134 Acute Viral Syndromes

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Acute infections with viruses produce a variety of clinical manifestations with a wide spectrum of clinical severities. Viral upper respiratory tract infections in immunocompetent hosts are usually trivial, although they may be life-threatening and associated with subsequent lower respiratory tract infection and disseminated disease in immunocompromised hosts. Respiratory virus infections, including those responsible for MERS and SARS, are described elsewhere in this book.

Viral infections can affect virtually every organ system and have a variety of clinical manifestations. These are described below.

VESICULAR RASH

Poxviruses Including Smallpox and Monkeypox

Poxviruses are double-stranded DNA viruses that are relevant because of concerns regarding possible bioterrorism with smallpox.[1,2] Additionally, outbreaks of monkeypox infection in humans have been detected, albeit rarely.[3] The poxviruses and their major clinical manifestations are listed in Table 134-1. In general, a common feature of poxviruses is that they cause vesicular skin eruptions.

Smallpox

The last case of endemic smallpox occurred in Somalia in 1977, and it was declared in 1980 that the disease was eradicated.[4] The virus (variola) has been maintained in some laboratories—the last known case of laboratory-acquired smallpox occurred in the United Kingdom in 1978. In part, as a result of this accident, the number of laboratories that retained the virus was reduced from 76 to 2. These laboratories are at the Centers for Disease Control and Prevention (CDC) in Atlanta in the United States and the Vektor Institute in Novosibirsk in Russia. It is not known if all the other laboratories destroyed their stocks of viruses—therefore, the potential exists for a deliberate release of variola as an act of bioterrorism.[1,5]

The incubation period for smallpox is 7 to 17 days (mean, 10-12 days).[4] A prodromal phase consisting of the abrupt onset of severe headaches, backaches, and fever occurs. The fever often reaches 40°C and then subsides. This is followed by a rash; initial lesions are small, red macules, which become vesicles over the next 2 to 3 days. The lesions first appear on the face and extremities and then cover the entire body including the palms and soles of feet. Subsequently, these lesions may umbilicate and crust.

The rash of smallpox could be confused with monkeypox, generalized vaccinia and eczema vaccinatum, chickenpox, coxsackievirus infection, herpes simplex virus (HSV) infection (especially eczema herpeticum), rickettsialpox, insect bites, drug eruptions, and acne. A classic feature of smallpox is that the lesions are all at the same stage of development. In contrast, chickenpox has individual lesions present at different stages of development. With chickenpox, fever occurs with the onset of the rash.

It is well known that smallpox is associated with significant mortality; however, it is not clear what the likelihood of mortality would be in patients who receive good supportive care, such as that which exists in modern intensive care units (ICUs). There are many reasons for the mortality associated with smallpox. Substantial amounts of fluid and protein are lost by febrile patients with numerous weeping lesions. In some patients, death may occur before the appearance of any rash since this prodromal period is associated with significant viremia. A hemorrhagic form of smallpox is also associated with high mortality.[4] Encephalitis occurs in less than 1% of infected patients. Secondary bacterial infections of the skin lesions may occur and are heralded by a second temperature spike.[4] Although cough is not usually a prominent symptom of smallpox, secondary bacterial pneumonia may occur, particularly in patients with severe disease.

The CDC recommends an algorithmic approach for the diagnosis of smallpox. Patients are subdivided into low-risk, moderate-risk, and high-risk groups depending on a variety of variables (Boxes 134-1 and 134-2). Patients at low or moderate risk of smallpox should undergo polymerase chain reaction (PCR) testing of the skin lesion for varicella-zoster virus (VZV) infection, HSV, and enterovirus. Patients at moderate risk undergo consultation by infectious disease or dermatology specialists. Electron microscopy should be performed if PCR for these viruses is negative. If rapid testing for VZV and HSV is negative for moderate-risk patients, the adequacy of specimen collection should be confirmed. If there is ongoing clinical suspicion of smallpox, local and state health departments should be consulted. For patients at high risk of smallpox, all testing should be performed at the CDC. This testing should include variola real-time PCR, *Orthopoxvirus* real-time PCR, and nonvariola *Orthopoxvirus* real-time PCR, in addition to tests for VZV, HSV, and enteroviruses.

There is no approved treatment for smallpox.[4] Prevention of secondary cases is crucial. A suspected case of smallpox should be managed in a negative-pressure room. Additionally, strict respiratory and contact isolation is essential (detailed instructions are available at http://www.bt.cdc.gov/agent/smallpox).[4]

Vaccinia

Vaccinia is the poxvirus used in smallpox immunizations. The primary vaccination results in a vesicle at the site of vaccination, usually within 3 to 5 days. This vesicle becomes pustular or is surrounded by induration or congestion 6 to 8 days after vaccination. In rare cases, a generalized rash characterized by multiple small, vesicular lesions occurs. Occasionally, severe complications result from smallpox vaccinations. If vaccinia is administered to patients with an immunologic deficiency, progressive necrosis at the site of vaccination may occur (vaccinia necrosum). Second, lesions may spread to other parts of the body. Such cases may be fatal. Patients with eczema may develop dissemination of vaccinia virus in the abnormal skin, leading to a generalized rash (eczema vaccinatum or Kaposi varicelliform eruption). Vaccinia immunoglobulin (0.6 mL/kg every 24 hours) can be prescribed for disseminated infection.

Encephalitis due to vaccinia may occur 1 to 2 weeks after vaccination and is associated with a mortality of 10% to 30%. Myocardial infarction, pericarditis, myocarditis, and dilated cardiomyopathy have been observed after smallpox vaccinations. In 2003, 37,901 potential bioterrorism first responders received the smallpox vaccine in the United States. There were 822 reports of adverse events; 100 of the 822 were serious, resulting in 85 hospitalizations, 2 permanent disabilities, 10 life-threatening illnesses, and 3 deaths. Among the 100 serious adverse events, 21 cases were myocarditis and/or pericarditis, 10 cases were ischemic cardiac events, 2 cases were generalized vaccinia, and 1 case was postvaccinial encephalitis. Serious adverse events were

TABLE 134-1 Common Clinical Manifestations of Poxviruses

VIRUS	CLINICAL MANIFESTATIONS
Variola (smallpox)	Diffuse vesicular rash; systemic disease
Monkeypox	Vesicular rash
Vaccinia (cowpox)	Vesicular rash; postinfectious encephalitis
Parapoxvirus	Orf (localized vesicular lesion)
Molluscipoxvirus	Molluscum contagiosum
Tanapox virus	Vesicular rash

BOX 134-1 Criteria for the Suspicion of Smallpox in Patients with Acute Generalized Vesicular or Pustular Rash

MAJOR SMALLPOX CRITERIA
Febrile prodrome
>101°F, 1-4 days before rash onset, with headache, backache, or abdominal pain
Firm, deep-seated, well-circumscribed vesicles/pustules
Lesions in the same stage of development in any one area of the body

MINOR SMALLPOX CRITERIA
Centrifugal distribution
First lesions in the pharynx, oral mucosa
Patient appears "toxic"
Slow evolution of the rash
1-2 days each stage: macule, papule, vesicle
Lesions on palms and soles

BOX 134-2 Categorization of Risk of Smallpox from Clinical Criteria*

HIGH RISK OF SMALLPOX
Febrile prodrome *and*
Classic smallpox lesion *and*
Lesions in the same stage of development

MODERATE RISK OF SMALLPOX
Febrile prodrome *and* one other *major* smallpox criterion *or*
Febrile prodrome *and* four or more minor smallpox criteria

LOW RISK OF SMALLPOX
No febrile prodrome *or*
Febrile prodrome *and* fewer than four minor smallpox criteria

*The major and minor criteria are listed in Box 134-1.

more common among older revaccinees than in younger first-time recipients.[6]

From December 2002 to January 2004, the U.S. Department of Defense vaccinated 578,286 military personnel with vaccinia.[6] Thirty cases of suspected contact transfer of vaccinia were reported.[6] *Contact transfer* is the spread of vaccinia from a recipient of the smallpox vaccine to another person. This spread occurs because the live virus used in the vaccine is present on the skin at the site of the vaccination. Spread of the virus to other parts of the body (autoinoculation) also can occur via the same mechanism. No cases of vaccinia necrosum or eczema vaccinatum were observed in the people with contact transfer of the virus.

Monkeypox

Monkeypox was first recognized in 1958 as a disease of primates. Subsequently, the disease was recognized in rodents. Beginning in 1970, cases in humans were reported in Central Africa.[7] In 2003, cases occurred in the United States in residents of the Midwest who had contact with imported prairie dogs.[3] Patients developed vesicular skin lesions and fever/sweats. Although case fatality rates of 4% to 22% have been observed in outbreaks of the infection in Africa, none of the 11 patients in the American outbreak died.[3]

Herpesviruses

HSV, VZV, and herpes B virus are all capable of causing vesicular skin rash and other systemic manifestations of disease. The herpesviruses are large, enveloped DNA viruses that exhibit lifelong latent infection.[8,9] The eight known human herpesviruses are HSV types 1 and 2; VZV; cytomegalovirus (CMV); human herpesvirus (HHV) types 6, 7, and 8; and Epstein-Barr virus (EBV).

Herpes Simplex Virus

HSV infections are found worldwide. Characteristically, HSV-1 is associated with orolabial disease, and HSV-2 is associated with genital infection, although this is not a rigid distinction. Primary infections (first infections with HSV-1 or HSV-2) are usually associated with mucosal lesions and systemic signs and symptoms. Mucosal and cutaneous lesions are vesicular and usually localized, although disseminated infection may occur rarely. Patients with atopic eczema or severe burns may develop extensive infections.

Primary HSV infections may have severe complications. Aseptic meningitis may occur and is more common with HSV-2. Meningeal symptoms usually start 3 to 12 days after the onset of genital lesions. Transverse myelitis and autonomic nervous system dysfunction may also occur in conjunction with primary genital HSV infection. HSV encephalitis in adults usually is not associated with primary infection. Potentially, reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with the extension of virus into the central nervous system (CNS) via the enervation of the middle cranial fossa. Occasionally, patients with primary HSV infection develop hepatitis, pneumonia, or thrombocytopenia. These complications may be life-threatening and require ICU admission.

By virtue of the establishment of latency, HSV-1 or HSV-2 may reactivate. HSV reactivations may be less severe than primary infections. In immunocompromised hosts, however, reactivation of HSV-1 or HSV-2 may be associated with disseminated infection or severe local esophagitis, hepatitis, or pneumonia. Neonatal herpes, occurring in infants of mothers with primary or reactivated infection at the time of delivery, carries a high risk of disseminated fatal infection.

HSV-1 encephalitis is frequently seen in the ICU and is characterized by confusion or coma, accompanied by cerebrospinal fluid (CSF) lymphocytosis. Magnetic resonance imaging (MRI) of the brain may show temporal lobe lesions. Testing of CSF by PCR for HSV-1 is typically positive.

Diagnosis of HSV-1 or HSV-2 infections causing vesicular skin lesions can be suspected clinically by the presence of multiple vesicular lesions on an erythematous base, occurring in the orolabial or anogenital areas. A precise diagnosis can be established easily by PCR on scrapings from the lesions. Results can be available within hours of specimen collection.

Varicella-Zoster Virus

Primary VZV infections cause chickenpox, whereas reactivated infections cause shingles (zoster). Chickenpox is characterized by multiple vesicular lesions, whereas shingles is characterized by a unilateral vesicular eruption with a dermatomal distribution. Immunocompromised patients with shingles may develop disseminated cutaneous infection that may resemble chickenpox.

Chickenpox is usually associated with fever, constitutional symptoms, and a vesicular skin rash. Most skin lesions are small vesicular lesions with an erythematous base. Successive crops of lesions occur over 2 to 4 days, so lesions at all stages from fresh vesicles to crusted lesions are present simultaneously.

Secondary bacterial infections of vesicular lesions are relatively common, with infections involving *Staphylococcus aureus* and *Streptococcus pyogenes* being the most common. One manifestation of secondary bacterial infection is the occurrence of fever after the fever associated with the onset of chickenpox has subsided. Severe infection often results in toxic shock syndrome.[10,11]

Chickenpox is associated with pneumonia in 1 in 400 cases of infection.[12,13] A larger proportion of people may have some pulmonary involvement, but it is typically asymptomatic. Pregnant women and immunocompromised patients are at high risk of life-threatening pneumonia. Chickenpox pneumonia is generally manifested by cough and shortness of breath 3 to 5 days after the onset of the rash. Chest radiography typically shows a reticulonodular infiltrate. Respiratory failure may occur.

Neurologic complications of chickenpox include encephalitis, acute cerebellar ataxia (1 in about 4000 cases),[14] and cerebral angiitis. Encephalitis due to VZV is less common than pneumonia but nevertheless may be life-threatening. The typical manifestation is onset of headaches followed by depression occurring in adults within 2 weeks of the chickenpox. Acute cerebellar ataxia is more common in children 1 to 3 weeks after the onset of chickenpox. Ataxia and slurred speech may occur but usually with complete resolution.

As with HSV infections, the rash of chickenpox or shingles can usually be diagnosed confidently on clinical grounds or confirmed by PCR of scrapings of skin lesions. PCR can also be performed on CSF to diagnose VZV encephalitis.[14]

Herpes B Virus (Cercopithecine Herpesvirus 1)

Herpes B virus (cercopithecine herpesvirus 1) infection is a relatively benign disease in monkeys. However, herpes B virus infection in humans, usually occurring from monkey bites or scratches, is a severe and potentially fatal disease. Monkeys of the *Macaca* genus (rhesus and cynomolgus monkeys) are considered to be at the highest risk. An incubation period of 2 to 14 days is usually observed after the bite or scratch. Initial symptoms are nonspecific but include fever, malaise, and headache. A cluster of small vesicles may occur at the bite site. Severe encephalomyelitis may ensue, with death occurring in days. In the United States, only one reference laboratory is equipped to identify the virus. Prompt and exhaustive cleaning of wounds, followed by early initiation of acyclovir or valacyclovir, may prevent the occurrence of severe disease. Additional information with contacts is available at http://www.cdc.gov/niosh/docs/99-100/.[15,16]

FEVER IN IMMUNOCOMPROMISED PATIENTS

Numerous viruses can cause fever as a presenting symptom. In the absence of specific manifestations such as pneumonia or encephalitis, viral infections are rarely life-threatening. The onset of fever in immunocompromised individuals may, however, be the harbinger of severe overwhelming viral infection.

Cytomegalovirus

CMV infection is a classic cause of severe infection in immunocompromised hosts, especially transplant recipients and patients with human immunodeficiency virus (HIV) infection.[17-19] Infection can be primary or due to reactivation. The risk of end organ CMV infection depends on the degree of immunosuppression and whether the infection is primary or reactivated. For solid organ transplant recipients, there is a significant risk of primary infection in patients who were seronegative for CMV before transplantation and received an organ from a seropositive donor.[17,19]

The organs commonly affected by CMV infection include the esophagus, colon, retina, and lungs. Virtually any organ can be infected, including the CNS. Some patients present with fever, malaise, and hematologic abnormalities, without specific end organ abnormalities.

Given the high risk of CMV infections in solid organ transplant recipients, strategies should be employed to prevent CMV infections.[17,20,21] Two options are prophylaxis or preemptive therapy. *Prophylaxis* implies the administration of preventive therapy to all persons at risk.[17] In contrast, *preemptive* therapy is the administration of antiviral therapy only to persons at highest risk, as determined by a positive result on a regularly monitored blood test for CMV infection.[17] Such therapy is given even if the patient is asymptomatic. Detection of CMV by PCR is used most often for early detection of CMV infection.

Epstein-Barr Virus

Primary EBV infection may be associated with fever, malaise, and hematologic abnormalities in immunocompromised patients (and also in some immunocompetent individuals). EBV infection may be associated with the development of malignancies such as posttransplant lymphoproliferative disorder.[22-24] In some transplant populations, regular quantitative monitoring of EBV in peripheral blood by PCR is performed to determine the risk of significant EBV infection.[25]

Human Herpesvirus 6

HHV-6 is a ubiquitous viral infection that usually occurs in infancy. Primary HHV-6 infection and possibly reactivation of infection in immunocompromised patients can be associated with serious disease.[26,27] HHV-6 seems to have neurotropism—in addition to fever, HHV-6 infection may be associated with confusion, coma, and seizures.[28,29] Occasionally, CSF examination is normal except for increased protein and the finding of HHV-6 by PCR.

Human Herpesvirus 8

HHV-8 is associated with Kaposi sarcoma, primary effusion lymphoma, and Castleman syndrome.[30,31] It may be transmitted via organ allograft in solid organ transplantation. Primary infection in immunosuppressed patients may be associated with high fever, thrombocytopenia and other severe cytopenias, and mental state abnormalities.[32] Detection of HHV-8 by PCR in whole blood can establish the diagnosis.

West Nile Virus and Zika Virus

In the 1990s, West Nile virus infection was detected in North America for the first time.[33,34] Although many cases of infection were directly from the vector of infection (mosquitoes), other cases were via blood transfusion or organ allograft.[35,36] West Nile virus exhibits neurotropism; infected patients may experience confusion and headaches in addition to fever and other more general symptoms.

Although Zika virus was described some decades ago, it has come to significant attention in 2015 and 2016. Most infected patients have minor symptoms with rash and fever. However, some adult patients may have more significant infection. In utero transmission may result in microcephaly and significant developmental problems in the child.

Adenovirus

Adenoviruses have a myriad of presentations in immunocompetent and immunocompromised hosts. Adenovirus infection in immunocompetent individuals is rarely associated with severe disease.[37] Although adenovirus infection in immunocompromised hosts may have trivial manifestations, severe diseases may certainly occur. In recipients of hematologic stem cell transplantation, adenoviruses may cause interstitial pneumonitis, hepatitis including ascending cholangiohepatitis, hemorrhagic cystitis, nephritis, hemorrhagic colitis, CNS disease, and disseminated disease.[37] In solid organ transplant recipients, the primary site of adenovirus disease is usually related to the transplanted organ. Clinical manifestations of adenovirus infections described in solid organ transplantations include pneumonia, hepatitis, nephritis, hemorrhagic cystitis, enteritis, and disseminated disease.[37]

Adenovirus infection in patients with HIV may cause pneumonia, hepatitis, meningoencephalitis, nephritis, and gastrointestinal and disseminated disease.[37]

Polyomaviruses

The most commonly encountered polyomaviruses are JC virus and BK virus. JC virus may be associated with progressive multifocal leukoencephalopathy, a progressive and ultimately fatal neurologic disease occurring in profoundly immunosuppressed individuals, such as patients with advanced HIV infection. BK virus is associated most commonly with renal infection in renal transplant recipients.[38] This infection is usually not accompanied by systemic manifestations such as fever. Infected patients have steadily rising serum creatinine. This presentation may be mistaken for acute rejection. Treatment with augmented immunosuppression is contraindicated, however, in patients with BK virus–associated nephropathy. Instead, immunosuppression should be minimized.

VIRAL HEMORRHAGIC FEVERS

Hemorrhagic fevers may be due to Filoviridae, Bunyaviridae, Arenaviridae, or Flaviviridae. Dengue hemorrhagic fever is not discussed in this chapter because it is reviewed in detail elsewhere in this book.

Marburg and Ebola Virus Hemorrhagic Fevers

Marburg virus and Ebola virus are members of the *Filovirus* genus. Marburg virus appears to have originated in Uganda and Western Kenya, where it infected monkeys and subsequently humans. *Marburg* refers to a town in Germany where monkeys from Uganda infected medical researchers, who subsequently infected hospital staff. The major subtypes of Ebola virus have occurred in Central Africa. An additional subtype (Reston) was discovered in Reston, Virginia, among infected monkeys imported from the Philippines.[39] The source of this infection has not been definitively determined.

Marburg and Ebola virus infections have an incubation period of 5 to 10 days and begin with the abrupt onset of fever, myalgia, and headache. Somnolence and delirium usually follow. Most patients have abdominal pain and diarrhea. Many have a maculopapular rash on the trunk. Hemorrhagic manifestations such as bleeding around needle puncture sites and from the mucous membranes become prominent. Most patients have significant thrombocytopenia, leukopenia, and elevated transaminase levels. Viral culture, serology, and PCR have all been used to establish the diagnosis. At present, management is purely supportive. Additionally, strict contact isolation precautions are necessary.

Hanta Fever and Crimean-Congo Hemorrhagic Fever

Hantavirus and Crimean-Congo hemorrhagic fever (CCHF) virus (CCHFV) are from the Bunyaviridae family of viruses. Hantaviruses cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). There are several human pathogenic strains of hantavirus. The subtypes Hantaan, Dobrava, and Seoul cause moderate to severe HFRS in Asia and Europe, whereas Puumala causes a mild form of HFRS.[40] Unlike other Bunyaviridae, hantaviruses do not appear to have an arthropod vector and are usually transmitted via aerosols of virus-contaminated rodent urine or feces. The incubation period is typically 2 weeks. Initially, patients develop fever, headache, dizziness, blurred vision, abdominal pain, and back pain. Petechiae may be evident on the palate and the trunk; most patients have significant thrombocytopenia. After 4 to 7 days, significant hypotension can occur. In patients who survive, oliguria and mucosal hemorrhage occur, followed by polyuria. Sin Nombre virus and Andes virus cause HPS in North America and South America, respectively.[40]

CCHF is a severe hemorrhagic fever with a mortality rate ranging from 3% to 30%; it has been described in parts of Africa, Asia, Eastern Europe, and the Middle East.[41] It has the most extensive geographic distribution of medically important tickborne viral diseases. CCHF occurs through tick (*Hyalomma* spp.) bites, by contact with blood or tissues from viremic livestock, and after contact with patients with CCHF during the acute phase of infection.[41] Patients have severe thrombocytopenia, disseminated intravascular coagulation, and extensive bleeding, with increased levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase. Diagnosis is made by enzyme-linked immunoassay (ELISA) and PCR. The clinical course of CCHF is composed of an incubation period (3-7 days), a prehemorrhagic period (3-7 days) characterized by flu-like symptoms, a hemorrhagic period (2-3 days), and a convalescence period. Supportive therapy is the most essential part of the management of CCHF. Ribavirin (30 mg/kg as an initial dose, then 15 mg/kg 6-hourly for 4 days, then 7.5 mg/kg 8-hourly for 6 days) is the recommended antiviral agent for severe CCHF, although its mechanism of action is unknown.[41]

Lassa Fever and South American Hemorrhagic Fevers

Lassa fever and South American hemorrhagic fevers are due to the Arenaviridae. Lassa fever occurs in West Africa. South American hemorrhagic fevers occur in Argentina, Bolivia, and Venezuela. Lassa fever is transmitted via rodents, but subsequent nosocomial transmission has been extensive. Many cases of Lassa fever are only mildly symptomatic. Some patients develop high fever, pharyngitis, and retrosternal chest pain accompanied by significant mucosal bleeding. Hypotension, renal failure, and pulmonary edema may follow. Serology can be used to establish the diagnosis, but the virus is also easily isolated from blood during the first week of illness, when viremia is often striking. Use of ribavirin has been associated with a decrease in mortality.[42]

South American hemorrhagic fevers (Argentine, Bolivian, and Venezuelan) usually present with unremitting fever accompanied by a variety of nonspecific symptoms. Petechiae are often present on the palate and the skin, especially the axilla; mucosal bleeding may result. Pulmonary edema may occur. Management is extremely difficult owing to the combination of hypotension and refractory pulmonary edema. The diagnosis can be established by serologic tests. No specific therapy is available.

2009 PANDEMIC INFLUENZA A AND AVIAN INFLUENZA A

The rapid dramatic increase in the frequency of severe illness due to the 2009 influenza A(H1N1) has affected intensive care facilities around the world.[43-45] Suggested risk factors for severe illness associated with the 2009 H1N1 infection include age (<5 years or ≥65 years), pregnancy, chronic cardiovascular conditions, chronic lung disorders, diabetes, immunosuppression, morbid obesity, hemoglobinopathy, chronic renal disease, chronic hepatic disease, and a long history of smoking.[46] Therapy with neuraminidase inhibitors (e.g., oseltamivir, zanamivir) is especially important for patients with such risk factors, as well as pregnant women. Epidemiologic studies estimated the case fatality ratio to be 0.05% to 0.5%.[47] However, as more than three-quarters of cases of the 2009 influenza A(H1N1) pandemic occurred in persons younger than 30 (with a peak in the group aged 10 to 19 years), years of life lost are estimated to be 3 to 5 times higher than for typical seasonal influenza and of the same order as the 1968 pandemic.[47]

Avian influenza A(H5N1) virus remains a cause for concern. The first human case of influenza A(H5N1) virus infection was documented in Hong Kong in 1997.[48] Since its reemergence in 2003, it has caused human cases in 15 countries (e.g., China, Egypt, Indonesia, Iraq, Nigeria, Thailand, Turkey, Vietnam) around the world.[49-53] The cumulative number of cases of avian influenza A(H5N1) virus infections

reported to the WHO as of June 8, 2010, was 499, with 295 subsequent deaths representing a mortality rate of approximately 60% (http://www.who.int/csr/disease/avian_influenza/country/en/). Although it has limited ability for human-to-human transmission, the continued circulation of influenza A(H5N1) virus increases the possibility of the reassortment of this virus with other circulating human influenza A viruses and increases the threat of a global influenza pandemic.[50]

HENDRA AND NIPAH VIRUSES

These paramyxoviruses have been associated with deaths due to encephalitis or an acute pulmonary syndrome in Australia (Hendra virus) and Malaysia, Singapore, India, and Bangladesh (Nipah virus). The reservoir for these closely related viruses appears to be fruit bats. Viral transmission appears to occur from bats to horses (Hendra virus) or pigs (Nipah virus). Humans exposed to ill horses or pigs have developed the fatal infection. In Bangladesh, nosocomial transmission of Nipah virus may have occurred.

OTHER ACUTE VIRAL SYNDROMES

Many viruses can cause aseptic meningitis, encephalitis, pneumonia, or hepatitis. These viruses are summarized in Tables 134-2, 134-3, and 134-4.

ANTIVIRAL DRUGS

Since the advent of HIV infection, there has been an increase in the development of drugs active against viruses. This section describes the currently available antiviral drugs, with the exception of drugs for HIV and viral hepatitis.

Acyclovir

Acyclovir is a deoxyguanosine analog that inhibits viral DNA polymerase. When incorporated into viral DNA, it acts as a chain terminator. Acyclovir has its greatest clinical utility against HSV-1, HSV-2, and VZV. It has some activity against CMV, but it is far inferior to ganciclovir for infections with this virus. Acyclovir-resistant HSV has been well described, whereas acyclovir-resistant VZV is rare. Acyclovir is available in oral and intravenous (IV) forms. It penetrates the CSF reasonably well, and CSF levels are about 50% of plasma levels.[43] Dosing for acute mucosal HSV infections is 200 mg, five times a day, administered orally, and for VZV infections is 800 mg, five times a day, administered orally. In HSV encephalitis, the usual dose is 10 mg/kg given IV every 8 hours. Dose reduction is required in the presence of renal dysfunction. In the absence of appropriate reduction in dosage for renal dysfunction, neurotoxicity is observed, usually manifesting as confusion, hallucinations, and occurrence of tremors. As acyclovir can cause crystalline nephropathy, patients receiving the drug should be well hydrated.

Valacyclovir

Because the bioavailability of orally administered acyclovir is low, valacyclovir (the L-valyl ester prodrug of acyclovir) was developed. It is usually administered twice daily for HSV infections and three times daily for VZV infections. Valacyclovir is also used for the prevention of CMV disease in renal transplant recipients.[54]

Famciclovir

Famciclovir lacks antiviral activity but is the prodrug of penciclovir, which is active against HSV and VZV. Similar to acyclovir, penciclovir is an inhibitor of viral DNA synthesis. In general, acyclovir-resistant strains are also resistant to penciclovir. Dose adjustment of famciclovir is needed in renal insufficiency.

TABLE 134-2 Viruses That Cause Aseptic Meningitis or Encephalitis

VIRUS	IMPORTANT CLINICAL FEATURES
Enteroviruses	Common cause of aseptic meningitis; rapid diagnosis available via PCR of CSF
HSV	In adults usually due to reactivation; rapid diagnosis available via PCR of CSF
VZV	Uncommonly may cause encephalitis after chickenpox
HHV-6	Causes encephalitis in transplant recipients
JK virus	Causes progressive multifocal leukoencephalopathy
Japanese encephalitis	Endemic in parts of Asia
St. Louis encephalitis	Outbreaks have occurred in all U.S. states
West Nile virus	Now common in U.S. and Canada
Tickborne encephalitis	Several foci of infection
Nipah virus	Zoonosis occurring in Malaysia, Singapore, India, and Bangladesh
Hendra virus	Zoonosis occurring in Australia
Rabies virus	Well-known zoonosis
California encephalitis	La Crosse virus is responsible for most cases
Human immunodeficiency virus	May cause acute encephalitis

CSF, cerebrospinal fluid; HSV, herpes simplex virus; HHV-6, human herpesvirus 6; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

TABLE 134-3 Viruses That Cause Pneumonia

VIRUS	IMPORTANT CLINICAL FEATURES
Respiratory syncytial virus	Common cause of infection in infants
Influenza	Well-known cause of respiratory infection
Parainfluenza virus	Croup and pneumonia
Measles virus	Leading cause of pneumonia in children in underdeveloped nations
Coronaviruses	Severe acute respiratory syndrome
CMV	Important cause of pneumonia in immunosuppressed hosts
VZV	Pneumonia can complicate chickenpox
Adenovirus	Ubiquitous virus; severe pneumonia in immunosuppressed hosts
Hantavirus	Severe pneumonia in immunocompetent hosts
Hendra virus	Zoonosis in Australia

CMV, cytomegalovirus; VZV, varicella-zoster virus.

TABLE 134-4 Viruses That Cause Hepatitis

VIRUS	IMPORTANT CLINICAL FEATURES
Hepatitis A virus	Fecal-oral transmission
Hepatitis B virus	Parenteral, sexual, vertical transmission
Hepatitis C virus	Parenteral transmission
Hepatitis D virus	Requires coinfection with hepatitis B
Hepatitis E virus	Fecal-oral transmission

Ganciclovir

Similar to acyclovir, ganciclovir is a deoxyguanosine analog. It has activity against HSV and VZV. Its primary use has been in the treatment or prevention of CMV infections. Ganciclovir acts by inhibiting viral DNA polymerases. Patients with end organ disease due to CMV are treated initially with ganciclovir, 5 mg/kg IV every 12 hours. Alterations in dose and frequency are required in patients with renal dysfunction. Typically, maintenance therapy is given at a reduced frequency (e.g., once per day) in patients who have received 2 to 3 weeks of induction therapy. Myelosuppression is the major toxicity of ganciclovir. Neutropenia typically begins to occur in the second week of ganciclovir therapy. Regular monitoring of hematologic parameters is mandatory for patients receiving ganciclovir. CNS abnormalities such as headaches and confusion have been well described in patients receiving ganciclovir. In addition to an IV preparation, ganciclovir is available in an orally administered form. This form may be useful as a prophylaxis against CMV infections.[17] Ganciclovir also can be administered into the eyes via an ocular implant.[55,56] Ganciclovir is less active against acyclovir-resistant HSV strains than against acyclovir-susceptible strains. Resistance of CMV to ganciclovir has been well described, and mutations in the *UL97* phosphotransferase gene are generally associated with ganciclovir resistance.[17,57] Risk factors for ganciclovir resistance include prolonged exposure to ganciclovir (usually several months), ongoing active viral replication due to severe immunosuppression, lack of prior CMV immunity, and inadequate antiviral drug delivery with oral ganciclovir.[17]

Valganciclovir

The oral bioavailability of ganciclovir is poor. Valganciclovir, a prodrug of ganciclovir, can be used to enhance bioavailability. Valganciclovir is widely used as a prophylaxis against CMV infections.[17] However, a meta-analysis demonstrated that valganciclovir for CMV prevention in solid organ transplant patients had no superior efficacy and significantly higher risk of absolute neutropenia, CMV late-onset disease, and CMV tissue-invasive disease compared to other standard therapies (e.g., valacyclovir, ganciclovir).[58] A recent study has suggested the safety and efficacy of valganciclovir for preemptive therapy and treatment of CMV disease in solid organ transplant recipients.[59]

Foscarnet

Foscarnet is used most frequently in patients with CMV infection refractory to or intolerant of ganciclovir. Foscarnet also has activity against HSV and VZV, including acyclovir-resistant and ganciclovir-resistant strains. Although foscarnet and ganciclovir may have synergistic activity against CMV, there is no proven usefulness of their combination in therapy.[60] Use of the combination of ganciclovir and foscarnet is associated with greater toxicity than use of ganciclovir alone.[60] Foscarnet is available in an IV formulation only. Toxicity is common with foscarnet. Nephrotoxicity is a major dose-limiting side effect. Electrolyte abnormalities are also common, especially hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia, which may be symptomatic. Foscarnet may produce painful genital ulcerations; saline loading may diminish the likelihood of nephrotoxicity or genital ulceration.

Cidofovir

Cidofovir is a nucleotide analog that is active against many herpesviruses and other DNA viruses, including polyomaviruses, poxviruses, and adenovirus. It is active against acyclovir-resistant and ganciclovir-resistant HSV and CMV. Cidofovir is administered via IV once a week or once every 2 weeks. Its use is accompanied by high rates of nephrotoxicity. Neutropenia occurs in 20% of patients receiving this drug.

Ribavirin

Ribavirin has found wide use as part of a combination therapy for hepatitis C virus infection, but it is discussed here in the context of its use against other viruses. In vitro, ribavirin has activity against a wide range of DNA and RNA viruses. Ribavirin (aerosolized) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of bronchiolitis and pneumonia due to respiratory syncytial virus. It has been used systemically in the treatment of some hemorrhagic fevers. Systemic ribavirin administration is associated with hemolytic anemia. Use of aerosolized ribavirin is controversial because of the drug's teratogenicity. Healthcare workers may potentially be exposed to the drug when it is used in conjunction with mechanical ventilation; use of aerosol containment systems are thus recommended.

Antiinfluenza Drugs

Amantadine, rimantadine, zanamivir, and oseltamivir are used in the treatment of influenza and for postexposure prophylaxis. Amantadine and rimantadine are active only against influenza A virus, whereas zanamivir and oseltamivir are active against influenza A and B viruses. In patients who have not received reduced doses of amantadine or rimantadine in the setting of renal dysfunction, serious neurotoxic reactions (including confusion and seizures) have been observed. Extensive experience with oseltamivir has been gained in recent years, and the drug has been found to be generally safe.

IV formulations of zanamivir or peramivir are now available on a compassionate-use basis for treating seriously ill patients, and peramivir was recently authorized for emergency use in hospitalized patients in the United States and licensed for use in Japan.[46] The efficacy of IV peramivir appeared to be similar to that of oseltamivir for seasonal influenza, but peramivir is less active for oseltamivir-resistant viruses than for oseltamivir-susceptible viruses. Thus IV zanamivir is the preferred option for seriously ill patients with suspected or documented oseltamivir resistance.[46]

Acknowledgment

The contributions of Dr. Yoshiro Hayashi to a previous edition of this book are gratefully acknowledged.

KEY POINTS

1. For a generalized vesicular rash, scraping the base of the lesion and using polymerase chain reaction (PCR) to detect herpesviruses can assist in the rapid diagnosis of chickenpox or disseminated herpesvirus infections.
2. Cytomegalovirus (CMV) infection should be rapidly excluded as a cause of fever in an immunocompromised patient by way of detection of CMV DNA in peripheral blood by PCR.
3. Travelers from Africa, Asia, or South America who present with thrombocytopenia and fever should be assessed for Dengue and the viruses that cause hemorrhagic fevers. Strict contact isolation should be considered.
4. Herpes simplex virus (HSV), varicella-zoster virus (VZV), and enteroviruses can be detected by PCR of cerebrospinal fluid, enabling a rapid diagnosis.
5. Dosage adjustment is necessary for most commonly used antiviral agents in patients with renal dysfunction. Failure to adjust dosage may lead to adverse effects such as neurotoxicity.