survey representing the 1998-1999 season, 142 cases, most occurring in children younger than 5 years, are reported.[67] LCMV is an infrequently recognized cause of meningoencephalitis. This virus is found in the urine, droppings, and saliva of infected mice, guinea pigs, and hamsters, and disease in humans arises after exposure to these substances.

Postinfectious encephalomyelitis refers to an acute self-limited demyelinating process most commonly following viral respiratory infections and varicella. In contrast, subacute sclerosing panencephalitis (SSPE) and progressive multifocal leukoencephalopathy (PML) are two chronic, usually fatal, demyelinating diseases due to measles and JC virus, respectively. SSPE most commonly follows 5 to 10 years after natural measles infection. SSPE is extremely rare in the United States; however, it may occur as often as one case per a population of 10,000 in areas of the world where MMR vaccine is not widely used.[68] PML is also rare, usually affecting those with acquired immune deficiency syndrome (AIDS) or, rarely, those with other serious immunodeficiencies.

Transverse myelitis has been most frequently associated with enteroviruses; however, VZV,[69,70] CMV, influenza A,[71] and hepatitis A[72] have been reported causes. even in immunologically normal individuals.

Clinical Presentation

Historical clues and physical findings can be helpful in focusing the search for an etiological agent. Travel or residence in areas where arboviruses are endemic during the appropriate season for arthropod transmission (typically summer months) and a history or evidence of insect bites should raise suspicion for arboviruses. Seasonality also plays a role in enteroviral diseases because in temperate climates enteroviruses are more prevalent during summer and fall months. History of a mother with recent symptoms consistent with viral illness (fever, sore throat, gastroenteritis, rash) should raise suspicion of enterovirus in a neonate with encephalitis or sepsislike illness. VZV encephalitis and myelitis typically follow chickenpox or zoster by weeks to months and commonly occur in older individuals or those with immunosuppression, such as transplant recipients.[73] VZV encephalitis may be complicated by CNS vasculopathy and resulting infarctions. Chronic encephalitis/meningitis due to enteroviruses occur in individuals with agammaglobulinemia. Chronic or relapsing encephalitis may also be due to VZV, measles (SSPE), or rubella (progressive rubella panencephalitis), though the latter two are extremely rare with the current widespread use of the MMR vaccine. HIV itself may cause encephalopathy/encephalitis or may also be associated with certain opportunistic infections such as PML. Significant exposure to rodent droppings should raise concern for LCMV. Finally, history of exposure to a bat should raise the concern for rabies.

The classic clinical presentation of viral meningitis is characterized by acute onset of fever, headache, photophobia, vomiting, and nuchal rigidity. A more chronic presentation might indicate enteroviral disease in an immunosuppressed host, whereas recurrent aseptic meningitis can be associated with HSV 2. Encephalitis is characterized by acute onset of fever, signs of encephalopathy such as depressed consciousness, focal neurologic findings, and seizures. A chronic progressive presentation might indicate more unusual causes, such as PML and SSPE. Transverse myelitis is characterized by an abrupt onset of weakness of the limbs progressing to flaccid paralysis. Diminished deep tendon reflexes progress to nonexistent, and there is associated sensory deficit. VZV myelitis usually follows varicella or zoster by 1 to 2 weeks.

Cerebrospinal fluid (CSF) findings in aseptic meningitis typically include a normal glucose level, a normal to slightly elevated protein level, and a pleocytosis of up to 1000 cells/mm^3. The pleocytosis is classically monocytic (>80%); however, there can be an initial predominance of polymorphonuclear cells in the first 48 hours of illness.[74] CSF findings in encephalitis can be normal or there may be pleocytosis and elevated protein levels.

The results of brain computed tomography (CT) and magnetic resonance imaging (MRI) studies are usually normal in viral meningitis, whereas disease is often seen in the setting of viral encephalitides. In general, CT scan is relatively insensitive for detecting acute encephalitis. MRI is the more sensitive study for detecting disease because of its ability to detect altered water content.[75] In acute viral encephalitis early findings include edema with minimal contrast enhancement. As disease progresses, edema and enhancement become more obvious and may be accompanied by mass effect, hemorrhagic changes, and necrosis. As the inflammation resolves, atrophy may become prominent. In HSV, imaging studies may reveal edema and enhancement, often times first involving the temporal lobes with subsequent spread to other areas of the brain. Changes can ultimately progress to atrophy, multicystic encephalomalacia, and gyriform high attenuation, especially in children.[76,77] In postinfectious encephalomyelitis,

the lesions may be seen throughout the CNS. The lesions are more readily elucidated by MRI and primarily involve the white matter, although gray matter may also be involved.

Exotic Viral Diseases

With both the increase in foreign travel and the threat of bioterrorism, the potential to treat a child with an exotic viral disease exists. Although discussion of these infections, which include Andes virus, B virus, monkeypox, and the hemorrhagic fever viruses (Ebola virus, Marburg virus, Lassa virus, Crimean-Congo hemorrhagic fever virus, Argentine hemorrhagic fever virus, and Bolivian hemorrhagic fever virus) is beyond the scope of this chapter, these infections should be kept in mind. If one of these agents is suspected, then the patient and patient garments should be contained in a single room, and infection control, infectious diseases, or the public health department should be called immediately.[78-81]

Diagnosis

The key to diagnosis of viral pathogens is high-quality specimens obtained early in the course of disease. There are five main ways to diagnose a viral infection: (1) identification of the virus in cell culture through observation of characteristic cytopathic effect; (2) identification of the virus by assays that link specific antibodies to the viral antigens (complement fixation, neutralization, immunofluorescence assays, enzyme-linked immunosorbent assay [ELISA]); (3) microscopic identification of characteristic viral inclusion bodies; (4) serological procedures that show either an early antibody (immunoglobulin M [IgM]) or a fourfold or higher rise in IgG antibody titers between an acute phase and convalescent phase (at least 10 to 14 days later) serum; and (5) molecular techniques that amplify target viral DNA or RNA.

If a viral cause is suspected, a few diagnostic studies can be performed immediately. Acute-phase serum should be held for later interpretation. It is critical that this specimen is drawn before administration of intravenous immunoglobulin (IVIG) or blood products. Viral cultures should be collected from the appropriate sites with Dacron swabs with plastic shafts (both cotton and wood inhibit viral growth). The virology laboratory should be informed of the diagnosis or suspected pathogens because the cell lines chosen for inoculation vary by what virus is suspected. Nasal washes and swabs of the base of a vesicle or ulcer (for VZV, HSV) should include good cellular content because fluorescent antibody assays stain cells and the more cells available, the more sensitive the assay. Table 88–2 outlines appropriate samples and testing for a number of specific viral pathogens.

Myocarditis

Isolation of virus from the myocardium provides a definite viral diagnosis of myocarditis; however, recovery of viruses from the myocardium by culture is rarely possible, even in cases of histologically proven myocarditis. Viral culture of peripheral specimens such as stool and nasopharyngeal secretions or the demonstration of a fourfold rise in specific viral antibody titers provides an indirect determination of causality; however, the sensitivity is also low, 16% to 26%[8,12] and 30% to 40%, respectively.

Molecular biologic techniques such as PCR and in situ hybridization have expanded the number of viruses implicated in the etiology of myocarditis. In addition, because of the increased sensitivity of PCR, the application of PCR for viral nucleic acid in myocardial tissue provides a virologic diagnosis in up to 60% of cases.[8]

Hepatitis

Viral diagnosis relies on serological testings, the detection of viral nucleic acid in serum, and the detection of viral antigens or nucleic acids in tissue obtained from a liver biopsy specimen. Hepatitis A virus (HAV) infection is confirmed with the detection of anti-HAV IgM antibodies. In patients with acute hepatitis A, anti-HAV IgM antibodies are detectable in the serum at the onset of symptoms, peak 1 week after onset of symptoms, and become undetectable by 3 to 6 months after infection. The presence of HBsAg in serum indicates active HBV replication and is present in acute and chronic HBV infection. Because of the destruction of actively infected hepatocytes, HBsAg may be absent in FHF, and the only marker of acute HBV infection may be anti-hepatitis B core antibody (anti-HBcAb) (anti-HBV core) IgM antibodies. Hepatitis B DNA can also be detected in serum and liver tissue by PCR. Absence of HBsAg or HBV-DNA in the serum does not rule out HBV as the cause of FHF because HBV DNA has been shown in liver tissue of patients with non-A and non-B FHF in whom serologic markers did not suggest HBV infection.[82] Hepatitis D, a hepatotropic virus that causes infection only in the presence of active hepatitis B infection, should be looked for in patients with acute HBV hepatitis because coinfection or superinfection with HDV may result in more severe disease.[83] Hepatitis D coinfection can be determined with anti-HDV antibodies or HDV-RNA in serum.[84]

Although the newer generation antibody assays for hepatitis C are more sensitive than past assays, anti-HBcAbs may not be detectable early in disease. Therefore when the epidemiologic findings suggest possible infection with HCV, serum and liver tissue should be analyzed for HCV-RNA by PCR. Detection of HEV-RNA in blood or liver confirms acute infection with HEV. HSV hepatitis is frequently a result of newly acquired infection; thus serologic testing may not be helpful. Ulcerative mucosal lesions, if present, should be cultured for HSV. Liver tissue should be sent for viral culture and PCR for HSV. PCR may also determine HSV in blood.

Pneumonia/Pneumonitis

Fluorescence assays on nasal wash specimens are the diagnostic test of choice because most of these pathogens are concentrated in the nasopharynx. The sensitivity of indirect immunofluorescence assays is greater than 90% to 95% sensitive for RSV; parainfluenza 1,2,3; and influenza

TABLE 88–2

Diagnostic Tests and the Specimens Used for Various Viral Agents

Viral Agent	Diagnostic Tests	Specimens Used
Adenovirus	FA, PCR, culture, shell vial	NP, BAL fluid, tissue
Arboviruses (California encephalitis, Colorado tick fever, EEE, SLE, WEE, West Nile)	Serology, PCR, and immunohistochemistry for some	Serum (acute and convalescent), CSF
Enteroviruses (echoviruses, Coxsackie viruses, enteroviruses)	PCR, culture, serology available for some	CSF, pharynx, stool,* serum (acute and convalescent)
Hantavirus	Culture, PCR, serology	BAL fluid, serum
Hepatitis viruses	Serology for all	Serum
• HAV	Anti-HAV IgM	Serum
• HBV	HBsAg, anti-HBcAb IgM, PCR	Serum, liver
• HCV	Anti-HCV, PCR	Serum, liver
• HDV	Anti-HDV, PCR	Serum, liver
• HEV	Anti-HEV IgM, PCR	Serum, liver
• HGV	PCR (not widely available)	Serum
Herpes viruses		
• CMV	FA, PCR, culture, shell vial, serology, buffy coat antigen	NP, BAL, blood, tissue, urine, plasma
• EBV	PCR, serology, in situ hybridization	Serum, tissue, CSF
• HHV-6	PCR	Plasma or serum, CSF
• HSV 1 and 2	PCR, FA, culture	CSF, base of lesion, tissue, NP, conjunctiva, stool (neonates)
• VZV	Culture, FA	Base of lesion, tissue
Influenza A and B	FA, culture, IA (rapid)	NP, BAL fluid, tissue
JC Virus	Brain biopsy†, PCR	Brain, CSF
LCMV	Serology	Serum
Measles (rubeola)	Serology, culture (rarely grows)	Serum
• SSPE	Oligoclonal bands, IgG, measles titer	CSF
Mumps	Serology, culture (rarely grows)	Serum, pharynx, urine, CSF
Parainfluenza	FA, cultures	NP, tissue, BAL fluid
Parvovirus	PCR, serology	Blood, serum
Rabies virus	CSF antibody, virus isolation/culture (rarely helpful), fluorescent microscopy (consult ID)	Punch biopsy (nape of neck), brain, saliva, CSF, urine
Retroviruses		
• HIV	PCR, serology	Serum, plasma, blood, CSF,
• HTLV	PCR, serology	Serum, tissue
Rotavirus	EIA	Stool
RSV	FA, culture, shell vial, IA (rapid)	NP, BAL, tissue
Rubella	Serology, culture	Serum, NP, pharynx, CSF, blood, urine

*Enteroviruses are shed in the stool for weeks and may not be diagnostic.
†Gold standard.
BAL, bronchoalveolar lavage; *CSF,* cerebrospinal fluid; *CMV,* cytomegalovirus; *EEE,* eastern equine encephalitis; *EBV,* Epstein-Barr virus; *EIA,* enzyme immunoassay; *FA,* fluorescence assay; *HAV,* hepatitis A virus; *HBcAb*, hepatitis B core antibody; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis D virus; *HEV,* hepatitis E virus; *HGV,* hepatitis G virus; *HHV-6,* human herpesvirus 6; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *HTLV,* human T-lymphotropic virus; *IA,* immunoassay; *ID,* infectious disease; *IgM,* immunoglobulin M; *JCV,* JC virus; *LCMV,* lymphocytic choriomeningitis virus; *NP*, nasopharyngeal; *PCR,* polymerase chain reaction; *RSV,* respiratory syncytial virus; *SLE,* St. Louis encephalitis; *SSPE,* subacute sclerosing panencephalitis; *VZV,* varicella-zoster virus; *WEE,* western equine encephalitis.

A and B. A rapid immunoassay for RSV and influenza is also available. Adenovirus immunofluorescence assays are available in some laboratories, but sensitivity is generally lower (around 70%). Shell vial assays can increase sensitivity, and although they are usually performed for CMV, they can also be performed for adenovirus. The same samples can be sent for culture in addition to immunofluorescence studies, and this should be done for immunocompromised and severely ill children. The diagnosis of Hantavirus can be made by culture of the virus (which is difficult), PCR for Hantavirus RNA, or serologic testing. The SARS virus can be identified by PCR amplification, culture of the virus

in respiratory secretions, or serologic testing. These tests can be performed through each state's health department in association with the Centers for Disease Control (CDC) (Table 88–2) (ref:www.cdc.gov/SARS).

Meningitis/Encephalitis

CSF, blood, and throat swabs should be collected for evaluation. One can make a diagnosis of enterovirus by culturing the virus from CSF or by detecting virus in CSF using reverse transcriptase-PCR. Because of the greater sensitivity of PCR, compared with culture,[85,86] it should be used whenever possible. Viral culture of a throat swab may also reveal enterovirus and is indicative of a current or recent infection. Rectal or stool viral cultures are less helpful because enteroviruses may be shed in the stool for weeks after infection. DNA PCR of CSF offers relatively sensitive and specific diagnosis of herpesviruses.[52] Detection of viral specific antibodies in the CSF can add supporting evidence. Additionally, the detection of HHV-6 DNA in plasma or serum by PCR confirms active systemic viral replication. Arboviruses are typically diagnosed through detection of antibodies in acute and convalescent serum specimens. CSF may also be tested for antibodies. PCR and immunohistochemistry have also been used to diagnose arboviral infections and are available in some settings. Diagnosis of LCMV is made through serologic testing. The JC virus can be detected in CSF with PCR, and this appears to be a relatively sensitive and specific method for diagnosing PML.[87,88] Definitive diagnosis, however, is usually made with brain biopsy. Diagnosis of SSPE is made with the evaluation of CSF for oligoclonal bands, IgG level, and specific measles antibody titer.

Treatment

In general, for most life-threatening viral infections the primary treatment is supportive. Because of improvements in intensive medical care, death from these illnesses has decreased even without the availability of specific antiviral therapy. Despite recent advances, there are no effective antiviral medications for many viral infections. There are, however, antivirals for most of the herpes group viruses and many of the respiratory viruses. For most infections, efficacy of antiviral therapy is decreased if therapy is delayed, so early diagnosis and rapid initiation of therapy are essential. Consultation with an infectious disease specialist is recommended because some antiviral agents are not commercially available and new treatment modalities continue to be identified. A listing of antiviral agents, indications, and dosages is provided in Table 88–3.

Myocarditis

Mechanical circulatory support should be considered for children with fulminant myocarditis unresponsive to standard management. Aggressive therapy is warranted because both adults and children who survive their illness have a good prognosis for return to normal ventricular function.[89,90] Cardiac transplantation may be necessary for those children refractory to other management.

Current recommendations do not support the use of immunosuppressive therapy[14,91] or nonsteroidal anti-inflammatory agents,[92] particularly early in the course of myocarditis.

Treatment with high-dose IVIG has been associated with improved left ventricular function in several small studies in children and adults.[93,94] IVIG is generally well tolerated and warrants investigation in larger, controlled studies. Several immune modulators such as interferon-α and interleukin-2 are being investigated for use in treatment of myocarditis.[92] Specific antiviral therapy is indicated when the inciting viral agent has been identified.

Hepatitis

The role of antiviral therapy in FHF is limited. Acyclovir should be initiated if HSV is suspected or confirmed, and pleconaril has shown some benefit in enteroviral sepsis.[95]

Controlled trials with plasma exchange and plasmapheresis have shown improved hemodynamic parameters, decreased intracranial pressure, and improved survival.[96] Experimental therapies such as hepatocyte transplantation and artificial hepatic support systems are in development and have shown promise in early studies.[97] Currently, orthotopic liver transplantation provides the primary treatment modality. For a detailed discussion of the management of FHF see Chapter 79 and reference 90.

Pneumonitis

The cornerstone of treatment remains supportive with oxygen, fluids, bronchodilators, and mechanical ventilation. Corticosteroids are generally of no proven benefit in viral-mediated pneumonia, and the data to suggest benefit in bronchiolitis remain controversial.[98-101]

Generally treatment of RSV with ribavirin in immunocompetent hosts has not shown clinical benefit,[102] despite initial studies that had suggested a modest clinical benefit and led to the licensing of ribavirin.[103-105] Evidence is developing, however, that a combination of inhaled ribavirin with either intravenous RSV immunoglobulin or monoclonal antibody may substantially decrease the high death rate of RSV pneumonia in bone marrow transplant subjects from 50% to 70% with ribavirin alone to 9% to 42% in combination.[106-109]

Patients whose symptoms are suggestive of SARS should be immediately isolated in a negative pressure room with the use of airborne precautions (N95 respirator or PAPR [powered air purifying respirator]) and contact precautions (gowns and gloves).[67,101,109a] Both hospital infection control and the local public health department need to be contacted immediately. Treatment of SARS remains controversial. The CDC website (www.cdc.gov) and infectious diseases consultation should be accessed for up-to-date diagnostics, treatment, and isolation guidelines.

Encephalitis

Untreated, HSV encephalitis carries a death rate in excess of 70%[110] and even treated, death and complications for

TABLE 88–3

Antiviral Agents and Indications for Use

Virus	Drug of Choice/Dose	Alternate Agents
Adenovirus	There is no currently approved therapy for the treatment of adenoviral infections.	Both ribavirin and cidofovir have in vitro activity against adenovirus. Small case series in immunocompromised children have suggested potential efficacy with intravenous ribavirin (25 mg/kg loading dose then 10 mg/kg/daily—available on compassionate use basis) or cidofovir (5 mg/kg once weekly)[115,116]
Enterovirus	There is no currently approved therapy for the treatment of enteroviral infections	Pleconoril (VP63843) (5 mg/kg po or per nanogram tid, maximum dose 400 mg) has not yet been approved by the FDA but is available on a compassionate-use basis for neonatal enteroviral sepsis, myocarditis, chronic meningocephalitis, severe infections in patients with bone marrow transplants, and vaccine-associated paralytic polio
Hantavirus	Intravenous ribavirin has shown benefit in hantavirus renal syndrome,[117] but not in hantavirus pulmonary syndrome[112]	
Herpesvirus		
CMV	Ganciclovir (5 mg/kg q 12 hr × 2-3 wk, then 5 mg/kg q 24 hr) is primary therapy for CMV disease; IVIG (500 mg/kg qod × 2 wk then once weekly) or CMV-IG (150 mg/kg, same schedule) should be given concurrently for CMV pneumonia in immunocompromised patients	Foscarnet (90 mg/kg q 12 hr × 2-3 wk, then 90 mg/kg q 24 hr), cidofovir (5 mg/kg/wk—high risk of renal toxicity, use with probenecid and saline hydration); increased efficacy of cidofovir suggested in allogeneic stem cell transplant recipients with CMV pneumonia in one small study[113]
HSV	Acyclovir (20 mg/kg/dose IV q 8 hr) for encephalitis in neonates and children younger than 12 yr and for neonates with disseminated disease	No specific dosing recommendations are available for HSV-associated hepatitis and pneumonitis; at least 10 mg/kg/dose should be considered outside of the neonatal period
HHV-6	Foscarnet and ganciclovir have in vitro activity; case reports and series show variable clinical response with one or both drugs in combination	
VZV	Acyclovir (10-12 mg/kg/dose q 8 hr) High dose (20 mg/kg/dose) should be used for VZV encephalitis or for disease in immunocompromised children	
Influenza A/B	Oseltamivir (2 mg/kg bid × 5 days—max, 75 mg bid)	Rimantadine or amantidine (5 mg/kg/day div bid—max, 75 mg bid)—influenza A only
JC Virus	No effective therapy	In HIV infection, treatment with combination antiretroviral therapy may improve survival; potential role for cidofovir[114]
Parainfluenza		Treatment for parainfluenza pneumonia should include coverage for copathogens; ribavirin and IVIG remain controversial, with a recent review showing no benefit[34]
RSV	Aerosolized ribavirin (6 g reconstituted in 100 ml tid × 5 days) has been used with modest efficacy in patients with severe RSV pneumonia and in immuno-compromised patients—not recommended for uncomplicated disease	Combination therapy with ribavirin and palivizumab (RSV monoclonal antibody) or ribavirin and RSV-IG may improve outcome of RSV pneumonia in immunocompromised patients—under investigation

CMV, cytomegalovirus; *div,* divided; *HHV-6,* human herpesvirus 6; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *IG,* immunoglobulin; *IV,* intravenous; *IVIG,* intravenous immunoglobulin; *JCV,* JC virus; *max,* maximum; *RSV,* respiratory syncytial virus.

those who survive remain on the order of 15% and 20%, respectively.[111] Similarly, despite treatment, neonatal HSV CNS disease carries significant risk of death and morbidity, ranging from 0% to 15% and 43% to 68%, respectively.[49] Early identification of patients and rapid initiation of acyclovir have been associated with better outcome.[110,111] Unless an alternative cause is clear, high-dose acyclovir should be initiated in all children with encephalitis until HSV can be ruled out. Other specific antiviral therapy may be directed as outlined in Table 88–3.

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