Medical Virology for 2nd Year M.D. Students

Parvoviruses and Adenoviruses

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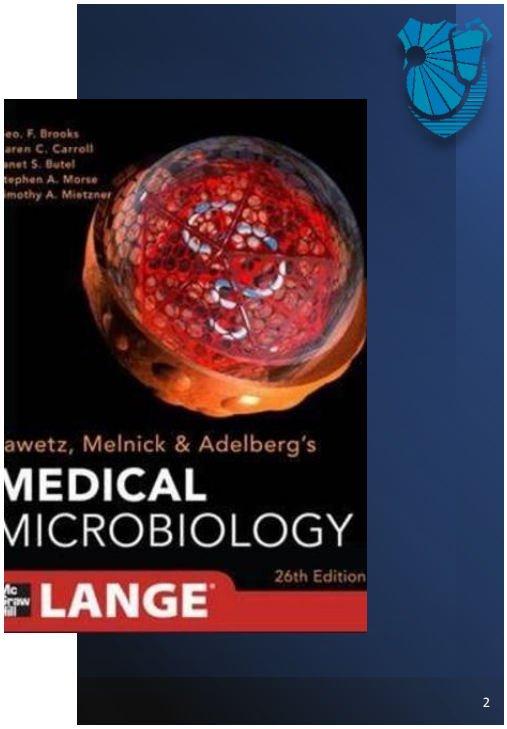
Important Note:
The Required Material for the Exams:
Section IV (Virology) in the provided textbook: Jawetz Medical Microbiology

References

- Jawetz, Melnick & Adelberg's Medical Microbiology. 26th edition. New York : London: McGraw-Hill Medical ; McGraw-Hill, 2013.
- Recent original and review articles in high impact and well renowned scientific journals



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Parvoviruses – General Properties

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

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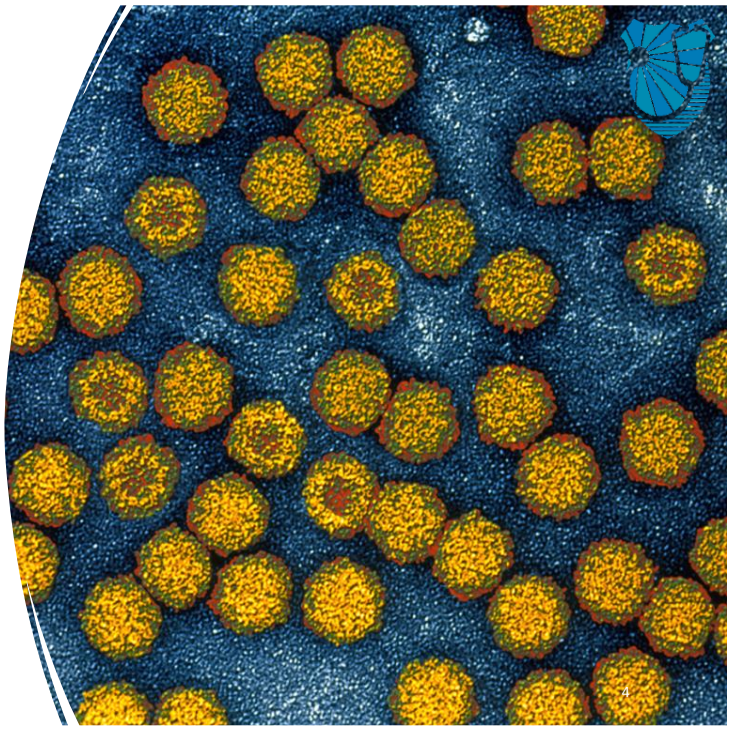
Colored transmission electron micrograph (TEM) of parvovirus B19 particles



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Parvoviruses – General Properties

Virions are extremely resistant to inactivation

They are stable between a pH of 3 and 9 and withstand heating at 56°C for 60 minutes, but they can be inactivated by formalin, β-propiolactone, and oxidizing agents

The major capsid protein, VP2, represents about 90% of virion protein

The genome is about 5 kb, linear, single-stranded DNA

Autonomous parvoviruses have 5k+ genomes compared to 4k+ genome in defective parvoviruses; also, the autonomous viruses encapsidate DNA strands complementary to viral mRNA, while defective parvoviruses have DNA of both polarities

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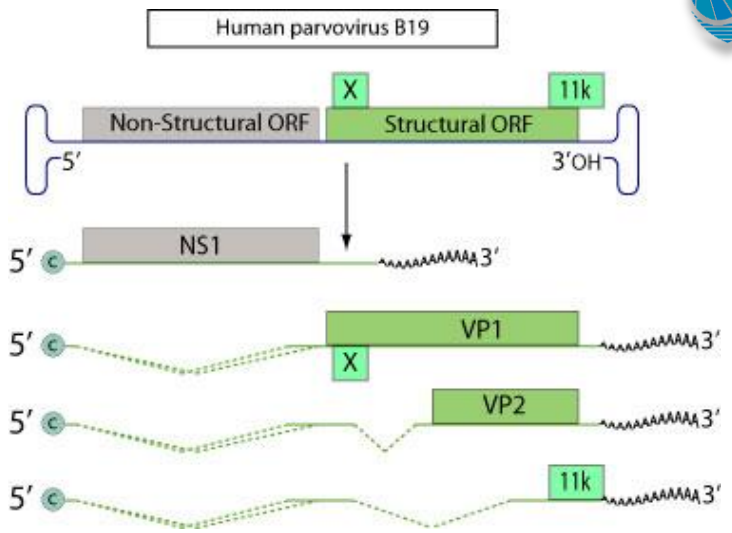
Parvoviruses – General Properties



Source: *ViralZone (https://viralzone.expasy.org/103?outline=all_by_species)*

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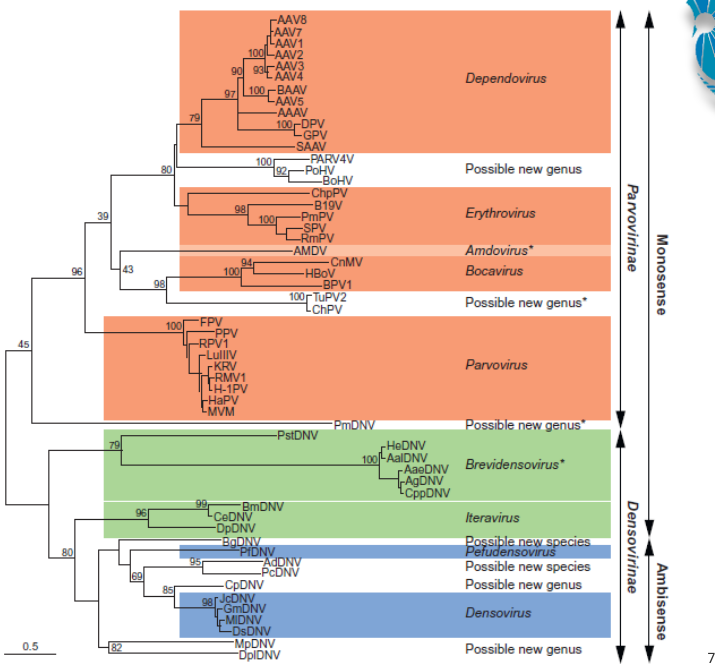
Parvoviruses – Classification



Source: *Family - Parvoviridae. In Virus Taxonomy, King, A.M.Q., Adams, M.J., Carstens, E.B., Lefkowitz, E.J., Eds. Elsevier: San Diego, 2012; https://doi.org/10.1016/B978-0-12-384684-6.00039-2pp. 405-425.*

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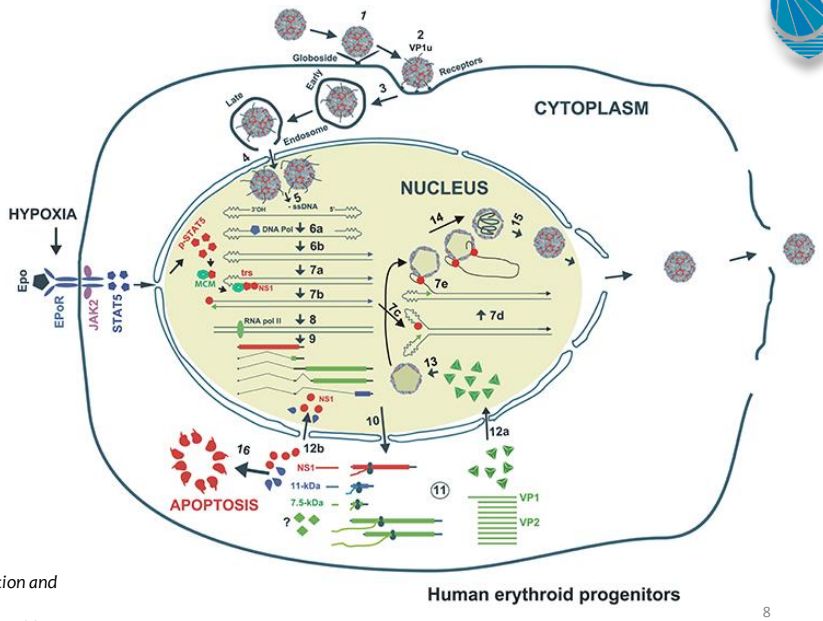
Parvovirus Replication

P antigen (globoside) is expressed on mature erythrocytes, erythroid progenitors, megakaryocytes, endothelial cells, placenta, and fetal liver and heart



Source: *Ganaie SS, Qiu J. Recent Advances in Replication and Infection of Human Parvovirus B19. Front Cell Infect Microbiol. 2018 Jun 5;8:166. doi: 10.3389/fcimb.2018.00166*

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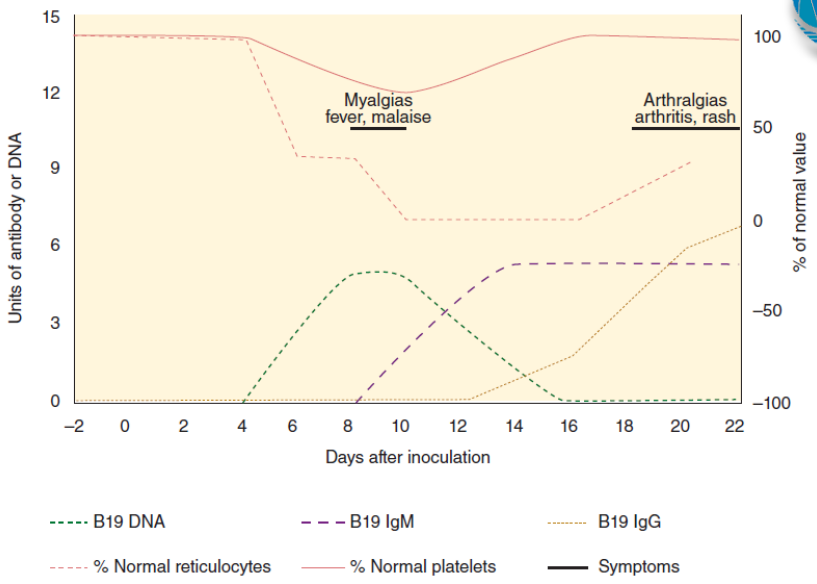
Clinical and laboratory findings during B19 infection in adult volunteers

Parvoviruses – Pathogenesis and Pathology



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Human Diseases Associated with B19 Parvovirus

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

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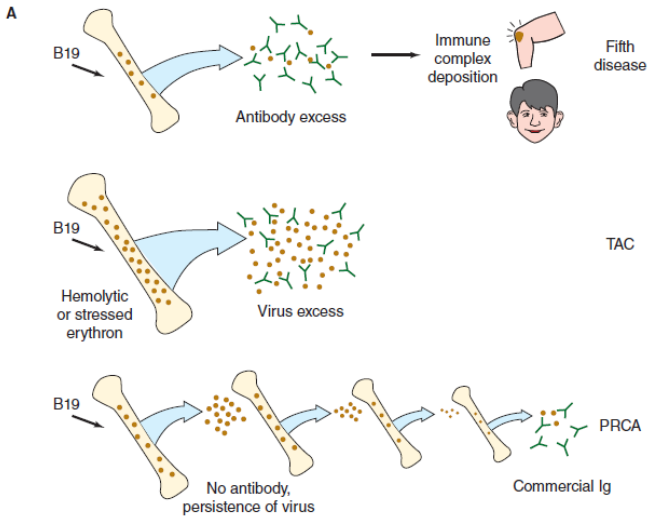
Pathogenesis of diseases caused by B19 parvovirus



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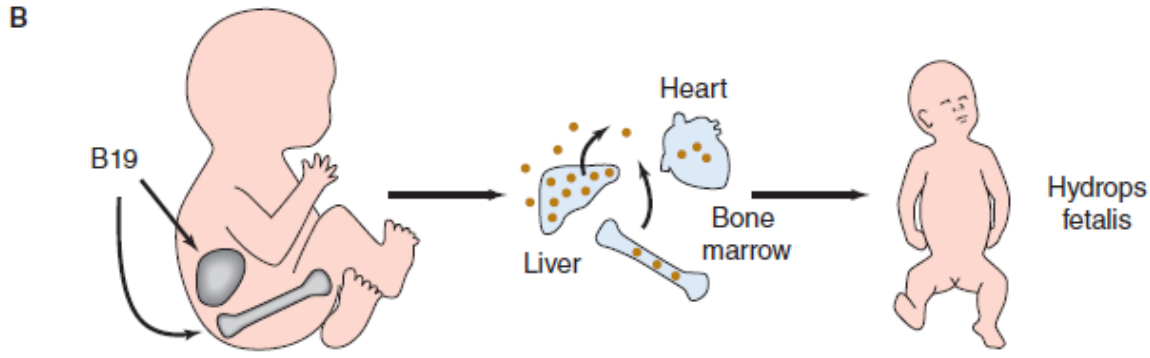
Pathogenesis of diseases caused by B19 parvovirus



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Clinical Findings: Erythema Infectiosum (Fifth Disease)

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Parvoviruses – Clinical Findings

A. Erythema Infectiosum (Fifth Disease)

B. Transient Aplastic Crisis: an abrupt cessation of RBC synthesis in the BM and is reflected in the absence of erythroid precursors in the BM, accompanied by a rapid worsening of anemia. It may complicate chronic hemolytic anemia, such as in patients with sickle cell disease, thalassemias, and acquired hemolytic anemias in adults.

C. Pure red cell aplasia: persistent infections with subsequent chronic suppression of BM resulting in chronic anemia in immunocompromised patients.

D. Congenital B19 infection

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Human Bocavirus Infections

Human bocavirus has been detected in 1.5% to 11.3% of respiratory tract samples from young children with respiratory infections.

It is prevalent among children with acute wheezing. However, bocavirus is often found in mixed infections with other viruses, so it remains unclear if bocavirus is the cause of acute respiratory disease in children.

The virus has been detected in about 3% of stool samples from children with acute gastroenteritis. Coinfection rates with other enteric pathogens were high, so any causative role of bocavirus in gastroenteritis is unknown.

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Parvoviruses – Diagnosis

- PCR (the most sensitive), probe hybridization of serum or tissue extracts, and in situ hybridization of fixed tissue.
- Serologic assays; Antigen detection assays; Immunohistochemistry.
- Virus isolation is not used to detect infection.
- The only assay currently available for human bocavirus is PCR.

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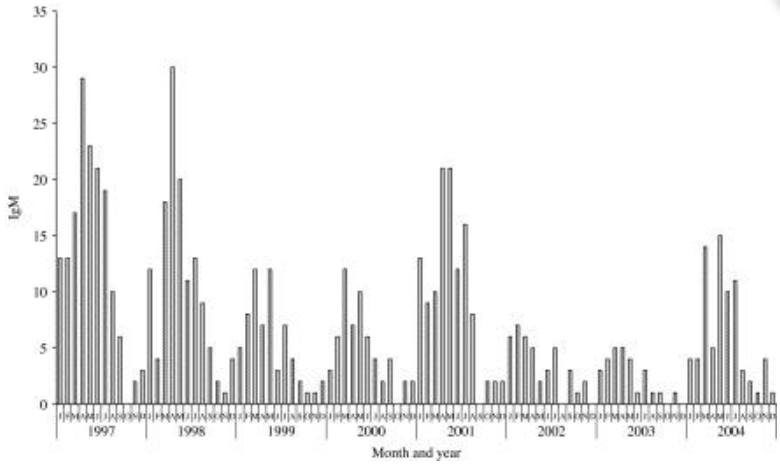
Parvoviruses – Epidemiology

Estimates of attack rates in susceptible contacts range from 20% to 50%



Source: *Enders M, Weidner A, Enders G. Current epidemiological aspects of human parvovirus B19 infection during pregnancy and childhood in the western part of Germany. Epidemiol Infect. 2007 May;135(4):563-9. doi: 10.1017/S095026880600731X. Epub 2006 Oct 26.*

Parvoviruses – Treatment, Prevention and Control

Symptomatic Rx (Tx)

There is no treatment for human bocavirus infections

There is no vaccine against human parvovirus

There is no antiviral drug therapy

Intravenous Immunoglobulin Therapy for Pure Red Cell Aplasia Related to Human Parvovirus B19 Infection: A Retrospective Study of 10 Patients and Review of the Literature

Yoann Crabol,[1] Benjamin Terrier,[1] Flore Rozenberg,[2] Vincent Pestre,[1] Christophe Legendre,[3] Olivier Hermine,[4] Catherine Montagnier-Petrissans,[5] Loïc Guillevin,[1] and Luc Mouthon[1]; for the Groupe d'experts de l'Assistance Publique-Hôpitaux de Paris

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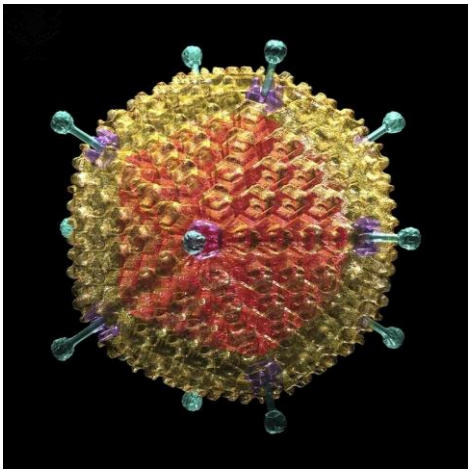
Adenoviruses – General Properties

Virion: Icosahedral, 70–90 nm in diameter, 252 capsomeres; fiber projects from each vertex
Composition: DNA (13%), protein (87%)
Genome: Double-stranded DNA, linear, 26–45 kbp, protein bound to termini, infectious
Proteins: Important antigens (hexon, penton base, fiber) are associated with the major outer capsid proteins
Envelope: None
Replication: Nucleus
Outstanding characteristic: Excellent models for molecular studies of eukaryotic cell processes



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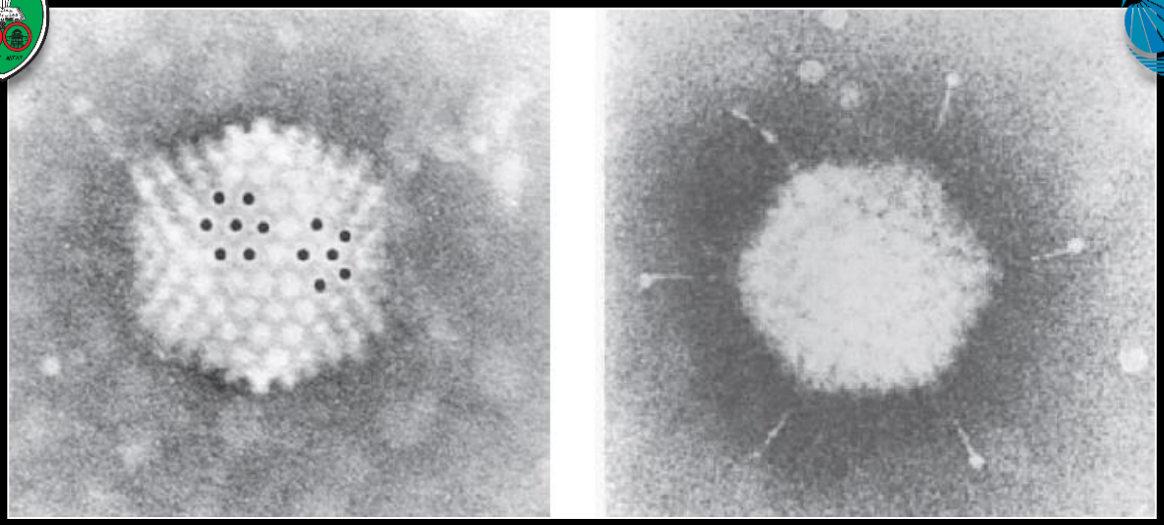

Electron micrographs of adenovirus

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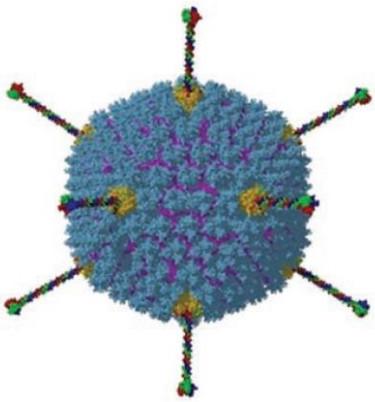
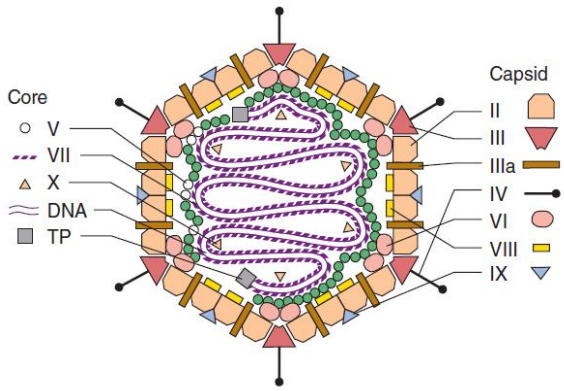
Models of the adenovirus virion





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Classification Schemes for Human Adenoviruses

Group	Serotypes	Hemagglutination		Percentage of G + C[a] in DNA	Oncogenic Potential	
		Group	Result		Tumorigenicity in Vivo[b]	Transformation of Cells
A	12, 18, 31	IV	None	48–49	High	+
B	3, 7, 11, 14, 16, 21, 34, 35, 50	I	Monkey (complete)	50–52	Moderate	+
C	1, 2, 5, 6	III	Rat (partial)	57–59	Low or none	+
D	8–10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51	II	Rat (complete)	57–61	Low or none[c]	+
E	4	III	Rat (partial)	57	Low or none	+
F	40, 41	III	Rat (partial)	57–59	Low or none	+

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Adenoviruses – Replication

1) Fiber attaches cellular receptors (e.g. coxsackie–adenovirus receptor, a member of the IgSF); the interaction of the penton base with cellular integrins promotes the internalization step
2) Adsorbed virus is internalized into endosomes; the majority of particles (~90%) move rapidly from endosomes into the cytosol (half-life ~5 minutes) facilitated by the acidic pH of the endosome
3) Uncoating starts in the cytoplasm and is completed in the nucleus, with release of the DNA
4) The steps that occur before the onset of viral DNA synthesis are defined as **early events**; initiated to induce the host cell to enter the S phase, to express viral evade mechanisms, and to synthesize viral gene products needed for viral DNA replication

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Adenoviruses – Replication

5) The E transcripts come from seven separated regions of the viral genome with synthesis of more than 20 early proteins, many of which are NS

6) The E1A early gene is important; it must be expressed for the other early regions to be transcribed

7) The E1B early region encodes proteins that block cell death (apoptosis); this is necessary to prevent premature cell death that would adversely affect virus yields

8) The E1A and E1B regions contain the only adenovirus genes involved in **cell transformation**; those gene products bind cellular proteins (e.g., pRb, p300, p53) that regulate cell cycle progression

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Adenoviruses – Replication

9) Viral DNA replication takes place in the nucleus. The virus-encoded, covalently linked terminal protein functions as a primer for initiation of viral DNA synthesis

10) Late events begin concomitantly with the onset of viral DNA synthesis. The major late promoter controls the expression of the late ("L") genes coding for viral structural proteins.

11) There is a single large primary transcript (~29,000 nucleotides in length) that is processed by splicing to generate at least 18 different late mRNAs.

12) A complex involving the E1B 55-kDa polypeptide and the E4 34-kDa polypeptide inhibits the cytoplasmic accumulation of cellular mRNAs

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Adenoviruses – Replication

13) Virion morphogenesis occurs in the nucleus. Each hexon capsomere is a trimer of identical polypeptides. The penton is composed of five penton base polypeptides and three fiber polypeptides

14) A late L4-encoded "scaffold protein" assists in the aggregation of hexon polypeptides but is not part of the final structure

15) Capsomeres self-assemble into empty-shell capsids in the nucleus. Naked DNA then enters the preformed capsid

16) A cis-acting DNA element near the left-hand end of the viral chromosome serves as a packaging signal, necessary for the DNA–capsid recognition event. Another viral scaffolding protein, encoded in the L1 group, facilitates DNA encapsidation.

17) Finally, precursor core proteins are cleaved "virus-encoded cysteine proteinas", which allows the particle to tighten its configuration, and the pentons are added

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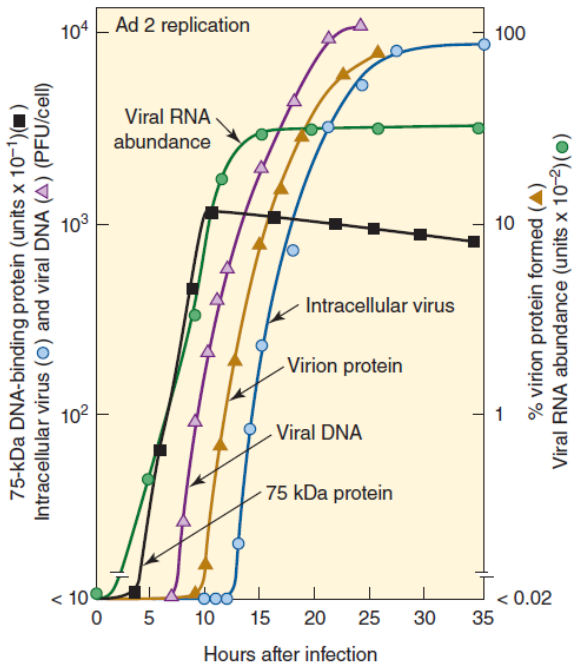
Time course of adenovirus replication cycle



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Adenoviruses – Replication

- The mature particle is then stable, infectious, and resistant to nucleases
- The adenovirus infectious cycle takes about 24 hours
- The small, abundant viral RNAs afford protection from the antiviral effect of interferon by preventing activation of an interferon-inducible kinase that phosphorylates and inactivates eukaryotic initiation factor 2
- Adenovirus E3 region proteins, which are nonessential for viral growth in tissue culture, inhibit cytolysis of infected cells by host responses. The E3 gp19-kDa protein blocks movement of MHC-I to the cell surface
- The cytopathic effect usually consists of marked rounding, enlargement, and aggregation of affected cells into grapelike clusters.
- Adenoviruses are not thought to be important in human cancer causation

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Adenoviruses – Pathogenesis

- Adenoviruses infect and replicate in epithelial cells of the respiratory tract, eye, gastrointestinal tract, and urinary tract.
- They usually do not spread beyond the regional lymph nodes.
- Group C viruses persist as latent infections for years in adenoids and tonsils and are shed in the feces for many months after the initial infection. In fact, the name "adenovirus" reflects the recovery of the initial isolate from explants of human adenoids.
- Most human adenoviruses replicate in intestinal epithelium after ingestion but usually produce subclinical infections rather than overt symptoms.

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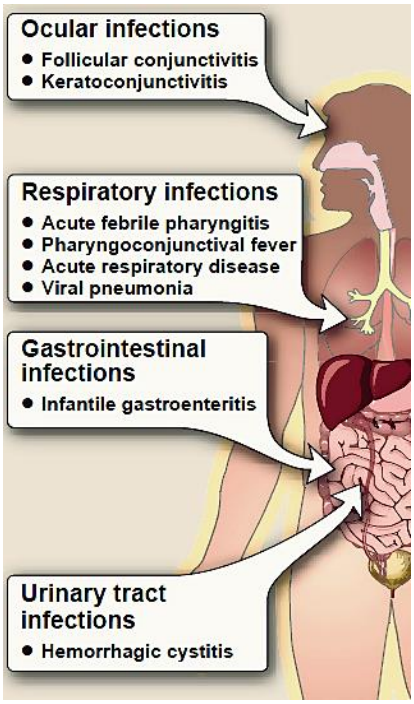
Adenoviruses – Clinical Findings

- About one-third of the known human serotypes are commonly associated with human illness.
- A single serotype may cause different clinical diseases and, conversely, that more than one type may cause the same clinical illness.
- Adenoviruses 1–7 are the most common types worldwide
- Adenoviruses are responsible for about 5% of acute respiratory disease in young children, but they account for much less in adults.
- Most infections are mild and self-limited.



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Adenoviruses – Clinical Findings

- In respiratory disease, typical symptoms include cough, nasal congestion, fever, and sore throat. This syndrome is most commonly manifested in infants and children
- Adenoviruses—particularly types 3, 7, and 21—are thought to be responsible for about 10–20% of pneumonias in childhood. Adenoviral pneumonia has been reported to have a mortality rate up to 10% in the very young
- Adenoviruses are the cause of an acute respiratory disease syndrome among military recruits (caused by types 4 and 7 and occasionally by type 3)
- Pharyngoconjunctival fever tends to occur in outbreaks, such as at children's summer camps ("swimming pool conjunctivitis"), and is associated with types 3 and 7. The duration of conjunctivitis is 1–2 weeks, and complete recovery with no lasting sequelae is the common outcome

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Adenoviruses – Clinical Findings

- A more serious disease is epidemic keratoconjunctivitis. It is caused by types 8, 19, and 37. This disease occurs mainly in adults and is highly contagious. Adenoviruses can remain viable for several weeks on sinks and hand towels, and these may be sources of transmission.
- The disease is characterized by acute conjunctivitis followed by keratitis that usually resolves in 2 weeks but may leave subepithelial opacities in the cornea for up to 2 years.
- Many adenoviruses replicate in intestinal cells and are present in stools, but the presence of most serotypes is not associated with gastrointestinal disease. However, two serotypes (types 40 and 41) have been etiologically associated with infantile gastroenteritis and may account for 5–15% of cases of viral gastroenteritis in young children.

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Adenoviruses – Clinical Findings

- Types 11 and 21 may cause acute hemorrhagic cystitis in children. Virus commonly occurs in the urine of such patients.
- In immunocompromised patients (transplant, AIDS) severe fatal pneumonia, hepatitis, myocardial infection, and severe GI disease

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Adenoviruses – Immunity
In contrast to most respiratory infectious agents, the adenoviruses induce effective and long-lasting immunity against reinfection
Maternal antibodies usually protect infants against severe adenovirus respiratory infections
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Adenoviruses – Laboratory Diagnosis

- Duration of adenovirus excretion varies among different illnesses: 1–3 days, throat of adults with common cold; 3–5 days, throat, stool, and eye, for pharyngoconjunctival fever; 2 weeks, eye, for keratoconjunctivitis; 3–6 weeks, throat and stool of children with respiratory illnesses; 2–12 months, urine, throat, and stool of immunocompromised patients.
- Virus culture can be done, Established human epithelial cell lines, such as HEp-2, HeLa, and KB, are sensitive but are difficult to maintain without degeneration for the length of time (28 days) required to detect some slow-growing natural isolates.

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Adenoviruses – Laboratory Diagnosis

- Infectious adenovirus detection may be made rapidly using the shell vial technique
- PCR assays are routinely used for diagnosis of adenovirus infections in tissue samples or body fluids, usually by using primers from a conserved viral sequence that can detect all serotypes
- PCR assays have been described that use single primer pairs that target conserved segments that bracket a hypervariable region in the hexon gene. The assays can detect all known serotypes of human adenoviruses, and sequencing of the amplicon allows serotype identification.

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Adenoviruses – Laboratory Diagnosis

- Hybridization or restriction endonuclease digestion patterns can identify an isolate as an adenovirus and group it.
- The fastidious enteric adenoviruses can be detected by direct examination of fecal extracts by electron microscopy, by enzyme-linked immunosorbent assay, or by latex agglutination test.
- Because adenoviruses can persist in the gut and in lymphoid tissue for long periods and because recrudescent viral shedding can be precipitated by other infections, the significance of a viral isolation must be interpreted with caution
- Fourfold or greater rise in complement-fixing antibody titer between acute-phase and convalescent-phase sera indicates recent infection with an adenovirus, but it gives no clue about the specific type involved

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Adenoviruses – Epidemiology

- Perennial mostly sporadic
- The most common serotypes: 1, 2, 3, 5, 7, 40 and 41
- Transmission via direct contact, fecal–oral route, by respiratory droplets, or contaminated fomites
- Many infections are subclinical
- Although adenoviruses cause only 2–5% of all respiratory illness in the general population, respiratory disease caused by types 3, 4, and 7 is common among military recruits

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Adenoviruses – Treatment, Prevention and Control

- There is no specific treatment for adenovirus infections
- Careful hand washing is the easiest way to prevent infections
- Disinfection of surfaces
- In group settings, paper towel use
- Chlorination of swimming pools and waste water
- Strict asepsis during eye examinations, coupled with adequate sterilization of equipment

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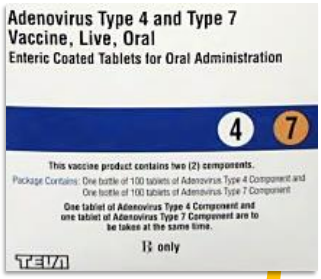
Adenoviruses – Treatment, Prevention and Control

- Attempts to control adenovirus infections in the military have focused on vaccines
- Live adenovirus vaccine containing types 4 and 7, encased in gelatin-coated capsules and given orally, was introduced in 1971
- Released in the intestine, where it replicates and induces neutralizing Ab
- It does not spread from a vaccinated person to contacts
- Stopped in 1999 and re-introduced in 2011; high efficacy



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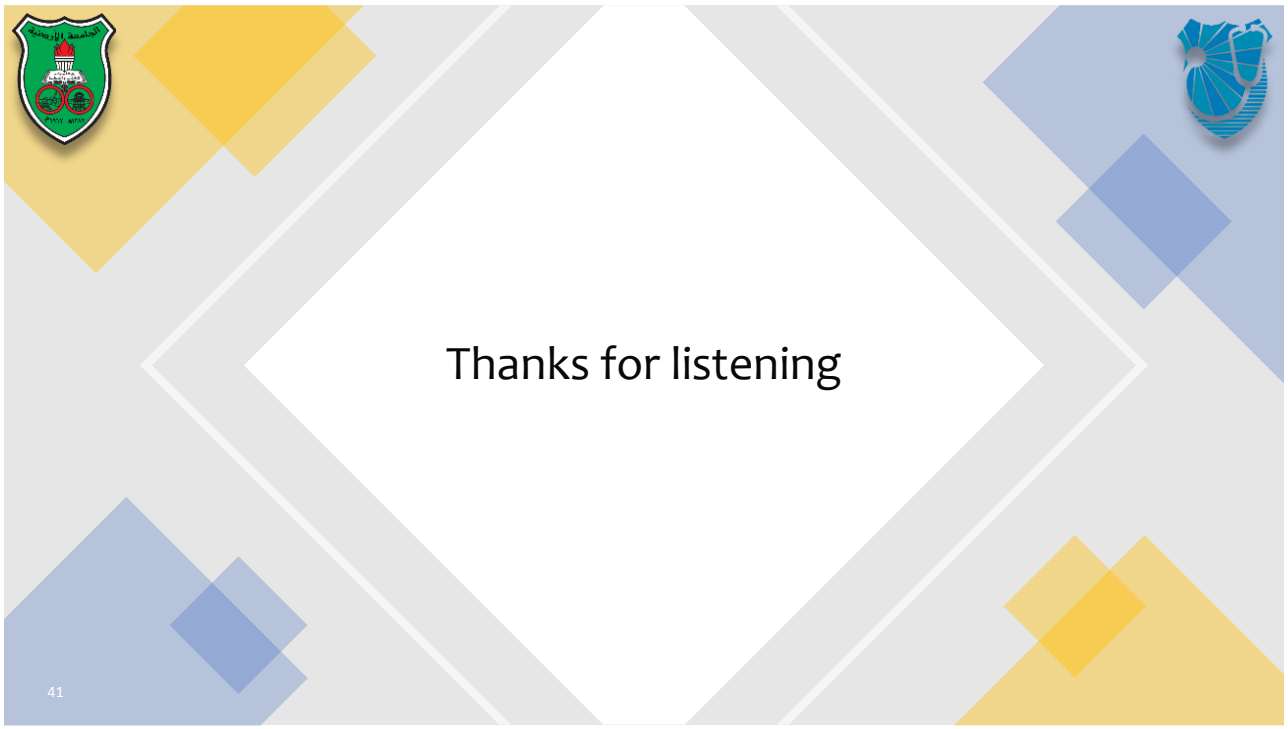

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