Viral Sepsis

P. Amin and V. Amin

Introduction

Viruses are the smallest infective agents currently known to affect humans and animals. The virus has a centrally situated nucleic acid, which is encased within a capsid consisting of a protein core. Viruses are obligatory intracellular microorganisms that live inside cells, using components of the nucleic acid and protein generating system of the host to replicate and trigger cell destruction leading to diseases. Alternatively, the host's defense mechanisms lead to cell destruction in an attempt to clear cells infected by the viruses. The nucleic acid is RNA or DNA, which may be single-stranded or double-stranded [1]. The pathophysiology of viral infections may be attributed to the degeneration and cellular necrosis of the infected cells, leading to local and systemic inflammatory responses. The body's defense mechanisms include phagocytosis, humoral and cell-mediated responses and the production of interferons [2]. Interferons prevent the local spread of viruses, whereas antibodies prevent viremia, ensure long-term immunity and sensitize infected cells to be destroyed by T-cells and macrophages [3, 4]. Cell-mediated immunity leads to an increase in cytotoxic cells that then release lymphokines, including interferon.

Epidemiology

Most of the infective viruses are constantly present in human or animal reservoirs; under certain conditions they are then transmitted to susceptible individuals. During epidemics, such as influenza, measles, mumps, severe acute respiratory syndrome (SARS), a large proportion of the susceptible community is affected by aerosol transmission [5]. Antigenic drift is the reason underlying the epidemic spread of

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J.-L. Vincent (ed.), *Annual Update in Intensive Care and Emergency Medicine 2015*,
DOI 10.1007/978-3-319-13761-2_4

variation in structure, leading to different subtypes (e. g., influenza virus) [6]. An epidemic is said to occur when the number of cases is in excess of the expected number for that population based on past experience. When multiple continents are involved, the disease is said to be a pandemic, e. g., human immunodeficiency virus (HIV).

There are two major forms of transmission by which viruses can be classified: Viruses that stay within a single species and viruses that alternately infect different host species [7]. There are a few exclusions, such as rabies and influenza viruses, which spread across species. Animal reservoirs are an important source of transmission for diseases like rabies, arboviruses and certain hemorrhagic viruses. Humans are an important pool of chronic carriers of viruses, such as hepatitis B virus (HBV), HIV and some herpesviruses [8–10].

Certain host factors predispose the individual to increased severity of that infection (e. g., smoking and respiratory syncytial virus [RSV] infections; alcohol and hepatitis; development of paralytic poliomyelitis in exercised limbs; reactivation of Epstein-Barr virus (EBV) may be a risk factor for developing lymphoma).

Method of Transmission

Respiratory This is the most common route of transmission in viral illnesses. The virus may be present in saliva or respiratory secretions and may spread by a bite as in rabies, or by kissing as with EBV, or may be spread as an aerosol, e. g., influenza and measles. Hantavirus may spread by aerosols formed from the urine of rodents in the soil. Viruses that spread by the aerosol route clearly increase the risk of spread to health care workers and other indoor patients.

Gastrointestinal This is the second most common mode of spread of viral infections. The major enteric viruses are coxsackie, echo, rotaviruses, poliomyelitis, Norwalk viruses, hepatitis A, E and sometimes B.

Personal Contact Some of the viruses that are thought to be transmitted by aerosol or from gastrointestinal sources may actually spread by personal contact. The recent epidemic of Ebola virus, which is known to be highly infective, has spread to healthcare workers and other patients, as body fluids are highly infective in this illness.

Skin This is another important portal of entry of viruses, but need not necessarily be through intact skin. Virus may enter the body by bites, as in rabies, arboviruses in mosquito or tick bites, or by needlestick injury or blood transfusions, e. g., in HIV or hepatitis B and C. The skin also serves as a portal of exit from ruptured skin vesicles disseminating the disease to the community, e. g., small pox, chicken pox, herpes simplex virus (HSV).

Genital Viruses that are transmitted both heterosexually and homosexually include HSV, HIV, HBV, and cytomegalovirus (CMV). These viruses are spread not only sexually, but also to babies during passage through the cervical canal. Some of the above viruses, including rubella and varicella, may lead to intra-uterine infection through trans-placental transmission.

Arthropod Borne Mosquito, ticks and flies may transmit viruses like Dengue, yellow fever, and Crimean-Congo hemorrhagic fever (CCHF).

Nosocomial Infection About 5% of nosocomial infections may be due to viral infections; however, the incidence may be underestimated because of difficulty in diagnosis and limitations in the availability of diagnostic tools. These viruses include the respiratory viruses (e. g., HSV, CMV), hepatitis virus (e. g., HBV and hepatitis C virus [HCV]), enteric viruses (e. g., rotavirus) and picornavirus. There is a potential 0.3% risk of transmitting HIV to other patients and healthcare workers. Cases of slow virus Creutzfeldt-Jakob disease have occurred following corneal transplantation. Ebola and Marburg viruses have also been transmitted as nosocomial infections. The most frequently studied virus implicated in nosocomial spread is RSV in the pediatric ward, neonatal intensive care unit (ICU) and adult ICU.

Incubation Period

Viruses that have short incubation periods of 2 to 5 days, usually affect the respiratory system. Infections that spread by the hematogenous route to distal organs like the brain may take 2–3 weeks. Incubation periods in HIV infection may be spread over a few months. Viruses like the rabies virus, which spreads through the nerves, may have an incubation period of as little as 2 weeks to as much as a year. Knowledge of the incubation period is important to determine the infectivity of the microbe. The extent of infectivity depends on the preservation of the virus and its exodus to the environment.

The Immune System

The immune system plays a major role in the defense mechanism and pathophysiology of the disease caused by viruses. The primary host defenses against virus infection are physical/chemical barriers to infection and the immune system [11]. Virus infection in humans usually evokes two types of immune response. The initial rapid-onset 'innate' response against the virus involves the synthesis of proteins, namely interferons, and the stimulation of 'natural killer (NK)' lymphocytes [12, 13]. In some cases, the innate response may be enough to prevent a wide spread infection. However, if the infection evolves beyond the first few rounds of viral replication, the 'adaptive immune response' comes into play [14]. The adaptive

immune response itself has two components: The humoral response and the cell-mediated response. Both of these components of the adaptive immune response result in the production of long lasting memory cells that provides immunity to successive infections by same virus. These extremely precise cell-surface detecting receptors detect the antigen or certain viral proteins specific to that virus [4]. This process leads to an immunological memory, which then forms the origin for vaccination [3]. The innate immune system provides universal host protection from infectious diseases. It identifies the presence of pathogens using numerous methods of detection. The major targets of innate immune recognition are viral nucleic acids. Generally, the innate immune system detects structural features of viral RNA and DNA that are distinct from the host nucleic acid [15, 16].

Detection of viral pathogens by the innate immune system has two major consequences: First, it leads to the induction of the innate antiviral mechanisms, most of which are mediated primarily by interferons. Subsequently, it leads to the activation of the adaptive immune response, which can offer a more directed, antigen-specific, and long-term antiviral immunity. The primary aim of the body's defense mechanism is to eradicate the infected cells. This is accomplished by cell-intrinsic mechanisms that are brought about by type-I interferons in the infected cells. It can also be implemented by cytotoxic lymphocytes, such as NK cells and CD8 T cells [17]. Prevention of entry of the virus into the host cell is an important protection process. Neutralizing antibodies primarily carry this out. Other methods that interfere with viral replication, gene expression and exit from the infected cells vary depending on the virus and the host. Acute phase proteins and the complement system play an active role in innate immune response. Leukocytes, including neutrophils, monocytes, macrophages, dendritic cells, NK cells and NK T cells, are the principal innate immune cell types that respond to viral infection [14]. C-type lectins on their cell surface recognize viral protein or nucleic acid content and, in the case of NK and NK T cells, changes on the cell surfaces of infected cells [18]. These cells enter tissues invaded by these microorganisms from the plasma through the action of cytokines that are released during infection. The adaptive immune system displays two distinct cell types: B and T lymphocytes. On exposure to a virus, B-lymphocytes stimulate the release of a soluble form of antibody able to bind the circulating virions, effectively leading to eradication of the virus. An antiviral B-lymphocyte response is effectively sensitive in preventing or limiting reinfection and forms the basis of vaccination against specific viruses [19].

Viruses are essentially intracellular organisms that reproduce within cells of the infected host and use the cellular constituents to produce the next generation virions. This process of replication can take place rapidly or slowly over time. This progression over a time frame determines the rapidity of evolution of illness. In acute viral infections, the multiplication of the virus and the host response will result in eradicating the virus and clearing the infection or if the infection is overwhelming will lead to the severe sepsis or death of the host. The tissue injury caused by viruses at the site of infection is due to the cytotoxic injury of virus multiplication and the host's immune response to infection. In chronic infection, the time frame of virus multiplication in the host is usually assessed in weeks, months, or even years,

with the host immune response spanning over prolonged periods. Viruses causing chronic and lasting infection have developed processes to subdue or alter the immune response whereby these viruses persist in the patient. The immune responses encountered both in acute and chronic viral infections can lead to tissue injury. The classic example of chronic viral infection leading to immune-mediated tissue destruction over years is hepatitis C cirrhosis. These immune responses, seen in a host of viral infections, may be responsible for the associated autoimmune diseases associated with certain viruses [20].

T-lymphocytes and cell-mediated immunity are concerned with virus-infected cells rather than free virus. Virus-immune T lymphocytes recognize viral antigens in association with self-major histocompatibility complex (MHC) class I glycoproteins [21]. These T lymphocytes perform key regulatory functions of the immune system. Through these T-cell receptors, the CD4 and CD8 molecules participate in an immune response leading to an interaction with antigen presenting cells, release of cytokines, proliferation of a host of cells with cytolytic destruction of target cells [22]. A major development is the understanding of the structure and functioning of the MHC, the T-cell receptor and cell surface components, such as CD3, CD4, and lymphocyte function-associated antigen-1.

Classification of Viruses

Viruses are divided into two large groups (Table 1)
- RNA containing viruses.
- DNA containing viruses.

Baltimore Classification

In this classification, viruses are divided into seven groups based on their nucleic acid and m-RNA production.
- Double stranded (ds)-DNA viruses.
- Single stranded (ss)-DNA viruses.
- ds-RNA viruses.
- ss-RNA viruses with positive strands (positive polarity).
- ss-RNA viruses with negative strands (negative polarity).
- ss-RNA viruses associated with the reverse transcriptase enzyme.
- ds-DNA viruses associated with the reverse transcriptase enzyme.

Poxviruses

Orthopox:	smallpox virus (variola), vaccinia virus, cowpox virus, and monkeypox virus.
Para pox:	orf virus, pseudocowpox, bovine papular stomatitis virus.
Yabapox:	Tanapox virus, Yaba monkey tumor virus.
Mollusc pox:	molluscum contagiosum virus.

Papovavirus
Papillomavirus, polyomavirus, various neoplasms in mammals.

Hepadnaviruses
A family of enveloped, ds-DNA viruses, including HBV.

Herpesviridae
At least five species of herpesviridae are extremely widespread among humans: HSV-1 and HSV-2 (both of which can cause orolabial herpes and genital herpes), varicella zoster virus (VZV, which causes chicken-pox and shingles), EBV virus (which causes mononucleosis), and CMV.

Adenoviruses
These cause a wide range of illnesses, from mild respiratory infections in young children to life-threatening multi-organ disease in people with a weakened immune system.

Papillomaviridae
Non-enveloped DNA virus, collectively known as papillomaviruses. Causes small benign tumors, known as papillomas or warts (e. g., human papillomavirus [HPV] 1, HPV6 or HPV11). Papillomas caused by some types, however, such as HPV 16 and 18, carry a risk of becoming cancerous.

Table 1 Classification of viruses

ds-DNA viruses associated with the reverse transcriptase enzyme	ds-DNA	ss-DNA	ds-RNA	ss-RNA(−) with transcriptase enzyme	ss-RNA(+)	ss-RNA with reverse transcriptase enzyme
Hepatitis B (HBV) only	Poxviridae	Parvoviridae	Reoviridae	Orthomyxoviridae	Picornaviridae	Retro viruses
	Papovaviridae			Paramyxoviridae	Caliciviridae	
	Hepadnaviridae			Rhabdoviridae	Astroviridae	
	Herpesviridae			Filoviridae	Coronaviridae	
	Adenoviridae			Arenaviridae	Flaviviridae	
	Papilloma viridae			Bunyaviridae	Togaviridae	

ds: double stranded; ss: single stranded.

Parvoviridae
Parvovirus B19 causes a childhood exanthem (erythema infectiosum).

Reoviridae
A family of viruses that can affect the gastrointestinal system (such as rotavirus) and respiratory tract.

Orthomyxoviruses
A family of RNA viruses that includes influenzavirus A, influenzavirus B, influenzavirus C. These viruses cause influenza in vertebrates, including birds (avian influenza), humans, and other mammals.

Paramyxoviruses
Includes mumps virus, measles virus, RSV, parainfluenza virus and human metapneumovirus, which is the major cause of bronchiolitis croup and pneumonia in infants and children.

Rhabdoviridae
Rhabdoviruses carry their genetic material in the form of negative-sense ss-RNA. Rhabdoviruses include rabies virus and vesicular stomatitis virus (VSV).

Filoviridae
Filamentous infectious viral particles (virions), encode their genome in the form of negative-sense ss-RNA. Two members of the family that are commonly known are Ebola virus and Marburg virus causing viral hemorrhagic fevers.

Arenavirus
Lymphocytic choriomeningitis virus infection can cause aseptic meningitis. Hemorrhagic fever syndromes are derived from infections by viruses, such as Lassa virus.

Bunyaviridae
A family of negative-stranded, enveloped RNA viruses. Although generally found in arthropods or rodents, certain viruses in this family occasionally infect humans. *Bunyaviridae* are vector-borne viruses. With the exception of hantaviruses, transmission occurs via an arthropod vector (sandfly, mosquito or tick). Hantaviruses are transmitted through contact with mice feces. Human infections with certain bunyaviridae, like CCHF virus, are associated with high levels of morbidity and mortality.

Picornavirus
Picornaviruses are non-enveloped, positive-stranded RNA viruses. The diseases they cause are varied, ranging from acute ‘common-cold’-like illnesses to polio.

Caliciviridae

A family of viruses with ss-RNA. Transmission of caliciviruses is generally by the fecal-oral route but can also be via the respiratory route. Calicivirus infections commonly cause acute gastroenteritis (e. g., the Norwalk virus).

Astrovirus

The *Astroviridae* comprise a third family of non-enveloped viruses the genome of which is composed of plus-sense ss-RNA. Astroviruses are now recognized as a cause of gastroenteritis in children and adults.

Coronaviridae

A family of enveloped, positive-stranded RNA viruses. Coronaviruses are transmitted by the fecal-oral route or by aerosols of respiratory secretions. Although most diseases are mild, sometimes they can cause more severe situations in humans, such as, for example, the infection of the respiratory tract known as SARS.

Flaviviridae

A family of viruses that are primarily spread through arthropod vectors (mainly ticks and mosquitoes). Major diseases caused by the *Flaviviridae* family include: Dengue fever, Japanese encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, St. Louis encephalitis, tick-borne encephalitis, West Nile encephalitis, yellow fever, HCV Infection.

Togaviridae

A family of viruses, including the following genera: Genus *Alphavirus,* type species, *Sindbis virus*, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, O'nyong 'nyong virus, Chikungunya, Semliki Forest virus; genus *Rubivirus,* type species *Rubella virus*.

Retroviridae

A family of enveloped viruses that replicate in a host cell through the process of reverse transcription, e. g., HIV.

Viral Diagnostic Methods

Viral testing is now essential in the management of patients with infections. Multiple test methods continue to be used and molecular tests are up-and-coming as a leading technology. A number of molecular assays are either in use or are in the process of being developed for *in vitro* diagnosis [23]. For the diagnosis of acute viral infections, the samples are usually collected from the site of disease (e. g., cerebrospinal fluid [CSF] in viral meningitis). Viral culture is technically difficult as viruses are labile and may not survive the process of transfer. Samples may be sent for serological tests, viral antigens and nucleic acid testing. Immunofluorescence is

another technique used to determine viral activity [24].Viral diagnostic techniques are shown in Box 1.

Box 1. Techniques Used in Diagnostic Virology

- Cell culture
- Antigen detection
  - Fluorescent antibody staining
  - Immunoperoxidase antibody staining
  - Enzyme immunoassay
- Nucleic acid detection
  - Polymerase chain reaction
  - Other nucleic acid amplification methods
- Electron microscopy
- Cytology
- Histology
  - Immunohistochemistry
  - In situ hybridization
- Serology

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Identification in Cell Culture

Virus growth in cell culture often produces a distinctive cytopathic effect (CPE) that can provide a presumptive identification, but CPE is not specific (i. e., many viruses cause it). If the virus does not produce a CPE, its presence can be detected by:

1. hemadsorption
2. interference with formation of a CPE by a second virus;
3. a decrease in acid production by infected, dying cells. This can be detected visually by a color change in the phenol red (a pH indicator) in the culture medium.

Definitive identification of the virus grown in cell culture is made by complement fixation, hemagglutination inhibition, and neutralization of CPE. Other tests, such as fluorescent antibody, radioimmunoassay, ELISA and immunoelectron microscopy are also used in certain circumstances.

Microscopic Identification

1. Inclusion bodies – developed by aggregates of virus particles – can be demonstrated in the nucleus or cytoplasm of infected cells. These non-specific inclusion bodies are seen in the nucleus, in certain herpes viruses and the Negri bodies seen in the cytoplasm of cells in patients with rabies virus infection.

2. In cases of RSV, measles and herpes multinucleated giant cells may be seen.
3. Fluorescent antibody staining of cells in culture can provide definitive diagnosis.
4. Electron microscopy can detect virus particles that have specific morphology and size, e. g., Ebola virus.

Serologic Studies

1. The detection of IgM may be an indicator of current infection.
2. The detection of IgG is more an indicator of past infection rather than current infection.

A four-fold rise in antibody titer in the convalescent serum sample compared with the acute sample may help in making the diagnosis.

Detection of Viral Antigens and Nucleic Acids

The presence of viral proteins, such as p24 of HIV, HBV surface antigen and NS1 antigen for Dengue are regularly used in diagnosis. The presence of viral DNA or RNA is increasingly used to confirm viral infections. Using labeled probes to determine viral load, assay of CMV and HIV RNA has ensured specific and rapid diagnosis of certain viral illnesses.

Serious Community-Acquired Viral Infections

Viral infections cause many community-acquired infections, particularly serious respiratory viral infections. Among the causes of serious community-acquired pneumonia requiring hospital admission, viruses account for 15–40% of all cases in which the underlying etiology is known [25].

Viruses that invade through the airway can be grouped as follows:

1. Upper airway infections
   - Viruses that limit their action to the epithelial surface: Common cold viruses (human rhinoviruses, Coxsackie A and echoviruses) and mild cases of influenza and parainfluenza. These viruses have mild clinical presentation with a generally favorable course and outcome.
   - Viruses that invade the epithelium and spread to other parts of the body: Viruses producing measles, mumps, rubella, herpes viruses (HSV, VZV], EBV and some cases of CMV [26].
2. Lower airway infections and pneumonias
   These form the most common serious respiratory disorders in immunocompetent adults – 'febrile respiratory illnesses'. The viruses included in this group are myxoviruses (including the different types associated with influenza A, B and C), adenoviruses (23 different types, of which 18 have been isolated in humans), parainfluenza viruses, and pneumonic conditions caused by HSV, VZV, EBV and CMV [26].

Influenza

The seasonal 'flu' virus is an RNA virus with three known subtypes (A, B and C) belonging to the family *Orthomyxoviridae*. These viruses have considerable genetic variability and have a capacity to cause epidemics and pandemics. Typically infection manifests as self-limiting upper airway disease presenting with fever, chills, malaise, headache, muscle pain and non-productive cough that lasts for 3 or 4 days. A very small proportion of infections can lead to complications, such as bacterial pneumonia, sepsis and acute respiratory distress syndrome (ARDS). Influenza virus is transmitted via the aerial route and hence is responsible for large epidemics. The virulence and antigenicity of the virus, the immune condition of the host, and the environment all interact, conditioning person- to-person transmission of the disease [27].

Diagnosis is based on clinical manifestations and tests, such as antigen determination tests, nucleic acid tests, polymerase chain reaction (PCR) amplification or viral cultures. Treatment consists of neuraminidase inhibitors (oseltamivir and zanamivir), which are preferred to amantadine and rimantadine because of resistance.

Extracorporeal membrane oxygenation (ECMO) is a potential modality of therapy in patients with influenza and severe ARDS, which has been associated with encouraging results. In a study in New Zealand and Australia, ECMO-treated patients with influenza A(H1N1)-associated ARDS were often young adults with severe hypoxemia and had an overall survival rate greater than 70% [28]. This method was applied in Europe [29], the United States [30], South America [31], Canada [32] and Asia [33] as the H1N1 pandemic spread. In H1N1 patients, survival rates ranged from 56 to 79% across the centers, independent of the applied strategy of mechanical ventilation.

Respiratory Syncytial Virus and Parainfluenza Virus

These are RNA viruses with structural similarities and belong to the same family, *Paramyxoviridae*. They share features relating to epidemiology, pathogenesis and clinical manifestations. Both these microorganisms cause serious disease, particularly in elderly patients or individuals with high risk of serious respiratory infection (e. g., COPD, cystic fibrosis, post-lung transplant). Clinically, these infections present as a febrile illness with bronchospasm, bronchiolitis, pneumonia, and may progress to ARDS [34]. Transmission is via fomites or infected secretions. Diagnosis is based on clinical signs, antigenic detection tests, viral isolation and PCR. Treatment consists of supportive measures, the administration of bronchodilators, corticosteroids, and the use of nebulized ribavirin in high-risk patients. Mortality rate is close to 10% in elderly individuals [34].

Coronavirus-SARS (SARS-CoV)

The SARS virus is an RNA virus. It was first described after an outbreak in Asia in 2003. It exhibits a biphasic clinical course with prodromic manifestations (fever, chills, muscle pain, nausea, headache). It usually progresses within about 7–8 days to respiratory distress with severe hypoxemia (in 45% of the cases) respiratory failure and ARDS (in 20%) [35]. Transmission is via droplets, the aerial route and by contact. PCR, immunofluorescence, viral cultures and enzyme-linked immunosorbent assay (ELISA) establish diagnosis. Treatment is fundamentally supportive. Steroids have been tried with questionable efficacy. Mortality rate is about 11%.

Other Respiratory Viruses

Adenoviruses can cause lower airway disease. Infections may rarely progress to pneumonia that can deteriorate towards ARDS. Extrapulmonary symptoms include gastritis, hepatitis, meningitis, and hemorrhagic cystitis. Diagnosis is established by PCR and viral cultures. Transmission is via droplets and contact. Treatment is supportive; cidofovir and ganciclovir appear to have activity *in vitro*.

Hantavirus produces two different clinical conditions: Hemorrhagic fever with renal failure syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). The clinical picture is characterized by prodromic manifestations (fever, chills, muscle pain, abdominal pain), rapid progression towards respiratory failure, ARDS, coagulopathy and shock. Transmission is through contact with urine or excrement from infected mice. Diagnosis is based on serological tests. Treatment is supportive and the administration of ribavirin in HFRS (not effective in HCPS) [26].

Viral Encephalitis

Acute viral encephalitis can be caused by a number of viruses (Box 2) but the most important is herpes simplex encephalitis (HSE). The outcome of any central nervous system (CNS) viral infection is dependent on the immune status of the host and the virulence of the infecting virus. In immunocompromised patients (e. g., acquired immunodeficiency disease [AIDS], bone marrow and solid organ transplants) one can encounter varicella and CMV infections [36].

Box 2. Causes of Viral Encephalitis

Herpes simplex virus (HSV-1, HSV-2)

Other herpes viruses – varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6)

Adenoviruses, influenza A

Enteroviruses, poliovirus, measles, mumps and rubella viruses

Rabies

Arboviruses, e. g., Japanese B encephalitis, West Nile encephalitis virus, tick-borne encephalitis viruses

Bunyaviruses e. g., La Crosse strain of California virus

Reoviruses e. g., Colorado tick fever virus

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Presentation of acute encephalitis may include a history of headache, fever, neurological signs, seizures. Other diagnostic signs include CSF pleocytosis, focal abnormalities seen on electroencephalogram (EEG) and changes seen on either computed tomography (CT) or magnetic resonance imaging (MRI). PCR has a specificity of about 95% to detect HSV-1 [37, 38].

General management includes the treatment of raised intracranial pressure (ICP) with intravenous mannitol and/or steroids, control of seizures with appropriate anticonvulsants and correction of fluid and electrolyte imbalances. Acyclovir treatment should be started as soon as a diagnosis of HSE is considered. Intravenous acyclovir at a dose of 10 mg/kg three times daily should be continued for at least 14 days [37].

Arthropod-Borne Viruses

Arthropod-borne viruses (arboviruses) are viruses that can be transmitted to man by arthropod vectors [39]. Arboviruses are mostly RNA viruses that belong to four families: *Flaviviridae* (e. g., yellow fever, Dengue, Japanese encephalitis); *Bunyaviridae* (e. g., Sandfly fever, Rift Valley fever, CCHF); *Reoviridae* (e. g., Colorado Tick virus); and *Togaviridae* (e. g., Eastern equine encephalitis [EEE], Western equine encephalitis [WEE]). They have a similar mode of transmission, through the bite of bloodsucking arthropods (mosquitoes, ticks, midges, and sandflies).

Arthropod-borne viruses and non-arthropod borne viruses can be categorized into arboviral encephalitides and viral hemorrhagic fever.

Arboviral Encephalitides

Chikungunya

Chikungunya (CHIKV) is an alphavirus of the family *Togaviridae,* transmitted principally by the *Aedes aegypti* mosquito. Clinical presentation includes sudden onset of high fever (> 102 °F), severe poly-arthralgia, headache, myalgia, back pain, rash (~ 50% of cases) [40]. Symptoms typically resolve within 7–10 days. The joint pain and stiffness may last longer. Complications include:

- *CNS*: Meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, paresis, palsies, and neuropathy.
- *Ocular:* Optic neuritis, iridocyclitis, episcleritis, retinitis and uveitis
- *Renal:* Nephritis and acute renal failure
- *Other:* Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and hypoadrenalism.

Infections with CHIKV are confirmed by the detection of the virus, viral RNA, or CHIKV-specific antibodies in patient samples. Treatment is symptomatic and supportive.

Japanese encephalitis virus

Japanese encephalitis virus (JEV) is an ss-RNA virus that belongs to the genus *Flavivirus* and is closely related to West Nile and Saint-Louis encephalitis viruses. The *Culex* mosquito transmits the virus and it is the most common vaccine-preventable cause of encephalitis in Asia. Among patients who develop clinical symptoms, the incubation period is 5–15 days. Clinical features consist of acute encephalitis, acute flaccid paralysis, similar to poliomyelitis, status epilepticus, increased ICP, and brainstem herniation. About 20–30% of patients die, and 30–50% of survivors have neurologic or psychiatric sequelae [41, 42]. There is no specific antiviral treatment for Japanese encephalitis; therapy consists of supportive care and management of complications.

Viral Hemorrhagic Fever

Viral hemorrhagic fever refers to a group of illnesses that are caused by several distinct families of viruses (Fig. 1). It is typically a combination of endothelial dysfunction causing a capillary leak syndrome and a bleeding diathesis, caused by thrombocytopenia and disseminated intravascular coagulation (DIC) [43]. Viruses that cause viral hemorrhagic fever are present globally and manifest symptoms pertaining to the virus in that geographic area. Viral hemorrhagic fevers continue to pose a major threat in most world regions today.

Ebola Virus Disease

Ebola virus disease, formerly known as Ebola hemorrhagic fever, is a severe, often fatal illness in humans. Ebola and Marburg viruses are non-segmented, negative-sense, ss-RNA viruses that resemble rhabdoviruses and paramyxoviruses in their genome organization and replication mechanisms [44].

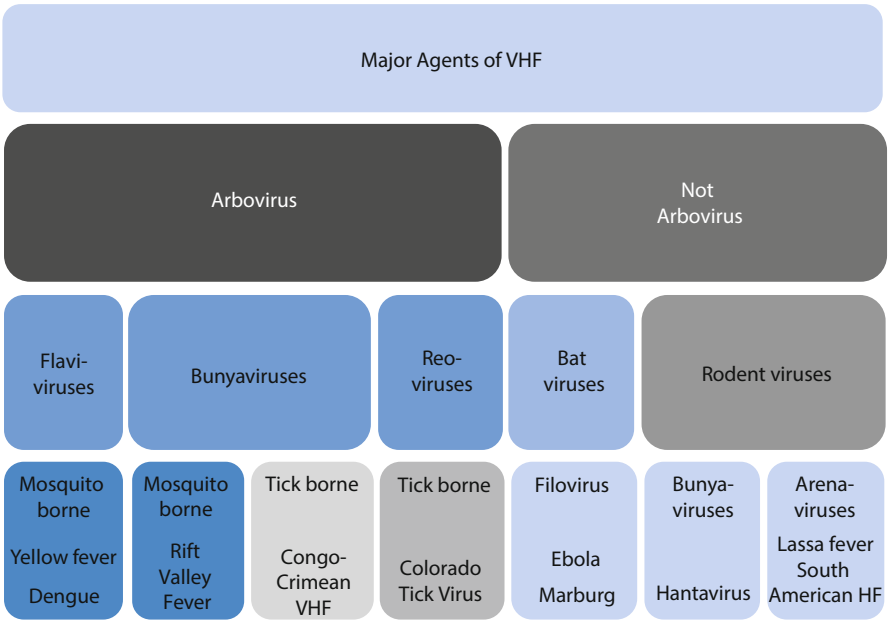


Fig. 1 Agents of viral hemorrhagic fever (VHF). Togaviruses are not included as they do not cause viral hemorrhagic fever. From [43] with permission

Ebola virus is subdivided into five species: Bundibugyo ebolavirus, Zaire ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus.

Ebola virus causes severe hemorrhagic fever with up to 90% mortality. Ebola virus disease outbreaks occur primarily in remote villages in Central and West Africa, near tropical rainforests [45]. Transmission of the disease generally results from contact with blood, secretions or tissues from patients or infected animals. In Africa, infection has been documented through the handling of infected chimpanzees, gorillas, fruit bats, monkeys, antelope and porcupines found ill or dead in the rainforest. Ebola virus disease can then spread in the community through human-to-human transmission, with infection resulting from direct contact with blood, secretions, organs or other body fluids of infected people, and indirect contact with environments contaminated with such fluids. The incubation period is 2 to 21 days.

Ebola virus disease is characterized by a severe febrile illness, with profound gastrointestinal manifestations, and is complicated by intravascular volume depletion, shock, electrolyte abnormalities and organ dysfunction. Both internal and external bleeding occur due to coagulopathy [46].

Diagnosis is performed by antibody-capture ELISA, antigen detection tests, serum neutralization test, reverse transcriptase PCR (RT-PCR) assay, electron microscopy and virus isolation by cell culture. Samples from patients are an extreme biohazard risk; testing should be conducted under maximum biological containment conditions [46].

Treatment for Ebola virus disease is mainly supportive and involves a combination of fluid resuscitation, administration of analgesics and standard nursing measures. There are currently no specific antiviral drugs for the treatment of Ebola virus disease.

Dengue

Dengue virus is a member of the Flaviviridae family composed of ss-RNA. It is transmitted by *Aedes aegypti* mosquitoes. It has four serotypes (DEN-1, 2, 3, 4). Dengue virus infections cause a spectrum of illnesses ranging from asymptomatic to Dengue fever, Dengue hemorrhagic fever, and Dengue shock syndrome [47] (Table 2). While Dengue fever is a self-limiting febrile illness, Dengue hemorrhagic fever is often characterized by prominent hemorrhagic manifestations associated with increased vascular permeability. The incubation period is typically 4–7 days.

After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases: Febrile, critical, recovery (Fig. 2). Dengue fever is characterized by the sudden onset of fever and other non-specific symptoms, such as headache, flushed face. During the first 24–48 h, a petechial rash or maculopapular rash can frequently be seen during the period of defervescence. The fever may continue for 5–7 days. Hemorrhagic complications may also appear, such as bleeding from the gums, nosebleeds, and bruising. Mortality from Dengue fever is low, whereas mortality from Dengue hemorrhagic fever is fairly high. Spontaneous bleeding, plasma leakage, fever, and thrombocytopenia characterize Dengue hemorrhagic fever. Dengue shock syndrome is the most severe

Table 2 Dengue clinical syndromes. From [68] with permission

DHF grade	Duration of fever, d	Hemorrhage	Thrombocytopenia: platelets/mm^3	Increased vascular permeability
I	$>2, \leq 7$	Positive tourniquet test only	$\leq 100{,}000$	Plasma leakage[a]
II	$>2, \leq 7$	Spontaneous bleeding[b]	$\leq 100{,}000$	Plasma leakage[a]
III (DSS)	$>2, \leq 7$	Positive tourniquet test and/or spontaneous bleeding[b]	$\leq 100{,}000$	Plasma leakage[a] and circulatory failure with pulse pressure ≤ 20 mmHg or hypotension for age
IV (DSS)	$>2, \leq 7$	Positive tourniquet test and/or spontaneous bleeding[b]	$\leq 100{,}000$	Plasma leakage[a] and profound shock with undetectable pulse and blood pressure

[a] As demonstrated by any of the following: elevation of the admission hematocrit to $\geq 20\%$ above the expected mean for age, sex, and population; reduction of the hematocrit to $\geq 20\%$ of the baseline value after fluid resuscitation; and clinical signs of plasma leakage, such as pleural effusion or ascites.

[b] For example, skin petechiae, bruising, or mucosal/gastrointestinal bleeding.

DHF: Dengue hemorrhagic fever.

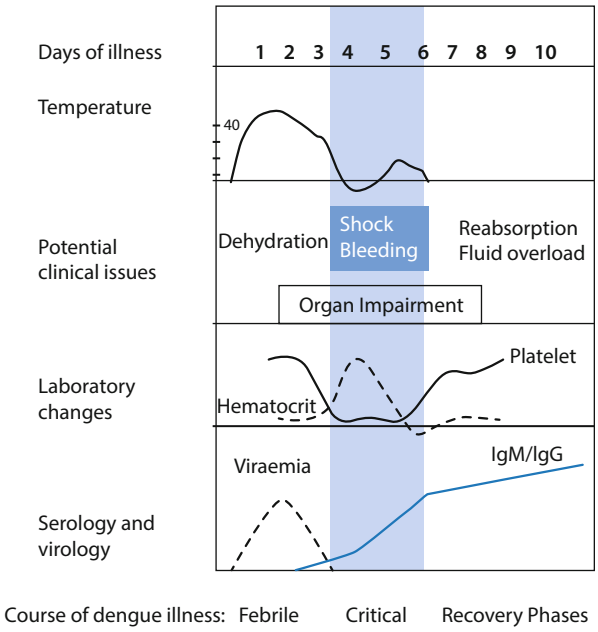


Fig. 2 The course of Dengue illness. IgM: immunoglobulin M; IgG: immunoglobulin G. Temperature is given in degrees Celsius (°C). From [69] with permission

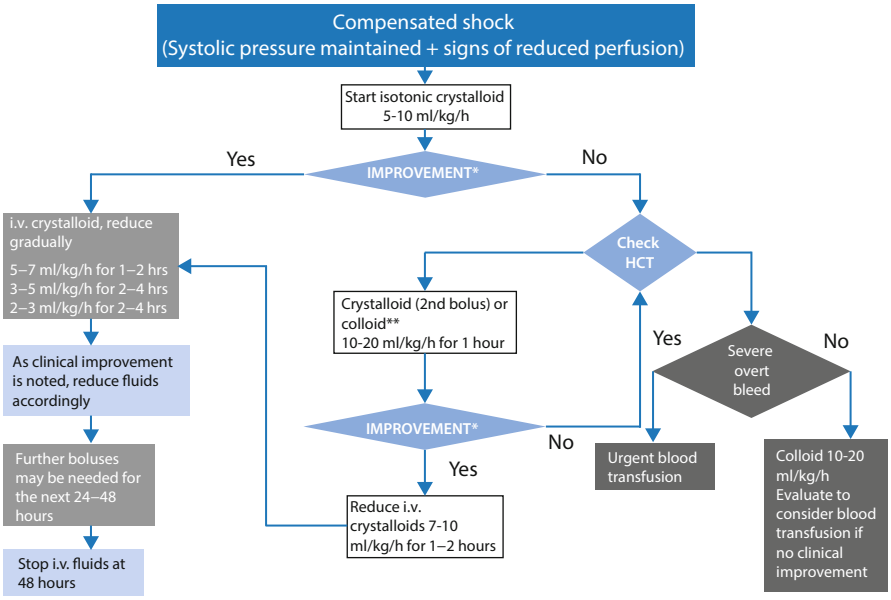
form of Dengue hemorrhagic fever and is characterized by the presence of all four Dengue hemorrhagic fever clinical manifestations (increased vascular permeability, thrombocytopenia, fever lasting two to seven days, hemorrhagic tendency) and circulatory failure [48].

Laboratory abnormalities include thrombocytopenia, leukocytopenia, and increased levels of hepatic aminotransferase. Serological detection is based on IgM-capture ELISA and IgG ELISA or a hemagglutination inhibition test, detection of the genomic sequence by RT-PCR or viral isolation [49].

There are no specific antivirals that can be used in Dengue syndrome. However, supportive care, paracetamol and other analgesics and antipyretics can be used to treat the fever. During episodes of Dengue hemorrhagic fever/Dengue shock syndrome, patients will need comprehensive ICU care with intensive algorithm-based fluid therapy (Fig. 3), vasopressors, and mechanical ventilation.

Crimean-Congo Hemorrhagic Fever

The CCHF virus is a *Nairovirus* in the *Bunyaviridae* family and causes severe disease in human beings, with a reported mortality rate of 3–30%. Human beings become infected through tick bites. CCHF virus circulates in an enzootic tick–vertebrate–tick cycle, and the virus causes no disease in animals [50]. CCHF virus has been detected in the sera of horses, donkeys, goats, cattle, sheep, and pigs in various regions of Europe, Asia, and Africa. Birds may have a role in the transportation of CCHF virus-infected ticks between different countries. The major at-risk groups are farmers living in endemic areas. Hospital healthcare workers are at serious risk:



*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
**Colloid is preferable if the patient has already received previous boluses of crystalloid

Fig. 3 Algorithm for fluid management of compensated shock in adults. i.v.: intravenous; HCT: hematocrit; ↑: increased; ↓: decreased. From [69] with permission

8.7% of healthcare workers who were exposed to infected blood and 33% of those who had a needlestick injury developed the disease.

Laboratory methods include virus isolation, serological assays, and molecular assays. Immunofluorescence assays (IFAs) using specific monoclonal antibodies may enable virus visualization under microscopy.

The antiviral drug, ribavirin, is currently used in the treatment of CCHF. Patients need to be aggressively fluid resuscitated. Replacement therapy with blood components is the basis of management in severe CCHF. Suspected and diagnosed patients with CCHF should be isolated [51].

Hospital-Based Viral Infections

HSV1

Ventilator-associated pneumonia (VAP) has always been attributed to bacteria, although on numerous occasions the etiology of VAP remains undetermined. With the advent of better diagnostic tools, recent data indicate that viruses may be implicated in nosocomial infections in non-immunocompromised patients. There are, however, no standardized diagnostic tools. No publication has established a causal

relationship between isolation and the infectious episode. In a French prospective study, isolated viruses including rhinovirus, herpes simples, influenza, RSV, enterovirus, parainfluenza, adenovirus, coronavirus and CMV were detected in 25% of the patients [52].

Numerous studies have implicated HSV1 as the most likely virus to cause VAP. The reported frequency varies between 5–64%, with a median of 15–20% [53–57]. Reactivation of a latent virus appears to be the initial mechanism in all patients with HSV1 pneumonia in the ICU. Reactivation is due to instrumentation of the airways and begins by the 3rd–5th day peaking by day 12 [58]. Risk factors for HSV1 include mucocutaneous herpetic lesions, tracheal mucosal lesions, high sequential organ failure assessment (SOFA) and/or APACHE II scores, mechanical ventilation for more than 7 days, old age and prior corticosteroid use [58].

Cytomegalovirus

The seroprevalence of CMV in adults is in the range of 50–90% [59]. As with all herpesviruses, primary CMV infection remains latent lifelong and undergoes episodes of reactivation, and may progress to symptomatic disease. In the last decade, CMV reactivation has been reported in immunocompetent critically ill patients. The incidence is variable, depending on the diagnostic method used (culture or PCR), and ranges from 12–33% [60]. The incidence of active CMV disease was found to be high in a series of 242 immunocompetent patients subjected to ventilation for over 48 hours (16.1%) [61]. CMV should be suspected as the cause of VAP in the presence of persistent infiltrates, a lack of clinical improvement and negative bacterial cultures [62]. Reactivation of CMV occurs between days 14 and 21 of the ICU stay. Reactivation may begin in the lung parenchyma and is usually activated by sepsis. This process can cause a persistent increase in cytokine-mediated inflammatory response. Risk factors for reactivation are blood transfusion, age, previous hospitalization, prior corticosteroid use and burn injury. Several observational studies have shown an association between CMV infection in critically ill patients and poor clinical outcomes [63].

Five drugs – ganciclovir/valganciclovir, cidofovir, foscarnet and fomivirsen – have been approved so far for the treatment of human CMV [64]. Ganciclovir is favored over alternative agents based on its potent activity against CMV and availability of intravenous formulation [65]. Preemptive therapy and prophylaxis appear effective for prevention of symptomatic CMV infection in non-immunocompromised patients. In experimental studies, early prophylactic administration of high-dose ganciclovir was significantly more effective in preventing both CMV reactivation and subsequent pulmonary fibrosis than delayed treatment.

Other Viruses

In a recent study, 19% of ventilated patients with suspected VAP yielded positive serological tests for *Acanthamoeba polyphaga*, a mimivirus. Risk factors consisted of duration of mechanical ventilation, prior bronchoalveolar lavage and absence of enteral nutrition. These patients had mortality rates of about 50% [66].

A host of other viruses may spread between patients by various routes, including community-acquired viruses, as has been seen with measles, during the SARS epidemic, influenza, Avian flu, etc. Nosocomial infections may spread through needlestick injury or exposure to contaminated body fluids, as in HBV, hepatitis C and HIV. All of the above can be associated with a risk of transmission to healthcare workers.

Conclusion

Septic processes remain one of the main causes of morbidity-mortality in ICUs throughout the world. Viruses play a significant role in serious infections warranting admissions to the ICU. The role viruses play in unidentified sepsis may be just the tip of the iceberg. Diagnostic dilemmas and non-availability of appropriate laboratory tests may prevent early and definitive diagnosis of viral sepsis. The limited availability of effective anti-viral agents or vaccines limits therapy. However, certain viruses do respond effectively to appropriate agents (e. g., HSV and VRZ to acyclovir, CCHF to ribavirin, CMV to ganciclovir). ECMO played an important role in improving survival globally in the recent H1N1 epidemic. Advances in HIV therapy provide new hope to the large population of AIDS patients worldwide. A similar hope can be seen for patients with chronic hepatitis B and C infection. In the ICU, healthcare workers need to be cautioned during epidemics of influenza and Ebola virus, ensuring that ICUs follow the necessary protocols to prevent transmission. These microorganisms have been around since even before the era of dinosaurs and have found the means to survival for generations by mutations and alterations in their genetic structure. The question is, can humanity find the means to counter them?

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