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CHAPTER 8

Viruses Including Human Immunodeficiency Virus

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INTRODUCTION

Viral agents are common and do not require an immunocompromised host to cause infection. Viruses are nonliving entities that replicate only when they are inside host cells, often using the molecular machinery

of the host genome to replicate. The viral genome consists of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) which can be comprised of a single or double strand of either nucleic acid. Viral capsids are polyhedral structures composed of proteins that enclose the nucleic acid of the virus. Viruses can also have an envelope which is derived from phospholipids and proteins of the host cell membranes. Electron microscopy (EM) was once used as a method of identification and some viruses have a distinct morphology which will be discussed in their sections [1,2]. This chapter discusses the following points which are necessary when diagnosing an infection and providing adequate antibiotic treatment:

- Basic physical, chemical, and structural characteristics.
- Epidemiology of each infection.
- Pathophysiology changes associated with infection, including host-related factors.
- Clinical manifestations of infection.
- The biochemical assays useful in differentiating genera from other closely related.

DIAGNOSTIC APPROACH

Viruses are small entities (20–300 nm) that infect and replicate within host cells, using host cellular machinery to synthesize new infectious particles and create progeny virions (virus particles). On one hand, a virus represents an inert biochemical complex of macromolecules, since it cannot replicate outside of a living cell. However, viruses are known to infect all living organisms. Indeed, a broad array of viruses contribute to manifestations of human disease. The extent of infection and related disease state depends upon the number of virions infecting the host, as well as specific host responses that contribute to associated manifestation of pathology. Diagnosis can be made by serology, growth in cell culture, cytopathic effect (CPE) including presence of intranuclear or intracytoplasmic inclusions and immunohistochemical staining of tissue biopsies or molecular methods.

RIBONUCLEIC ACID VIRUSES

These viruses contain only RNA as the genomic content.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS). HIV is a single-stranded RNA virus and requires the enzyme reverse transcriptase for replication. Primary infection is considered an asymptomatic phase during which the virus is replicating, followed by an increased viral load and finally immune dysfunction and AIDS. HIV-1 is the predominant strain in the United States, Europe, and Australia while HIV-2 is predominantly found in West African nations. After infection with HIV-1, specific indicators arise in the blood with HIV-1 RNA first, followed by protein p24 antigen, and then antibodies directed toward HIV-1 epitopes.

Replication of the virus requires attachment of glycoproteins to host receptors. The protein gp120 attaches to the host cellular receptor on CD4+ cells. This binding allows for the interaction with the chemokine co-receptor sites CXCR4 and CCR5. Rapid evolution of the virus can cause viral turnover and a high mutation rate in some patients allowing for immune escape. Transmission can include sexual contact through mucosal membranes. Although rare, accidental transmission through needle sticks in laboratories has been noted. Congenital HIV can occur in neonates born to HIV positive mothers, particularly those with uncontrolled HIV.

Screening tests for HIV measure the presence of specific antibody in the patient's serum, detectable after the host has been exposed to the virus for some time (window period). Enzyme immunoassays (EIAs) have developed over time from first to third generation assays. With each new generation the tests have become more sensitive and were associated with a concomitant decrease in the window period. The fourth generation tests detect HIV antibody and the p24 antigen, and the fifth generation additionally differentiates between antibody and antigen allowing assessment of the acuteness of the infection and also differentiates between HIV-1 and HIV-2. Both of these new assays decrease the window period almost to the extent of molecular testing. Either an indirect immunofluorescence assay (IFA) or western blot (WB) can be used to confirm detection of antibodies to HIV-1. The WB requires reactivity to at least two of the three following bands p24, gp41, and gp120/160. The confirmatory test for the fourth and fifth generation assays is the multispot test which also differentiates HIV-1 and HIV-2.

Molecular testing is now more accessible and both RNA and DNA testing can be performed. Real-time reverse transcriptase PCR can

determine HIV-1 RNA viral load in plasma which is helpful in staging a patient during disease progression and in following response to treatment. Blood should be collected in a tube containing EDTA. DNA testing can be used to identify disease in newborns, since the presence of DNA is an indicator of replication and incorporation of virus in the host cell genome.

The HIV has a tendency to mutate and become resistant to commonly used antivirals, therefore, genotype or phenotype testing is often needed to guide treatment. Genotypic assays employ molecular methods to identify viruses resistant to protease inhibitors, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and integrase inhibitors by sequencing the patient's HIV virus. Phenotypic assays require the growth of the virus in various concentrations of the antiviral drug to determine susceptibility of the virus and are therefore more time consuming and costly.

There are multiple antivirals that are available which target the viral replication including nucleoside analogs, protease inhibitors, and reverse transcriptase inhibitors. Tenofovir disoproxil/emtricitabine is a new antiviral combination drug containing a reverse transcriptase inhibitor and a nucleoside reverse transcriptase inhibitor. This antiviral can treat HIV infection and reduce the risk of HIV transmission (see Chapter 7: Antibiotics, Antimicrobial Resistance, Antibiotic Susceptibility Testing, and Therapeutic Drug Monitoring for Selected Drugs).

Influenza Virus

Orthomyxoviruses are enveloped, single-stranded RNA viruses which have a lipid bilayer containing hemagglutinin (HA) and neuraminidase (NA) glycoproteins. There are currently 16 HA subtypes and 9 NA subtypes. The influenza virus is divided into types A, B, and C, of which in types A and B the HA and NA antigens undergo genetic variation; the C type is generally antigenically stable.

Influenza initially causes upper respiratory tract infections which can spread to the lower respiratory tract and cause severe desquamation of bronchial or alveolar epithelium. Complications of influenza can result in pneumonia or with bacterial pneumonia and possible neurologic syndromes. Transmission occurs through airborne droplets or direct contact with infected patients. The natural hosts of the virus are avian and mammalian species.

Novel strains of influenza occur when HA and NA antigens change to the various subtypes which permits evasion of host immune responses

and allows for reinfection. Cell cultures were previously useful for isolation and diagnosis of the influenza virus. Various cells were used to identify CPEs of the influenza virus including primary monkey kidney cells, human diploid lung fibroblasts, 549 human carcinoma cells, and Madin–Darby canine kidney cells. Unfortunately, culture requires several weeks. Presumptive identification of the presence of influenza virus can be made by hemagglutination using chicken red blood cells, although other viruses such as parainfluenza, mumps, and measles produce HAs.

Antigen testing is commonly used, particularly in the out-patient setting or emergency rooms, for the rapid detection of influenza, however, sensitivity is low. Molecular testing is more sensitive and is available in formats that require testing in a molecular lab as well those that can be performed as a point of care test (see Chapter 12: Overview of Molecular Diagnostics Principles). Both antigen tests and molecular methods can differentiate Influenza A from B; however, molecular tests can also identify the most common subtypes by their HA and NA, which is useful for epidemiologic purposes (H1N1 or H3N2).

Treatment for influenzae is oseltamivir which should be administered within 48 hours of illness onset. An inactivated and recombinant influenza vaccine is available as well as a nasal spray which is a live attenuated influenza vaccine. Most hospitals require personnel to be vaccinated to prevent spread to other caregivers and patients.

Respiratory Syncytial Virus and Metapneumovirus

These viruses belong to the *Paramyxoviridae* family and are enveloped, single-stranded RNA viruses. Respiratory syncytial virus (RSV) is the cause of severe acute lower respiratory tract illnesses in children including bronchiolitis, tracheobronchitis, and pneumonia. In adults, patients who are at-risk are those who live in nursing homes, and those with underlying heart and lung conditions. Metapneumovirus is the cause of the common cold and causes lower and upper respiratory tract illnesses. Transmission occurs through airborne droplets or direct contact with infected patients.

Cytopathological effects of RSV include formation of multinucleated giant cells, or syncytia, in cell culture. Cells available for tissue culture include human heteroploid cells such as HEp-2, HeLa, and A549 cells. Rapid antigen tests are available as IFAs, EIA, and chromatographic immunoassay. Molecular methods can determine the presence of the virus and is often included in respiratory multiplex assays.

Parainfluenza and Mumps

The human parainfluenza (HPIV) and mumps virus also belong to the *Paramyxoviridae* family of enveloped viruses. HPIV 1–4 are associated with upper respiratory tract infection in pediatric and adult patients. Disease is self-limiting and reinfection is possible due to the lack of long-term immunity. HPIV is the most common cause of croup in infants to children 6 years of age. Mumps can be asymptomatic in up to 30% of cases. Nonspecific or respiratory symptoms are common and slightly elevated temperature and enlargement of parotid glands are a common characteristic of infection. HPIV and mumps are transmitted via airborne droplets or contact with contaminated fomites.

A live virus vaccine for measles, mumps, and rubella (MMR) is available. Molecular methods are more sensitive and specific for diagnosis of HPIV and can differentiate the types 1–4. Treatment includes ribavirin.

Measles and Rubella

Measles virus is part of the family *Paramyxoviridae* and is highly contagious, transmitted via aerosols. Measles, also known as rubeola, occurs as acute respiratory illness with a prodrome of fever that can reach 105°F with malaise, cough, coryza, and conjunctivitis. Pathognomonic enanthema or Koplik spots are followed by a maculopapular rash. Exanthema will occur on the face and upper body followed by the trunk and upper, then lower extremities. Lesions persist for about 10 days and will finally resolve to fine desquamation. Complications that can occur include otitis media, bronchopneumonia, laryngotracheobronchitis, diarrhea, and acute disseminated encephalomyelitis and subacute sclerosing panencephalitis. Serology testing for measles-specific IgM can be used for diagnosis as well as molecular methods.

Rubella belongs to the *Togaviridae* family and is transmitted through direct contact of nasal and throat secretions and inhalation of droplets. Rubella, also known as German measles, occurs as a mild, maculopapular rash with lymphadenopathy and fever. The rash will start on the face and last about 3 days. Complications that can occur include thrombocytopenic purpura and encephalitis. Infection during pregnancy can lead to congenital defects in infants with shedding of the virus for a long period of time. Prenatal screening for immunity by serum IgG tests is recommended for all pregnant women at the initial prenatal visit. Viral detection can be made from throat, nasal, or urine sample by molecular methods and serology which tests for presence of rubella-specific IgM. A live virus vaccine for MMR is available.

Flaviviridae

The flavivirus family includes West Nile virus, Dengue virus, Yellow fever, St. Louis encephalitis, Chikungunya, and Zika virus. These are considered arboviruses which originated from ARthropod-BORne virus, and are transmitted via mosquitoes. Flaviviruses are enveloped single-stranded RNA viruses that cause mostly asymptomatic infection. While many infections are asymptomatic, infection may begin as a nonspecific, febrile illness and develop as a severe and life-threatening disease. Since these viruses are not endemic in the community, diagnosis is made by antibody testing (IgG) in the serum. Testing should be limited to the warm season when mosquitoes are viable. Characteristics of various flavivirus are summarized in [Table 8.1](#).

Enterovirus and Parechovirus

These viruses belong to the *Picornaviridae* family and are small, nonenveloped viruses that are comprised of a single-stranded RNA genome. Viruses included in this family are enterovirus, echovirus, parechovirus, poliovirus, and coxsackie virus. Many infections are asymptomatic and disease can be localized or systemic. Neurologic syndromes include meningitis, encephalitis, and acute flaccid paralysis. Respiratory syndromes can include the common cold, hand-foot-and-mouth disease, pharyngitis,

Table 8.1 Characteristics of various flavivirus

Flavivirus	Vector	Location
Dengue virus	<i>Aedes aegypti</i> , <i>Aedes albopictus</i>	Central America, South America, Caribbean, Southeast Asia, US states Florida, Hawaii, Texas
Yellow fever virus	<i>Aedes aegypti</i>	Sub-Saharan Africa, South and Central America, Caribbean islands
Zika virus	<i>Aedes</i> spp., <i>Culex</i> spp., <i>Anopheles</i> spp.	South America, Central America, Mexico, US states Texas and Florida
West Nile virus	<i>Aedes</i> spp., <i>Culex</i> spp., <i>Anopheles</i> spp.	North America, Africa, Europe, Middle East, West Asia
Chikungunya virus	<i>Aedes</i> spp., <i>Culex</i> spp., <i>Anopheles</i> spp.	Africa, South America, Central America, North America, Asia, Europe, Pacific Islands
St. Louis encephalitis virus	<i>Culex</i>	United States, Canada, Mexico

Table 8.2 Characteristics of enteroviruses

Enterovirus	Species	Serotypes infecting humans
EV A	Coxsackie viruses Enteroviruses	20
EV B	Coxsackie viruses Echoviruses Enteroviruses	59
EV C	Coxsackie viruses Polioviruses Enteroviruses	23
EV D	Enteroviruses	4, including EV-D68
Rhinovirus	A and B	107
Human parechovirus	HPeV	19

bronchiolitis, rhinitis, and pneumonia as well as cardiovascular such as myocarditis. Poliovirus causes paralytic poliomyelitis, aseptic meningitis, and febrile illness. Echovirus causes aseptic meningitis, rash, febrile illness, conjunctivitis, and severe generalized neonatal disease.

Transmission of the enterovirus is largely by the fecal-oral route, except for the respiratory enterovirus strain, EV-D68, transmitted through airborne droplets. Enteroviruses are more prevalent in the summer and fall months. Rhinovirus can occur year round. Poliovirus is spread through fecal-oral route and is more common in areas with poor sanitation. Eradication efforts have decreased polio cases 106 total cases in 2015 according to the Polio Global Eradication Initiative [3].

Primary monkey kidney cells can be used to grow most enteroviruses in cell culture from cerebrospinal fluid (CSF), blood, respiratory, throat swabs, and stool specimens. Antibody testing is recommended for diagnosis of coxsackie viral myocarditis since not all strains will grow in cell culture. Molecular methods are the preferred method for diagnosis of meningitis and disseminated disease, however, not all commercially available enterovirus PCR assays include parechovirus, mostly seen in neonates. Although supportive treatment is usually used ribavirin can also be used. There is a vaccine against poliovirus, but not the other enteroviruses. Characteristics of enteroviruses are listed in [Table 8.2](#).

Coronavirus

Human corona viruses are endemic in the human population. The causative agent of severe acute respiratory syndrome (SARS) is SARS virus

which emerged in the Guangdong province of China. Middle East Respiratory Syndrome (MERS) was initially isolated in Saudi Arabia. Birds and wild mammals are natural reservoirs and can be transmitted as a zoonotic virus via airborne transmission.

Endemic human corona viruses cause upper respiratory tract infections in patients. Symptoms include fever, cough, sore throat, rhinorrhea, and croup in children. Infections occur more often in the winter months. SARS virus was transmitted via airborne transmission and caused the SARS pandemic which spread to 26 countries with about 700 deaths according to the The Center for Disease Control and Prevention (CDC). Symptoms include fever, malaise, nonproductive cough followed by rapid respiratory deterioration. MERS virus also causes illness with high mortality rates especially in patients with comorbidities. Symptoms include fever, cough, pneumonia, and respiratory deterioration. Molecular methods such as RT-PCR are available for detection.

Hepatitis A and Hepatitis E

Hepatitis A (HepA) and Hepatitis E (HepE) viruses are both nonenveloped viruses belonging to different families. HepA is part of the *Picornaviridae* family, while HepE is part of the *Hepeviridae* family. HepA and HepE are commonly seen in waterborne outbreaks associated with contaminated food and transmitted through the fecal-oral route. HepA virus can be excreted in high titers in feces allowing for person to person spread. HepE can be ingested in meat from infected animals, mainly in Western Europe and Japan. Zoonotic infections from pigs and deer can also occur.

HepA and HepE viruses cause viral hepatitis with initial presentation of fever, headache, anorexia, nausea, and abdominal discomfort with more severe disease in older patients. HepA will infect the cells lining the alimentary tract and will replicate in the liver. Serology is available for testing. A vaccine is available for prevention of HepA virus.

Hepatitis C

Hepatitis C (HepC) virus is part of the *Flaviviridae* family and is its own genus, *Hepadnavirus*. HepC is the most common blood borne infections in the United States. Infection can range from asymptomatic carriers, to clearance of virus, and chronic infection. Chronic infection will cause liver damage and leads to cirrhosis and is the leading cause of liver transplantations. HepC is transmitted by intravenous drug use, multiple sexual partners, or contact with an infected partner.

Diagnosis is made by an initial screen using serology and if positive molecular testing for confirmation. Both qualitative and quantitative testing can be done to determine presence of virus and viral load respectively. Treatment can include direct acting antiviral drugs including second generation drugs such as sofosbovir, a viral protein inhibitor, as well as ribavirin. HepC virus genotyping may be important to determine the severity and aggressiveness of infection, as well as for understanding response to antiviral therapy. HepC virus genotypes are separated into six distinct genotypes, 1–6, where genotype 1 is the most common in the United States, but can be the most difficult to treat, while 2 and 3 respond well to ribavirin therapy [4].

Filoviruses

Ebola virus and Marburg viruses belong to the *Filoviridae* family. Symptoms are similar but vary greatly between individual patients. The incubation period can be between 4 and 16 days and resembles a flu-like illness followed by nausea, vomiting, sore throat, and diarrhea. A maculopapular rash will follow with mucosal membrane hemorrhage and gastrointestinal bleeding. Death will occur after shock between 6 and 16 days after onset of illness. Virus detection requires molecular methods in specimen collected during the acute stage of illness. During the most current outbreak of 2014–16, the CDC recommended that patients with suspected ebola virus be tested only in special Laboratory Response Network laboratories located in specific cities [5]. In addition, hospitals were asked to care for these patients in areas in which the staff engaged in testing was limited, equipment used was segregated, and performed in dedicated places for these individuals.

DEOXYRIBONUCLEIC ACID VIRUSES

DNA viruses contain only DNA as part of their genetic makeup. Various DNA viruses are discussed in this section.

Herpes Simplex Virus

Human simplex virus (HSV)-1 and HSV-2 belong to the family *Herpesviridae*. Primary infection for HSV-1 can be acquired in childhood without symptoms and can cause fever or submandibular lymphadenopathy in older children. Primary infection with HSV-2 occurs as herpes genitalis, fever, and lymphadenopathy with healing lesions that typically last approximately 3 weeks.

After primary infection, the virus will become latent in the dorsal root ganglia, recurring periodically. HSV-1 is typically associated with orolabial recurrence while genital recurrence is usually caused by HSV-2. However, genital infections caused by HSV-1 are becoming more common. Neonatal herpes can occur during vaginal delivery. Risk of infection is higher with mothers who have a primary infection. Disease can range from localized infection in the skin, eyes, and mucosa to manifestations that can at times occur as CNS or disseminated disease. HSV can cause central nervous system (CNS) disease in an immunocompromised host. HSV encephalitis can be fatal in about 70% of cases without therapy. With therapy this is reduced to about 20%. HSV meningitis is usually self-limiting and may be seen as sequelae to genital herpes. HSV meningitis may recur in up to 25% of cases after an asymptomatic period of months to years.

Transmission occurs through direct contact with secretions from an infected person. The incidence of asymptomatic carriers is high. Although HSV multiplies rapidly compared to other viruses and can grow in Rabbit Kidney cells in as fast as 24 hours, molecular methods are the most appropriate method for diagnosis of encephalitis or meningitis. EM images are reminiscent of a round wheel but are indistinguishable from the other herpes viruses. Tzanck smears (demonstrating multinucleated giant cells) are still used for diagnosis of fresh, untreated, un-roofed skin lesions, or superficial surfaces in newborns. Therapy should be started on clinical grounds if early PCR is negative. Treatment available includes acyclovir and valacyclovir.

Varicella Zoster Virus

Varicella Zoster virus (VZV) is part of the family of *Herpesviridae*. Varicella, or chicken pox, is the initial disease of VZV. Primary infection occurs in childhood. Incubation time is 10–21 days during which skin vesicles produced are highly infectious. VZV will become latent and remain in the ganglia. Encephalitis can occur during chicken pox and occurs with acute cerebellar ataxia. Reactivation will occur in the ganglion and tracks down the sensory nerve to the area of the skin innervated by the nerve forming a rash. VZV is acquired by airborne transmission. Latent VZV infection establishes in the dorsal root ganglia. Although clinically different from HSV due to the presence of a dermatomal rash, the Tzanck smear described for HSV, can also be used for VZV, however, differentiation of the two agents would not be possible using this technique. Treatment includes acyclovir.

Cytomegalovirus

Cytomegalovirus (CMV) is in the family *Herpesviridae*, and was formally called HHV-5. CMV can be asymptomatic but is the most common viral cause of congenital defects. Congenital defects include microcephaly, intracerebral calcification, hepatosplenomegaly, and cytomegalic inclusion disease. The risk for severe birth defects is highest when mother has primary infection during pregnancy. CMV is an opportunistic pathogen and will cause pneumonitis, pneumonia, and mortality if not treated. CNS or GI disease as well as disseminated disease can occur in immunocompromised patients.

Transmission is through sexual contact, or via any body fluids that allow transfer by direct contact with the infected person. The fetus can be infected via mother's viremia or through viral ascension from the cervix.

Cell culture can be done in human fibroblast cells. The cytopathogenic effect of CMV results in intranuclear inclusions usually identified by antibody staining. In tissue biopsy these inclusions are called the "owl's-eye." However, due to the slow growth of the virus in tissue culture this method of diagnosis has fallen out of favor. Serology can be useful for testing the immune status of pregnant women and pretransplant patients, however, molecular methods can detect virus in body fluids including CSF and quantitation in plasma is useful in following treatment. Treatment can include ganciclovir, valganciclovir, foscarnet, and cidofovir. Genotypic resistance testing can identify the presence of nucleic acid mutations in the genes *UL97* and *UL54*. Mutations in *UL97* encode resistance to ganciclovir, while mutations in *UL54* encode resistance to ganciclovir, cidofovir, and foscarnet.

Human Herpes Virus 6–8

Human herpes virus (HHV)-6 and HHV-7 belong to the *Roseolovirus* genus. HHV-8 is part of the *Rhadinovirus* genus. HHV-6 is associated with the acute phase exanthema subitum, known as roseola. Symptoms are more severe in immunocompromised patients. Symptoms of primary infection include fever, rhinorrhea, diarrhea, and roseola. In immunocompromised patients, HHV-6 can reactivate and cause encephalitis, pneumonitis, graft-versus-host disease, and bone marrow suppression. HHV-7 can cause roseola, febrile illness, and seizures in children. Reactivation is possible in immunocompromised patients. HHV-8 is associated with all forms of Kaposi's sarcoma, an angioproliferative disease which occurs as brown lesions on the skin, internal organs, and extremities.

HHV-6 and HHV-7 are both found in the saliva and therefore airborne transmission is a likely route of infection. Reactivation of both agents is possible in immunocompromised patients. Greater than 90% of the population is seropositive for HHV-6 and the virus can be transmitted to the fetus during pregnancy. HHV-7 can also be found in the saliva, but congenital disease has not been recorded. HHV-8 can be found in the saliva, breast milk, and semen. Transmission can occur through injection drug use and blood transfusion.

Molecular methods are the appropriate tests for these viruses. CPEs in cell culture occurs as multinucleated giant cells. Treatment includes antivirals targeting HHV-6 and HHV-7 which include foscarnet, cidofovir, and ganciclovir.

Hepatitis B and Hepatitis D

Hepatitis B (HepB) is a part of the *Hepadnaviridae* family. HepB infects hepatocytes with disease ranging from asymptomatic to acute infection that resolves to a chronic infection. There are three phases of chronic Hepatitis B Virus (HBV) disease: the immune tolerant phase, the immune clearance phase, and the inactive carrier phase. Hepatitis D requires HepB to replicate and is only transmitted to patients already infected with HepB. The most common modes of transmission are from mother to child, early childhood infections from close contact, sexual contact, and transfer in shared needles during intravenous drug use. Assays are available to test for HepB proteins and specific antibodies in serum. Quantitative molecular methods are commonly used once diagnosis is made.

Various proteins can be detected during the course of infection. HepB surface antigen (HBsAg) and the HepB envelope antigen (HBeAg) are present in the serum during primary infection. The presence of HBsAg is useful in diagnosis. The presence of HBeAg can indicate viral replication producing a highly infectious patient. Serology testing for HepB-specific antibodies is used to determine the stages of diseases and establish the immunity after vaccination. The first IgM antibodies to appear are anti-Hepatitis B core (anti-HBc) which can persist for weeks after initial infection. The presence of anti-HBs indicates immunity from infection or vaccination. As acute infection resolves, anti-HBe is detected and HBsAg disappears. Persistence of HBsAg indicates a carrier state or, if symptoms are present, a chronically infected patient. Nearly 80% of primary liver cancer (Hepatocellular carcinoma) is associated with chronic

HBV infection. Treatment includes lamivudine, adefovir, tenofovir, and telbivudine. In addition a subunit vaccine derived from HBsAg for HeB is available.

Adenovirus

Adenoviruses belong to the *Adenoviridae* family. Infection can be asymptomatic and cause respiratory infections and diarrheal illness. Symptoms include fever, pharyngitis, and cervical adenopathy. Other infections include involvement of the eye, gastrointestinal tract, urinary tract, CNS, liver, and genital tract. Gastroenteritis is normally caused by the adenovirus serotype 40/41. Transmission includes airborne transmission and fecal-oral route.

Adenovirus can grow in tissue culture in human heteroploid cells such as Hep-2. CPEs are composed of aggregates of refractile cells. Molecular methods are available for testing and can be done on serum, CSF, respiratory, and stool samples. Treatment can include ganciclovir, ribavirin, and cidofovir.

Papovavirus

Double-stranded DNA viruses also include the papillomaviruses and the polyomaviruses.

Human Papillomaviruses

Multiple papillomaviruses have an oncogenic potential, especially the high risk serotypes HPV-16 and HPV-18. Hepatitis B Virus (HPV) infects and replicates in the squamous epithelium and mucosal membranes which causes benign warts and papillomas. HPV can cause oncogenic cervical cancer. Transmission occurs through direct contact of infected epithelia especially through sexual contact.

Cytology of the exfoliated cervical epithelial cells shows characteristic features using Papanicolaou stain. CPEs are characterized by high nucleus/cytoplasm ratios. Molecular testing can be used for diagnosis and to specifically identify the high risk serotypes. A vaccine is available for HPV Gardasil (Merck, West Point, PA) which targets HPV types 6, 11, 16, and 18.

Polyomavirus

Polyomaviruses are part of the *Polyomaviridae* family. BK virus establishes latent infection in the kidney and is shed in the urine. Disseminated disease usually occurs in immunocompromised patients, BK virus causes renal disease in kidney transplant patients and JC virus causes neurologic

symptoms and progressive multifocal leukoencephalopathy in HIV infected patients, both with poor prognosis.

Infectious spread likely occurs via airborne transmission through direct contact of bodily fluids; although spread can also occur through organ transplantation or through occurrence as congenital infections. Urine cytology can identify large cells in the urine (decoy cells) however diagnosis is usually made by real-time PCR of urine and/or blood. JC virus can be detected in the CSF by molecular methods.

Rabies Virus

Rabies belongs to the genus *Lyssavirus* and is a zoonotic disease which causes acute, fatal viral encephalomyelitis. Transmission occurs from small rodents that vary based on geography. In the United States, rabies can be transferred from skunks in California and North and South Central states, gray foxes in Texas and Arizona, raccoons on the East coast, Arctic and red foxes in Alaska, and mongooses in Puerto Rico.

The rabies virus infects the CNS and occurs with fever, headache, and weakness. Progression of the disease results in insomnia, anxiety, confusion, paralysis, hallucinations, agitation, hypersalivation, and hydrophobia. Death typically occurs within days of onset of these symptoms. Diagnosis requires saliva, serum, CSF and a skin biopsy of hair follicles at the nape of the neck. The serum and saliva are tested for antibodies to the rabies virus, while the skin biopsy is examined for rabies antigen. Brain biopsy of the infected animal may demonstrate Rabies inclusions or Negri bodies. EM images will show morphology reminiscent of a bullet. Characteristics of DNA viruses and RNA viruses are summarized in [Table 8.3](#).

KEY POINTS

- Viruses are nonliving entities that replicate inside host cells, using the molecular machinery of the host to replicate single or double-stranded RNA or DNA. Glycoproteins present on the viral capsid surface interact with specific host membrane molecules, allowing adhesion and subsequent infection.
- RNA viruses, such as the HIV that causes AIDS, may be found both as free virus particles and as virions within infected host cells.
- The orthomyxoviruses are enveloped, single-stranded RNA viruses which have a lipid bilayer containing HA and NA glycoproteins. The influenza virus is a prime example, with surface antigens that change under pressure of immune recognition.

Table 8.3 Characteristics of viruses

Family	Genome	Envelope	Cell line	Cytopathic effect
Deoxyribonucleic acid viruses				
<i>Herpesviridae</i> HSV, ^a VZV, CMV, EBV, ^b HHV-6–8 ^b	dsDNA	+	HDF	Nuclear inclusions (Cowdry)
<i>Adenoviridae</i>	dsDNA	–	Hep-2	Grape-like clusters
<i>Papillomaviridae</i>	dsDNA	–	–	–
<i>Poxviridae</i> Small pox, Molluscum	dsDNA	–	–	–
<i>Polyomaviridae</i> BK, JC	dsDNA	–	–	Decoy cells
Ribonucleic acid viruses				
<i>Orthomyxoviridae</i> Influenza	ssRNA	+	PMK	Hemadsorption
<i>Paramyxoviridae</i> Measles, ^c Mumps, Parainfluenza	ssRNA	–	PMK	Cytoplasmic inclusions, syncytia
<i>Picornaviridae</i> Entero, Coxsackie, ^d Rhino	ssRNA	–	PMK	Tear-shaped cells
<i>Rhabdoviridae</i> Rabies	ssRNA	+	–	Negri bodies, bullet shaped
<i>Togaviridae</i> Arbo, Rubella	ssRNA	+	–	–
<i>Retroviridae</i> HIV	ssRNA	+	–	–
<i>Reoviridae</i> Rotavirus	dsRNA	–	–	–

^aRapid rounding of all cells.

^bNo growth cell culture.

^cMeasles nuclear and cytoplasmic inclusions, Warthin–Finkeldy cells.

^dFocal swollen cells; *HDF*, human diploid fibroblast; *PMK*, primary monkey kidney cells; *Hep-2*, human epithelial type 2.

- The arbovirus flavivirus family includes West Nile virus, Dengue virus, Yellow Fever St. Louis encephalitis, and Zika virus. These are transmitted via arthropod vectors.
- The *Paramyxoviridae* family of enveloped viruses includes the parainfluenza, mumps, measles, rubella, and RSV. Transmission typically occurs through airborne droplets or direct contact with infected patients.
- The *Picornaviridae* family is small, nonenveloped single-stranded RNA viruses which include enterovirus, echovirus, parechovirus, poliovirus, and coxsackie virus. Clinical symptoms postinfection range from respiratory disorder to rashes.
- Corona viruses, represented by the agent causing SARS, are zoonotic viruses that can be spread via airborne transmission.
- The Hepatitis viruses represent a broad group of agents that span multiple families. All replicate in the liver, with resultant typical chronic infection.

- DNA viruses contain only DNA. A common member of this class is the *Herpesviridae* family, which includes the HSV agents.
- Other DNA viruses include those of the *Hepadnaviridae* family (Hepatitis) and the *Herpesviridae* family (Varicella Zoster and CMV). Transmission is acquired through contact with body fluids, typically via sexual or other means.
- The Roseolovirus HHVs typically cause clinical exanthems, seen due to CPEs postinfection of host cells.
- Other DNA viruses of clinical note include [1] adenoviruses (*Adenoviridae* family) that lead to respiratory infections and can cause diarrheal illness; [2] human papillomaviruses with oncogenic capabilities; and [3] polyomavirus (*Polyomaviridae*) which cause renal and neurological disorders.
- Molecular diagnostics allows rapid detection by matching of nucleic acid sequences, by detection of viral antigens released during the infection process, or by detection of increased antibody presence with specificity for viral proteins.
- Common antiviral therapeutics function via direct inhibition of reverse transcriptase. Alternative antiviral agents utilize nucleoside analogs to disrupt DNA polymerase activity to limit virion replication.

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