SHEET N 7

MICROBIOLOGY (Virology)

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

DOCTOR : Malek

Parvovirus

Taxonomy

Paroviridae family contains:

1) **parvovirinae subfamily (members that can infect vertebrates).**
2) **densovirinae subfamily that infects insects mainly.**

Parvovirinae comprise five genera that can infect humans: Erythrovirus, Bocavirus, Dependovirus, Amdovirus and Protoparvovirus.

1) Erythrovirus genus: Parvovirus B19 is the most common member of the Erythrovirus genus. There are three human genotypes in this genus:

Genotype 1: (b19)

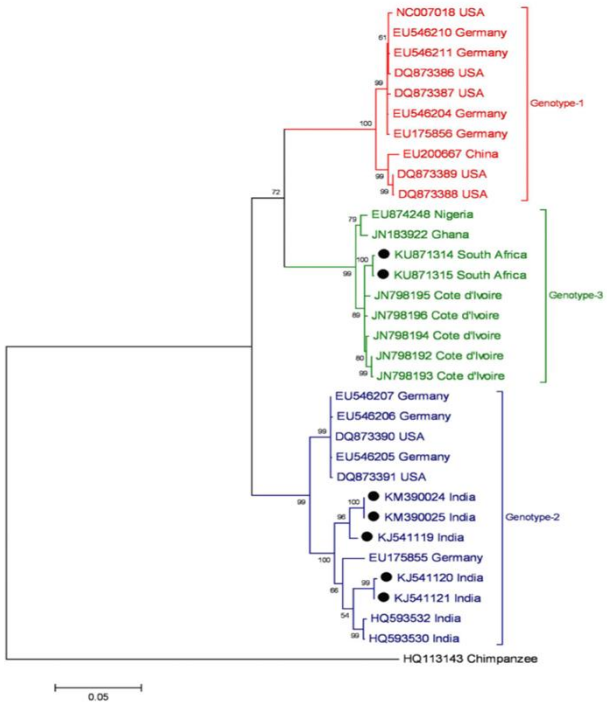
Prototype strain: AU , very low diversity, the most known and studied genotype, also the dominant human pathogen of parvovirinae.

Genotype 2:

Prototype strain: LALI ,higher diversity than genotype 1

Genotype 3:

Prototype strain: V9 , higher diversity than genotype 1



2) Bocavirus genus:

the three human bocaviruses are in the Bocavirus genus. Recently identified, can cause lower respiratory tract infections & may be associated with GI tract infections.

3) **Dependovirus genus:**
   The genus Dependovirus contains members that are defective and depend on a helper virus (an adenovirus or herpesvirus) for replication.
   - Human "adeno-associated viruses" have not been linked with any disease.
4) **Amdovirus**
5) **Protoparvovirus**

Parvovirus (erythrovirus B19)

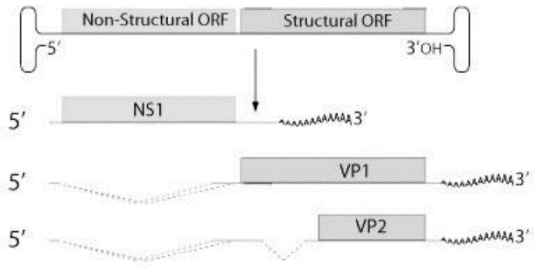
Discovery

- **Cosart & collegues were the first to identify B19 parvovirus, while screening of sera for Hepatitis B surface antigens using ouchterlony immunodiffusion technique, the sample which contains the new isolate was number 19 in panel B (B19 virus)**.

General properties

- The simplest DNA animal viruses, **ssDNA viruse, icosahedral and non-enveloped.**
- Its replication is **dependent** on replicating host cells or by co-infecting helper viruses, and **classification is based on host range & dependence on other viruses to replicate**.
- Virions are **extremely resistant** to inactivation by heat, solvents, detergents and some treatments, (stable between a pH of 3 and 9 and withstand heating at 56°C for 60 minutes).

Genome and proteins:



1.Genome:

- **Linear ssDNA, Have ends nucleotide repeats on the 5' & 3' ends, and two large, two small open reading frames (ORF), on the left side NS1 ORF, on the right side vp1 & vp2 ORF. Which both originate from the same ORF.**

2.Structural proteins:

Virions contain two coat proteins that are encoded by an overlapping, in-frame DNA sequence:

- **VP1**:

The minor structural protein, represents 4% of the virion protein. It is bigger in size because additional 227 amino acids on N terminus. The N terminus of VP1 is located on

the external part of virion capsid and contains many neutralizing epitopes which are linear in nature.

- **VP2**:

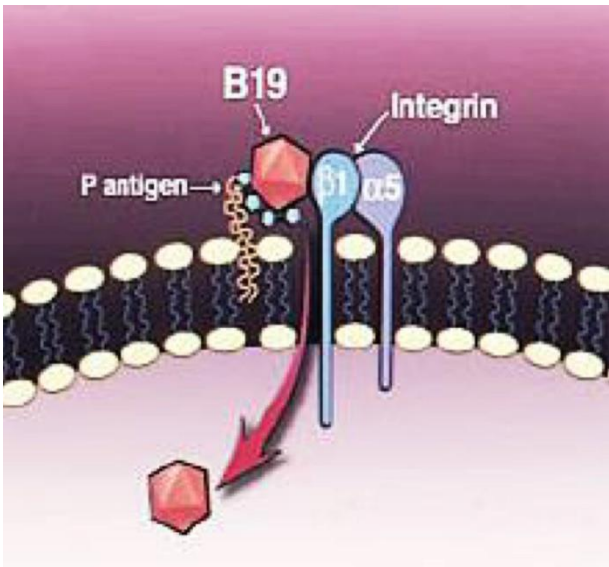
The major capsid protein, VP2, represents about 96% of virion protein. VP2 is identical in sequence to the carboxy portion of VP1, and it is smaller than VP1. **VP2 epitopes are conformational**.

3.Non structural proteins: (NS1) : DNA binding proteins that are involved in replication, Antigenic domains of NS1 are located on its carboxy terminus.

Important Properties of Parvoviruses

Virion: Icosahedral, 18–26 nm in diameter, 32 capsomeres
Composition: DNA (20%), protein (80%)
Genome: Single-stranded DNA, linear, 5.6 kb, MW 1.5–2.0 million
Proteins: One major (VP2) and one minor (VP1)
Envelope: None
Replication: Nucleus, dependent on functions of dividing host cells
Outstanding characteristics: Very simple viruses Human pathogen, B19, has tropism for red blood cell progenitors One genus contains viruses that are replication-defective and require a helper virus

Replication



- It is difficult to culture human B19 parvovirus; only primary erythroid progenitors are known to be permissive for B19 infection.
- **The cellular receptor for B19 is blood group P antigen (globoside).** P antigen is expressed on mature **erythrocytes, erythroid progenitors, fetal liver, heart, platelets and trophoblasts,** which helps explain the narrow tissue tropism of B19 virus**.**
- **The α5β1 integrin is believed to be a co-receptor for B19 entry**. P antigen only is not enough for the virus to enter, co receptors are need.
- If an individual doesn't have P antigen virus receptor he wil be **resistant to B19 infection**.
- Viral DNA replication occurs in the **nucleus**. They **must infect dividing** cells with cellular DNA polymerases are involved because parvovirus is dependent on active replication. The non-structural protein, NS1, is required for virus replication. Viral replication results in cell death**.**

- during replication equal numbers of + & - strands of DNA are packaged randomly into single virion particle, so when we extract viral DNA, complement strands may hyberdize together & form dsDNA. And that what happens also when the virus loses its capsid**.**

Human Diseases Associated with B19 Parvovirus (min 14:03-33:38)

Syndrome	Host or Condition	Clinical Features
Erythema infectiosum	Children (fifth disease) Adults	Cutaneous rash Arthralgia-arthritis
Transient aplastic crisis	Underlying hemolysis	Severe acute anemia
Pure red cell aplasia	Immunodeficiencies	Chronic anemia
Hydrops fetalis	Fetus	Fatal anemia

- Being infected with B19 Parvovirus is common globally, specifically when there is a shifting between the seasons usually in the late winter, spring and early summer in the form of epidemics.
- So, these epidemics have a seasonal variation and reaches the peak each (3-5) years as a cycle in the temperate regions.
- Immature cells in the erythroid lineage are targets for B19 parvovirus infection.

- The major sites of B19 virus replication in patients are adult marrow, and the fetal liver.

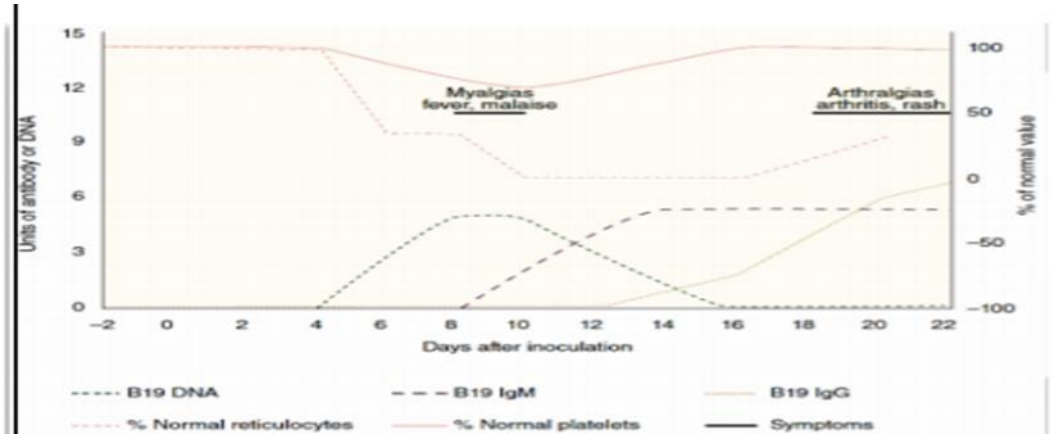
- Being infected with B19 Parvovirus is common between young children, and its main manifestation is ***Erythema infectiosum*** or "the fifth disease" or "slapped cheek syndrome" – all of these names are for the same manifestation-.

- The infection of patients with short life span RBCs will cause ***Transient aplastic crisis.***

- In both ***Erythema infectiosum*** and ***Transient aplastic crisis*** the disease is self-limiting in spite of that the severity of the disease is higher in the ***Transient aplastic crisis.***
- The incubation period of B19 is from (6-10 days), and the transmission usually occurs through the respiratory route "secretions, saliva" that are released from the infected peoples, so the chance to infect the surrounding people in the crowded places is high. There is no evidence of virus excretion in feces or urine.

- If the pregnant woman gets infected then there is a high chance to transmit the infection to the fetus “vertical transmission”, and this happens in 30% in each exposure to the virus.

- In the general population, the seroprevalence of B19 - the number of persons in a population who test positive for a specific disease based on serology (blood serum) specimens “Wikipedia”- is more than 33% in the children under the 5 years, and 90% in the people who are older than 50 years, and 50-60% in the women that are in the productive age because they have B19 IgG, so half of them are susceptible to the infection.



- Also, can be transmitted parenterally by blood transfusion when the donor has the virus is in his blood, and the incidence of B19 when the donor is healthy is from (1/20000 – 1/50000), and the risk of transmission is high when the blood components of the hemophiliacs patients who need a repeated blood transfusion -several units rather than one blood unit-.
- We can detect the virus in these blood units through nucleic acid amplification testing (NAT) by which we can detect the presence of some factors such as Factor 8 or 9 or if the clotting factor concentrates and if there are immunoglobulins against the virus.
- Many infections are subclinical (with no symptoms) and acute, but in the immunocompromised patients they are life threatening, and chronic especially in the patients with short life span RBCs.

Now let’s discuss each syndrome by details:

A) Erythema infectiosum

This disease is the most common manifestation of B19 infection. It is most common in children of early school age and occasionally affects adults ” normal individuals”, both in sporadic and epidemic forms and the main symptoms are fever, headache, conjunctivitis, cough, myalgia, diarrhea and the other signs of upper respiratory tract infection AND also the appearance of specific rash associated with B19 infections on

the face (erythematous facial rash -redness and swelling in the face- and perioral pallor and this gives the “slapped cheek” appearance.

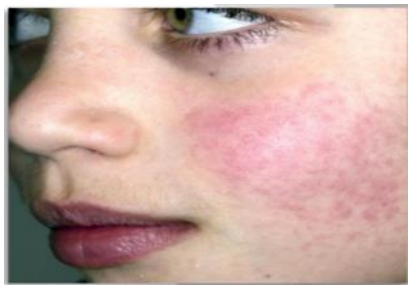
- In a certain study, they give some immunocompetent people a dose of B19 virus by their nose and start monitoring them, the incubation period is usually is usually 1–2 weeks but may extend to 3 weeks. (this period differs from one person to another depending on the infection dose of each one).

  The first phase “non-specific” of illness at the end of the first week includes: fever, malaise, myalgia, chills, and itching and the Viremia occurs 1 week after infection and persists for about 5 days with the upper respiratory as the site of viral shedding. Reaches the peak after 8-9 days and the viral levels increase from 10 billion to 1000,000 billions/ml of the blood and the reticulocytopenia (abnormal decrease of reticulocytes in the body “reticulocytes are immature RBCs”) is taking place with also a decrease in the hemoglobin and transient decrease in the neutrophils, lymphocytes and platelets
  And the IgM antibodies become detectable 2 weeks after the incubation, and the IgG within 15 days post-infection.

  After an incubation period of about 17-18 days, a second phase of illness begins.

Then the erythematous facial rash and lacelike rash will appear on the limbs or trunk and rarely on the palm of the hand and the soles of feet and the rash will stay for after 2–4 days and accompanied with fever.

Arthralgia-arthritis in adults especially young women, so many adults will have arthropathy with B19 and severe pain in the joints and absent skin rash (joint symptom happens in 1/3 of B19 infected adults, but in children, arthralgia is not common “less than 10% of them



will have arthralgia” in certain joints like the proximal interphalangeal joint in the feet and hands, wrist, knees, elbows, ankles with swollen and redness, and these symptoms are self-limited and rarely they persist for months or years in contrast to the adults)

Some people say that there is a role of B19 in some autoimmune diseases that contain joint involvement like rheumatoid arthritis and chronic juvenile arthritis, but these claims still unsured and under studies.

B) Transient Aplastic Crisis (TAC)

Parvovirus B19 is the cause of transient aplastic crisis that may complicate in cases of chronic hemolytic anemia (such as in patients with sickle cell disease, thalassemia, and acquired hemolytic anemias in adults after BMT with absence of erythroid precursors in the marrow, accompanied by a rapid worsening of anemia)

And it is also acute and self-limited but the symptoms are severe only in patients with chronic hemolytic anemia because of the short life span of their erythrocytes.

The syndrome is a severe drop of red blood cell synthesis “Anemia” and circulating reticulocytes.

In the normal situation the symptoms will not appear because of the normal life span of the RBCs, symptoms of transient aplastic crisis occur during the viremic phase of infection.

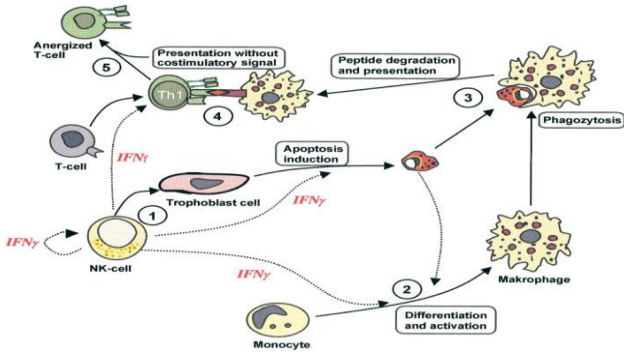
Persistent infections will cause chronic suppression of BM and chronic severe anemia in immunocompromised patients (congenital immunodeficiency, malignancies, AIDS, and organ transplants), which is called **pure red cell aplasia**.

C) Hydrops fetalis:

The infection during pregnancy of susceptible women (seronegative women) will result in either apportion or fetal death due to fatal anemia or transfusion congenital dependent anemia or hepatomegaly OR hydrops fetalis.

The manifestations are inflammatory response then trophoblast apoptosis (because the trophoblast can express the receptor for B19), so the result is a poor outcome baby.

الصورة من خارج السلايدات فقط للتوضيح

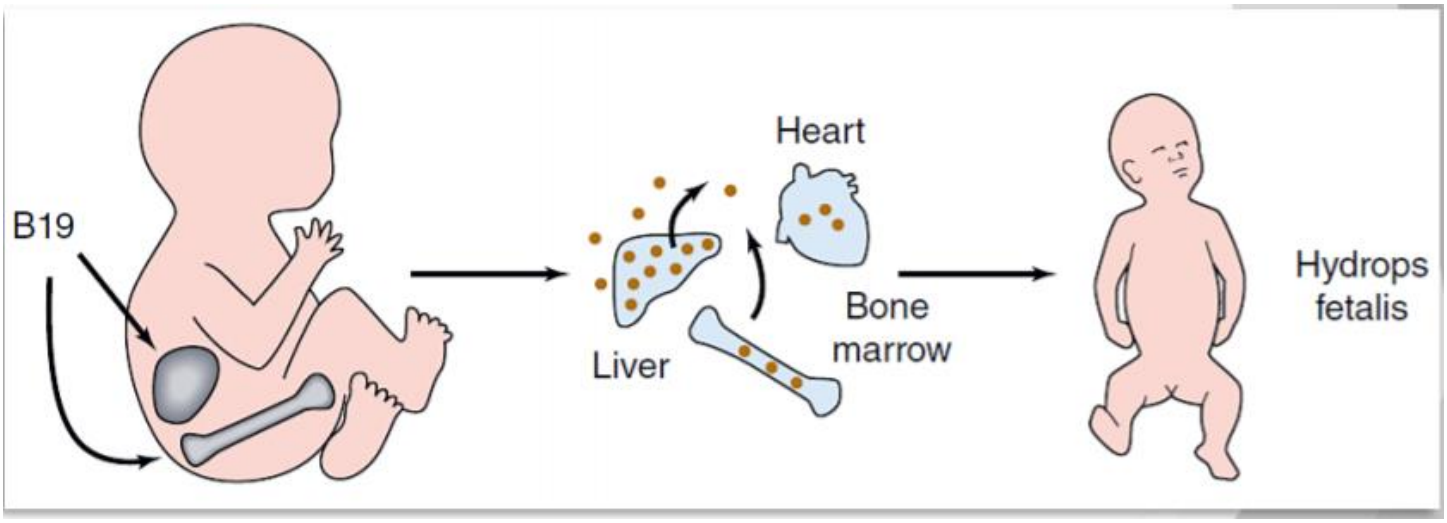


The rate of transmission as we mentioned before from the mother to her fetus is 30%, and the risk of fetal death is 10% and the highest risk happens if the infection occurs before the 20th week of pregnancy (The fetus is high vulnerable to B19 infection during the second

trimester of pregnancy because of the rapid expansion of target cells of B19 “RBCs and erythrocytes precursors”) and as the gestational proceeds, the risk decreases.

Maternal–fetal transmission may occur most commonly in pregnant women with high plasma viral loads.

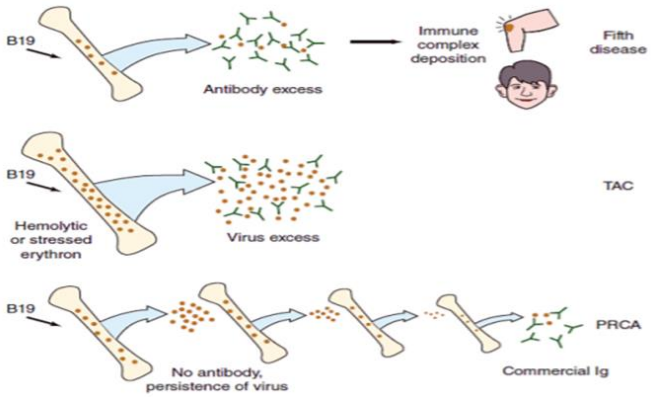
A high number of Hydrops fetalis cases that result because of the late infection in the pregnancy will be resolved spontaneously, and infection of **the immunocompromised patients** -regardless of its causative either congenital or acquired- will result in pure red cell aplasia:



D) Pure red cell aplasia

Specifically, in AIDS patients, on the contrast of normal people, the acute infection will not be resolved and will become chronic with severe anemia and low to medium level viremia that will persist for months or years which reflects that the immune system is unable to clear the virus and, then will be either selective aplasia for RBCs precursors in the bone marrow or pancytopenia (is a condition that occurs when a person has low counts for all three types of blood cells: red blood cells, white blood cells, and platelets.
Pancytopenia is usually due to a problem with the bone marrow that produces the blood cells. -additional information-)

In some cases, we can treat the patients through the administration of intravenous immunoglobulins that will help in the elimination of viremia.



Human bocavirus

- Human bocavirus has been firstly identified in 2005, and detected in 1.5% to 11.3% of respiratory tract samples from young children (6-24 months) with respiratory infections.
- It is prevalent among children with acute wheezing.
- The virus has been detected in about 3% of stool samples from children with acute gastroenteritis. Bocavirus can be isolated from GI specimens but **its association with gastroenteritis is not yet fully determined.**
- Co-infection rates with other enteric pathogens were high, so any causative role of bocavirus in gastroenteritis is unknown.

Laboratory diagnosis of parvovirus infections

Different techniques can be used:

1) Immune electron microscopy: (not routinly done because it needs experience)

2) serology testing & antigen detection:

- Testing for IgG & IgM to check if the patient is immune against parvo.
- Serologic assays based on recombinant parvovirus B19 antigens are used to measure antibodies. **VP2 virus-like particles appear to be optimal as antigen for antibody detection**. Detection of **B19 IgM** antibody is indicative of recent infection; it is present for 2–3 months after infection.
- **B19 IgG** antibody against conformational epitopes on VP1 and VP2 persists for years, although antibody responses against linear epitopes decline within months post-infection. **Antibody may not be found in immunodeficient patients with chronic B19 infections**. In those patients, chronic infection is diagnosed by **detecting viral DNA**.
- Antigen detection assays can identify high-titered B19 virus in clinical samples. **Immunohistochemistry** has been used to detect B19 antigens in fetal tissues and bone marrow.

3) Nucleic acid amplification testing (most sensitive)

- The most sensitive tests **detect viral DNA.**
- Available tests are PCR, probe hybridization of serum or tissue extracts, and in situ hybridization of fixed tissue. **PCR is the most sensitive assay.**
- B19 DNA has been detected in serum, blood cells, tissue samples, and respiratory secretions. During acute infections, viral loads in the blood can reach approximately 10^11 genome copies/mL.
- **The only assay currently available for human bocavirus is PCR.** Bocavirus DNA has been found in serum, saliva, stool samples, and respiratory specimens. Bocavirus genome is smaller that Parvo's.

- **Note:** B19 and bocaviruses are difficult to grow. **Virus isolation is not used to detect infection.**

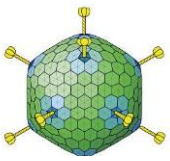
Epidemiology of parvovirus infections

- The B19 virus is widespread. Infections can occur throughout the year in all age groups.
- Up to 60% of all adults and 90% of elderly people are seropositive.
- B19 infection is transmitted via the **respiratory tract**. Transfer among siblings and children in schools and daycare centers is the **main path of transmission**.
- **Many infections are subclinical**.
- Whereas patients with **aplastic crisis** are likely to be infectious during the course of their illness, patients with **fifth disease** are probably no longer infectious by the time of onset of rash.
- **The epidemiology of human bocavirus is not know**n. It has been found in young children and appears to be global in distribution.

Treatment, prevention and concentration of parvovirus infections

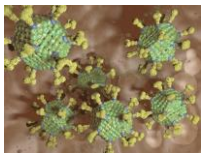
- **Infection is mostly asymptomatic**, it is mild when it is symptomatic as a fibril illness, can be accompanied with rash sometimes.
- **In most cases it is self limited** so there is no need for specific treatment. **NSAIDs** can relieve symptomatic individuals especially those with arthropathy or arthritis.
- **Treatment is needed when the virus is life threatening** like in immunocompromised patients, and treatment depends on manifestation and immune status of the patient.
- **Fifth disease and transient aplastic crisis** are treated symptomatically. The latter may require transfusion therapy, that can give temporary relief in anemic patients, and in fetal anemia we can use intrauterine transfusion (should be monitored closely because it is associated with risk).
- **Commercial immunoglobulin preparations** contain neutralizing antibodies to human parvovirus. They can sometimes ameliorate persistent B19 infections in immunocompromised patients and in those with anemia.
- **Cases with chronic viremia in Pure Red Cell Aplasia patients can be given IV Ig.**
- **There is no treatment** for human **bocavirus** infections.
- **There is no vaccine against human parvovirus.** If we had a vaccine it would be against VP1 & VP2. Although VP1 constitutes 4% of the capsid, it contains strong neutralizing epitopes, so it is a candidate for the vaccine.
- There is no antiviral drug therapy.

Adenoviridae Introduction



-First found in adenoid tissue (tonsils), latency resistant infection could happen the[illegible]
-Naked viruses. (non-enveloped)
-Icosahedral
-Contain single linear double-stranded DNA genome, 40 genes, 36k bases, with:
1) early genes (E genes: E1, E2, E3, E4).
2) late genes (L2 to L5).
-Its protein capsid contains 252 capsomeres: 240 hexones (that contain specific antigens) that are found on the triangular faces of the virus, & 12 pentones on the vertices that also contain specific antigens, from each pentose there is a rod-like fiber with a terminal head that make interactions with host cell receptors.
*how the virus enters the cell? By fibers attachment with the coxsackievirus and adenovirus receptor (CAR) on host cells
-1-5% of the produced progeny are infectious.

(At the 12 vertices of the capsid, there are protruding fibers that contain type-specific antigens which are important in serotyping.)



ADENOVIRUS (Ad)-CLASSIFICATION

There are **57 serotypes** in the **seven species** of human Ads: للحفظ

species A (Ad12, 18, 31).
species B (Ad3, 7, 11, 14, 16, 34, 35, 50, 55).
species C (Ad1, 2, 5, 6).
species D (Ad8 to 10, 13, 15, 17, 19, 20, 22 to 30, 32, 33, 36 to 39, 42 to 49, 51, 53, 54, 56).
species E (Ad4).
Species F (Ad40 and 41).
Species G (Ad52).

- **7/14/4/21 serotype:** make epidemic infections (in winter to early summer)
-species C (1/2/5/6) make endemic infections (all year around)
-**species D** can be latent reactivated.
-**species F (40/41)**, called enteric adenoviruses, cause adenovirus-associated gastroenteritis (endemic)
- **7/4 serotypes** infect military recruits.
- **8/9/37 serotypes:** cause large epidemics of keratoconjunctivitis
- **3/4/7 serotypes:** cause keratoconjunctivitis associated with contaminated swimming pool water
- respiratory tract infections are associated with **B/C/D species**.
- immunocompromised patients may have **D** serotypes infections.
- most infections (except epidemic ones) happen all-year around.

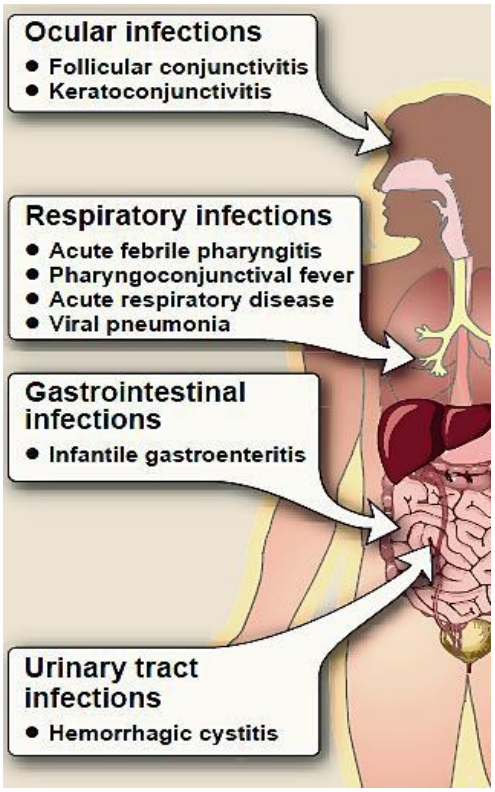
Adenovirus Pathogenesis

-Adenoviruses infect and replicate in epithelial cells of the **respiratory tract, eye, gastrointestinal tract and urinary bladder.**
-Usually, adenoviruses cause localized infection and do not spread systemically.
-Most human adenoviruses replicate in intestinal epithelium after ingestion but usually produce subclinical infections rather than overt symptoms.
- half of cases are asymptomatic.

Adenovirus Transmission

-The site of the clinical syndrome caused by an adenovirus infection is generally related to the mode of virus transmission.
-Most adenoviruses are primarily agents of **respiratory disease,** which are transmitted via the respiratory route. The **GI disease** is transmitted via the fecal-oral route.
-Similarly, **ocular infections** are transmitted by direct inoculation of the eye by virus-contaminated hands, ophthalmologic instruments, or bodies of water in which groups of children swim together.
-transmission could be airborne (by air droplets or aerosols) or by contaminated fingers or ophthalmic solutions.
-Shedding of the virus can be prolonged which cause more transmission
-adenovirus may cause **latent infection** in the adenoidal and tonsillar tissues of the throat.

Adenovirus Summary of clinical features



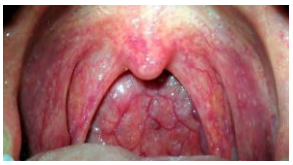
In the **upper respiratory tract** it cause pharyngitis, pharyngoconjunctival fever. And acute respiratory disease (fever, sore throat, coryza (runny nose), conjunctivitis, lymphadenopathy and malaise.
In the **lower respiratory tract** it cause bronchitis and pneumonia.
It also cause cervical adenopathy, cough, and tonsillitis, and pertussis-like syndrome.
-may cause fatalities.
-symptoms can resolve in two weeks, but some symptoms like photophobia and foreign-body sensation can persist for months or years.
In gastrointestinal infections the incubation period is 3-10 days, symptoms are watery diarrhea, mild fever, abdominal pain, respiratory symptoms.
-other RARE symptoms: meningoencephalitis, encephalitis, acute myocarditis, arthritis.

Adenovirus Respiratory Disease

The most common manifestation of adenovirus infection of infants and young children is acute febrile pharyngitis, characterized by a cough, sore throat, nasal congestion, and fever.

Some adenovirus types tend additionally to produce conjunctivitis, in which case the syndrome is referred to as pharyngoconjunctival fever.

Adenoviruses are thought to be responsible for about 10–20% of pneumonias in childhood.
Adenoviral pneumonia has been reported to have an 8–10% mortality rate in the very young.




Adenovirus Ocular Disease

In addition to the conjunctivitis that accompanies the upper respiratory infection, a similar condition may occur as a separate disease. It is self-limiting and has no permanent sequelae.
A more serious infection is epidemic keratoconjunctivitis, which involves the corneal epithelium, and may be followed by corneal opacity lasting several years.
The epidemic nature of this disease results from transmission via shared towels or ophthalmic solutions, person-to-person contact, or improper sterilized ophthalmologic instruments.

Adenovirus GI Disease

Most human adenoviruses multiply in the GI tract and can be found in stools; however, these are generally asymptomatic infections.
Two serotypes (types 40 and 41) have been associated specifically with infantile gastroenteritis and may account for 5–15% of cases of viral gastroenteritis in young children.
Clinical manifestations include: Long-lasting diarrhea, less frequent vomiting, frequent development of dehydration, and abdominal pains and distension.

Acute Hemorrhagic Cystitis

An illness that is associated with Ad11.
Characterized by gross hematuria.
Its significance lies in the potential confusion with other, more serious diseases of the kidney (such as glomerulonephritis).
This self-limited disease is usually not accompanied by fever or hypertension, and tests of renal excretory and concentrating functions have been essentially normal.

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Epidemiology, Diagnosis, Treatment and Prevention

Adenoviruses exist in all parts of the world and they are present year-round.
The most common serotypes in clinical samples are the low-numbered respiratory types (1, 2, 3, 5, and 7) and the gastroenteritis types.
Dx: Ag detection or PCR.

There is no specific treatment for adenovirus infections. Careful hand washing is the easiest way to prevent infections. Live adenovirus vaccine containing types 4 and 7 is available.

-ganciclovir, verapin, hepaverin, cidofovir, ribavirin, all are tested to treat adenovirus infections and gave a mixed results.