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Virology

Doctor 2018 | Medicine | JU

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Please note that this sheet includes the points which the professor mentioned and focused on during the lecture. Any piece of information in the slides that was not mentioned will not be included in the sheet (this is in compliance with what the professor said was required). For those interested in further reading, you may refer to the slides.

- **Revision of Varicella Zoster Virus: (Important Points)**

- ✓ Causes **Varicella (chickenpox)** and **Zoster (shingles)**.
- ✓ Zoster (shingles) is a manifestation of the **reactivation** of VZV.
- ✓ There is a **varicella vaccine (live-attenuated)**.
- ✓ This vaccine is not given in many countries (not part of the childhood vaccination program) because the disease does not have many complications. If complications do occur, they mainly include: aseptic meningitis and pneumonia. But mortality rates are very low.

➤ **We will now proceed with the rest of the Herpesviridae family:**

- **Cytomegalovirus (CMV):**

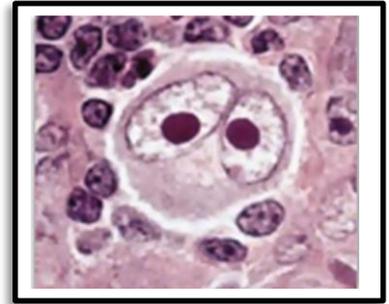
- ✓ **IMPORTANT: It is the most common cause of congenital infections** (1% of live births in the US). Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the CMVs.

- **Recall: TORCH:** which is an acronym for the most important infectious agents responsible for congenital malformations
 - ✓ **T:** Toxoplasma
 - ✓ **O:** Others (e.g. Hepatitis B, Parvoviruses, treponema, HIV)
 - ✓ **R:** Rubella
 - ✓ **C:** Cytomegalovirus (**The most common cause among TORCH agents**)
 - ✓ **H:** Herpes Simplex Virus (HSV)

Pathology and Pathogenesis:

CMV produces a characteristic cytopathic effect:

Perinuclear cytoplasmic inclusions (looks like an owl's eyes, thus infected cells are described as having “**an owl-eye appearance**”) in addition to the intranuclear inclusions typical of herpesviruses. (*Notice the adjacent image*)



Cells infected with CMV may become **very large** (hence the name: cyto**MEGALO**virus because it causes -megaly (enlargement) of the infected cells (cyto-)). Also, formation of **multinucleated cells** may occur.

Primary infection with CMV will mostly give rise to infectious **mononucleosis-like syndrome** (similar to mononucleosis whose clinical features include the **classical triad of:** **1. Fever** **2. Pharyngitis** **3. Cervical lymphadenopathy**)

Recall: The most common (classical) cause of infectious mononucleosis is EBV.

- Other viruses may cause what is called: **infectious mononucleosis-like syndrome**. Examples of such viruses include:
 - ✓ Herpes simplex virus
 - ✓ CMV
 - ✓ HIV

Most cases of CMV **primary** infections, especially those during childhood, are **asymptomatic (subclinical)**. Severe CMV infections are frequently found in adults who are immunosuppressed.

Latency mostly occurs in **renal cells** (although it may also occur in a variety of other human cells by CMV). **This latency (and reactivation)** is of significance in **immunocompromised patients** (such as those receiving organ transplants, on chemotherapy, and those with AIDS). To test for reactivation, we take urine samples (kidney samples) and test for the presence of CMV. Latency is not significant in immunocompetent patients.

So, most CMV infections occur in immunocompromised patients, where it is mostly due to reactivation. It causes **pneumonia** and **retinitis**.

We also fear congenital CMV infections. A high percentage of babies with this disease will exhibit developmental defects and mental retardation.

Pneumonia is the most common complication.

Lab Diagnosis

1. **Serological diagnosis:** serological detection of IgM suggests a current infection.
2. **Molecular diagnosis:** qualitative and quantitative PCR for CMV
(a patient may be infected with CMV but does not show any significant sign of disease, and shedding of the virus would be minimal. While the titer of the virus would be high in immunocompromised patients indicating disease by CMV. qPCR would help in quantification in such cases).

- ✓ Generally, when giving a **blood unit** to a patient, we initially screen the blood sample for **several viruses** (and other agents) including:
Hepatitis B and C, HIV and treponema (the latter is not a virus).
- ✓ If the patient receiving the blood unit is **immunocompromised** (especially HIV-infected patients), we must additionally screen for **CMV** (and possibly parvoviruses). This is because CMV is generally a threat to immunocompromised patients. **Thus, the blood sample to be given to an immunocompromised patient must also be CMV-negative.**

Treatment

- **Nucleoside analogues** (which are used in treatment of herpesviruses):

Mechanism of Action

- ✓ **Nucleotides** are the building blocks for nucleic acids (DNA and RNA)
- ✓ **Analogue:** a compound with structural similarities to another compound.
- ✓ At high concentrations, nucleoside analogues **effectively compete** with normal nucleotides for incorporation into nucleic acids, causing the **polymerase** to add these nucleoside analogues to the growing nucleic acid chain.
- ✓ However, these nucleoside analogues **lack a free hydroxyl group** which is the site of addition of the following nucleotide, causing chain termination.
- ✓ **Summary of mechanism: Chain termination**

- **Would such drugs affect the host?**

Well, yes. BUT, these drugs are administered as **pro-drugs**, which are only activated in **virally-infected cells** due to the presence of viral enzymes such as **thymidine kinase**, causing the potency of the drug to be 1000 times higher in virally-infected cells than it would be in normal host cells.

- **Examples of such drugs (used in treatment of CMV): Ganciclovir**, Acyclovir and Valaciclovir. (The professor mainly focused on **Ganciclovir**)

Epidemiology:

CMV is present **all over the world**, throughout the year, with no seasonal variation. In developing countries, the seroprevalence is high in early childhood (most infections are asymptomatic).

Transmission of CMV is mainly through **saliva**.

- **Epstein Barr Virus (EBV):**

- ✓ **Primary infection: **Infectious mononucleosis****
(**triad of infectious mononucleosis: fever, pharyngitis, cervical lymphadenopathy**)

- ✓ **EBV is the first **oncovirus**** to be identified in humans (i.e. the first virus linked to cancers in humans). The cancers it causes are mainly **lymphomas** (Burkitt lymphoma, Hodgkin and non-Hodgkin lymphomas), and it is also associated with **nasopharyngeal carcinoma**, and gastric carcinoma.

Other oncoviruses include:

- ✓ **HPV** (cervical, penile, and oral cancer)
- ✓ **HTLV-1** (t cell leukemia)
- ✓ **Hepatitis B and C** (hepatocellular carcinoma)
- ✓ **Polyomavirus** (Merkel cell carcinoma)
- ✓ From the Herpesviridae family: **EBV**, and **Kaposi sarcoma herpesviruses**
- ✓ Another pathogen (not a virus) that causes cancer: **H.pylori** (gastric cancer and lymphoma), the most common pathogen associated with cancer.

- ✓ **Main target cells** are **B lymphocytes** because they have the receptor for EBV, which is **CD21 (complement receptor 2 (CR2))**.

Pathogenesis and Pathology

Infections in early childhood are mostly asymptomatic. The disease usually peaks at another age (15-18 years old), and in this case it is symptomatic and causes infectious mononucleosis, also called “**kissing disease**” (because it can be **transmitted through saliva**). The peak at this age is due to sexual debut.

Clinical Findings

Infectious Mononucleosis.

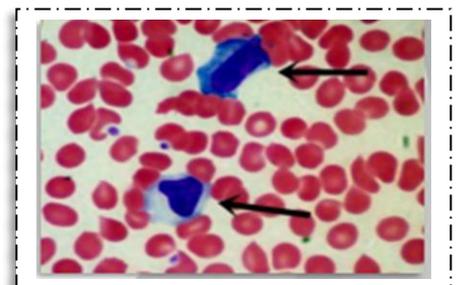
Note: During the disease, there is an increase in the number of circulating white blood cells, with a predominance of lymphocytes. Many of these are **large, atypical T lymphocytes**. Their histologic morphology may confuse the viewer with (lympho)blasts (another type of cells). **The reason for this confusion:**

1. T lymphocytes generally have scanty cytoplasm, but this is not the case here.
2. In this case, T lymphocytes exhibit **more compact chromatin in the nucleus** than usual (compact chromatin is a feature of lymphoblasts).

Therefore, T lymphocytes in this special case display common morphological features with blast cells, hence, they are atypical T lymphocytes. This similarity may confuse the case with lymphoma or leukemia.

Those atypical T lymphocytes are a reaction of T cells that are trying to get rid of B cells infected with the virus. So, these atypical T lymphocytes are **CYTOTOXIC T lymphocytes**.

Do NOT confuse the target cells (B cells) with the atypical T cells (which are a reaction to kill infected B cells).



As we mentioned earlier, EBV causes **pharyngitis** (one of the symptoms of infectious mononucleosis), as you can see in the following image.



Other clinical findings include:

✓ Cancer:

Burkitt lymphoma (a tumor of the jaw, mostly in African children and young adults).

Nasopharyngeal carcinoma

- ✓ EBV may be associated with a non-malignant condition called: **Oral hairy leukoplakia** (affects HIV-infected individuals) which appears as white patches on the tongue. It is surgically removed for aesthetic purposes. There is no risk for it to become malignant.

Burkitt lymphoma:



Oral hairy leukoplakia:



Diagnosis

- ✓ Molecular assays for identification of the virus
- ✓ Isolation of the virus
- ✓ Serology (antibodies against different viral antigens). Specific antibodies are directed against the viral capsid antigen, EBNA or EBER antigen.

✓ **Less-specific heterophile agglutination test (monospot test)**

Heterophile antibodies: antibodies that can react (recognize) antigens of different species (In the case of EBV, heterophile antibodies are formed in the human body against EBV, but they can also recognize antigens of other species like sheep or horses and can therefore agglutinate sheep or horse RBCs. Agglutination of sheep/horse RBCs indicates the presence of heterophile antibodies, which confirms infection with EBV.

Treatment

No specific antiviral therapy. Treatment is supportive.

There is no EBV vaccine available.

Nucleoside analogues may be tried (like Acyclovir).

• Human Herpes Virus 6 and 7 (HHV-6, HHV-7)

Both cause **exanthem subitum** (**Roseola Infantum** or "**sixth disease**"), a mild childhood disease characterized by a **skin rash** and **high fever**. The fever may be so severe as to cause **febrile seizures** in children. The disease is benign and patients recover completely.

- ✓ The receptor for **HHV-6** is **CD46**.
- ✓ The receptor for **HHV-7** is **CD4**.



Other examples of rash-causing childhood diseases:

- ✓ **First disease:** Measles
- ✓ **Second disease:** Scarlet fever
- ✓ **Third disease:** German measles (Rubella)
- ✓ **Fourth disease:** Dukes' disease
- ✓ **Fifth disease:** Erythema infectiosum (B19 parvovirus).
- ✓ **Sixth disease:** Roseola infantum

Transmission (of both HHV-6 and HHV-7) occurs via **oral secretions**.

• Human Herpesvirus 8 (KSHV*)

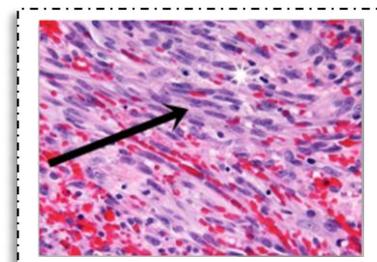
KSHV: Kaposi Sarcoma-associated Herpesvirus

- ✓ Mostly associated with **immunodeficiency (especially HIV infection/AIDS stage)**.
- ✓ **Kaposi sarcoma** (a malignant tumor) mainly affects the **blood vessels** (endothelium) and could be present in internal organs (e.g. stomach or lungs). This cancer has two forms, both of which are malignant.
- ✓ The course of Kaposi sarcoma associated with AIDS patients is more aggressive (with **multiple lesions**) and occurs at younger ages than cases of Kaposi Sarcoma in non-AIDS patients (in which the course of disease is more gradual).
- ✓ Patients also have **cachexia** (wasting disease) caused by the **interleukin TNF**.

Kaposi Sarcoma:



- ✓ It is **lymphotropic** and is **more closely related to EBV**.
- ✓ KSHV is the cause of Kaposi sarcomas, and is involved in the pathogenesis of body-cavity based **lymphomas (primary effusion lymphomas)** occurring in AIDS patients and of **Multicentric Castleman disease**.
- ✓ Contact with **oral secretions** is the most common route of transmission. The virus can also be transmitted **sexually, vertically** or by **blood**.
- ✓ Diagnosis is by **histopathology** or **PCR**. In histopathology, we see characteristic spindle cells, but we must further verify using immunostains or molecular detection.



• Herpes B virus:

- ✓ Infection occurs naturally in **monkeys**.
- ✓ Transmission from **monkey to human** (NOT human to human)
- ✓ Rare cases
- ✓ **Mortality rates are high**. (highly pathogenic for humans)
- ✓ Animal workers and people handling macaque monkeys including **veterinarians**, medical researchers, pet owners and **zoo workers are at risk**.
- ✓ No vaccine is available.

❖ Togaviridae

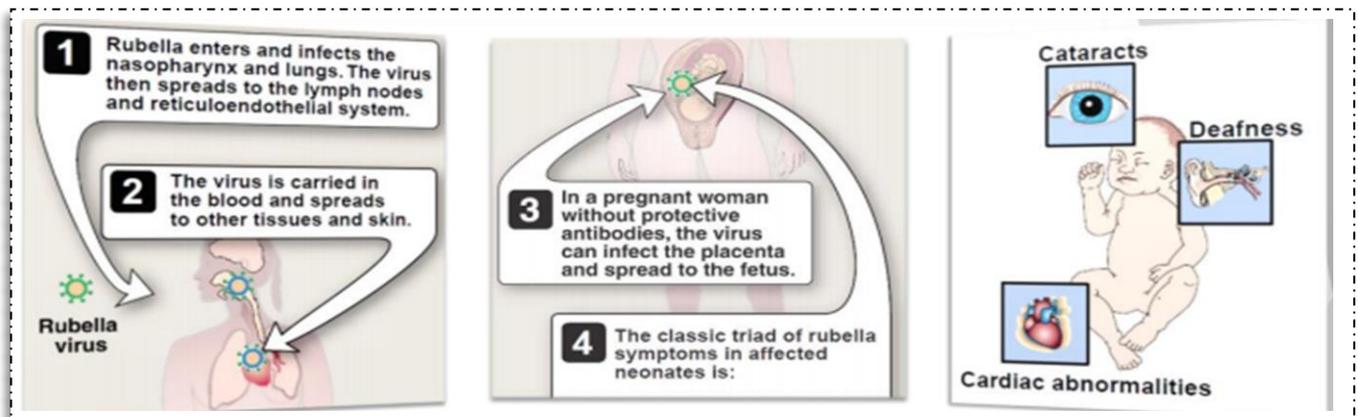
- ✓ The togaviruses are enveloped +ssRNA viruses that contribute significantly to human disease.
- ✓ Togaviridae is divided into two genera: **Alphavirus** and **Rubivirus**.

• Alphavirus:

- ✓ The alphaviruses are **arthropod-borne viruses (arboviruses)**, which are transmitted to humans and domestic animals by **mosquitoes**.
- ✓ The majority of infections are **subclinical**, however, several clinical syndromes are associated with alphavirus infections of humans. These include: **acute encephalitis (equine encephalitis virus)**; **acute arthropathy (Chikungunya virus)** (Chikungunya= bent over) because it is associated with joint infections (causes patient to stay in a bent-over position), and a febrile illness with a **flulike syndrome**.

• Rubella Virus:

- ✓ Rubella (German Measles) is especially dangerous in pregnant woman who have not been vaccinated or exposed to Rubella before.
- ✓ “Infection with Rubella” and “vaccination” confer **long-life immunity**, because only one antigenic type of the virus exists.
- ✓ 20%-50% of the cases are asymptomatic (subclinical).
- ✓ It is not a severe disease, and is dangerous if the infection occurs in fetuses, as it can result in **mortality**, or **congenital rubella syndrome** (which includes a **triad of: 1. Cataracts 2. Deafness 3. Cardiac abnormalities**)
- ✓ It normally does not have lethal complications. Arthropathies may occur for a few months and then resolve after that.



❖ Respiratory, GI and CNS Viruses

➤ Paramyxoviridae:

The paramyxoviruses include the most important agents of **respiratory infections (upper and lower) of infants and young children**, as well as the causative agents of two of the common contagious diseases of childhood (**mumps and measles**).

All members of the paramyxoviridae family initiate infection **via the respiratory tract**.

The paramyxoviruses are **enveloped -ssRNA viruses with a non-segmented genome**.

This family includes:

- ✓ The **parainfluenza viruses** (4 types), and they are **very commonly associated with laryngeal infection (in the larynx) and epiglottitis**.
- ✓ Other members of the family include **measles and mumps viruses, the respiratory syncytial virus and metapneumovirus**.

- Measles virus:

The cellular receptor for measles virus is CD46 (the same receptor for HHV-6).

CD46 is involved in complement regulation.

(CD46, as we mentioned, is also the receptor for the Roseola virus, because the skin rash resembles small roses).



Measles virus is transmitted by sneeze- or cough-produced respiratory droplets.

The disease (**Measles or Rubeola or First Disease**) is extremely infectious, and almost all infected individuals develop clinical illness if not vaccinated. Infection is mostly symptomatic.

- Recall: In **German measles**, a percentage of the infections may be **asymptomatic**.
- A percentage of **mumps** infections can also be **asymptomatic**.
- Measles infections **are mostly symptomatic**
- The majority of Chickenpox (primary) infections are symptomatic (almost no asymptomatic cases).

Measles begins with a prodrome of **fever, upper respiratory tract symptoms, and conjunctivitis**. Then, a **generalized macular rash** appears, beginning at the **head** and **traveling slowly to the lower extremities**. During this, typical lesions are found in the buccal mucosa called **Koplik spots** (small white spots on bright red mucous membranes of the mouth and throat), and these spots are **PATHOGNOMONIC** for measles. The presence of these spots are enough to diagnose measles without any lab methods.



The major morbidity and mortality caused by measles are associated with various **complications** of infection, especially pneumonia and encephalitis. The most important

of these is **postinfectious encephalomyelitis**, which is an autoimmune reaction against **myelin basic proteins**.

Measles is more severe than German measles as a disease. Patients with measles may need hospitalization, and some will develop complications such as those previously mentioned.

- ✓ **Diagnosis of measles can be achieved clinically in most cases**, especially in an epidemic situation. (Recall: **H1N1** is also an example of a virus that can be diagnosed clinically in an epidemic situation). The presence of **Koplik spots** provides a **definitive diagnosis**.
- ✓ Previous exposure to measles **confers long-life immunity** (single serotype). **A live attenuated measles vaccine is available (given as part of the MMR vaccine – measles, mumps, rubella)**
- **Mumps virus:**

Mumps is an acute contagious disease characterized by enlargement of one or both **salivary glands (the main target)**, but the infection is widespread in the body and complications may occur in the **pancreas (pancreatitis)**, **CNS (causing aseptic meningitis)** and **testes**.

Orchitis (inflammation of the testis) in male patients caused by mumps may cause **sterility**.

- ✓ (**Note for exam questions: PAY ATTENTION** to whether the patient described in the question is **male or female**. For instance, if a question asks for potential complications of mumps, and you happen to find both orchitis and aseptic meningitis in the options, both of which are correct, re-read the question and identify the gender of the patient. In such a question, the patient will most likely be a female, thus you should exclude orchitis (testicular inflammation))
- ✓ Before the mumps vaccine was developed, mumps was the most common cause of aseptic meningitis.
- ✓ More than one third of all mumps infections are **asymptomatic**.
- ✓ Transmission is through respiratory droplet.

Diagnosis can usually be made on the basis of **clinical findings**. Serological or molecular diagnosis may be used.

Immunity is permanent after a single infection.

An effective **attenuated live-virus vaccine** is available. Mumps vaccine is **available in combination with measles and rubella (MMR) live-virus vaccines**. **Two doses of MMR are recommended for school entry.**

- Parainfluenza viruses (PIVs 1-4)

- ✓ Associated with upper and lower respiratory infection (**laryngeal infection**), It can cause common cold and more severe disease (croup disease).
- ✓ **Croup Disease:** also known as **laryngotracheobronchitis**, characterized by a voice similar to frog chirps. (especially with types 1 and 2)
- ✓ **Primary infection:** Rhinitis, pharyngitis, **croup (especially types 1 and 2), bronchiolitis or pneumonia (especially type 3).**
- ✓ **Most common** complication is **otitis media.**
- ✓ **PIV 4** does not cause serious disease.

- Respiratory syncytial virus

- ✓ One of the **most common causes** of lower respiratory tract infection in infants, and is specifically associated with **bronchiolitis.**

- ❖ Although the airways of very young infants are narrow and more readily obstructed by inflammation and edema, only a subset of young babies develops severe RSV disease.
- ❖ It has been reported that susceptibility to **bronchiolitis** is genetically linked to polymorphisms in innate immunity genes.
- ❖ RSV is an important cause of **otitis media.**
- ❖ In the epidemic situation, it can be diagnosed by clinical findings, but there are lab methods such as **DFA** (direct fluorescent antibody) and **RT-PCR.**
- ❖ **Treatment:** supportive treatment (removal of secretions, administration of oxygen), and we can give the patient antiviral drugs: **ribavirin** or monoclonal antibody (**Palivizumab**) which will reduce the shedding of the virus.

- Metapneumovirus:

- It causes mostly common cold and is a newly discovered virus.
- **People at risk:** elderly, children and immunocompromised patient.
- There is good percentage of **asymptomatic** infection.

❖ **Coronaviridae Family**

It is called coronavirus because it appears like solar corona (=crown) in the electron microscope.

- ❖ **Most coronaviruses are found in Bats.**
- ❖ Part of these viruses infected humans thousands of years ago, and now all are established in the human population.
- ❖ **It is mostly associated with common cold. Remember, it is the second most common cause of common cold after Rhinovirus.**
- ❖ Between different periods, there is contact between human and bats, some of these bats' viruses can infect the humans such as these two emerging coronaviruses: **SARS coronavirus** (severe acute respiratory syndrome) and **MERS coronavirus** (middle east respiratory syndrome).
- ❖ Recent emerging infections are from bats, mostly through **network reservoirs** (Bats infect another animal and that animal infects humans).
- ❖ Other strains of the virus that **are associated with the common cold** are **NL63** which also causes croup disease (laryngotracheobronchitis), **229E**, **OC43** and **HKU1**.
- ❖ **Structure:** Enveloped viruses with a positive-sense single-stranded RNA genome.
- ❖ The receptor for SARS coronavirus is Angiotensin-converting enzyme.



Clinical Features of Coronavirus Infections

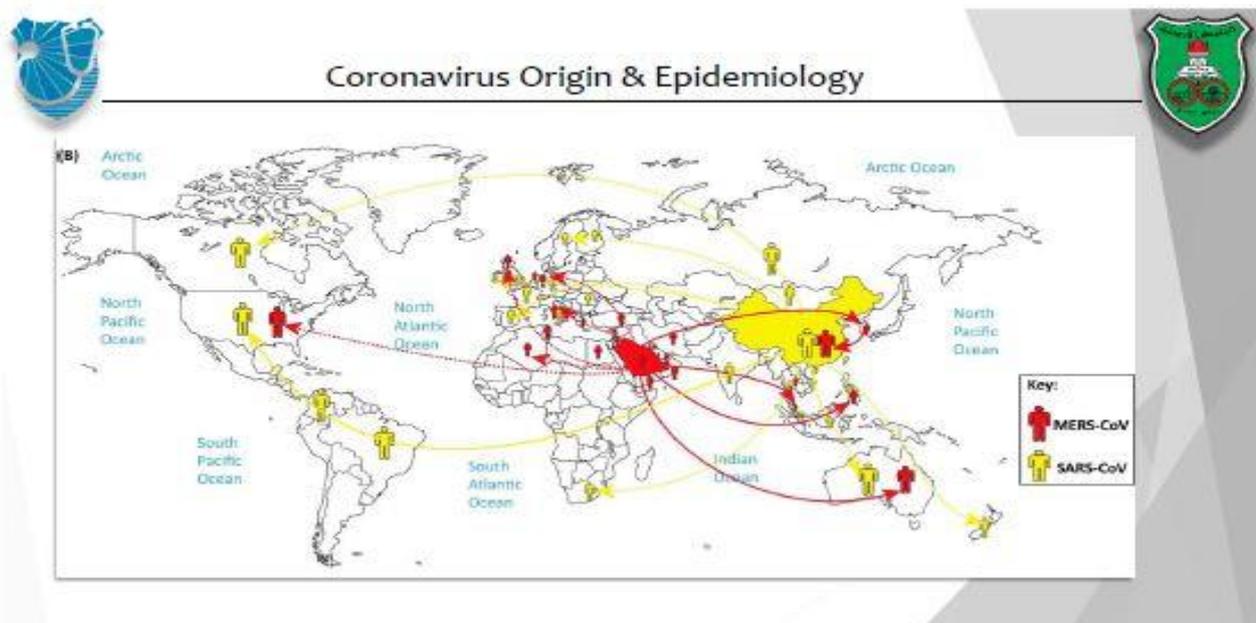


HCoV	Clinical Symptoms	Case Fatality Rate	Incubation Period	Median Time to Death
229E	Coryza	N/A	2-5 days	-
OC43	Coryza	N/A	2-5 days	-
SARS-CoV	Fever, myalgia, headache, chills, cough, dyspnea, respiratory distress, diarrhea	9%	2-11 days	23 days
NL63	Coryza, Croup	N/A	2-4 days	-
HKU1	Coryza	N/A	2-4 days	-
MERS-CoV	Fever, myalgia, headache, chills, cough, dyspnea, pneumonia, vomiting, diarrhea	36%	2-13 days	14 days

Important note regarding the table:

- ✓ Note that the viruses that are associated with the common cold (coryza) **don't** show any fatality, but **SARS and MERS strains show a percentage of fatality.**
- ✓ People at risk of MERS: **Health care workers** (doctors, nurses ...) and it is present in our region, so, we should take precautions.
- **The reservoir of coronavirus is Bats**, but the SARS coronavirus is transmitted to a type of cats called civet cat and from this cat is transmitted to humans. MERS corona virus reservoir is bats and then it is transmitted to camels and then from camels to humans.
- Epidemiology: we have cases of MERS in our region (ex: Saudi Arabia and Jordan...), other strains that are associated with common cold are distributed all over the world, SARS decreased because it was controlled in 2000.

Management of coronavirus infections: Supportive.



❖ GI viruses

- ❖ **Norovirus** (member of caliciviridae family) **is the most common cause of adult viral gastroenteritis.**
- ✓ Structure: **Naked** positive sense single-stranded RNA virus.

- ✓ **Door** handles appear to be efficient vectors for viral **transfer**.
- ✓ Most of the infections are through person-to-person contact, water-borne and food-borne transmission.
- ✓ Clinical features: watery diarrhea and treated by oral rehydration.
- ❖ **Rotavirus** is a member of the **REOviridae** family (**which is the only family of viruses that contains a double-stranded segmented RNA genome**), **it is the most common cause of Viral infantile gastroenteritis.**
- ✓ It has seasonal variation, occurs mostly in winter.
- ✓ Death is associated with the loss of fluid, so, the treatment is oral rehydration, and it is possible to cause malabsorption because of the disruption of the villi. In this case, we see fat in the stool.
- ✓ Diagnosis: antigen or molecular detection.
- ✓ There is a **live attenuated vaccine** for Rotavirus and is given orally.
- ✓ **Astroviruses (their shape is like a star): you only need to know that they cause gastroenteritis.**

❖ Arboviruses

- ✓ **They are arthropod-borne in mosquitoes and ticks** which transmit **Lyme disease** that is caused by *Borrelia mayonii*.
- ✓ The life cycle of the arboviruses is based on the ability of these viruses to multiply in both the **vertebrate host** and the **blood sucking vector**.
- ✓ Only the female of the species serves as a vector of the virus, because only she requires a blood meal to develop the eggs (in order for progeny to be produced)
- ✓ Arboviruses have a development in insects and humans, and usually, humans are dead end-hosts because the virus cannot be transmitted between humans.
- **Arboviruses include: Togaviridae and Flaviviridae.**
- ❖ **Togaviridae** (alphaviruses): **ssRNA (+)**, associated with arthritis and encephalitis.

❖ Flaviviridae

- **Yellow fever virus** disturbed the construction of the Panama canal, because the workers were infected with this virus and developed yellow fever, but the project continued because they controlled the mosquito that contained the virus.
- **Dengue fever:**
 - ✓ Caused by **Dengue virus**.
 - ✓ **The most common arbovirus globally (common in India and Sri Lanka).**
 - It is called **Breakbone fever (a mosquito-borne infection)** because one of the symptoms is severe pain in the bones and joints, also it is characterized by fever, severe headache, muscle and joint pain, nausea and vomiting, eye pain, and rash.
 - Dengue is endemic in more than 100 countries and is considered the most prevalent of all arboviruses in humans.
 - Control depends on antimosquito measures.
- **West-Nile fever:**
 - ✓ Caused by **West Nile virus**.
 - ✓ **A Mosquito-borne virus.**
 - ✓ It occurs in Europe, the Middle East, Africa, the former Soviet Union, Southwest Asia, and, more recently, the United States.
 - ✓ It appeared unexpectedly in the New York City area in 1999, resulting in seven deaths and extensive mortality in a range of domestic and exotic **birds**.
 - ✓ Sequence analysis of virus isolates showed that it originated in **the Middle East**; it probably crossed the Atlantic in an infected bird, mosquito, or human traveler.
 - ✓ About 80% of West Nile infections are **asymptomatic**, with about 20% causing **West Nile fever** (fever, headache, skin rash, and LAP) and less than 1% causing **neuro-invasive disease (meningitis, encephalitis)**.

• Zika Fever

- ✓ Caused by **Zika virus**.
- ✓ Associated with congenital abnormalities, mostly **transmitted by mosquitos**.
- ✓ Other non-vector modes of Zika virus transmission include **congenital** (vertical) and sexual.
- ✓ Infection is likely asymptomatic in about 80% of cases.
- ✓ When symptoms occur, they are typically mild, self-limiting, and nonspecific.
- ✓ Rash, a prominent feature, is maculopapular and pruritic in most cases.
- ✓ Spontaneous resolution within 1–4 days of onset.
- ✓ **Congenital infection association with microcephaly.**

❖ Ebola Virus

- ❖ It is a member of family called **Filoviridae** (filo because it has a filamentous shape).
- ❖ It is transmitted by respiratory droplets, body contact and Fomites (instruments used by the patients like towels).
- ❖ Characterized by fever, headache, sore throat, and myalgia followed by abdominal pain, vomiting, diarrhea, and rash, with both internal and external bleeding, often leading to shock and death.
- ❖ Very high titers of virus are present in many tissues, including the liver, spleen, lungs, and kidneys, and in blood and other fluids.
- ❖ Ebola virus has a tropism for cells of the macrophage system, dendritic cells. Interstitial fibroblast and endothelial cells.
- ❖ **Filoviruses have the highest mortality rates of all the viral hemorrhagic fevers.**

❖ Rabies Virus

An enveloped negative sense single -stranded RNA virus (bullet shape).

Main source of infection is **Dogs**, but it is also found in foxes, rakoons and bats. Pathogenesis: from the animal bite (because shedding of the virus occurs in the **salivary gland**), it replicates in the **muscles**, then moves from the peripheral nervous system by **retrograde transport** to the **CNS** causing **encephalitis**. If the bite occurs in the face (**which is close to CNS**), then the incubation period will be **shorter** than if it occurs in the lower limb (here, the incubation period can be around months). **Wound cleaning is very important after animal bite.**

- ✓ So, after replicating in the muscles the virus then spreads through peripheral nerves to the salivary glands and other tissues.
 - ✓ **The organ with the highest titers of virus is the salivary gland.** Other organs where rabies virus has been found include pancreas, kidney, heart, retina, and cornea.
 - ✓ **The incubation period (typically 1–3 months but may vary from 1 week to 1 year) depends on the host's age, genetics, and immune status, the viral strain, amount of inoculum, the severity of lacerations, and the distance the virus has to travel from its point of entry to the CNS.**
-
- There is a higher attack rate and shorter incubation period in persons bitten on the face or head; the lowest mortality occurs in those bitten on the legs.
 - Pathognomonic features of rabies: presence of Negri bodies (**eosinophilic cytoplasmic inclusions**).
 - **The presence of such inclusions is pathognomonic of rabies** but is not observed in at least 20% of cases.
 - Remember: nuclear inclusions caused by **DNA viruses** NOT RNA viruses.
 - **VERY IMPORTANT:** Some important pathognomonic features that we took in previous lectures: **Dendritic Ulcer by HSV, kolpik spots by measles.**

- **The clinical spectrum of rabies can be divided into three phases:**
- **Prodrome:** malaise, anorexia, headache, photophobia, nausea and vomiting, sore throat, and fever.
- **Acute neurologic phase:** CNS signs including nervousness, apprehension, hallucinations, and bizarre behavior. Sympathetic overactivity is observed, including lacrimation, pupillary dilatation, and increased salivation and perspiration. Hydrophobia (afraid from water, because when he drinks water, laryngeal muscles contract and he feels suffocated) and aerophobia are common as well.
- **Coma and death:** The major cause of death is cardiorespiratory arrest.

Rabies Diagnosis:

A) Clinical through history of exposure. B) Rabies antigens or nucleic acid detection. C) Serology D) Virus isolation.

Rabies Management: cleaning of the wound, Active and passive immunization.

Prevention of initial exposure is, however, the most important mechanism for controlling human rabies.

❖ Prion diseases (Transmissible Spongiform Encephalopathies)

Most common human prion disease is Creutzfeldt–Jakob Disease.

- It is caused by misfolded forms of the **prion protein** not nucleic acid.
- Normally, this protein is found in our bodies.
- It is **not immunogenic** and the **sterilization for this protein is so hard**.
- It has many beta pleated sheets in comparison with alpha helices.
- The disease is confined to the central nervous system.

Kuru occurred only in the eastern high lands of New Guinea and was spread by customs surrounding **ritual cannibalism** of dead relatives. Since the practice has ceased, the disease has disappeared.

The prion diseases are uniformly fatal. No human or animal has ever recovered from a prion disease once neurologic dysfunction is manifest (mortality rate is 100%).

- ✓ Prions are resistant to formaldehyde, dry heat and boiling, proteases..etc.
- ✓ Prions are sensitive to phenol.

Through 2006, over 150 people had been diagnosed with new variant CJD in England, and most had died.

HIV (Revision)

The difference between **AIDS** and **HIV infection**:

- ❖ HIV infection is just **the entry of the virus** into the target cells (any cell that has CD4 as a main receptor and has a co-receptor (which is one of the chemokine receptors such as CCR5 or CXCR4 and there are others)), and these receptors **are mainly found in T helper cells**, macrophages and dendritic cells.
- ❖ So, the entry of virus is called **HIV infection**, but once it causes severe immunodeficiency defined by the presence of **less than 200 CD4 T cells** per microliter, here it is called **AIDS**, or the presence of **AIDS defining conditions** that indicate a presence of less than 200 CD4 T cells per microliter. Some examples of these conditions:
 - ❖ **Esophageal candidiasis, Kaposi sarcoma and progressive multifocal encephalopathy** (caused by JC virus).
 - ❖ Mode of transmission: sexual, blood, vertical, injection drug use, needle stick injury.
 - ❖ Most **common** mode of transmission is **heterosexual transmission**.
 - ❖ We said before that **blood transfusion is the riskiest mode** of HIV transmission. So, if we give a blood unit full of HIV infection, 95% of patients will develop an HIV infection. However, we can see here that heterosexual transmission is the most common mode of transmission, that's because it is something so common, much more than blood transfusion.
- ❖ Finally, HIV genome: the three major proteins encoded within the retroviral **genome: Gag, Pol, and Env**.
- ❖ **Pol** is the reverse transcriptase.
- ❖ **Env**: the envelope glycoproteins (gp120, gp41) that bind to cellular receptors.

Good Luck