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Viral infections in the intensive care unit (ICU) have gained a higher profile recently. This is due, in part, to novel and emerging pathogens, an aging population, and increased numbers of immunocompromised hosts, but most of the apparent increase is due to ready availability of molecular testing. Many cases of sepsis that would have been unidentified previously are now known to be viruses. Intensivists thus must have a thorough understanding of viral syndromes.

Although viruses can infect every organ system (Table 96.1), three syndromes predominate in immunocompetent adults. These are respiratory, central nervous system (CNS), and gastrointestinal infection. Other populations, such as transplant and human immunodeficiency virus (HIV) patients, are discussed in Chapter 46.

**OBJECTIVES**

This chapter will:
1. Describe the diagnosis and treatment of viral influenza.
2. Explain the evaluation and management of viral meningoencephalitis.
3. Describe the initial approach to viral hepatitis.

**Central Nervous System Infections**

The most common acute viral infections of the CNS are aseptic meningitis and encephalitis. Meningitis is inflammation of the meningeal layers surrounding the brain, involving headache, fevers, and meningismus. Encephalitis involves the brain parenchyma and alterations of the cerebral function. Other symptoms of encephalitis include fevers, headache, seizures, and focal neurologic deficits. Inflammation rarely confines itself to the meninges or parenchyma. As such, there is significant clinical overlap between these entities, termed “meningoencephalitis.” Nonetheless, the predominating features are useful for clinical distinction and treatment decisions.

Distinguishing viral from other causes of meningoencephalitis is challenging. History, exposures, imaging, and laboratory work are helpful in determining a cause. History and exposures for common entities are detailed later. Temporal lobe encephalitis on imaging is suggestive of a viral cause, particularly herpes simplex virus (HSV). Another useful clue is the finding of hydrocephalus, rarely seen with viral CNS infections.

Cerebrospinal fluid (CSF) analysis is the most important test for identifying a cause for CNS infections. The characteristic CSF profile for viral infection in lymphocyte-predominant leukocytosis (neutrophils may predominate very early in infection, but this will shift rapidly) is elevated protein less than 150 mg/dL, normal glucose concentration,
and low to absent red blood cells (RBCs). Culture (the gold standard, but not always widely available) and molecular identification methods (e.g., polymerase chain reaction [PCR]) provide more definitive identification of the responsible pathogen.  

### Herpes Simplex Virus

Herpes simplex virus (HSV) is unique from other CNS viral infections in many ways. First, it is treated more easily with a readily available antiviral, acyclovir, making identification critical. Second, it is extremely common and demonstrates no seasonal predominance pattern and thus must be considered in all patients presenting with meningoencephalitis. Third, the clinical distinction between meningitis and encephalitis in this syndrome is clinically significant, because encephalitis can be fatal without treatment where meningitis is self-limited.  

### Encephalitis

Recognition and treatment of HSV encephalitis is critical. Without treatment, mortality approaches 70%, and even with treatment, mortality rates can be as high as 30%.

### TABLE 96.1

| SYNDROME/PRESENTATION | COMMON VIRUSES | TREATMENT |
|-----------------------|----------------|-----------|
| **Respiratory Failure** |                |           |
| Hypoxic respiratory failure-pneumonia | Hypoxic respiratory failure: Influenza A and B, RSV A and B, coronavirus, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome coronavirus, Adenovirus, cytomegalovirus, Varicella, HSV, Paninfluenza 1-4, Metapneumovirus, measles especially in immunocompromised patients | Supportive: adequate oxygen delivery |
| Hypercapnic-hypoxic respiratory failure | VAP: HSV, CMV, Mimivirus | Antivirals: Neuraminidase inhibitors (NAIs) (Oseltamivir, Zanamivir, peramivir, Laninamivir). For resistant influenza viruses may consider combination therapy of NAI with ribavirin and/or novel antivirals such as Favipiravir |
| Asthma/COPD exacerbation | Hypercapnic-hypoxic respiratory failure: Influenza A and B, coronavirus, rhinovirus, Parainfluenza 1-4, RSV A and B | |
| **Adult Respiratory Distress Syndrome (ARDS)** | ARDS: Influenza virus, Hantavirus [Hantavirus pulmonary syndrome (HPS)], varicella, herpes simplex virus, SARS, MERS-CoV | Ribavirin for RSV in immunocompromised patients and children and may also be considered for other viruses such as in SARS or MERS-CoV - lopinavir in combination regimens has also been used Acyclovir for VZV pneumonitis (limited efficacy it is still widely recommended as early primary therapy) |
| **Without lung disease (restrictive disease): Guillain-Barré syndrome (GBS)** | GBS: HSV, VZV, CMV, EBV, influenza, Hantavirus acute and chronic hepatitis B, Rare causes: West Nile virus, Parvovirus B19, Hantavirus, rubella, dengue | Ganciclovir for CMV pneumonitis in solid organ transplant patients appears to reduce morbidity Corticosteroids: For influenza, SARS and VZV pneumonitis to reduce inflammatory tissue injury in severe pneumonia Immunotherapies: Palivizumab is approved for high-risk pediatric patients with RSV infection; IVIG for certain respiratory viruses including influenza and GBS, plasma exchange for GBS. Combinations of ganciclovir with immunoglobulin or cytomegalovirus immunoglobulin may be of value in patients with bone marrow transplants and CMV pneumonitis. Others: Vitamin A for severe measles |
| **Neurological syndromes** | HSV: 40% to 50% of encephalitis cases where a cause is determined, and 10% to 20% overall VZV (the most common cause of encephalitis among immunocompromised patients and the second most common viral cause of sporadic encephalitis not occurring during an outbreak) | Supportive: Treatment of neurologic (eg, cerebral edema, high intracranial pressure, and seizures) and systemic (eg, hypoxemia, low cerebral perfusion pressure, and fever) complications |
### Table 96.1

| SYNDROME/PRESENTATION | COMMON VIRUSES | TREATMENT |
|-----------------------|----------------|-----------|
| Clinical presentation: usually as altered mental status, seizures, coma, neuropathies | Enteroviruses (Enterovirus 71, Coxsackie, Echovirus, poliovirus; as a group, enteroviruses) are collectively the third most common cause of sporadic viral encephalitis and the most common cause of aseptic meningitis. Arboviruses (JEV, WNV, TBEV, MVEV, LCEV, SLEV, EEEV; the most common pathogens to cause encephalitis that is restricted to certain geographic regions) Influenza (encephalitis is very uncommon complication of seasonal influenza infections but because influenza itself is common 4-19% of patients with severe or fatal H1N1 reported neurologic complications) Other viruses: West Nile virus, CMV, mumps, measles, rubella, rabies, JC virus (PML), acute HIV infection | Antivirals: Acyclovir: early aggressive antiviral therapy with acyclovir for HSV, VZV improves mortality and reduces subsequent cognitive impairment |
| Virus related shock Cardiogenic shock Myocarditis | Enteroviruses (Enterovirus 71, Coxsackie viruses group A and B, Echovirus), Influenza, Adenovirus, Parvovirus, RSV, CMV, HIV-1, hepatitis A and C viruses, vaccinia virus (after smallpox vaccine) | Foscarnet: HHV-6, combination therapy with foscarnet and ganciclovir is recommended for CMV encephalitis Oseltamivir: severe influenza Pleconaril: severe Enterovirus infections Corticosteroids: complicated HSV encephalitis (data based on retrospective studies), VZV encephalitis (for inflammatory vasculopathy), uncomplicated zoster (variable results), severe influenza, WNV (case report), postinfectious encephalitis Immunotherapies: immunomodulatory therapy with either intravenous immune globulin or plasma exchange for patients with postinfectious encephalitis who fail corticosteroid treatment (data based on case series) or for WNV encephalitis (Case reports) Others: Vitamin A for severe measles |
| Distributive shock-Hemorrhagic fever | Arenaviruses (South American HF-Junin; Lassa Fever), Bunyaviruses (Rift valley fever, Crimean Congo HF-CCHF), HF with renal syndrome, Hantavirus, Filoviruses (Ebola, Marburg), Flaviviruses (Yellow fever, Dengue HF) | Supportive Antivirals: Rifampin: for RSV myocarditis Pleconaril: severe Enterovirus infections Oseltamivir: severe influenza ART: HIV-1 Corticosteroids: do not reduce mortality (data based on small RCT of poor quality) Immunotherapies: IVIG (data based on in vitro data, case series, limited RCT.) Combination therapy of IVIG with rifampin has been described in case series. Others: herbal medicines, mechanical ventricular assist devices until resolution or cardiac transplantation is available, novel therapies e.g pleconaril Supportive: adequate oxygen delivery, blood products. Passive transfer of antibodies (plasma, IVIG) may be of value in Bunyaviruses, Junin virus, Lassa virus, Hantavirus HF, Flaviviruses (Yellow fever, Dengue HF) Antivirals: ribavirin for CCHF , Lassa virus, Hantavirus HF Ribavirin plus interferon may be considered for Lassa virus |
Moreover, survivors frequently are left with neurologic and psychiatric sequelae.6,7 Gender, exposures, geography, and timing are not useful in predicting which patients have HSV encephalitis. There is a well-described bimodal distribution with regard to age, with peaks occurring in children younger than age 20 and adults older than age 50,1 but any patient, regardless of age, should have CNS samples sent for HSV PCR if encephalitis is suspected.8

Physical exam features are typical for encephalitis, including fever, altered mental status, focal deficits, and seizures. Oral lesions may or may not be seen. HSV-1 has a particular association with several behavioral syndromes, including hypomania, disinhibition (specifically the Klüver-Bucy syndrome), and amnesia, likely stemming from its predilection to affect the limbic system.9,10 Magnetic resonance imaging (MRI) demonstrating unilateral temporal lobe abnormalities supports the diagnosis, with or without mass effect. These findings are seen less commonly on CT.11 Treatment should be prompt to reduce sequelae of infection; Table 96.2 summarizes the dosing regimens. Initiation of therapy should not be delayed while awaiting confirmatory testing.8 Acyclovir infusion should be slow and with additional intravenous fluid boluses to prevent crystal formation and reduce risk of renal failure. Treatment should be 14 to 21 days in duration because of observed relapse in shorter courses of therapy.12 As of now this treatment is recommended to be parenteral throughout the duration of therapy.

| SYNDROME/PRESENTATION | COMMON VIRUSES | TREATMENT |
|-----------------------|----------------|-----------|
| Hypovolemic/distributive shock in the setting of acute liver failure secondary to viral hepatitis | Hepatitis A, B, C, D, E, G, herpes group (CMV, HSV and Epstein Barr virus), adenovirus and influenza virus | Supportive: hemodynamic management, ventilation, prevention and treatment of hemorrhage, dialysis, therapy of co-existent sepsis and electrolyte disturbance, and management of intracranial pressure Orthotopic liver transplantation Antivirals (may be used for acute flare up of chronic viral hepatitis e.g. in immunocompromised patients) |
| Clinical presentation: nausea and vomiting with progression to encephalopathy and coma; may be new onset or acute decompensation of chronic liver failure due to viral hepatitis/ cirrhosis | | |
| Hypovolemic/distributive shock in the setting of acute pancreatitis | Mumps (the most common virus associated with pancreatitis, occurring even in the absence of parotitis), Enteroviruses (Coxsackie B), cytomegalovirus, varicella zoster, HSV-1, Epstein-Barr virus, influenza A, Parainfluenza, adenovirus, measles. In fulminant hepatic failure due to hepatitis A (HAV) or hepatitis E (HEV) pancreatitis occurs in up to 34% of the cases | Supportive Antivirals Oseltamivir: severe influenza Pleconaril: severe Enterovirus infections Acyclovir: VZV |
| Shock in the setting of adrenal insufficiency caused by viral infection (rare) | CMV in HIV-1 infection | Treatment of CMV itself is generally not warranted, unless there is evidence of CMV disease elsewhere. However, it is critical to treat the underlying human immunodeficiency virus infection with antiretroviral agents to attempt immune restitution. |
| Rhabdomyolysis | | |
| Special Immunocompromised host | | |
| Trauma/Burn | | |
| Pregnancy | | |
| Transplantation | | |

Abbreviations: ADEM, acute disseminated encephalomyelitis; AIDs, Adult Respiratory Distress Syndrome; CMV, Cytomegalovirus; CCHF, Crimean Congo Hemorrhagic Fever; COPD, Chronic Obstructive Pulmonary Disease; DRC, disseminated intravascular coagulopathy; EBV, Epstein Barr virus; GBS, Guillain-Barré syndrome; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatic C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HAV-6, Herpes Virus 6; HAV-8, Herpes Virus 8; HF, Hemorrhagic Fever; HSV, Herpes Simplex Virus; NAIs, Neuraminidase inhibitors; ICU, Intensive Care Unit; JEV, Japanese Encephalitis Virus; MVEV, Murray Valley encephalitis virus; PTLD, post-transplant lymphoproliferative disorder; RCT, Randomized Controlled trials; RSV, Respiratory Syncytial Virus; SARS, Severe Acute Respiratory Syndrome; TBEV, tick-borne encephalitis virus; VZV, Varicella-Zoster Virus; WNV, West Nile virus.

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| SYNDROME/PRESENTATION | COMMON VIRUSES | TREATMENT |
|-----------------------|----------------|-----------|
| Hypovolemic/distributive shock in the setting of acute liver failure secondary to viral hepatitis | Hepatitis A, B, C, D, E, G, herpes group (CMV, HSV and Epstein Barr virus), adenovirus and influenza virus | Supportive: hemodynamic management, ventilation, prevention and treatment of hemorrhage, dialysis, therapy of co-existent sepsis and electrolyte disturbance, and management of intracranial pressure Orthotopic liver transplantation Antivirals (may be used for acute flare up of chronic viral hepatitis e.g. in immunocompromised patients) |
| Clinical presentation: nausea and vomiting with progression to encephalopathy and coma; may be new onset or acute decompensation of chronic liver failure due to viral hepatitis/ cirrhosis | | |
| Hypovolemic/distributive shock in the setting of acute pancreatitis | Mumps (the most common virus associated with pancreatitis, occurring even in the absence of parotitis), Enteroviruses (Coxsackie B), cytomegalovirus, varicella zoster, HSV-1, Epstein-Barr virus, influenza A, Parainfluenza, adenovirus, measles. In fulminant hepatic failure due to hepatitis A (HAV) or hepatitis E (HEV) pancreatitis occurs in up to 34% of the cases | Supportive Antivirals Oseltamivir: severe influenza Pleconaril: severe Enterovirus infections Acyclovir: VZV |
| Shock in the setting of adrenal insufficiency caused by viral infection (rare) | CMV in HIV-1 infection | Treatment of CMV itself is generally not warranted, unless there is evidence of CMV disease elsewhere. However, it is critical to treat the underlying human immunodeficiency virus infection with antiretroviral agents to attempt immune restitution. |
| Rhabdomyolysis | | |
| Special Immunocompromised host | | |
| Trauma/Burn | | |
| Pregnancy | | |
| Transplantation | | |

Abbreviations: ADEM, acute disseminated encephalomyelitis; AIDs, Adult Respiratory Distress Syndrome; CMV, Cytomegalovirus; CCHF, Crimean Congo Hemorrhagic Fever; COPD, Chronic Obstructive Pulmonary Disease; DRC, disseminated intravascular coagulopathy; EBV, Epstein Barr virus; GBS, Guillain-Barré syndrome; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatic C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HAV-6, Herpes Virus 6; HAV-8, Herpes Virus 8; HF, Hemorrhagic Fever; HSV, Herpes Simplex Virus; NAIs, Neuraminidase inhibitors; ICU, Intensive Care Unit; JEV, Japanese Encephalitis Virus; MVEV, Murray Valley encephalitis virus; PTLD, post-transplant lymphoproliferative disorder; RCT, Randomized Controlled trials; RSV, Respiratory Syncytial Virus; SARS, Severe Acute Respiratory Syndrome; TBEV, tick-borne encephalitis virus; VZV, Varicella-Zoster Virus; WNV, West Nile virus.

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| SYNDROME/PRESENTATION | COMMON VIRUSES | TREATMENT |
|-----------------------|----------------|-----------|
| Hypovolemic/distributive shock in the setting of acute liver failure secondary to viral hepatitis | Hepatitis A, B, C, D, E, G, herpes group (CMV, HSV and Epstein Barr virus), adenovirus and influenza virus | Supportive: hemodynamic management, ventilation, prevention and treatment of hemorrhage, dialysis, therapy of co-existent sepsis and electrolyte disturbance, and management of intracranial pressure Orthotopic liver transplantation Antivirals (may be used for acute flare up of chronic viral hepatitis e.g. in immunocompromised patients) |
| Clinical presentation: nausea and vomiting with progression to encephalopathy and coma; may be new onset or acute decompensation of chronic liver failure due to viral hepatitis/ cirrhosis | | |
| Hypovolemic/distributive shock in the setting of acute pancreatitis | Mumps (the most common virus associated with pancreatitis, occurring even in the absence of parotitis), Enteroviruses (Coxsackie B), cytomegalovirus, varicella zoster, HSV-1, Epstein-Barr virus, influenza A, Parainfluenza, adenovirus, measles. In fulminant hepatic failure due to hepatitis A (HAV) or hepatitis E (HEV) pancreatitis occurs in up to 34% of the cases | Supportive Antivirals Oseltamivir: severe influenza Pleconaril: severe Enterovirus infections Acyclovir: VZV |
| Shock in the setting of adrenal insufficiency caused by viral infection (rare) | CMV in HIV-1 infection | Treatment of CMV itself is generally not warranted, unless there is evidence of CMV disease elsewhere. However, it is critical to treat the underlying human immunodeficiency virus infection with antiretroviral agents to attempt immune restitution. |
| Rhabdomyolysis | | |
| Special Immunocompromised host | | |
| Trauma/Burn | | |
| Pregnancy | | |
| Transplantation | | |

Abbreviations: ADEM, acute disseminated encephalomyelitis; AIDs, Adult Respiratory Distress Syndrome; CMV, Cytomegalovirus; CCHF, Crimean Congo Hemorrhagic Fever; COPD, Chronic Obstructive Pulmonary Disease; DRC, disseminated intravascular coagulopathy; EBV, Epstein Barr virus; GBS, Guillain-Barré syndrome; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatic C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HAV-6, Herpes Virus 6; HAV-8, Herpes Virus 8; HF, Hemorrhagic Fever; HSV, Herpes Simplex Virus; NAIs, Neuraminidase inhibitors; ICU, Intensive Care Unit; JEV, Japanese Encephalitis Virus; MVEV, Murray Valley encephalitis virus; PTLD, post-transplant lymphoproliferative disorder; RCT, Randomized Controlled trials; RSV, Respiratory Syncytial Virus; SARS, Severe Acute Respiratory Syndrome; TBEV, tick-borne encephalitis virus; VZV, Varicella-Zoster Virus; WNV, West Nile virus.

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### TABLE 96.2

| Treatment of Herpes Simplex Virus With Acyclovir[^15] |
|-----------------------------------------------|
| **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **INTERMITTENT HEMODIALYSIS** | **CONTINUOUS RENAL REPLACEMENT THERAPY** |
| >50 mL/min | 25–49 mL/min | 10–24 mL/min | <10 mL/min OR ANURIA | 5 mg/kg IV q24h; on dialysis days, give after HD | 10 mg/kg IV q24h |

[^15]: Weight is adjusted body weight for all calculations. Data from Wilson JW, Estes LL. *Mayo Clinic Antimicrobial Therapy Quick Guide*: Oxford: University Press; 2011.

### TABLE 96.3

| Treatment of Varicella Zoster Virus With Acyclovir |
|-----------------------------------------------|
| **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **INTERMITTENT HEMODIALYSIS** | **CONTINUOUS RENAL REPLACEMENT THERAPY** |
| >10–12 mg/kg IV q8h | 10 mg/kg IV q12h | 10 mg/kg IV q24h | 5 mg/kg IV q24h | 5 mg/kg IV q24h; on dialysis days, give after HD | 10 mg/kg IV q24h |

[^15]: Weight is adjusted body weight for all calculations. Given doses for VZV are for disseminated disease and not specific for encephalitis. Data from Wilson JW, Estes LL. *Mayo Clinic Antimicrobial Therapy Quick Guide*: Oxford University Press; 2011.

### Meningitis

Although HSV-1 drives encephalitis, HSV-2 is associated more commonly with meningitis. The typical description of HSV meningitis is a recurrent infectious aseptic meningitis. Episodes of transient neurologic abnormalities associated with fever, headache, and meningitis may occur for 2 to 5 days at a time and spontaneously resolve. Incidence is lower than for HSV encephalitis, and demographic and seasonal features are difficult to determine. History, however, may elicit known genital herpes or lesions in a significant proportion of patients. Currently, a standardized guideline-based treatment approach to HSV meningitis does not exist. Initial treatment may be with acyclovir IV as described for encephalitis (see Table 96.2). However, after stability, these patients can be transitioned to oral therapy on discharge for 10 to 14 days of total acyclovir.

### Varicella Zoster Virus

Immunocompetent persons have been reported to develop varicella zoster virus (VZV) meningitis; this is typically self-limited and of little consequence. VZV encephalitis typically is associated with disseminated disease in a host with an active zoster outbreak. This can occur in immunocompetent hosts, although most cases occur in the immune compromised. Diagnosis can be accomplished via CSF PCR. Clinical trials have not established the efficacy or need for treatment of VZV encephalitis in immunocompetent hosts, but in patients with normal renal function, acyclovir 10 to 12 mg/kg IV q8h is the treatment of choice; renal function adjustments are presented in Table 96.3. Duration of therapy is 10 to 14 days.

### Other Causes of Aseptic Meningitis

Aside from HSV, other significant causes of aseptic meningitis include the *Enterovirus* family (most common), HIV, and the viruses that cause encephalitis. Treatment of these is largely supportive. HIV screening in these patients is prudent, because this can seem to be asymptomatic meningitis, and because immunocompromised hosts are susceptible to a range of other viral and other causes of meningitis. Some vaccine-preventable illnesses that cause meningitis are poised to reemerge secondary to lower immunization rates. Mumps may occur with meningitis, but it is typically a self-limited process.

Human herpesvirus 6 (HHV-6) is an increasingly more frequently seen pathogen because of molecular testing. Clinical disease is seen almost exclusively in the immunocompromised host.

### Other Causes of Viral Encephalitis

A number of other viruses can cause encephalitis, including enterovirus, influenza, arenaviruses, and arboviruses. For all of these, treatment is supportive. Diagnosis depends on molecular testing of CSF, clinical signs and symptoms, and history. Historical factors of concern include travel history, geography, any animal exposures, or sick contacts. Any patient with suspected viral meningitis should be treated with acyclovir until HSV as a cause has been ruled out. As for meningitis, HIV screening in this population is prudent because a number of other causes (e.g., JC virus) can occur in the HIV-positive population. Guillain-Barré syndrome (GBS) is infrequently a sequela of encephalitis. Enterovirus and West Nile virus, in particular, have a predilection for this aftereffect. In patients with rapidly ascending flaccid paralysis and a history compatible with recent encephalitic infection, this should be considered as a potential diagnosis.

One special cause of encephalitis worth mentioning is rabies. Rabies has the distinction of being the single deadliest viral illness known, with only one documented survivor. Treatment is limited to early postexposure prophylaxis with vaccination and wound cleaning. However, for a patient with rabies and active encephalitis, there are no treatments.
that have proven reliably effective. Any samples being handled sent for laboratory testing with rabies virus should be marked as such because of the risk to lab workers.\(^{18}\)

**RESPIRATORY VIRAL ILLNESS**

Many pneumonias (community and hospital acquired), chronic obstructive pulmonary disease (COPD) exacerbations, and acute respiratory distress syndrome (ARDS) can be caused by a plethora of viruses, including influenza, coronavirus, rhinovirus, parainfluenza, Hantavirus, human metapneumovirus, and respiratory syncytial virus. Some of these have classic associations, such as Hantavirus and Sin Nombre virus, with an ARDS-like syndrome after exposure to rodents,\(^{19}\) or Middle Eastern Respiratory Syndrome after exposure to camels.\(^{20}\) Most, however, are seasonal and circulating in the community.

Despite the diversity in viral infections causing respiratory illness, most share a common treatment: supportive care. Although there are continuing attempts to make effective antivirals,\(^{21}\) currently influenza is the only common respiratory infection in which antiviral therapy is part of standard medical practice for immunocompetent adults. In select patients, RSV treatment with ribavirin is being attempted, but this is not yet standard of care.

The lack of guided treatment does not, however, preclude the need to effectively diagnose the responsible cause. Continuing antibacterial therapy in patients with viral respiratory infection has no beneficial effect on outcomes and increases the risk of multi-drug-resistant organism colonization.\(^{22}\) Identification of a viral infection can be used as a basis for early de-escalation of antibiotics. Although studies on rapid influenza and bacterial respiratory pathogen testing have shown mixed results on antimicrobial prescribing in practice,\(^{23,24}\) the Infectious Disease Society of America (IDSA) endorses their use as part of antimicrobial stewardship practice.\(^{25}\)

Despite this, providers should remember that these swabs are not 100% accurate. Nasopharyngeal swabs do not always correlate with findings on bronchoalveolar lavage.\(^{26}\) This may be due to postinfection shedding from resolved disease, inadequate movement of virus between upper and lower respiratory tracts, or other factors, but like all test results, these have to be interpreted in context.

**Influenza**

Influenza is a leading cause of morbidity and mortality in the United States and worldwide. Influenza’s genetic structure and high transmissibility allows for new strains to sweep the globe every several decades after an “antigenic shift” and resulting in a pandemic. Pandemics occurred in 1918, 1957, 1968, and most recently in 2009. Each was associated with unpredictable seasonality, and higher resource utilization and mortality. Pandemic strains become predominant seasonal circulating strains in intervening years, where cases follow a typical pattern of starting in late fall, peaking in mid to late winter, and disappearing by the end of spring. Particularly during “normal” seasonal influenza years, there is significant local variation in the onset and termination of the flu season.\(^{27,28}\)

Testing for influenza typically is restricted to the flu season, except for in the case of known contacts and during unusual outbreaks of activity. The effectiveness of antivirals even in that window has been called into question in several systematic reviews.\(^{29,30}\) Nonetheless, current IDSA treatment guidelines support their use for patients in the first 48 hours after symptom onset, and reports of reduced mortality during the H1N1 outbreak in 2009 and a favorable side effect profile have encouraged physicians to treat outside of this window.\(^{29,31–33}\) Currently, the preferred agents are neuraminidase inhibitors including oseltamivir, zanamivir, and peramivir. Dosing is summarized in Table 96.4. The 2009 H1N1 pandemic tested several novel methods of treatment for influenza-associated ARDS. Extracorporeal membrane oxygenation (ECMO) was one of the more effective strategies,\(^{34}\) and critically ill influenza patients appear to have a more clear benefit from ECMO than other adult populations. More research is needed in this area.

**Other Considerations**

As mentioned above, viral shedding can occur in noninfected or postinfected states, so a positive test result does not mean a viral cause of disease has been determined definitively. For example, it is not uncommon to identify CMV on BAL specimens in hosts who are asymptomatically shedding. The context of the host and pathogen should be considered. Clinically significant CMV reactivation is unusual in immune competent hosts, and detection in this setting does not equate to disease. Diagnosis of CMV pneumonia requires pneumonitis, usually identified via biopsy.\(^{35}\)

Another consideration in viral respiratory infections is concomitant bacterial superinfection. Viral pneumonia renders a host more susceptible to other infections, and severe bacterial pneumonias can develop concomitantly. This is well described with influenza, in which much of the 1918 H1N1 appeared to occur 7 to 14 days postinfection because of pneumonias, particularly *Streptococcus* pneumonia.\(^{36}\)

### TABLE 96.4

| AGENT     | CREATININE CLEARANCE > 60 mL/min | CREATININE CLEARANCE 31–60 mL/min | CREATININE CLEARANCE < 30 mL/min | IHD | CRRT |
|-----------|----------------------------------|----------------------------------|---------------------------------|-----|------|
| Oseltamivir | 75 mg BID                        | 30 mg BID                        | 30 mg daily                      |     |      |
| Zanamivir  | 10 mg BID                        | Unchanged                        | Unchanged                       |     |      |
| Peramivir  | 600 mg IV once                   | >=50: 600 mg IV once             | 100 mg IV once                  |     |      |
|            | 31-49: 200 mg IV once            |                                  |                                 |     |      |

Dosing given is for treatment, not prophylaxis. BID, twice daily; CRRT, continuous renal replacement therapy; HD, hemodialysis; IHD, intermittent hemodialysis; IV, intravenous.

Modified from Tunkel AR. Approach to the patient with central nervous system infection. *Principles and Practice of Infectious Diseases.* 2010:1079–1083; Wilson JW, Estes LL. *Mayo Clinic Antimicrobial Therapy Quick Guide.* Oxford University Press; 2011.
**TABLE 96.5**

| Treatment of Acute Hepatitis B With Lamivudine |
|-----------------------------------------------|
| **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **CREATININE CLEARANCE** | **CREATININE CLEARANCE < 15 mL/min OR ANURIA** | **INTERMITTENT HEMODIALYSIS** | **CONTINUOUS RENAL REPLACEMENT THERAPY** |
| > 50 mL/min | 30–49 mL/min | 15–29 mL/min | 5–14 mL/min: 35 mg load then 15 mg q24h | <5 mL/min: 35 mg load then 10 mg q24h |
| 100 mg q24h | 50 mg q24h | 25 mg q24h |

Note that lamivudine is also effective against HIV, and expert input from an HIV provider should be sought before treating a coinfected patient. Data from Wilson JW, Estes LL. *Mayo Clinic Antimicrobial Therapy Quick Guide*. Oxford University Press; 2011.

**GASTROINTESTINAL ILLNESS**

Most infectious gastrointestinal illnesses are caused by viruses. Noroviruses, for example, are the most common cause of gastroenteritis. Although more common in immunocompromised hosts, CMV can cause a treatable colitis without viremia in immunocompetent hosts. However, in immunologically normal hosts, the most commonly encountered illnesses with specific treatments are hepatitis infections.

**Acute Viral Hepatitis**

Acute viral hepatitis can be a manifestation of any of the viral hepatitisides (A, B, C, D, and E) in a normal host. In appropriate hosts and settings, other causes may include adenovirus, Epstein-Bar virus, CMV, HSV, VZV, or yellow fever, but the focus of this discussion is on the hepatitis viruses. Although genetically and structurally dissimilar, the five hepatitis viruses cause a common acute presentation. Viruses can be differentiated by molecular testing and serology, and history may provide a clue as to the responsible pathogen. Hepatitis A and E are transmitted via a fecal-oral route, whereas B, C, and D are transmitted via contact with infected fluids. Geography also provides some hints, because hepatitis B is the leading cause of fulminant disease in the developed world, whereas hepatitis E dominates in India.

Most acute infections are subclinical or self-limited, but a minority may go on to fulminant disease and critical illness. Initial symptoms include elevated transaminases, malaise, myalgias, arthralgias, and headache. Fever is more common in hepatitis A and E than B and C. Hepatitis B can be associated with serum sickness-like syndrome. Fulminant hepatitis is severe liver failure developing within 8 weeks of becoming symptomatic. Although chronic hepatitis C infection increases the risk of fulminant disease when the patient is infected acutely with another hepatitis virus, it rarely causes fulminant acute hepatitis on its own. Hepatitis C has a predilection for causing fulminant hepatitis in pregnant women. Although less common, it is prudent to test for HSV and VZV as causes for acute liver failure, because treatment options exist for these agents.

The liver failure seen in fulminant hepatitis includes encephalopathy, coagulopathy, cerebral edema, cardiovascular collapse, and hepatorenal syndrome. Mortality can be greater than 80%. Treatment is largely supportive. A small trial of antiviral therapy for fulminant HBV hepatitis was associated with lower mortality in a selected group of younger patients without preexisting liver disease or HIV. Patients in this study received 100 to 150 mg/day lamivudine in conjunction with pulse steroids, plasma exchange, hemodiafiltration, and use of experimental protease inhibitors to avoid disseminated intravascular coagulation (Table 96.5). Lamivudine was associated with a 0.25 (0.07–0.91) hazard ratio for mortality. Another retrospective study did not replicate this, finding no mortality benefit from viral suppression. However, the authors recommended considering nucleoside inhibitor therapy anyway, because it may reduce the risk of recurrence posttransplant. The American Association for the Study of Liver Disease suggests considering lamivudine (and possibly other agents) for acute hepatitis B but notes evidence is equivocal and rates this a level III recommendation. Given the paucity of evidence, such agents should be considered only in conjunction with expert consultation.

HSV- and VZV-induced fulminant failure should be treated with acyclovir 5 to 10 mg/kg IV every 8 hours for at least 7 days (see Table 96.2 for renal dose adjustment). The outcomes after transplantation for these viruses are not as clear, but these patients still should be considered for transplantation.

Other agents such as EBV, hepatitis A, E, and yellow fever have no specific treatments. Because of the high mortality of fulminant hepatitis, regardless of the cause, expert consultation should be sought to evaluate for liver transplantation.

**Chronic Viral Hepatitis**

Chronic viral hepatitis is seen most commonly with hepatitis C, although a minority of hepatitis B patients, as well as those with hepatitis B and E, can develop chronic disease. Chronic disease is defined as an infection persisting longer than 6 months. The indolent nature of these infections typically does not cause critical illness. Infection with chronic hepatitis C certainly can increase susceptibility and sequelae to other hepatic injuries, including toxic, ischemic, and coinfection with acute viral hepatitis but does not require directed treatment.

Chronic hepatitis B can be treated with interferon and/or antivirals. Identifying candidates for treatment and determining the best course of therapy is complicated, and many patients end up on indefinite therapy. Treatment interruption increases the risk of resistance and treatment failure and ideally should not be interrupted in the ICU. If this is necessary, seek expert hepatology and/or infectious disease input.

Novel direct acting agents have revolutionized the treatment of hepatitis C. These agents are generally well tolerated and require relatively short courses of therapy to achieve sustained virologic response. Patients who are on such agents ideally should have them continued in the ICU.
3. Early diagnosis allows for antiviral treatment of influenza.
4. Antiviral therapy may have a role in hepatitis, but the benefit of directed therapy is uncertain.

**Other Gastrointestinal Infections**

A variety of gastrointestinal viral infections can cause critical illness, such as norovirus-induced enteritis, or *Coxsackie* virus–induced pancreatitis. However, these entities typically require only supportive care in normal hosts. It is prudent to screen such individuals for HIV and assess for other occult immunocompromising conditions, but otherwise these patients do not require infection-directed treatment.

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A complete reference list can be found online at ExpertConsult.com.

**Key Points**

1. Viruses are a common cause of critical illness and should be evaluated to facilitate de-escalation of other therapies.
2. In meningoencephalitis, diagnosis and empiric treatment of HSV can reduce the burden associated with this illness.
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