# Unit 6 Lecture 16

# DNA Viral Diseases

Recall from unit one that viruses have DNA or RNA for their nucleic acid, but never both and that the DNA and RNA can be either single stranded or double stranded. This first section of viral diseases covers the DNA viruses. Families of DNA viruses are grouped according to the number of strands of DNA they possess, the presence or absence of an envelope, size, and the host cells they attack.

# Pox viruses

The Pox viruses are the largest viruses. They cause skin lesions that start as flat, red macules, enlarge into papules, fill with a clear fluid to become vesicles, and then fill with pus to become pustules which are also known as pox or pocks. The pox crust over and may scar. Most animal pox viruses, and there are many, are species specific, but some animal pox viruses can infect humans, (cowpox, monkeypox, and goatpox). Smallpox is species specific to humans.

A member of the Orthopoxvirus family, Smallpox has played and could still play an important role in the history of microbiology, immunization,

epidemiology, and medicine. Over eighty percent of the European population contracted smallpox during the Middle Ages. Later, explorers took smallpox to the new world and introduced it to a very susceptible population of Native Americans resulting in an estimated 3.5 million deaths. Over



time smallpox is believed to have killed about one BILLION people. The disease has been wiped out in the wild since 1978 as the result of a very intense vaccination program carried out by the World Health Organization (WHO). Two known repositories, one in Atlanta and the other in Russia, still have the "Demon in the Freezer". However, it has been postulated that rogue nations also have isolates and are developing it as a biological weapon of mass destruction. If an outbreak of variola major occurred now, it is estimated at least 30% of the population would die and majority of the rest of the population would be incapacitated for a time.

The portal of entry is inhalation of droplets containing the virus to the respiratory membranes or coming into contact with infected skin crusts. A rash develops into pustules. Variola major causes a more severe form of smallpox than variola minor. Symptoms include fever, malaise, and prostration. More severe symptoms are toxemia, shock, intravascular coagulation, and death. <u>Diagnosis</u> [Click on Powerpoint version under Diagnosis on WHO web page.] is based on signs and symptoms, and direct electron microscopy of material from lesion. Variola grows in chick embryos and tissue cultures. Serological identification can also be used in laboratory

diagnosis. Vaccinia, a mild poxvirus, is used in the vaccination program and it offers some protection against monkeypox. Survival of a smallpox infection renders life long immunity. Molluscum contagiosum is another pox virus that causes a benign epidermal tumor in humans.

# Human Herpes Viruses (Herpesviridae)

Many types of herpesvirus infect humans. They are often latent, that is they remain inactive in cells, sometimes for years and may reactivate as a result of aging, fever, ultraviolet light, immunosuppression, physical or emotional stress, or chemotherapy causing a recurrence of the disease. Herpesviruses cause a variety of human diseases including cold sores, genital herpes, chickenpox, shingles, mononucleosis, and cancer.

Herpes Simplex Virus Type 1 (HSV 1)

The portal of entry of HSV 1 is direct contact to skin or mucous membranes. The disease is manifested by fever blisters and cold sores on the lips and is thus called herpes labialis. Seventy to eighty percent of adults are positive for HSV 1 antibody. Encephalitis can occur in older children and adults and can result in a 70% mortality rate in untreated cases. Herpetic keratitis can lead to vision loss. The basis of laboratory diagnosis is serological testing and/or culture. Since transmission is by direct contact with infected secretions from a symptomatic or asymptomatic host, prevention dictates avoidance of contact of lesions. There is no vaccine, but treatment of the lesion with acyclovir reduces viral shedding and causes the virus to go into remission. HSV 1 produces a latent infection of neuronal cells in the dorsal root ganglia (usually trigeminal branch or peripheral sensory nerves) with reactivation probable. It is unknown why some suffer reactivation and others do not.

Herpes Simplex Virus Type 2 (HSV 2)

The portal of entry of HSV 2 is direct contact to skin or mucous membranes. It is estimated that 45 million infected individuals in U.S. have herpes genitalis. HSV 2 usually causes lesions on the genitalia, however HSV 1 can cause those same lesions and HSV 2 can cause oral lesions. Most HSV 2 infections are acquired as a sexually transmitted disease between the ages of 15 and 29. Neonatal herpes can be contracted *in utero*, during vaginal birth (untreated 70-80% mortality), or after birth. About 70% infants born with HSV 2 are born to women who have no history of HSV. Herpetic whitlow (also found in HSV 1 infections) produces a lesion on hands, fingers. The basis of laboratory diagnosis is serological testing (20% of adults are positive) and/or culture. Transmission of the disease but may not be fully protective. There is no vaccine and no permanent cure although acyclovir and related drugs reduce viral shedding. Latent infection of neuronal cells in

the dorsal root ganglia (sacral branch) leads to probable reactivation from the same reasons listed above.

Human herpesvirus type 3 is the Varicella-Zoster Virus (VZV) and causes chickenpox usually in children and herpes zoster (shingles) usually in adults. Shingles is a reactivation disease of <u>childhood chickenpox</u>. The portal of entry is via the respiratory tract. VZV causes a pox like lesion in chickenpox although this is not a pox virus. Shingles produces skin vesicles and nerve pain along one nerve tract. Symptoms appear in susceptible individuals ten to twenty-one days after contact with an individual who has active chickenpox or shingles. The basis of laboratory diagnosis is serological testing and/or tissue culture. A vaccine is available and recommended for those who have not had chickenpox. A recent vaccine has been made available to older individuals to prevent the reoccurrence of shingles. Supportive treatment is recommended in mild cases, aggressive treatment with anti-viral agents is used in the immunosuppressed. Use of aspirin is contraindicated in children due to possibility of Reye's syndrome. The virus tends to hibernate in the nerve ganglia, esp. trigeminal and thoracic nerves and is reactivated by stress, X-ray treatments, mechanical injury, etc.

Epstein-Barr (EB virus) is another humanherpes virus (type 4). Instead of infecting mucoepithelial cells, EBV primary target is the B-lymphocytes. The portal of entry is via the respiratory secretions. Twenty percent of the population are active carriers of this virus. Diseases caused by this virus include infectious mononucleosis (kissing disease), Burkitt's lymphoma and nasopharyngeal carcinoma. The severity of the disease is age dependent. The younger one is when initially contacting the disease, the milder the symptoms. The basis of laboratory diagnosis is the nonspecific heterophile antibody test or the specific IgG, IgM, and EBNA antibody detection tests. Seventy percent of the adult population demonstrates IgG antibodies.





Infection causes production of atypical lymphocytes. There are no vaccines and treatment is generally supportive.

In Cytomegalovirus (CMV - humanherpes virus type 5) infections, the usual portal of entry is intimate exposure or close contact. Vertical transmission (20% fetal infections) occurs when the mother is infected. Most diseases are asymptomatic. Mononucleosis can also occur. Disseminated CMV can occur in immunosuppressed (problem in contaminated bone marrow transplants) individuals. Congenital CMV leads to death or long-term neurological sequelae (3000-6000 cases per year in US). The basis of laboratory diagnosis is serologic testing. There are no vaccines and treatment for immunosuppressed with antiviral agents is often required to prevent death. CMV infects 7.5% of all neonates, making it the most prevalent viral infection in this age group.

Other Herpes viruses include HHV-6 which causes roseola infantum (Sixth's disease) and is associated with multiple sclerosis. HHV-8 causes Kaposi's sarcoma, a cancer often seen in AIDS patients. Although HHV-7 was isolated from T-cells of an AIDS patient, no known disease has been associated with it.

# Hepatitis B

Hepatitis B a member of the family Hepadnaviridae causes serum hepatitis. The portal of entry can be overt transmission from blood, serum or intimate contact. The main manifestation of the disease is jaundice due to hepatic disease, fever, and rash. Arthritis and death can occur. This is the only DNA virus to cause hepatitis. There are six known hepatitis viruses. The others are RNA viruses. More than one-third of the world has been infected with Hepatitis B virus. Hepatitis B is closely associated with Primary Hepatocellular Carcinoma. Diagnosis is based on serological testing and patient history. The reservoir is the chronic carrier. Prevention occurs by using universal precautions when handling infected materials or individuals or use of condoms when engaging in sexual intercourse. A vaccine (Hepatitis B recombinant vaccine) is available and must be taken by health care personnel.

# Adenoviruses

Adenoviruses are one of the viral causes of the common cold in addition to causing one form of "pink-eye". The portal of entry is either the respiratory tract or into the eye via respiratory secretions. Symptoms of the disease include acute rhinitis, cough, and fever. In Keratoconjunctivitis there is inflammation of conjunctiva and cornea. The basis of laboratory diagnosis is culture or PCR techniques. Prevention of transmission means controlling respiratory and ocular secretions. Reservoirs are the chronic respiratory carriers. There is a pooled inactivated vaccine and interferon has been used in the treatment. This viral agent has been and may again be used in gene therapy because it is a large virus, capable of carrying many genes.

# Papillomaviridae and Polyomaviridae

A wart, also known as a papilloma, is a benign growth of epithelium or mucous membrane caused by papillomavirus (Human Papilloma Virus-HPV). There are over one hundred types. Seed warts are most often found on fingers or toes; plantar warts on the soles of feet; flat warts on the trunk, face, elbow, or knees; and genital warts on the external genitalia. Thirty of the types cause genital warts of which thirteen are significant. Five and one half million new infections occur each year. Condyloma acuminata are large cauliflower-like genital warts. The portal of entry is a break in skin or mucous membranes. The basis of laboratory diagnosis is DNA probes, real time PCR or the PAP smear. Prevention of genital warts is by use of a condom. Cryotherapy, cauterization, or laser therapy is used to remove the wart. Genital warts are a known precursor to cervical cancer, especially with types 16, 18, 31, and 45. That is not to say that every woman who has genital warts will get cervical cancer. Rather, cases of cervical cancer are preceded by a history of genital warts. A vaccine has being developed that prevents nearly 100% of the growths that lead to the disease. Most people tend to clear the virus naturally (antibodies). For those who are past thirty years old, most positive cases usually represent chronic infections with an oncogenic strain.

Parvovirus B19 which causes erythema infectiosum (Fifth's disease: one of the five childhood diseases) is unique in that this virus has a single stranded DNA virus. The child presents a typical "slapped-cheek" appearance.

#### RNA VIRUSES

Like the DNA viruses, the <u>RNA viruses</u> are classified into families by the number of strands of nucleic acid they possess, the presence or absence of an envelope, size, and the host cells they attack. In addition, if the virus is single stranded, criteria on whether or not the RNA is a positive or negative as a coding nucleic acid strand is considered in the grouping.

# Influenza virus

The Influenza viruses A, B, C belong to the Orthomyxovirus family. These viruses are the cause of flu, a respiratory illness that especially affects the elderly. The portal of entry is via the respiratory secretions tract. Flu is a seasonal disease in the (U.S.) starting about the beginning of December. In this group of highly contagious respiratory illnesses, Type A is most prevalent. The patient complains of fever, coughing, headache, muscle ache, and pharyngitis. The basis of laboratory diagnosis is serologic testing and culture. Reservoirs include the pig, birds, and man. A new vaccine is produced every year due to the mutagenesis of the virus. Antigenic shift occurs about every ten years from reassortment of genomes of different strains that cause major changes in virus. Antigenic drift occurs every 2-3 years and is caused by point mutations. Both necessitate the production of a new vaccine each year. A rare side effect post vaccination is the development of Guillain-Barré. Since the disease is viral, antibiotics are not effective. If caught early however, amantadine or rimantadine can prevent viral uncoating. Most often supportive health care is the only treatment available. Secondary bacterial pneumonia in patients can be fatal. During the winter of 1918-19 the great flu pandemic occurred and killed estimated 40-95 million people that one season. This virus was an avian flu virus that jumped directly to humans.

# Paramyxoviruses

Parainfluenza viruses 1, 2, 3 belong to the Paramyxovirus family. The virus is spread through respiratory secretions inoculation of mucous membranes by contaminated hands. They usually cause minor upper respiratory diseases such as bronchitis, bronchopneumonia and Croup (larygotracheobronchitis).

Remember, antibiotics are not effective against viruses and there is no vaccine.

Another virus in the paramyxovirus family is the Mumps virus. The disease produces parotitis, a painful swelling at the angle of the jaw although most cases are subclinical. Some serious complications of the disease include viral encephalitis, deafness, and orchitis. Transmission is via moisture droplets getting to the respiratory tract. The basis of laboratory diagnosis is serologic testing. A vaccine, part of MMR, induces an artificially, active immune response. Eradication of mumps is possible.

A third paramyxovirus (Morbillivirus) causes measles which is also known as Rubeola or Red measles. Measles is acquired through respiratory tract secretions. Patients usually are children who exhibit a rash over the body and Koplik's spots (oral lesions). In severe cases Subacute Sclerosing Panencephalitis (SSPE) affects the cortex, the white mater of the brain and the brain stem. Diagnosis is made through clinical signs, and serological testing. Treatment consists of supportive therapy. Vaccination has reduced measles to all time low in this country and this disease could be eliminated like smallpox because humans serve as the only reservoir. As recently as 1999 there were still 30-40 million cases of measles a year worldwide with 1-2 million deaths in unvaccinated populations. The number of deaths has decreased to about 350 million cases per year due to an intensive vaccination program.

RSV (Respiratory Syncytial Virus) is the most prevalent virus in newborns causing coughing, wheezing, and dyspnea. It is the most common cause of fatal acute respiratory infection in infants and young children. Respiratory secretions are the mode of transfer. The basis of laboratory diagnosis is a fluorescent stain DNA probe or EIA which are both better than culture. No vaccine is available. Treatment is Ribavarin, an anti-viral agent and supportive therapy.



# Rabies

Rabies (Lyssavirus) is a rhabdovirus that causes a fatal meningoencephalitis if untreated. The <u>portal</u> <u>of entry</u> is usually though a bite into the skin. The reservoir is wild rabid animals, such as skunks, raccoons, or bats. Symptoms include pain in swallowing (which results in hydrophobia), seizures, paralysis, and death. To diagnose in humans, look for antibody production, which usually occurs too late in disease to effectively

treat. To diagnose in animals, look for Negri bodies in microscopic sections of infected animal brain. There is no cure for the patient except passive vaccination in suspect cases. Antibody can block the progression of the disease. A vaccination program is used for domestic animals.

# Togavirus

Rubella or German measles is a mild benign childhood disease caused by rubivirus, a member of the togavirus family. The problem that arises is if transplacental transfer occurs in first trimester, congenital defects result. The portal of entry is through the placenta or via respiratory secretions. Diagnosis is based on serological testing and culture. Prevention of acquiring the disease is through vaccination with MMR.

There are more than 500 different togaviruses in the <u>Arbovirus group</u>. The strains seen in this part of the country are WEE, EEE, St. Louis encephalitis, LaCrosse encephalitis, Colorado tick fever, and West Nile Virus. All arboviruses are spread through the bite of an infected arthropod *(arthropod borne)*. The disease can be asymptomatic to flulike symptoms headache, rash, fever, viral encephalitis, and death. More severe members of this group include Dengue fever and Yellow Fever. Dengue fever is also called breakbone fever because of the back and bone pain that lasts 6-7 days. The basis of laboratory diagnosis is via serological methods or PCR although sometimes cultural isolation is used. Since transmission is via mosquitoes, prevention lies in controlling the vector.

# ΗIV

HIV virus (Human Immunodeficiency Virus) (formally HTLV-III) causes AIDS. The portal of entry is varied but most often through the skin, mucous membrane, or blood. Homosexual men and intravenous drug abusers who share needles are at most risk. Antireceptor spikes unsafe Practice of sex, contact with contaminated blood, and congenital transfer are the methods of transmission. The virus is a retrovirus. The retrovirus is a single-



stranded RNA that converts to double-stranded DNA because of the enzyme reverse transcriptase. This virus also possesses a high rate of mutation preventing a vaccine from being produced. The virus has an affinity to the CD4 (Helper T cells). One of the tests performed is a CD4 level. Other lab tests involve serological methods. For a clinical definition and risk factors see the text. For treatment, anti-viral drugs such as AZT, ddl, (reverse transcriptase inhibitors) and newer classes of drugs such as the protease inhibitors help in keeping CD4 cells high enough to prevent secondary infections. However, it must be noted that there is no cure or vaccine at this time. Over 800,000 cases have been defined in the U.S. in the last twenty years. Over half have died. It is estimated that an additional 2 million have the virus, but the disease has not yet manifested itself in these individuals. Most individuals do not die from the virus, but from a secondary opportunistic bacterial or fungal infection.

# Polio

Poliovirus is acquired via the fecal-oral route. This virus has a tropism to the

brain and meninges that can result in neuromuscular paralysis or encephalitis. The muscles atrophy because of flaccid paralysis of the limbs. Life threatening situations arise when the virus affect the respiratory system. Usually a summertime disease, this disease can be and should be eliminated soon because of an intense vaccination program. Identification is via serological or culture methods. Other enteroviral infections are caused by the Coxsackie and ECHO viruses. The portal of entry is either respiratory or oral route. The symptoms of the diseases include fever, myalgia, malaise, and viral meningitis. The basis of laboratory diagnosis is culture. Hand, foot, and mouth disease is due to a Coxsackie A virus.

Human Rhinoviruses are a large group of picornaviruses associated with the common cold. The portal of entry is though respiratory secretions. Treatment is for relief of symptoms only. There are no anti-viral agents and antibiotics will not work. There is no vaccine. Hand washing and disinfection of contaminated objects are the best means of preventing the spread of the virus.

RNA viruses that cause hepatitis are Hepatitis A (infectious hepatitis) and Hepatitis C virus. Hepatitis A is transmitted via the fecal-oral route. Outbreaks occur because of poor hygiene in food handlers and faulty sewage treatment. Symptoms include yellow jaundice, GI disorders, and fever. Laboratory diagnosis is based on detection of anti-HAV IgM antibodies. An attenuated vaccine is available. Hepatitis C is referred to as post-transfusion hepatitis because it is primarily transmitted in contaminated blood. Prevention is achieved by testing blood prior to the transfusion. There is no anti-viral drug for these agents; only supportive for the patient. Infection with Hepatitis C can lead to liver cancer.

Rotavirus is primary cause worldwide of morbidity and mortality due to diarrhea. Over one million childhood deaths per year as a result of uncontrolled diarrhea are attributed to rotavirus infections in underdeveloped countries. Transmission is via the fecal-oral route. Good hygiene prevents transmission. The basis of laboratory diagnosis is primarily serological testing. Children exhibit malnutrition, failure to thrive, and stunted growth. The reservoirs are calves and pigs.

Hantaviruses are Bunyaviruses that are transmitted to humans via inhalation of virions in dried deer-mouse urine. They cause Hantavirus pulmonary syndrome.

<u>Ebola virus</u> and Marburg virus are filamentous viruses that cause hemorrhagic fever and are classified as filoviruses. There is no known treatment or prevention for hemorrhagic fever, although a vaccine is being tested on monkeys. The mortality rate is as high as ninety percent. Specimens containing these viruses require level IV isolation, which is not routinely available.