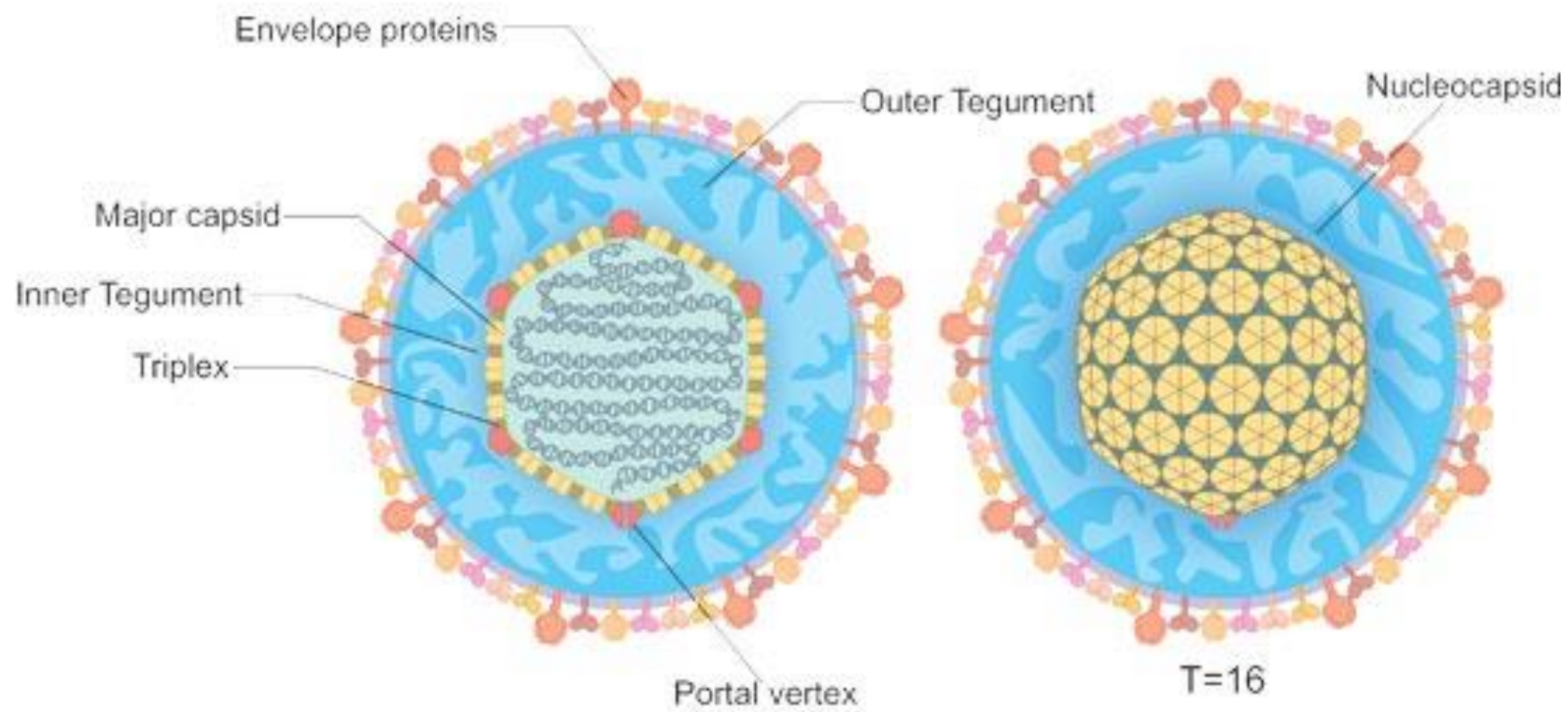


Practical lesson 21 : Microbiological diagnosis of infections caused by herpesviruses, picornaviruses and rhabdoviruses. Arboviruses

- **HERPESVIRUSES**

- The herpesvirus family contains six important human pathogens: herpes simplex virus types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 8 (the cause of Kaposi's sarcoma). All herpesviruses are structurally similar. Each has an icosahedral core surrounded by a lipoprotein envelope. The genome is linear double-stranded
- DNA. The virion does not contain a polymerase. They are large (120-200 nm in diameter), second in size only to poxviruses. They replicate in the nucleus, form intranuclear inclusions, and are the only viruses that obtain their envelope by budding from the nuclear membrane. The virions of herpesviruses possess a tegument located between the nucleocapsid and the envelope. This structure contains regulatory proteins, such as transcription and translation factors, which play a role in viral replication. Herpesviruses are noted for their ability to cause latent infections. In these infections, the acute disease is followed by an asymptomatic period during which the virus remains in a quiescent (latent) state. When the patient is exposed to an inciting agent or immunosuppression occurs, reactivation of virus replication and disease can occur. With some herpesviruses (e.g., herpes simplex virus), the symptoms of the subsequent episodes are similar to those of the initial one; however, with others (e.g., varicella-zoster virus), they are different
- Three of the herpesviruses, HSV types 1 and 2 and varicella-zoster virus (VZV), cause a vesicular rash, both in primary infections and in reactivations. Primary infections are usually more severe than reactivations. The other two herpesviruses, CMV and Epstein-Barr virus (EBV), do not cause a vesicular rash. Four herpesviruses, namely HSV types 1 and 2, VZV, and CMV, induce the formation of multinucleated giant cells, which can be seen microscopically in the lesions. The importance of giant cells is best illustrated by the Tzanck smear, which reveals multinucleated giant cells in a smear taken from the painful vesicles of the genitals caused by HSV type 2.
- The herpesvirus family can be subdivided into three categories based on the type of cell most often infected and the site of latency. The alpha herpesviruses, consisting of HSV types 1 and 2 and VZV, infect epithelial cells primarily and cause latent infection in neurons. The beta herpesviruses, consisting of CMVs and human herpesvirus 6, infect and become latent in a variety of tissues. The gamma herpesviruses, consisting of EBV and human herpesvirus 8 (HHV-8, Kaposi's sarcoma-associated virus), infect and become latent primarily in lymphoid cells. Certain herpesviruses are associated with or cause cancer in humans (Burkitt's lymphoma and nasopharyngeal carcinoma, and human herpesvirus 8 causes Kaposi's sarcoma). Several herpesviruses cause cancer in animals



- *HERPES SIMPLEX VIRUSES (HSV)*
- HSV type 1 (HSV-1) and type 2 (HSV-2) are distinguished by two main criteria: antigenicity and location of lesions. Lesions caused by HSV-1 are, in general, above the waist, whereas those caused by HSV-2 are below the waist.
- ***Diseases***
- HSV-1 causes acute gingivostomatitis, recurrent herpes labialis (cold sores), keratoconjunctivitis (keratitis), and encephalitis, primarily in adults. HSV-2 causes herpes genitalis (genital herpes), neonatal encephalitis and other forms of neonatal herpes, and aseptic meningitis. Infection by HSV-1 or HSV-2 is a common cause of erythema multiforme.
- ***Important Properties***
- HSV-1 and HSV-2 are structurally and morphologically indistinguishable. They can, however, be differentiated by the restriction endonuclease patterns of their genome DNA and by type-specific monoclonal antisera against glycoprotein G. Humans are the natural hosts of both HSV-1 and HSV-2.
- ***Pathogenesis & Immunity***
- The virus replicates in the skin or mucous membrane at the initial site of infection, and then migrates up the neuron by retrograde axonal flow and becomes latent in the sensory ganglion cells. In general, HSV-1 becomes latent in the trigeminal ganglia, whereas HSV-2 becomes latent in the lumbar and sacral ganglia. During latency, most- if not all-viral DNA is located in the cytoplasm rather than integrated into nuclear DNA. The virus can be reactivated from
- the latent state by a variety of inducers at which time it migrates down the neuron and replicates in the skin, causing lesions. The typical skin lesion is a vesicle that contains serous fluid filled with virus particles and cell debris. When the vesicle ruptures, virus is liberated and can be transmitted to other individuals. Multinucleated giant cells are typically found at the base of herpesvirus lesions.
- Immunity is type-specific, but some cross-protection exists. However, immunity is incomplete, and both reinfection and reactivation occur in the presence of circulating IgG. Cell-mediated immunity is important in limiting herpesviruses, because its suppression often results in reactivation, spread, and severe disease.
- Herpes labialis
- ***Laboratory Diagnosis***
- An important diagnostic procedure is isolation of the virus from the lesion by growth in cell culture. The typical cytopathic effect occurs in 1 to 3 days, after which the virus is identified by fluorescent antibody staining of the infected cells or by detecting virus-specific glycoproteins in enzyme-linked immunosorbent assays (ELISAs). HSV-1 can be distinguished from HSV-2 by using monoclonal antibody against glycoprotein G often in an ELISA test.
- A rapid presumptive diagnosis can be made from skin lesions by using the Tzanck smear, in which cells from the base of the vesicle are stained with Giemsa stain. The presence of multinucleated giant cells suggests herpesvirus infection

- ***Treatment***

- Acyclovir (acycloguanosine, 'Zovirax) is the treatment of choice for encephalitis and systemic disease caused by HSV-1. It is also useful for the treatment of primary and recurrent genital herpes; it shortens the duration of the lesions and reduces the extent of shedding of the virus but does not cure the latent state. Acyclovir is also used to treat neonatal infections caused by HSV-2. Mutants of HSV-1 resistant to acyclovir have been isolated from patients; fos-carnet can be used in these cases. Valacyclovir (Valtrex) and famciclovir (Famvir) are used in the treatment of genital herpes and in the suppression of recurrences.
- Note that no drug treatment of the primary infection prevents recurrences; drugs have no effect on the latent state, but prophylactic, long-term administration of acy-clovir, valacyclovir, or famciclovir can suppress clinical recurrences.

- ***Prevention***

- Valacyclovir (Valtrex) and famciclovir (Famvir) are used in the suppression of recurrent lesions, especially in those with frequent recurrences caused by HSV-2. Suppressive chemoprophylaxis also reduces shedding of the virus and, as a result, transmission to others. Prevention also involves avoiding contact with the vesicular lesion or ulcer. Cesarean section is recommended for women who are at term and who have genital lesions or positive viral cultures.
- Circumcision reduces the risk of infection by HSV-2. There is no vaccine against HSV-1 or HSV-2.

- *VARICELLA-ZOSTER VIRUS (VZV)*
- ***Disease***
- Varicella (chickenpox) is the primary disease; zoster (shin-gles) is the recurrent form.
- ***Important Properties***
- VZV is structurally and morphologically similar to other herpesviruses but is antigenically different. It has a single serotype. The same virus causes both varicella and zoster.
- Humans are the natural hosts.
- ***Laboratory Diagnosis***
- Although most diagnoses are made clinically, laboratory tests are available. A presumptive diagnosis can be made by using the Tzanck smear. Multinucleated giant cells are seen in VZV as well as HSV lesions (see Figure 37-2). The definitive diagnosis is made by isolation of the virus in cell culture and identification with specific antiserum. A rise in antibody titer can be used to diagnose varicella but is less useful in the diagnosis of zoster.
- ***Treatment***
- No antiviral therapy is necessary for chickenpox or zoster in immunocompetent children. Immunocompetent adults with either moderate or severe cases of chickenpox or
- zoster often are treated with acyclovir because it can reduce the duration and severity of symptoms. Immunocompromised children and adults with chickenpox, zoster, or disseminated disease should be treated with acyclovir. Disease caused by acyclovir-resistant strains of VZV can be treated with foscarnet. Two drugs similar to acyclovir, famciclovir (Famvir) and valacyclovir (Valtrex), can be used in patients with zoster to accelerate healing of the lesions, but none of these drugs can cure the latent state. There is some evidence that these drugs reduce the incidence of postzoster neuralgia.
- ***Prevention***
- There are two vaccines against VZV: one designed to prevent varicella, called Varivax, and the other designed to prevent zoster, called Zostavax. Both contain live, attenuated VZV, but the zoster vaccine contains 14 times more virus than the varicella vaccine. The zoster vaccine is effective in preventing the symptoms of zoster, but does not eradicate the latent state of VZV.
- The varicella vaccine is recommended for children between the ages of 1 and 12 years, whereas the zoster vaccine is recommended for people older than 60 years and who have had varicella. The varicella vaccine is given in two doses, whereas the zoster vaccine is given in one dose.

- *CYTOMEGALOVIRUS (CMV)*
- ***Diseases***
- CMV causes cytomegalic inclusion disease (especially congenital abnormalities) in neonates. It is the most common cause of congenital abnormalities in the United States.
- CMV is a very important cause of pneumonia and other diseases in immunocompromised patients such as recipients of bone marrow (stem cell) and solid organ transplants. It also causes heterophil-negative mononucleosis in immunocompetent individuals.
- ***Important Properties***
- CMV is structurally and morphologically similar to other herpesviruses but is antigenically different. It has a single serotype. Humans are the natural hosts; animal CMV strains do not infect humans. Giant cells are formed, hence the name cytomegalo.
- Summary of Replicative Cycle
- The cycle is similar to that of HSV (see page 290). One unique feature of CMV replication is that some of its "immediate early proteins" are translated from mRNAs brought into the infected cell by the parental virion rather than being translated from mRNAs synthesized in the newly infected cell.
- ***Transmission & Epidemiology***
- CMV is transmitted by a variety of modes. Early in life, it is transmitted across the placenta, within the birth canal, and quite commonly in breast milk. In young children, its most common mode of transmission is via saliva. Later in life it is transmitted sexually; it is present in both semen and cervical secretions. It can also be transmitted during blood transfusions and organ transplants. CMV infection occurs worldwide, and more than 80% of adults have antibody against this virus.
- ***Pathogenesis & Immunity***
- Infection of the fetus can cause cytomegalic inclusion disease, characterized by multinucleated giant cells with prominent intranuclear inclusions. Many organs are affected, and widespread congenital abnormalities result.
- Infection of the fetus occurs mainly when a primary infection occurs in the pregnant woman (i.e., when she has no antibodies that will neutralize the virus before it can infect the fetus). The fetus usually will not be infected if the pregnant woman has antibodies against the virus. Congenital abnormalities are more common when a fetus is infected during the first trimester than later in gestation, because the first trimester is when development of organs occurs and the death of any precursor cells can result in congenital defects.
- Infections of children and adults are usually asymptomatic, except in immunocompromised individuals. CMV enters a latent state primarily in monocytes and can be reactivated when cell-mediated immunity is decreased.

- ***Laboratory Diagnosis***

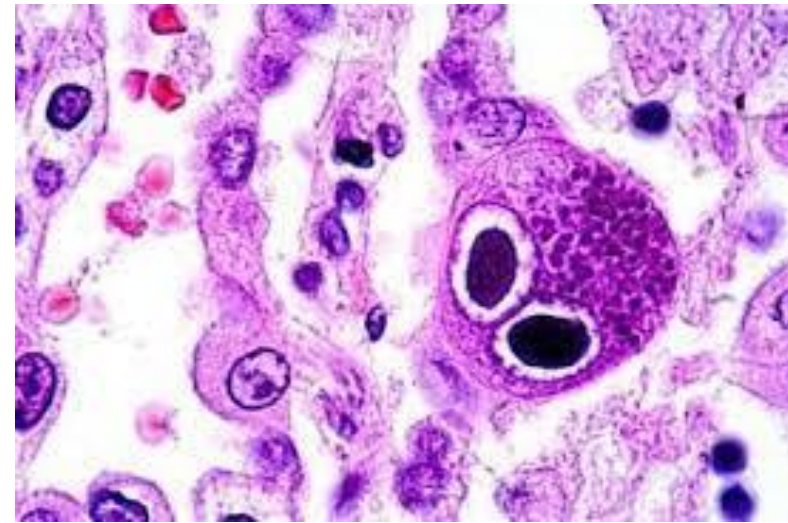
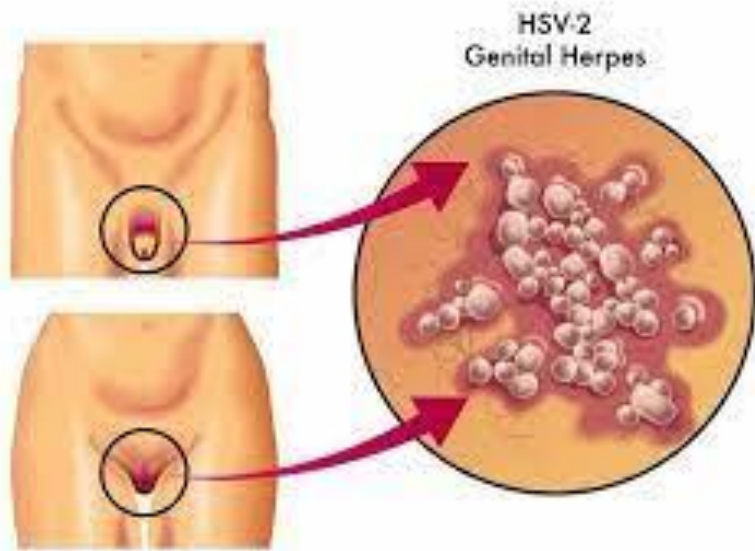
- The preferred approach involves culturing in special tubes called shell vials coupled with the use of immunofluorescent antibody, which can make a diagnosis in 72 hours. The
- virus obtained in the culture can then be used to determine the drug susceptibility to ganciclovir. Other diagnostic methods include fluorescent antibody and histologic staining of inclusion bodies in giant cells in urine and in tissue. The inclusion bodies are intranuclear and have an oval owl's eye shape. A fourfold or greater rise in antibody titer is also diagnostic. PCR-based assays for CMV DNA or RNA in tissue or body fluids, such as spinal fluid and amniotic fluid, are also very useful.

- ***Treatment***

- Ganciclovir (Cytovene) is moderately effective in the treatment of CMV retinitis and pneumonia in patients with AIDS. Valganciclovir, which can be taken orally, is also effective against CMV retinitis. CMV strains resistant to ganciclovir and valganciclovir have emerged, mostly due to mutations in the *UL97* gene that encodes the phosphokinase. Drug susceptibility testing can be done.
- Foscarnet (Foscavir) is also effective but causes more side effects. Unlike HSV and VZV, CMV is largely resistant to acyclovir. Cidofovir (Vistide) is also useful in the treatment of CMV retinitis. Fomivirsen (Vitravene) is an antisense DNA approved for the intraocular treatment of CMV retinitis. It is the first and, at present, the only antisense molecule to be approved for the treatment of human disease.

- ***Prevention***

- There is no vaccine. Ganciclovir can suppress progressive retinitis in AIDS patients. Infants with cytomegalic inclusion disease who are shedding virus in their urine should be kept isolated from other infants. Blood for transfusion to newborns should be CMV antibody-negative. If possible, only organs from CMV antibody-negative donors should be transplanted to antibody-negative recipients. A high-titer immune globulin preparation (CytoGam) is used to prevent disseminated CMV infections in organ transplant patients.



CMV is short for **cyto-megalo-virus**

CMV is preventable



Pregnant women who already have young children, or who work with young children, are at highest risk of catching CMV

CMV is found in home and daycare settings



Avoid contact with saliva - Kiss kids under the age of 6 on the forehead instead of lips or cheek



75% of toddlers have CMV in their urine or saliva in studies at child-care settings



Wash your hands after contact with bodily fluids of kids under the age of 6



Don't share utensils, drinks, or toothbrushes with kids under the age of 6



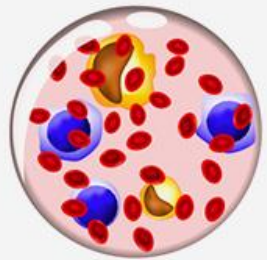
- *EPSTEIN-BARR VIRUS (EBV)*
- ***Diseases***
- EBV causes infectious mononucleosis. It is associated with Burkitt's lymphoma, other B-cell lymphomas, and nasopharyngeal carcinoma. EBV also causes hairy leukoplakia.
- ***Important Properties***
- EBV is structurally and morphologically similar to other herpesviruses but is antigenically different. The most important antigen is the viral capsid antigen (VCA), because it is used most often in diagnostic tests. The early antigens (EA), which are produced prior to viral DNA synthesis, and Epstein-Barr nuclear antigen (EBNA), which is located in the nucleus bound to chromosomes, are sometimes diagnostically helpful as well. Two other antigens, lymphocyte-determined membrane antigen and viral membrane antigen, have been detected also.
- Neutralizing activity is directed against the viral membrane antigen.
- Humans are the natural hosts. EBV infects mainly lymphoid cells, primarily B lymphocytes. EBV also infects the epithelial cells of the pharynx, resulting in the prominent sore throat. In latently infected cells, EB DNA is in the nucleus and is not integrated into cellular DNA. Some, but not all, genes are transcribed, and only a subset of those is translated into protein.
- ***Laboratory Diagnosis***
- The diagnosis of infectious mononucleosis in the clinical laboratory is based primarily on two approaches:
- In the hematologic approach, absolute lymphocytosis occurs, and as many as 30% abnormal lymphocytes are seen on a smear. These atypical lymphs are enlarged, have an expanded nucleus, and an abundant, often vacuolated cytoplasm. They are cytotoxic T cells that are reacting against the EBV-infected B cells. In the immunologic approach, there are two types of serologic tests: (a) The heterophil antibody test is useful for the early diagnosis of infectious mononucleosis because it is usually positive by week 2 of illness. However, because the antibody titer declines after recovery, it is not useful for detection of prior infection.
- ***Treatment***
- No antiviral therapy is necessary for uncomplicated infectious mononucleosis. Acyclovir has little activity against EBV, but administration of high doses may be useful in life-threatening EBV infections.
- ***Prevention***
- There is no EBV vaccine.

Mononucleosis

**Whitish coating
on the tonsils**



**Atypical white
blood cell**



Visual
Photophobia

Swelling
lymph nodes

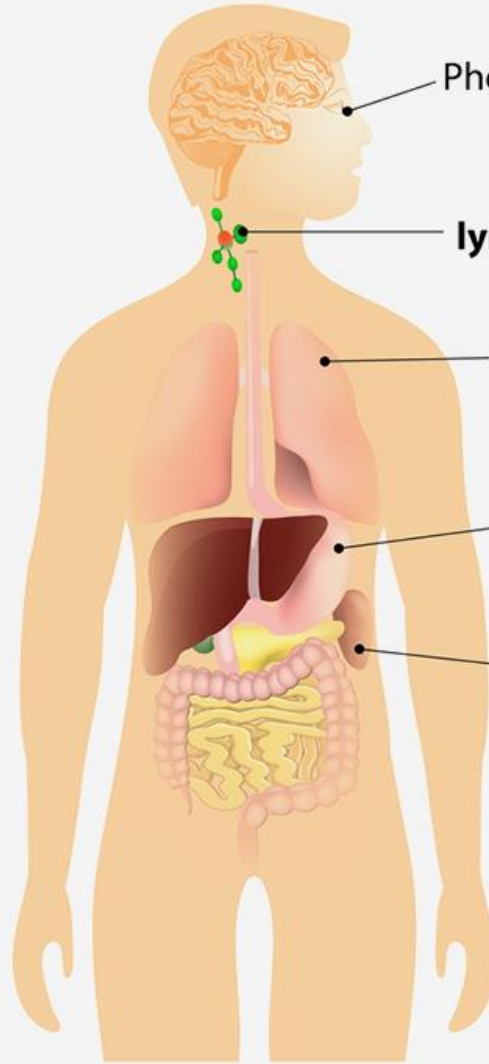
Respiratory
Cough

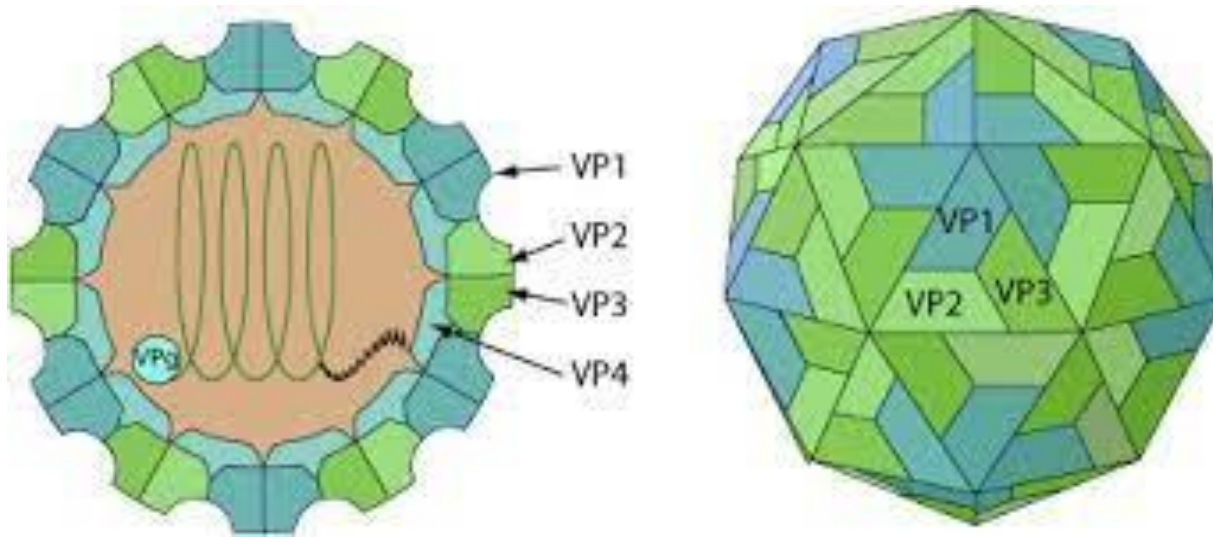
Gastric
Nausea

Spleen
Enlarged

Systemic:

- Chills
- Fever
- Aches
- Headache



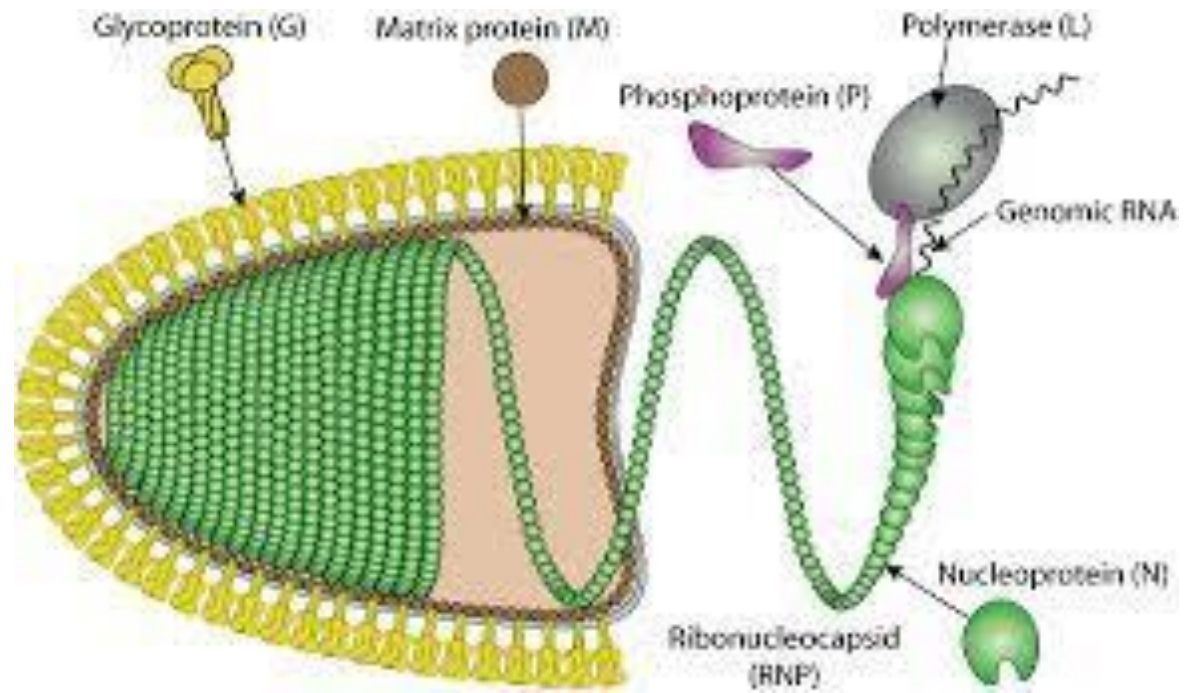


• **PICORNAVIRUSES**

- Picornaviruses are small (20-30 nm) nonenveloped viruses composed of an icosahedral nucleocapsid and a single-stranded RNA genome. The genome RNA has positive polarity (i.e., on entering the cell, it functions as the viral mRNA). There is no polymerase within the virion. Picor-naviruses replicate in the cytoplasm of cells. They are not inactivated by lipid solvents, such as ether, because they do not have an envelope.
- The picornavirus family includes two groups of medical importance: the enteroviruses and the rhinoviruses.
- Among the major enteroviruses are poliovirus, Coxsackie viruses, echoviruses, and hepatitis A virus . Enteroviruses infect primarily the enteric tract, whereas rhinoviruses are found in the
- nose and throat
- Enteroviruses replicate optimally at 37°C, whereas rhinoviruses grow better at 33°C, in accordance with the lower temperature of the nose. Enteroviruses are stable under acid conditions (pH 3-5), which enables them to survive exposure to gastric acid, whereas rhinoviruses are acid-labile. This explains why rhinovirus infections are restricted to the nose and throat.

- ENTEROVIRUSES
- 1. Poliovirus
- ***Disease***
- This virus causes poliomyelitis.
- Important Properties
- The host range is limited to primates (ie., humans and nonhuman primates such as apes and monkeys). This limitation is due to the binding of the viral capsid protein to a receptor found only on primate cell membranes. However, note that purified viral RNA (without the capsid protein) can enter and replicate in many nonprimate cells--the RNA can bypass the cell membrane receptor (i.e., it is "infectious RNA"). There are three serologic (antigenic) types based on different antigenic determinants on the outer capsid proteins. Because there is little cross-reaction, protection from disease requires the presence of antibody against each of the three types.
- ***Laboratory Diagnosis***
- The diagnosis is made either by isolation of the virus or by a rise in antibody titer. Virus can be recovered from the throat, stool, or spinal fluid by inoculation of cell cultures.
- The virus causes a cytopathic effect (CPE) and can be identified by neutralization of the CPE with specific antisera.
- ***Treatment***
- There is no antiviral therapy. Treatment is limited to symptomatic relief and respiratory support, if needed. Physiotherapy for the affected muscles is important.
- ***Prevention***
- Poliomyelitis can be prevented by both the killed vaccine (Salk vaccine, inactivated vaccine, IPV) and the live, attenuated vaccine (Sabin vaccine, oral vaccine, OPV)
- . Both vaccines induce humoral antibodies, which neutralize virus entering the blood and hence prevent central nervous system infection and disease. Both the killed and the live vaccines contain all three serotypes.
- At present, the inactivated vaccine is preferred for reasons that are described later.
- The current version of the inactivated vaccine is called enhanced polio vaccine, or eIPV. It has a higher seroconversion rate and induces a higher titer of antibody than the previous IPV.

- 2. Coxsackie Viruses
- Coxsackie viruses are named for the town of Coxsackie, NY, where they were first isolated.
- ***Diseases***
- Coxsackie viruses cause a variety of diseases. Group A viruses cause, for example, herpangina, acute hemorrhagic conjunctivitis, and hand-foot-and-mouth disease, whereas group B viruses cause pleurodynia, myocarditis, and peri-carditis. Both types cause nonspecific upper respiratory tract disease (common cold), febrile rashes, and aseptic meningitis. Coxsackie viruses and echoviruses (see next section) together cause approximately 90% of cases of viral (aseptic) meningitis.
- ***Important Properties***
- The size and structure of the virion and the nature of the genome RNA are similar to those of poliovirus. The classification of Coxsackie viruses into group A or B is based on pathogenicity in mice. Group A viruses cause widespread myositis and flaccid paralysis, which is rapidly fatal, whereas group B viruses cause generalized, less severe lesions of the heart, pancreas, and central nervous system and focal myositis. At least 24 serotypes of Coxsackie virus A and 6 serotypes of Coxsackie virus B are recognized.
- ***Laboratory Diagnosis***
- The diagnosis is made either by isolating the virus in cell culture or suckling mice or by observing a rise in titer of neutralizing antibodies. A rapid (2.5-hour) polymerase chain reaction (PCR)-based test for enteroviral RNA in the spinal fluid is useful for making a prompt diagnosis of viral meningitis because culture techniques typically take days to obtain a result.
- ***Treatment & Prevention***
- There is neither antiviral drug therapy nor a vaccine available against these viruses. No passive immunization is recommended.
- 3. Echoviruses
- The prefix ECHO is an acronym for enteric cytopathic human orphan. Although called "orphans" because they were not initially associated with any disease, they are now known to cause a variety of diseases such as aseptic meningitis, upper respiratory tract infection, febrile illness with and without rash, infantile diarrhea, and hemorrhagic conjunctivitis.
- The structure of echoviruses is similar to that of other enteroviruses. More than 30 serotypes have been isolated. In contrast to Coxsackie viruses, they are not pathogenic for mice. Unlike polioviruses, they do not cause disease in monkeys. They are transmitted by the fecal-oral route and occur worldwide. Pathogenesis is similar to that of the other enteroviruses.
- Along with Coxsackie viruses, echoviruses are one of the leading causes of aseptic (viral) meningitis. The diagnosis is made by isolation of the virus in cell culture.
- Serologic tests are of little value, because there are a large number of serotypes and no common antigen. There is no antiviral therapy or vaccine available.



- **RHABDOVIRUSES**
- RABIES VIRUS
- *Disease*
- This virus causes rabies, an encephalitis.
- *Important Properties*
- Rabies virus is the only medically important member of the rabdovirus family. It has a single-stranded RNA enclosed within a bullet-shaped capsid surrounded by a lipoprotein envelope. Because the genome RNA has negative polarity, the virion contains an RNA-dependent RNA polymerase. Rabies virus has a single antigenic type. The antigenicity resides in the envelope glycoprotein spikes. Rabies virus has a broad host range: It can infect all mammals, but only certain mammals are important sources of infection for humans (see later).
- Summary of Replicative Cycle
- Rabies virus attaches to the acetylcholine receptor on the cell surface. After entry into the cell, the virion RNA polymerase synthesizes five mRNAs that code for viral proteins.
- After replication of the genome viral RNA by a virus-encoded RNA polymerase, progeny RNA is assembled with virion proteins to form the nucleocapsid, and the envelope is acquired as the virion buds through the cell membrane.

- ***Transmission & Epidemiology***

- The virus is transmitted by the bite of a rabid animal that manifests aggressive, biting behavior induced by the viral encephalitis. The virus is in the saliva of the rabid animal.
- In the United States, transmission is usually from the bite of wild animals such as skunks, raccoons, and bats; dogs and cats are frequently immunized and therefore are rarely sources of human infection. In recent years, bats have been the source of most cases of human rabies in the United States. Rodents and rabbits do not transmit rabies. Human rabies has also occurred in the United States in people who have not been bitten, so-called "nonbite" exposures. The most important example of this type of transmission is exposure to aerosols of bat secretions containing rabies virus. Another rare example is transmission in transplants of corneas taken from patients who died of undiagnosed rabies.

- ***Laboratory Diagnosis***

- Rapid diagnosis of rabies infection in the animal is usually made by examination of brain tissue by using either PCR assay, fluorescent antibody to rabies virus, or histologic staining of Negri bodies in the cytoplasm of hippocampal neurons (see Figure 39-6). The virus can be isolated from the animal brain by growth in cell culture, but this takes too long to be useful in the decision of whether to give the vaccine. Rabies in humans can be diagnosed by PCR assay; by fluorescent antibody staining of a biopsy specimen, usually taken from the skin of the neck at the hairline; by isolation of the virus from sources such as saliva, spinal fluid, and brain tissue; or by a rise in titer of antibody to the virus. Negri bodies can be demonstrated in corneal scrapings and in autopsy specimens of the brain.

- ***Treatment***

- There is no antiviral therapy for a patient with rabies. Only supportive treatment is available.

- ***Prevention***

- In the United States, the rabies vaccine contains inactivated virus grown in human diploid cells. (Vaccine grown in monkey lung cells or chick embryo cells is also available.) In other countries, the duck embryo vaccine or various nerve tissue vaccines are available as well. Duck embryo vaccine has low immunogenicity, and the nerve tissue vaccines can cause an allergic encephalomyelitis as a result of a cross-reaction with human myelin. For these reasons, the human diploid cell vaccine (HDCV) is preferred.

- **ARBOVIRUSES**

- INTRODUCTION

- Arbovirus is an acronym for arthropod-borne virus and highlights the fact that these viruses are transmitted by arthropods, primarily mosquitoes and ticks. It is a collective name for a large group of diverse viruses, more than 600 atlast count. In general, they are named either for the diseases they cause (e.g., yellow fever virus) or for the place where they were first isolated (e.g., St. Louis encephalitis virus). A new group of viruses called roboviruses has recently
- emerged. The term robo refers to the fact that these viruses are rodent-borne (i.e., they are transmitted directly from rodents to humans without an arthropod vector). Transmission
- occurs when dried rodent excrement is inhaled into the human lung, as when sweeping the floor of a cabin. Two roboviruses cause a respiratory distress syndrome that is often fatal: Sin Nombre virus (a hantavirus) and Whitewater Arroyo virus (an arenavirus).

- ***Important Properties***

- Most arboviruses are classified in three families,1 namely, togaviruses, flaviviruses, and bunyaviruses (1) Togaviruses2 are characterized by an icosahedral nucleocapsid surrounded by an envelope and a singlestranded, positive-polarity RNA genome. They are 70 nm in diameter, in contrast to the flaviviruses, which are 40 to 50 nm in diameter (see later). Togaviruses are divided into two families, alphaviruses and rubiviruses. Only alphaviruses are considered here. (2) Flaviviruses3 are similar to togaviruses in that they also have an icosahedral nucleocapsid surrounded by an envelope and a single-stranded, positive-polarity RNA genome, but the flaviviruses are only 40 to 50 nm in diameter, whereas the togaviruses have a diameter of 70 nm.
- (3) Bunyaviruses4 have a helical nucleocapsid surrounded by an envelope and a genome consisting of three segments of negative-polarity RNA that are hydrogenbonded together.

Arthropod-borne viruses

(Arboviruses)



Dengue



Chikungunya



Yellow Fever



Zika



