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Viral Infections in ICU Patients

David E. Greenberg[1] and Stephen B. Greenberg[2,3]

NIAID[1], Laboratory of Clinical Infectious Diseases, Bethesda, Maryland 20892
Department of Medicine[2] and Department of Molecular Virology and Microbiology[3]
Baylor College of Medicine, Houston, Texas 77030

1 INTRODUCTION

Intensive care units (ICU) were used originally for mechanical ventilation of patients with poliomyelitis and for recovery of patients after anesthesia. Today, these units have been expanded to care for severely ill patients with a wide variety of clinical conditions requiring close monitoring and support. A variety of medical conditions and physiologic disturbances have benefited from this care. Many critically ill patients have underlying infections and of those with infections, viruses are the cause in a small but important percentage (1,2). The majority of viral infections which require care in an intensive care unit involve the respiratory or the central nervous system. However, other organ systems, such as the gastrointestinal tract, may be severely affected by viruses and require support or close monitoring. The conditions reviewed in this chapter are found in adults and do not include HIV infections. Table 1 is a summary of acute illnesses which may be caused by viruses and require treatment in an ICU in the Western Hemisphere. The syndromes and special hosts that are associated with severe viral infections may be diagnosed from epidemiologic clues and specific laboratory tests (3,4). Clinical signs and symptoms are rarely sufficient to make a specific diagnosis of a viral infection.

2 ACUTE RESPIRATORY FAILURE

2.1 Hypoxic → Viral Pneumonia

Although severe community-acquired pneumonia is usually caused by bacteria, viruses account for approximately 3-10% of cases in large series (5,6,7,8). The usual viral causes of pneumonia in adults are influenzavirus type A and B, parainfluenzaviruses, respiratory syncytial virus (RSV), and

adenoviruses (9,10,11). These pneumonias may be nosocomially acquired, especially during peak respiratory periods (12,13,14,15,16).

Viruses can cause an atypical pneumonia in otherwise healthy individuals or a pneumonia in immunocompromised hosts (17,18,19,20). The most common cause of viral pneumonia in adults is influenzavirus type A and B. Immunocompromised patients are more likely to have viral pneumonias caused by RSV, cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), adenovirus and rarely measles (21-35). Radiographic findings are variable and not virus specific. Computed tomographic findings are also variable and overlap by virus etiology. Viral pneumonia may have poorly defined nodules and patchy areas of peribronchial ground-glass opacity and air-space consolidation. Hyperinflation is common (36).

Influenzavirus pneumonia is more likely to occur in the elderly and immunocompromised patient. Predisposing conditions for influenza pneumonia include age >65 years, diabetes mellitus, chronic lung disease, pregnancy, and immunosuppression. Influenzavirus pneumonia can be overwhelming and rapidly fatal (37-39). Influenzavirus infection can lead to bacterial superinfection and pneumonia secondary to *Streptococcus pneumoniae* and less commonly, *Staphylococcus aureus.* Diagnosis can be made by obtaining respiratory secretions and testing for viral antigen or virus growth in cell culture, or by serologic tests such as HI or ELISA.

Table 1. Virus Infections in ICU Patients

Syndrome	Viruses Associated
•Acute Respiratory Failure	
Hypoxic → Pneumonia	Influenza A & B, RSV, coronavirus (SARS), adenovirus, CMV, VZV, HSV
Hypercapnic – Hypoxic →	
COPD/Asthma exacerbation	Influenza A & B, coronavirus, rhinovirus, adenovirus
Acute Respiratory Distress Syndrome	Influenza A & B, coronavirus, rhinovirus
Without lung disease	
Guillain-Barré Syndrome	HSV, CMV, EBV
	Hantavirus, influenzavirus
•Shock	
Cardiogenic → myocarditis	Enteroviruses
Distributive → "sepsis"	Dengue Fever, VHF
•Altered Mental Status	
Meningitis/Encephalitis	HSV, enteroviruses, arboviruses, West Nile Virus, rabies
•Fulminant hepatitis	Hepatitis B, D, E
•Rhabdomyolysis	Influenza A & B, CMV
•Acute Pancreatitis	Mumps, parainfluenza, enterovirus
•Bioterrorism Agents	Smallpox, VHF, encephalitides
Special or Immunocompromised Host	
•Burns/Trauma	HSV, CMV
•Pregnancy	VZV, CMV, HSV, influenzavirus
•Transplantation	CMV, HSV, RSV, influenzavirus A and B, HHV-6, BKV, adenovirus

Although there are several antiviral agents which are effective against influenzavirus, there are few controlled studies on treatment of influenzavirus pneumonia. The older drugs, amantadine and rimantadine are useful against influenzavirus type A only and are only available in oral formulation. The newer neuraminidase inhibitors, oseltamivir and zanamivir are effective against influenzavirus types A and B, and are also only available in oral form (40,41). Ribavirin can be given intravenously and has been shown to be effective in a few published cases of influenzavirus as well as RSV pneumonia (42-44).

Recent outbreaks of severe acute respiratory syndrome (SARS) have been published which have been associated with a new coronavirus   (45). A case fatality rate of 4% to 15% has been reported in series from China and Canada (46). SARS should be considered in patients with the following history: travel in the previous 10 days to places with documented or a suspected SARS case; or close contact with a person with known or suspected SARS. Clinical illness includes cough, shortness of breath, hypoxia, and radiographic evidence of pneumonia or ARDS without another cause (47-50). Because SARS has been shown to transmit to healthcare personnel, isolation of patients is required. Standard, contact, and airborne isolation precautions should be initiated in suspected cases. All cases require notification to the local public health department and the Centers for Disease Control.

2.2 Hypercapnic-Hypoxic

2.2.1 COPD/Asthma Exacerbation. Acute respiratory failure can occur in patients with chronic obstructive pulmonary disease (COPD) and lead to hospitalization and the need for mechanical ventilation (51). Patients with exacerbations of COPD often have a history of increased sputum production, dyspnea and cough. Documented viral infections occurs in up to 45% of episodes of exacerbation of COPD (52,53). The most frequently identified viruses in acutely ill COPD patients are rhinoviruses, parainfluenzaviruses, coronaviruses, and influenzaviruses type A and B (53). In severely ill adult patients requiring hospitalization and mechanical ventilation, influenzaviruses and coronaviruses are most common. The epidemiology of acute exacerbations in adult asthmatic patients is similar. With acute, severe, exacerbations of asthma, patients may require close monitoring and ventilatory support. Recent studies have confirmed the importance of rhinoviruses, parainfluenzaviruses, and influenzaviruses in over half the acute exacerbations in adult asthmatics (54).

2.2.2 Acute Respiratory Distress Syndrome (ARDS). ARDS is characterized by severe hypoxemia and diffuse infiltrates on chest x-ray in the absence of clinical heart failure. ARDS has many causes. Common illnesses associated with ARDS include sepsis, diffuse pneumonia, aspiration or severe trauma. Although bacteria are more often the cause of infections leading to ARDS, viruses have been identified, especially influenzavirus, Hantavirus, varicella, herpes simplex virus and SARS (55-57).

Hantaviruses cause very different illnesses in Europe and Asia as opposed to the Americas (58,59). Epidemics of hemorrhagic fever with renal syndrome (HFRS) are caused by Hantaan, Dobravna, and Seoul viruses. Hantavirus pulmonary syndrome (HPS) is spread by New World rats and mice carrying one of the dozen reported viruses of the Bunyavirus family. Sin Nombre virus is the major pathogen causing HPS in the United States (60). HPS causes a non-cardiogenic pulmonary edema after initial influenza-like symptoms. HPS has a higher mortality than HFRS. The virus is transmitted to humans by inhalation of aerosolized particles of rodent excreta or by direct rodent contact. HPS has been recognized in 31 states, most commonly in the western region of the United States. Laboratory abnormalities include thrombocytopenia, leukocytosis, hemoconcentration, and the presence of immunoblasts on peripheral smear (61,62). Diagnosis requires serologic detection of IgM and IgG antibodies to Sin Nombre virus. Mortality rates may approach 40%. Although there is no specific therapy, cardiopulmonary support in an ICU may be associated with improved survival.

2.3 Without Lung Disease.

Guillain-Barré Syndrome (GBS) is the most common cause of acute neurogenic respiratory failure. Ventilatory assistance will be necessary in up to one-third of patients with this acute inflammatory disseminated polyneuropathy (AIDP). If respiratory failure occurs, it usually does so during the first two weeks of the illness. An antecedent respiratory or gastrointestinal illness is commonly reported in the preceding four weeks prior to the onset of symptoms (63,64,65). Viruses commonly reported in GBS patients include influenzavirus, CMV, acute and chronic hepatitis B, EBV, and varicella-zoster virus (66-75). Rare cases have been reported and associated with West Nile virus, Parvovirus B19, Hantavirus, rubella, and dengue (76-80).

The care of these patients in ICUs has significantly reduced mortality rates. In patients requiring mechanical ventilation, plasma exchange has

shortened the duration of respiratory support (81). An alternative treatment to plasma exchange appears to be IVIg. Even with treatment, the rehabilitation process is long and residual weakness is found in approximately 15%.

3 SHOCK

3.1 Cardiogenic → Myocarditis

Cardiogenic shock may develop following acute myocardial infarction or severe heart failure from any cause. Clinically, Cardiogenic shock is manifested by peripheral hypoperfusion, cold extremities, cyanosis, or hypotension. Viral infection of the myocardium can lead to clinical myocarditis which is severe enough to manifest Cardiogenic shock either due to myocardial failure or tachyarrhythmias (82,83).

Although rarely proven, viruses are suspected as the major causes of acute myocarditis. A suspicion of viral myocarditis should be high in patients who had fever and myalgias preceding the development of cardiac symptoms. Evidence of myocardial damage with elevated creatine kinase and troponin levels is common. Patients may present with typical anginal chest pain and/or arrhythmias; making it difficult to rule out an acute myocardial infarction (84).

The viruses documented in myocarditis cases are predominantly enteroviruses, especially coxsackie B viruses (85). However, influenzavirus, adenoviruses, Parvovirus B19, and CMV have been reported, as well (86-92). Recent smallpox vaccine studies have also reminded us of the potential for myocarditis with vaccinia virus. Most patients with acute myocarditis have mild heart failure, but occasionally, the myocarditis and associated organ dysfunction is severe enough to require mechanical ventricular assist devices until resolution or cardiac transplantation is available.

3.2 Distributive "Sepsis"

3.2.1 Dengue Fever. Dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) have become increasingly prevalent in the past decade (93-95). The principal vector, *Aedes aegypti,* as well as *Aedes albopictus,* or the tiger mosquito, was brought to Houston, Texas from Japan in the 1980's. Clinically, dengue fever presents with high fever, severe headaches, myalgias, joint pains, maculopapular rash and leukopenia. Petechiae secondary to thrombocytopenia can be observed.

DHF/DSS are severe forms of the infection. The main pathophysiologic changes seen in DHF/DSS patients are abnormal hemostasis and plasma leakage.

With DHF/DSS, patients present with high fever, facial flushing and headache. Hemorrhagic manifestations such as bleeding at venipuncture sites, petechiae, epistaxis, gingival bleeding, and gastrointestinal hemorrhage may be observed. The tourniquet test is often positive. After the patient becomes afebrile, profuse sweating and a drop in blood pressure are observed. Once shock develops, the patient's condition deteriorates and death may occur without support. Recent series have reported DSS in the absence of thrombocytopenia and hemoconcentration. Mortality rates vary from 2-10% for DHF.

Risk factors for DHF/DSS in the Americas include 1) secondary infection with a different serotype; 2) sequential serotypes in secondary infections; 3) association with dengue 2 virus and, less frequently, dengue 3 virus; 4) longer interval between first and second infection; 5) young age; 6) lower frequency in blacks; and 7) individuals with a history of asthma, diabetes mellitus, or sickle cell anemia (93). To consider a case, the travel history and local disease occurrence must be known. Diagnosis is made by detection of IgM antibody. Paired sera for the testing of specific rises in IgG antibody will give a more specific diagnosis. Treatment for DHF/DSS is supportive.

3.2.2 Viral Hemorrhagic Fevers (VHF). Viral hemorrhagic fevers (VHF) are caused by RNA viruses and transmitted by rodent or arthropod vectors. In the case of Marburg and Ebola viruses, the reservoir and mode of transmission remain unknown. Case-fatality rates vary from 1% to 90%. Clinical syndromes include hemorrhage secondary to capillary leakage, hepatitis, encephalitis, and/or nephropathy. Disseminated intravascular coagulopathy (DIC) is common to many but not all of these viruses. The viruses found naturally in the Western hemisphere include yellow fever, dengue, Sin Nombre virus (Hantavirus), and South American hemorrhagic fever viruses (Guanarito, Sabia, Junin, and Machupo) (Table 2). Other viruses indigenous to Africa and Asia include Rift Valley fever, Crimean-congo hemorrhagic fever, Kyasanur Forest virus, Omsk hemorrhagic fever, hemorrhagic fever with renal syndrome, Lassa fever, and African hemorrhagic fever (Marburg and Ebola). The hemorrhagic fever viruses in Asia and Africa have the potential for introduction into the Western hemisphere or for use as biological warfare agents.

Table 2. Viral Hemorrhagic Fevers (VHF) in the Western Hemisphere

	Flaviviridae	Bunyaviridae	Arenaviridae
Disease	Yellow fever Dengue HF	Hantavirus Pulmonary Syndrome	Venezuelan, Brazilian, Argentine, & Bolivian HF
Clinical Syndromes	Hemorrhage, hepatitis, nephropathy	ARDS, hepatitis, nephropathy	Hemorrhage, encephalitis, nephropathy
Case-fatality Rate	2-20%	40-50%	10-33%
Treatment	Supportive care, close monitoring, no aspirin, no steroids, fluid resuscitation	Oxygenation and monitoring crystalloid fluid replacement, ribavirin IV (experimental)	Supportive therapy, specific immune human plasma (Argentine HF)

The viruses causing hemorrhagic fever cause microvascular damage and alterations in vascular permeability (96,97). Fever, prostration, and myalgias are common initial symptoms. Physical examination will often reveal hypotension, facial flushing, and petechiae. With progression to shock and generalized bleeding, there is often hematopoietic, neurologic and pulmonary involvement. Hepatitis is common and severe with yellow fever but not with the other VHF agents of the Western hemisphere. Increasing vascular permeability, loss of intravascular volume, and multiorgan failure are often the final pathway to death.

Routine laboratory tests yield nonspecific abnormalities, but thrombocytopenia and coagulation defects should suggest the diagnosis with the corresponding clinical presentation. Specific diagnosis requires isolation of the virus or staining of formalin-fixed tissue. Only the CDC and USAMRIID laboratories are under Biolevel safety 4 conditions which are necessary for attempting isolation of these viruses. RT-PCR assays for rapid diagnosis may become more widely available in the future.

The care of patients with VHF is largely supportive. Patients in shock and actively bleeding will require close monitoring, fluid resuscitation as well as transfusion of red cells, platelets, and clotting factors (98,99). No aspirin or corticosteroids should be used. Dopamine may be the pressor of choice in unresponsive shock. Only ribavirin has been used successfully in VHF, especially for Lassa fever patients. Experimental use of ribavirin in Hantavirus pulmonary syndrome is being evaluated. Specific immune human plasma has been successful in treating Argentine hemorrhagic fever and may be useful in Bolivian hemorrhagic fever.

All suspected VHF cases should be placed in isolation immediately. Respiratory precautions and placement in a negative pressure room should help reduce the spread to hospital personnel and close contacts. All specimens must be appropriately labeled. Decontamination of all areas where the patient has been is essential. Reporting all suspected cases to local, state, and federal authorities is necessary to alert the community of a possible outbreak.

4 ALTERED MENTAL STATUS

4.1 Viral Meningitis and Encephalitis

The differential diagnosis of viral meningitis and encephalitis includes a long list of viruses as well as bacteria and noninfectious conditions. Because the clinical presentation of viral meningitis and encephalitis overlaps with other infections and illnesses, the diagnostic evaluation and therapeutic management are complicated. The most common viral pathogens associated with meningitis or encephalitis and their epidemiology are listed in Table 3 (100-103).

Viral meningitis and encephalitis cases occur worldwide. In the United States, echoviruses and coxsackie viruses (non-polio enteroviruses) are the cause of many cases of meningitis and some cases of encephalitis. (104). Although outbreaks are more common in the summer months, CNS enteroviral illness occurs throughout the year. The most common cause of sporadic cases of encephalitis in adults is HSV-1. Over 50% of the cases of encephalitis in adults older than 50 years are caused by HSV-1 (105). Outbreaks of encephalitis can be caused by alphaviruses and/or flaviviruses such as St. Louis Encephalitis. West Nile virus infection and illness has only been reported in the United States since 1999 (106). However, severe CNS infections and deaths from West Nile virus are being reported with increased frequency throughout many states during 2002 and 2003 (107). Rare cases of rabies are reported annually in the United States, but the mortality rate in these patients approaches 100% (108,109).

The clinical presentation of viral meningitis and encephalitis often includes fever, headache, vomiting, altered mental status, and seizures. On neurologic examination, hyperreflexia, cognitive alterations, ataxia, and focal findings are common. Examination of the cerebrospinal fluid is necessary for evaluating these patients and sending specimens for diagnosis. Typically, patients with viral meningitis and encephalitis have elevated protein levels, normal glucose levels and a lymphocytosis. In

some cases, there may be a neutrophil pleocytosis and/or mild hypoglycorrhachia. These findings will often prompt clinicians to begin broad-spectrum antibiotics as well as antivirals until culture and PCR results are known. Magnetic resonance imaging (MRI) can demonstrate a pattern that suggests a specific pathogen such as HSV-1 or Japanese encephalitis. In other cases, the MRI may be normal. In herpes simplex encephalitis (HSE), 95% of patients have a history of change in the level of consciousness, 90% have fever, 85% have personality change, and 80% have headaches. Seizures have been reported in approximately two-thirds of patients. Other signs and symptoms include aphasia, amnesia and/or hallucinations. Typically, the CSF profile includes elevated opening pressure, lymphocytes, red blood cells and slightly elevated protein level. After 18 to 24 hours of symptoms, approximately 95% of CSF samples will have a positive PCR test (110). Serum antibody assays are not helpful in diagnosis. EEG shows lateralized epileptiform discharges (PLEDs) over the temporal or frontal area in 85% of patients with HSE. In the first 5 to 6 days of illness, the CT scan maybe normal. MRI is more likely to be abnormal earlier than the CT scan. Brain biopsy, although the definitive diagnostic procedure, is only performed when there is an atypical clinical, radiologic, or laboratory picture. The mortality rate has been reduced to 20% with acyclovir therapy. However, the mortality rate is higher in those older than 30 years and in those who were comatose before treatment was initiated.

West Nile virus had been a cause of encephalitis in Africa and the Middle East until 1999, when it was found in fatal cases of encephalitis in New York City (111,112). Over the next few years, hundreds of cases had been confirmed throughout most of the United States. West Nile virus is a member of the Flaviviridae family. Most infected patients are asymptomatic. Clinical illness is associated with fever, headache, anorexia and malaise. Lymphadenopathy has been reported in earlier epidemics. A maculopapular rash over the chest, back, and upper extremities is observed in approximately 50% of cases. Other signs and symptoms include conjunctivitis, nausea, abdominal pain, and diarrhea (113,114).

Meningitis, encephalitis, and acute flaccid paralysis have been reported with West Nile virus (115-117). CSF examination usually reveals a lymphocytic pleocytosis and elevated protein level. Guillain-Barré syndrome has also been reported. Diagnosis can be made by serologic tests, but cross-reactive antibodies to other flaviviruses have been observed. Detection of virus by RT-PCR is positive in less than 50% of cases.

Patients may need prolonged ventilation because of neurologic complications. No specific therapy has been found to be effective, although interferon, ribavirin and IVIg have been tested or proposed for clinical trials. Recovery may be prolonged with neurologic abnormalities being reported for up to one year following the illness.

Specimens should be collected for viral isolation and PCR testing. CSF PCR tests are available for detecting HSV-1, CMV, EBV, VZV, HHV-6, HHV-7, and the enteroviruses. In HSV-1 encephalitis, the sensitivity of CSF PCR approaches 95% (118). Less information is available on the sensitivity of CSF PCR tests for the other viruses.

For many patients with meningitis, admission to the hospital will not be necessary. Patients with suspected encephalitis should be admitted to the hospital and monitored closely. Initiation of empiric acyclovir intravenously should be considered. An MRI should then be reviewed for evidence of mass effect. If significant mass effect is present, then the CSF examination should be deferred and evidence of increased intracranial pressure (ICP) would require specific treatment (119). If no mass effect is found, then CSF examination should be performed and the appropriate tests ordered. If the HSV PCR test is negative, consider other diagnoses unless MRI is compatible with HSV.

Table 3. Epidemiology of Viral Encephalitis/Meningitis in the Western Hemisphere

Virus	Clinical Findings	Epidemiology
Enteroviruses	Myocarditis, rash pleurodynia	Summer and fall peaks both epidemic; sporadic cases
Herpes Simplex Type 1	Focal neurologic deficits	No seasonality; sporadic
Herpes Simplex Type 2	Primary genital lesions	No seasonality; sporadic
Varicella-Zoster virus	Rash	No seasonality; sporadic
EBV/CMV	Mononucleosis syndrome, immunosuppressed	No seasonality; sporadic
HHV-6	Focal neurologic	No seasonality; sporadic
EEE/WEE/VEE	Mosquito-borne, seizures	Summer; epidemic
SLE/WNV	Mosquito-borne, SIADH, acute flaccid paralysis	No seasonality; sporadic
California	Seizures	Northern Central US; summer; epidemic
Influenzavirus	Pneumonia	Winter; epidemic
LCM	---	Contact with rodents; winter; sporadic
Mumps	Parotitis	Spring/summer; sporadic
Rabies	Hydrophobia	History of animal bite; no seasonality; sporadic

5 FULMINANT HEPATITIS

In 1% to 2% of patients with acute hepatitis, acute liver failure or fulminant hepatitis will occur (120). Patients with fulminant hepatitis will often manifest encephalopathic changes, jaundice, and a prolonged prothrombin time. Levels of elevated aminotransferases do not have prognostic value and may decrease as the liver failure becomes worse. The viruses reported in cases of fulminant hepatitis are hepatitis B and D, A and E and rarely C (121,122). A recent study reports that approximately 12% of acute liver failure causes are attributable to viral hepatitis (123). Occasional cases of herpes simplex and varicella hepatitis have been reported in immunocompetent and immunosuppressed adults (124-126). A recent study has found HHV-6 antigens in explanted livers of patients with acute liver failure of unknown etiology (127).

6 RHABDOMYOLYSIS

Rhabdomyolysis is a syndrome characterized by muscle weakness, pain and cramps. Complications may be extramuscular and lead to acute renal failure and severe metabolic abnormalities (128,129). Rhabdomyolysis may be purely related to exertion, genetically determined or due to nonhereditary, nonexertional causes. Viruses have been reported to be rare precipitative causes of rhabdomyolysis (130,131). These viruses have been cytomegalovirus, measles, adenovirus, varicella, EBV, influenzavirus, parainfluenzavirus and enteroviruses (132-150).

7 PANCREATITIS

Acute pancreatitis is characterized by abdominal pain and elevated serum amylase and lipase (151). Depending upon the severity of the pancreatitis, the patient may need mechanical ventilation and support in an intensive care unit. The majority of cases are caused by gallstones and alcohol. Pancreatitic obstruction, drugs and toxins, metabolic and genetic disorders, trauma and iatrogenic causes account for most of the remaining cases. Several viruses are rare causes of acute pancreatitis: mumps, coxsackievirus, cytomegalovirus, hepatitis B, varicella-zoster virus, herpes simplex virus, hepatitis C, enterovirus 71, hepatitis E, hepatitis A, and adenovirus (152-160).

8 BIOTERRORISM AGENTS

The possible use of biological agents in a terrorist attack has become quite real since September 11, 2001 and the subsequent distribution of anthrax (161,162). Potential biological weapons have included both bacteria and viruses. The chief viral candidates with the greatest impact are smallpox, viral hemorrhagic fever agents such as Ebola virus, and equine encephalitis (163,164). Delivery of the virus weapon is likely to be by the respiratory route; contamination of food or water is less likely.

8.1 Smallpox

A single case of smallpox would have significant impact on the health care system (165). Smallpox is caused by variola virus and is highly infectious. Spread may occur by person-to-person or by fomites. After a 12 to 14 day incubation period, a prodromal illness marked by fever, rigors, malaise, headache and backache will last approximately three days. During this time, the physician examining the patient will consider a "flu-like" illness is most likely (166). A discrete centrifugal rash characterized by macules begins on the face, hands, and forearms (167). The macules become papules and then vesicles which spread over the whole body. Pustules and crusted lesions develop by the eighth day and thirteenth day, respectively. The rash can be distinguished from varicella (chickenpox) by being more peripheral and progressing at the same stage over the skin.

Mortality may reach 30% and is highest during the second week of illness. Pulmonary edema and hemoptysis were commonly reported in earlier outbreaks. Renal failure and electrolyte abnormalities also contributed to the morbidity in smallpox patients.

If a suspected case of smallpox were admitted to the hospital or ICU, the physician would need to notify local and national public health officials. Specimens should be sent for diagnosis to state and national laboratories where biosafety level 4 precautions are available.

A suspected case of smallpox needs to be placed in strict airborne and contact isolation and in a negative-pressure room. Patient transport should be limited. Dedicated equipment should be used. Linens from the patient should be autoclaved before laundering (Table 4). Isolation of the patient should be continued until all scabs separate.

Smallpox patients will need monitoring and excellent skin care. There is no currently approved antiviral treatment, although cidofovir has been

shown to be effective in vitro and in animal models (168,169). Vaccination of contacts should limit the development of clinical disease if administered within four days of exposure (170).

8.2 Viral Hemorrhagic Fevers (VHF)

VHF are caused by a diverse group of viruses that are transmitted by animal and arthropod vectors (171). VHF agents are potential biologic weapons because they are highly infectious, stable as aerosols, and cause high morbidity and mortality. These viral agents can infect by direct contact with needles, fluids and tissues of other infected patients, however aerosol infection in humans has not been reported with the exception of Hantavirus.

All suspected cases of VHF should be placed in isolation in negative-pressure rooms. Airborne, droplet and contact precautions should be instituted. Patient transport should be limited and masks should be placed if transport is essential. Dedicated equipment should be left in the patient's room. Disinfection of surfaces with 10% bleach solution or phenolic disinfectant is recommended. The patient should remain in isolation for the duration of the illness (Table 4).

Table 4. Isolation Guidelines for Presumed or Documented Viral Infections Related to Bioterrorism*

	Virus			
	Smallpox	VEE*	Viral Enceph.	VHF
Isolation Precautions				
Standard Precautions	X	X	X	X
Contact Precautions (gowns and gloves)	X			X
Airborne Precautions (negative pressure room & N95 masks for all individuals entering rm)	X			
Droplet Precautions (surgical mask)			X	
Patient Placement				
No restrictions				
Cohort "like" patients when private room unavailable	X		X	
Private Room	X	X		X
Negative Pressure	X			
Door closed at all times	X			
Patient Transport				
No restrictions			X	
Limit movement to essential medical purposes only	X	X		X
Place mask on patient to minimize dispersal of droplets		X		
Cleaning, Disinfection of Equipment				
Routine terminal cleaning of room with hospital approv. Disinfectant upon discharge	X	X	X	
Disinfect surfaces with bleach/water sol. 1:9 (10% sol.)				X
Dedicated equipment (disinfect prior to leaving room)	X			X
Linen management as with all other patients	X	X	X	X
Post-mortem Care				
Follow principles of Standard Precautions	X	X	X	X
Droplet Precautions				
Airborne Precautions (negative pressure room & N95 masks for all individuals entering rm)	X			

*Adapted from Karwa M, et al. Bioterrorism and Critical Care. Crit Care Clin 2003; 19:279-313, with permission)
*VEE = Venezuelan Equine Encephalitis

9 SPECIAL OR IMMUNOSUPPRESSED HOSTS

9.1 Burns/Trauma

Burn patients have been reported to have a high incidence of herpes simplex virus (HSV) infections manifested as ARDS and occasionally as pneumonia (172-174). Necrotizing tracheobronchitis, and facial rashes

have also been found in these patients (175-179). With acyclovir therapy, there has been reported clinical improvement. Isolation of HSV from bronchoalveolar lavage specimens is associated with the need for assisted ventilation in burn patients (180,181). However, there are conflicting studies on whether HSV activation is associated with increased mortality in these patients (182). A recent prospective study culturing for HSV in the respiratory tract of patients in critical care units showed HSV reactivation was frequent and associated with ARDS and increased length of stay in intensive care (183). This confirmed results from other older studies (184,185). Similar findings have also been found in critically ill surgical patients (186-188).

9.2 Pregnancy

There are numerous physiologic and immunologic changes in pregnancy that create a state of relative immunosuppression (189). Pregnant women are more susceptible to a variety of viral infections including pneumonia (189,190). Influenzavirus, VZV, and measles have all been reported as causes of pneumonia (191-194). Complications of VZV can be particularly devastating during pregnancy. Ninety percent of adults living in nontropical areas are immune to varicella, therefore most pregnant women are not susceptible (195). Pneumonia can occur a few days after the development of rash and fever and can lead to respiratory failure. Both the mother and fetus can suffer morbidity and mortality from varicella. Patients with the complication of varicella pneumonia should be treated aggressively with antiviral therapy and close monitoring (194-197). Acyclovir is generally accepted as the treatment of choice despite the lack of safety studies (198). In pregnant women with no history of VZV who have an exposure, the use of VZIG may be beneficial in preventing maternal infection (199). Another virus that may lead to admission to the ICU is HSV. HSV infection can affect both the mother and the developing fetus (200-202). HSV of the genital tract can be transferred to the newborn and result in severe and life-threatening disease (203). Although rare, HSV type 2 causing encephalitis following cesarean section has been reported (204). Finally, given recent concerns regarding bioterrorism, it is important to realize that smallpox has had high mortality in the pregnant woman compared to the non-pregnant woman (205).

9.3 Transplantation

Viral infections can cause severe morbidity and mortality in both solid-organ and stem cell transplant patients (206-211). These infections can manifest as either primary infection or reactivation of latent disease (212,213). Viral infections in transplant patients may present as a variety

of clinical syndromes that require ICU stays. These include pneumonia, encephalitis, hepatitis and gastroenteritis (180,214-219).

The variety of clinical presentations and radiographic features make diagnosis of specific viruses difficult. In the transplant patient, common community respiratory viruses such as influenzaviruses A and B, respiratory syncytial virus (RSV), adenovirus and parainfluenzavirus (PIV) can lead to fulminant pneumonia, respiratory failure and death (4,220-224). There has been increased mortality reported in hematopoietic stem cell transplant patients who develop RSV or PIV infection (225-227). Occasional cases with metapneumovirus have been reported in stem cell transplant recipients (228,229). Both ribavirin with and without IVIG have been used to treat RSV pneumonia; but mortality remains high (33,230,231).Treatment benefit is generally seen when used prior to the development of respiratory failure (232). Other respiratory viruses that can lead to severe pneumonia are rhinoviruses and adenoviruses (233). Solid organ transplant recipients also are at risk of developing severe lower respiratory tract viral infections. One study found a high incidence of influenza among lung transplant patients, but liver and kidney transplant patients also develop influenza (234).

The Herpesviruses cause a variety of clinical syndromes in transplant patients. CMV, EBV, VZV, HSV, HHV-6 and HHV-8 have all been reported to cause disease (188,235-238). CMV disease constitutes a serious problem in bone marrow transplant recipients with a 30-50% incidence of clinically significant infections (239,240). Pneumonitis is the most serious complication and was associated with high mortality prior to antiviral therapy (241). Ganciclovir and foscarnet have been frequently used for prophylaxis and treatment of CMV (242-245). Hyperimmune globulin in combination with antivirals has also been used for treatment of disease (246). Ganciclovir resistance in CMV has been reported and should be considered when clinical responses do not occur (247). EBV can reactivate in transplant recipients and lead to uncontrolled B-cell proliferation and post-transplant lymphoproliferative disorder (PTLD) (248). This can present as frank lymphoma with high mortality rates. Donor lymphocyte infusions and anti-CD20 antibody has been used for treatment (249). HSV can present as both severe mucocutaneous disease or in rare cases encephalitis (250). HSV disease results from reactivation of latent virus (251). Other viruses that cause encephalitis in transplant patients are CMV, VZV, EBV, HHV-6 and recently West Nile Virus (252). Cases of encephalitis usually require treatment in the ICU. In this patient population, viral pneumonia and encephalitis require care in an

ICU setting. Although viral culture has been the gold standard for diagnosis, PCR has become the new diagnostic standard (225,253).

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