Viral infection

**Content**
- Viral disease of
  - Respiratory system
  - Digestive system
  - Systemic with skin eruption
  - Systemic with hematopoietic disorder
  - Arbovirus and hemorrhagic fever
  - Warty growths
  - Central nervous system

**Viral structure**

**Mechanism of viral infection**
- Attachment
- Penetration
- Virus uncoating
- Replication and protein production
- Morphogenesis and maturation
- Release of virus

**Tissue change caused by viral infection**
- Cell necrosis
- Cell swelling
- Inclusion body formation
- Giant cell formation
- Latent viral infection
- Oncogenesis

**Classification of viral disease**
- Respiratory system
  - Adenovirus, Rhinovirus, Influenza, Respiratory syncytial virus
- Digestive system
  - Mumps virus, viral enteritis, hepatitis virus (A,B,C,D,E)
Classification of viral disease

• Systemic with skin eruption
  - Measles virus, Rubella virus, Varicella zoster virus, Herpes simplex virus 1 and 2
• Systemic with hematopoietic disorder
  - Cytomegalovirus, EBV
• Arbovirus and hemorrhagic fever
  - Dengue virus 1-4

Classification of viral disease

• Warty growths
  - Human papilloma virus, molluscum virus
• Central nervous system
  - Poliovirus, Rabies virus, Arbo viral encephalitis virus

Respiratory system

Rhinovirus

• Major cause of common cold
• More than 100 serotypes
• Binding to ICAM-1 receptor on epithelial cells of upper respiratory tract
• Bradykinin from host response → mucous secretion

Rhinovirus

• Clinical feature:
  Adult: rhinorrhea, nasal congestion, sore throat, cough, fever (20%)
  Child: fever (60%)
• Common complication:
  Adult: sinusitis
  Child: otitis media, lower respiratory symptom (bronchopneumonia)

Influenza virus

• Classify due to soluble (S) antigen of virion:
  - subtype A, B, C
• Classify due to glycoprotein envelope:
  - hemagglutinin (H=1-3)
  - neuraminidase (N=1-2)
  - eg. H1N1, H3N2
Influenza virus

• Cause of influenza
• Self limited infection of upper airway, but can extending to lower air way
• Destroy mucociliary function followed by secondary bacterial infection

Influenza virus

• Clinical feature:
  - rapid onset of fever, myalgia, headache, weakness, cough
  - progressive symptom 3-5 day
  - clinical subside 2 weeks

Influenza virus

• Histology
  - desquamation of ciliated columnar epithelium of nasophalynx, nasal cavity, bronchi
  - complication: pneumonia, lung hemorrhage, hyaline membrane disease
• Killed viral vaccine: protect 75%

Influenza virus

• Avian influenza (Bird flu)
  - caused by influenza virus type A, H5N1
  - disease of bird, chicken, duck
  - transmitted to human by direct contact with affected animals
  - virus dies from heat (70 c)

Influenza virus

• Avian influenza (Bird flu)
  - disease in animals
    low pathogenic
    highly pathogenic
  - disease in humans (2-3 days)
    fever, cough, sore throat, lymphopenia, severe pneumonia, res. failure, dead

Respiratory syncytial virus (RSV)

• Most common cause of self- limited respiratory tract infection in young children eg, bronchiolitis, pneumonia
• Transmitted by respiratory droplet and secretion
**Histopathology**

- **Upper respiratory tract**
  - mucosal hyperemia, swelling with predominant infiltration of lymphocytes, monocytes and plasma cells
  - mucous overproduction causing obstruction of nasal cavity, sinuses and eustachian tube

- **Lower respiratory tract**
  - laryngotracheobronchitis: swelling of vocal cord and abundant mucous secretion causing obstruction of small air way and atelectasis
  - pneumonia: interstitial infiltration of mainly lymphocytes

**Adenovirus**

- Classify 42 serotypes
- Common cause in child:
  - febrile common cold
  - pharyngoconjunctivitis
  - exudative tonsillitis
  - bronchiolitis
  - pneumonia

- Immunocompromised host:
  - high risk for severe pneumonia and frequently dead

**Mumps virus**

- Paramyxovirus family
- Cause of mumps with self limited disease in 2 weeks
- Clinical:
  - fever, malaise, headache, parotid swelling and pain
- Live attenuated mumps vaccine

**Digestive system**
Mumps

Pathogenesis

- Inhalation of respiratory droplet contains virus
- Dendritic cells at respiratory epithelium capture virus and drainage to lymph nodes
- Replication in lymph nodes
- Hematogeneous spread to parotid glands (parotitis), and other organs (CNS, pancreas, testis)

Histology

- Extrasalivary gland complication:
  - Aseptic meningitis (most common)
  - Orchitis
  - Oophoritis
  - Pancreatitis
- Parotitis: bilateral 75%
  - Desquamation of ductal epithelial cells
  - Interstitium edema with lymphocytes, and plasma cells infiltration
- Orchitis:
  - Testis edema, lymphocytes infiltration, hemorrhage
  - May be infarction → infertility (13%)

Parotitis

Viral enteritis and diarrhea

- Rotavirus
- Norwalk virus
- Corona virus
Rotavirus

- Reovirus family
- Most common cause of gastroenteritis in children < 1 year of age
- Clinical: fever, vomiting, watery nonbloody diarrhea
- Pathogenesis: reduce absorption of water and sodium from GI

Rotavirus

- Transmission by fecal-oral route
- Persistent symptom about 1 week
- Treatment: conservative with fluid replacement

Norwalk virus

- Common in childhood
- Clinical, transmission, pathogenesis, clinical course and treatment are similar to Rotavirus

Corona virus

- Caused by respiratory tract infection and diarrhea
- Self limited disease
- Intermittent epidemiology

Hepatitis virus

- Classified 6 types
  - Hepatitis virus types A, B, C, D, E, G

Hepatitis A virus (HAV)

- Transmitted by fecal-oral route (food, water)
- Common cause of acute hepatitis
- Clinical: fever, jaundice, nausea, vomiting
- Complete recovery
- No develop chronic hepatitis and hepatocellular carcinoma
Hepatitis B virus (HBV)

- Transmitted by blood transfusion, intravenous drug use, sexual activity, vertical transmission and contact body secretion eg. semen, saliva, breast milk
- Clinical: fever, jaundice, nausea, vomiting

Hepatitis B virus (HBV)

- Cause of:
  - acute hepatitis with resolution
  - chronic hepatitis, cirrhosis and hepatocellular carcinoma
  - fulminant hepatitis with massive liver necrosis
  - result for hepatitis D virus infection
  - carrier

Hepatitis C virus (HCV)

- Transmitted by blood transfusion, intravenous drug use, sexual activity, and contact body secretion eg. semen, saliva
- Asymptomatic of acute illness

Hepatitis C virus (HCV)

- Cause of:
  - Persistent infection and chronic hepatitis
  - cirrhosis and hepatocellular carcinoma

Hepatitis D virus (HDV)

- Transmitted by blood transfusion, intravenous drug use, sexual activity, and contact body secretion
- Infected with HBV:
  - coinfection: expose to serum containing both HBV and HDV
  - superinfection: chronic carrier of HBV with new infection of HDV
Hepatitis D virus (HDV)

- Clinical:
  - acute hepatitis
  - fulminant hepatitis
  - chronic hepatitis with cirrhosis

Hepatitis E virus (HEV)

- Transmitted by water-borne infection
- High mortality rate in pregnant women (20%)
- Self limited in most case
- Complete recovery
- No develop chronic hepatitis and hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hepatitis A Virus</th>
<th>Hepatitis B Virus</th>
<th>Hepatitis C Virus</th>
<th>Hepatitis D Virus</th>
<th>Hepatitis E Virus</th>
<th>Hepatitis G Virus</th>
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<tbody>
<tr>
<td>Transmissible</td>
<td>Fecal-oral</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Waterborne</td>
<td>Parenteral</td>
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<tr>
<td>Incubation period</td>
<td>2-6 wk</td>
<td>2-26 wk</td>
<td>2-7 wk</td>
<td>2-8 wk</td>
<td>Unknown</td>
<td></td>
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<td>Carrier state</td>
<td>None</td>
<td>0.1-1.0% of blood donors in U.S. and Western world</td>
<td>0.2-1.0% of blood donors in U.S. and Western world</td>
<td>5-10% in drug addicts and hemophiliacs</td>
<td>Unknown</td>
<td>1-2% of blood donors in U.S.</td>
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<tr>
<td>Chronic hepatitis</td>
<td>None</td>
<td>5-10% of acute infections</td>
<td>&gt;50%</td>
<td>&lt;5% confection, 80% upon superinfection</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Hepatocellular carcinoma</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No increase above HBV</td>
<td>Unknown, but unlikely</td>
<td>None</td>
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</tbody>
</table>

Systemic with skin eruption

Measles virus

- Cause of measles
- Infected by respiratory droplet
- Common in children
- Self limited disease

Measles virus

- Virus multiplies in upper respiratory epithelium, lymphoid tissue, and spread to blood
- Immunity protect reinfection
Measles virus
• Clinical:
  - conjunctivitis, cough, coryza, fever
  - at day 2-3: “Koplik spot” at buccal mucosa
  - at day 4-5: reddish-brown rash, enlarged cervical LN
  - 1 week: subside

Measles virus
• Complication:
  - pneumonia
  - encephalitis
  - keratitis
  - abnormal hemorrhage
  - secondary bacterial infection

Koplik spot

pathology
• Multinucleated giant cells with intranuclear and intracytoplasmic inclusion (Warthin-Finkeldey cells) in lymphoid organs and other organs

Measles

Warthin-Finkeldey cells
Rubella virus

- Cause of Rubella
- Systemic infection: rash, fever, swollen LN, joint pain, headache, conjunctivitis.
- Congenital rubella syndrome in the fetus of an infected pregnant woman (first 20th weeks)

Congenital rubella syndrome

- Fetal death, premature delivery, congenital anomalies
- Heart defects: VSD, PDA, pulmonary valvular stenosis
- Eye and ear defects: cataract, glaucoma, deafness
- CNS defects: microcephaly, mental retard

Herpes simplex virus

- HSV-1 and HSV-2
- HSV-1: fever blister or cold sores at facial skin eg. lip, nose
  - gingivostomatitis at gum, orophalynx
- HSV-2: genital herpes at genitalia (HSV-1 may be causes genital herpes)

Herpes simplex virus

- Transmitted by direct contact, sexual contact
- Blisters and secretion contains viral particles

Herpes simplex virus

- Gross:
  - group of intraepithelial vesicles (blisters) and frequently crust covering
  - may be ulcer
- Pathology:
  - pink to purple, glassy intranuclear inclusion (Cowdry type A)
  - mononucleated or multinucleated cells

HSV
**HSV**
glassy intranuclear inclusion (mononucleated or multinucleated cells)

**Pathogenesis**
- Initial infection in skin or mucous membrane
- Travel along sensory nerve ending and retrograde axonal flow to neuron in dorsal root ganglia (latent infection)
- Reactivate of latent infected neuron (e.g., stress, fever, UV)
- Newly replicated virus is transported anterograde to a site at or near portal of entry into body causing localized vesicles

**Neonatal herpes infection**
- Infected fetus by contact vaginal secretion contains viruses
- Clinical features:
  - Mucocutaneous vesicles
  - Virus spread to other organs e.g., brain, liver, lung
- High mortality rate

**Varicella zoster virus (VZV)**
- Cause of chickenpox, herpes zoster (shingles)
- Transmitted by inhalation of airborne respiratory droplets from an infected host or direct contact

**Varicella zoster virus (VZV)**
- Primary acute infection of VZV: “chickenpox”
- Reactivation of latent VZV: “shingles or herpes zoster” distributes to sensory nerves
Pathogenesis

- Primary infection (chickenpox)
- VZV spread from mucosal and epidermal lesions to local sensory nerves
- VZV remains latent in dorsal ganglion cells of sensory nerves
- Reactivation of VZV results in syndrome of herpes zoster (shingles)

Varicella zoster virus (VZV)

- Gross:
  - Chickenpox: diffuse, scattered vesicles
  - Shingles: vesicles distribution along the peripheral nerve (dermatome)
- Histology:
  - Intranuclear inclusion of infected cells (multinucleated cells)

Chickenpox

Shingles

VZV

Intranuclear inclusion
Cytomegalovirus (CMV)

- Produce a variety of disease depend on age, immune status
- Cause of asymptomatic in healthy person or severe systemic infection in neonates and immunocompromised host (opportunistic infection)

Cytomegalovirus (CMV)

- Transmitted by:
  - intrauterine transmission
  - perinatal transmission
  - breast milk
  - respiratory droplets
  - semen and vaginal fluid
  - blood transfusion
  - organs transplantation

Cytomegalovirus (CMV)

- Clinical feature depends on infected organs
- Congenital CMV infection
  - 90% asymptomatic
  - 10% symptomatic eg. Hemolytic anemia, jaundice, thrombocytopenia, pneumonia, hepatosplenomegaly, retinitis, brain damage, mental retard or dead

Histology

- Large purple intranuclear inclusion surrounded by clear halo and smaller basophilic intracytoplasmic inclusion
- Organ involvement: salivary glands, kidney, liver, pancreas, brain, ect.
Epstein-Barr Virus (EBV)

- Cause of infectious mononucleosis, self-limited disease
- EBV associated with hairy leukoplakia, lymphoma, and nasopharyngeal carcinoma
- Transmitted by contact saliva

Epstein-Barr Virus (EBV)

- Clinical of infectious mononucleosis:
  - fever
  - generalized lymphadenopathy
  - hepatosplenomegaly
  - sore throat (patch on tonsil)
  - may be CNS lesion
  - may be hepatitis, pneumonia

Pathogenesis

EBV replicates in B-lymphocytes in tonsil
B-lymphocytes disseminates in circulation
Atypical T lymphocytes in blood circulation

Arbovirus and hemorrhagic fever
**Dengue virus**
- Dengue virus 1-4
- Dengue fever is a vector-borne disease
- transmitted via bite of mosquitoes eg. *Aedes aegypti* *Aedes albopictus*
- Symptoms of dengue include:
  - high fever, headache
  - rash
  - nausea and vomiting
  - myalgia
  - leukopenia (neutropenia), thrombocytopenia

**Dengue virus**
- Infection with one serotype provides lifelong immunity to that particular serotype but not to the other three
- Previous infection with simple dengue fever greatly increases risk of developing DHF

**Human papilloma virus (HPV)**
- most common causes of sexually transmitted infection (STI) in the world
- HPV types cause benign skin wart, anogenital warts, anogenital cancer
- Warts: proliferative squamous epithelium producing nodules or flat lesions

**Human papilloma virus (HPV)**
- Skin warts
  - HPV types 1,2
  - common warts (verruca vulgaris): hands, trunk, extremities
  - plantar warts: plantar
  - no associated with cancer

**Human papilloma virus (HPV)**
- Anogenital warts (condyloma acuminatum)
  - HPV types 6,11
  - warts at penis, vulva, vagina, anus
  - no associated with cancer
- Anogenital cancer (squamous cell carcinoma)
  - HPV types 16,18,31,45
  - cause of cancer of anus, vulva, cervix and penis
Human papilloma virus (HPV)

• Transmitted by skin-to-skin contact during sexual intercourse
• Treated by electrocautery, laser treatment
• Histology: koilocytosis of infected cells

Skin warts

Anogenital warts (condylomata acuminata)

Koilocytosis of infected cells

Molluscum virus

• Cause of molluscum contagiosum
• Self-limited viral disease of skin
• Transmitted by skin or sexual contact
• Gross: raised, umbilicated, cutaneous nodules at skin (most perineum)
• Histology: intracytoplasmic inclusion bodies (molluscum bodies)

pathogenesis

transmitted primarily through direct skin contact with an infected individual

virus infects epidermis causing hyperplasia, hypertrophy and central degeneration of the epidermis

epidermis has molluscum bodies contain large numbers of maturing virions
**Molluscum contagiosum**

- Intracytoplasmic inclusion bodies (molluscum bodies)

**Central nervous system**

**Poliovirus**

- Causes poliomyelitis
- Transmitted by fecal-oral route
- Most asymptomatic
- 1/100 of infected patients → disease (spinal poliomyelitis, bulbar poliomyelitis)

**Pathogenesis**

Poliovirus infects oropharynx, secreted in saliva and swallowed

- Multiplies in intestinal mucosa and lymph nodes
- Hematogenous spreading
- Invade to CNS and replicate in spinal cord (spinal poliomyelitis), or brain stem (bulbar poliomyelitis)

* Virus destroys motor neuron in anterior horn of spinal cord or brain stem*
Poliomyelitis

- Clinical features
  - flaccid paralysis
  - muscle atrophy
  - hyporeflexia

Rabies virus

- Cause of rabies (encephalitis)
- Transmitted by saliva of dog or cat bites
- Clinical:
  - malaise, headache, fever, dysphagia
  - followed by period of acute neurologic symptom including disorientation, hallucination, seizure, coma and dead from res. failure

Rabies virus

- Post-exposure prophylaxis: combined immune serum and vaccine
- High mortality rate

pathogenesis

Rabies virus multiplies at site of local bite
  ↓ travel to CNS through the peripheral nerves
  ↓ replicates in neurons of CNS
  ↓ Clinical symptom

Negri bodies

Intracytoplasmic inclusion in neuron

Arbo viral encephalitis virus

- Japanese B caused by encephalitis
- Animal host: pig
- Carrier: mosquitoes
- Clinical: confusion, seizure, coma
- Pathology: mononuclear cells around vessels, necrosis of neuron and brain tissue