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*RESEARCH ARTICLE*

# ADENOVIRUS: EPIDEMIOLOGY, SPREAD OF NOVEL SEROTYPES AND IN ROLE WITH RESPIRATORY TRACT INFECTIONS

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## Abstract

Adenoviruses (AdVs) are the DNA viruses that can cause mild infections involving both upper or lower respiratory tract,gastrointestinal tract, or conjunctiva. Adenovirus plays a very notable role in respiratory tract disease in both pediatric and adult patients. It has been linked with outbreaks and epidemics in various patient populations, resulting in considerable morbidity and mortality. Fatality rates for severe untreated AdV pneumonia may exceed 50%. More than 50 serotypes of the AdV have been recognised. Different serotypes display different tissue tropisms that can correlate with the clinical manifestations of infection. In this paper, we discuss the epidemiology, pathogenesis,clinical presentation, respiratory tract illnesses and complications, and roles of diagnosis and potential treatment options. Treatment of AdV infections is controversial, as prospective, randomized therapeutic trials have not been conducted. Cidofovir is the drug of choice for severe AdV infections, but not all patients require treatment.The role of the past oral adenovirus vaccine and the military implications of its withdrawal from routine use in military recruits is discussed as well.



## Introduction:-

Adenoviruses are the DNA viruses those are responsible for varieties of human diseases that can affect the gastrointestinal tract, respiratory tract, and also the eye [1]. There are seven species of adenoviruses ,those categorized from A to G with their two subgroups [2, 3]. The classification of Adenovirus correlates with clinical presentation, epidemiological spread [4] and antigenic character, and also it can be identified by the genetic methods [5]. Species B, C, and E all are associated with the respiratory tract infections [6]

Adenovirus is an enigmatic pathogen in respiratory tract infections. For many years prior to its identification, it had the greatest impression on young, healthy men during initial weeks of their military basic training. It was the primary agent who is responsible for predictable outburst of acute respiratory illness in military recruits and was referred to as the “ARD syndrome” (acute respiratory disease of recruitssyndrome) [7].

Firstly Adenovirus was isolated from the adenoidal tissue and it was shown to have a unique cytopathic effect in the epithelial cell culture [8,9]. Since adenovirus initial isolation, further examination have led to isolation of the virus from a variety of tissue sites and in different clinical disease entities. This work has also help us to understand of the uniqueness of adenovirus life-cycle.

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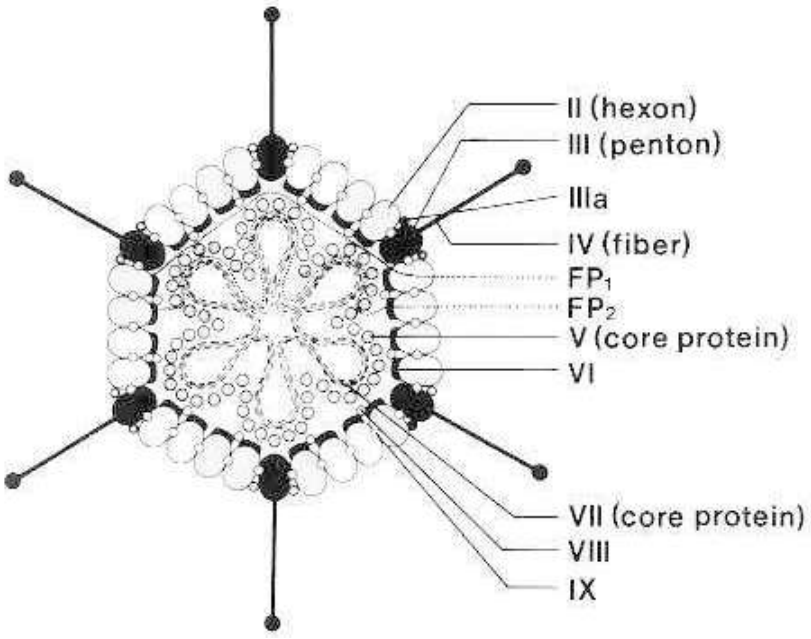
Currently, the most common noticeable clinical presentations of adenovirus infection are pneumonia,conjunctivitis, bronchitis/bronchiolitis, , pharyngoconjunctival fever, and upper respiratory tract infections or some common cold symptoms [8,9]. It has also been a conductive agent in epidemic outburst of conjunctivitis, acute lower respiratory tract infections, and febrile pharyngoconjunctival syndromes [7-9]. Six species of adenoviruses have also been associated which contain 51 serotypes [8,9]. Certain clinical presentations of the adenoviral respiratory tract infections are linked to some specific serotypes.

In this paper, we focus on the most clinically relevant serotypes that can cause respiratory tract infections. We also cover the pathogenesis of the virus, common clinical manifestations in the respiratory tract, their complications, and management in both pediatric and adult patients.

**Virus Structure**

The outer surface structure and genetic makeup of the virus play a critical role in its pathogenicity. The outer structure consists of a protein coat, called a capsid, which consists of hundreds of capsomeres [7].

The adenovirus particle basically made up of an icosahedral protein shell surrounding a protein core that contains the linear, double-stranded DNA genome (Fig. 1). The shell, which is 70 to 100 nm in diameter,that is consist of 252 structural capsomeres.




The 12 vertices of the icosahedron are settled by units called pentons, each of which has a slender projection called a fiber. The 240 capsomeres that make up the 20 faces and the edges of the isocahedron are called hexons because they form hexagonal arrays. The shell also contains some additional, minor polypeptide elements.

The core particle is made up of two major proteins (polypeptide V and polypeptide VII) and a minor arginine-rich protein (μ). A 55 kDa protein is covalently attached to the 5′ ends of the DNA.

In 2010, the structure of the human adenovirus was solved at the atomic level, making it the largest high-resolution model ever. The virus is composed ofaround 1 million amino acid residues and weighs around 150 MDa.

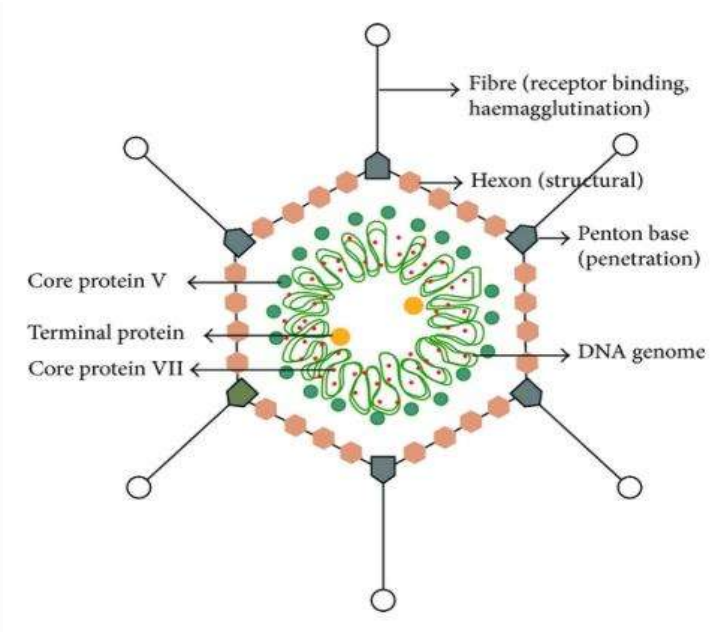



**Fig 1:-** Adeno virus structure & genome.

**Pathogenesis**

Hadv pathogenesis differs depending on the serotype,species and organ specificity and the disease patterns appear to occur within particular serotypes.(10) Adenovirus infections are divided into either localized to a single organ or can affect many organ systems, which may lead to spread disease, with mostly high morbidity and mortality rate.(11) The incubation period for Adenoviruses infection ranges from 2 to 21 days with an average of 7 to 13 days and the primary site of replication is the epithelial cells of the host gastrointestinal (GI) tract, respiratory tract, eyes, and urinary bladder.(7,12)

The family Adenoviridae consist of six subgroups—A, B, C, D, E, and F—which are further subdivided into 51 serotypes [8,9]. Some of those subgroups have been linked to different clinical syndromes, but more than half of the serotypes have not yet identified with a clinical disease process [14]. This is because adenovirus infections are responsible for three distinct types of infection of human cells: lytic infection, latent (chronic) infection, and oncogenic transformation of cells [8,9]. Adenovirus infect mucoepithelial cells in the respiratory trct,gastrointestinal tract, and conjunctiva or cornea, causing damage of these cells directly.

Only about 1% to 5% of the progeny are infectious and therefore able to continue the viral life-cycle. This lytic infection is responsible for most of the classic respiratory and enteric clinical illnesses [8,9]. Latent infection usually occurs in lymphoid tissue and results in a chronic, indolent infection, which is frequently asymptomatic and therefore hard to link to clinical disease. During this entire process, only a few viral particles are released, and the host tissues continue cell replication with minimal to no injury and therefore viral infection is sustained at a very low level in the host [8,9]. The last type of infection, oncogenic transformation, has been the main focus of adenoviral research, mostly because of its potential use in future gene therapy and other therapeutics. During this infection, the virus invades human cells and integrates into the cellular genome without production of infectious viral progeny. This may lead to a subsequent oncogenic transformation of the cell, without an acute clinical infection [7-9].

Oncogenic transformation is a unique feature of adenovirus that was initially noted by NIH investigators during their early research into the development of an adenovirus vaccine. During these studies, they found that the oncogenic simian virus 40 (SV40) could transform adenovirus 7 into a virus with oncogenic potential [7,8].

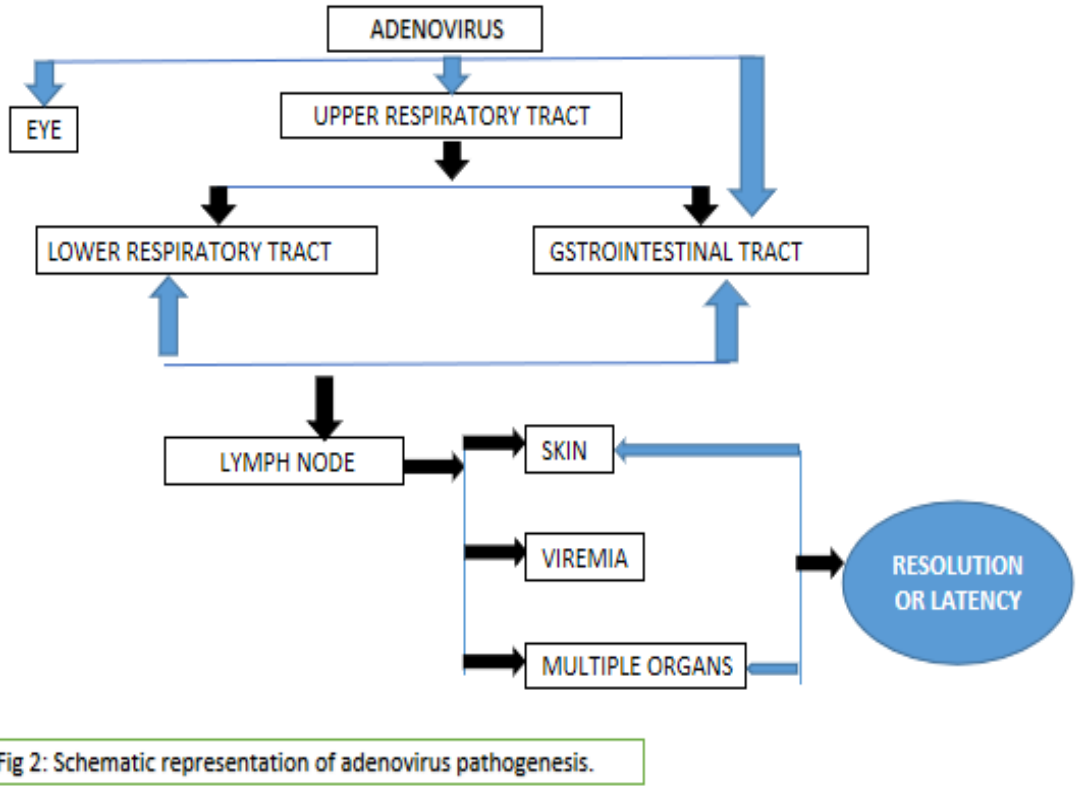



Fig 2: Schematic representation of adenovirus pathogenesis.

Human adenoviruses cause either lytic infection in the epithelial cells or the latent infection whichis takes place within the lymphoid cells (Ghebremedhin, 2014; Murali et al., 2014).(13,14) The lytic infection which is also called as viral reproduction cycle occurs when the Hadv enters the cells via ~120-nM clathrin-coated "pits and vesicles". Once in the cells, post internalization disruption of the early endosome occurs, favouring the virion to escape from the cytoplasm to the nucleus before destruction by lysosomal proteases. Then it replicates inside the nucleus of the host cell (human epithelial cells).(12,15) The virus can also inhibit the macromolecular synthesis and transport of messenger RNA (mRNA) from the nucleus to the cytoplasm of the host cell, thus facilitating host cellular death and cell lysis. After the virus actively replicates inside the host cell, it causes cellular death and cell lysis. Furthermore, the production of virions results in a host inflammatory response. Hadv can persist in susceptible cells in a latent state for long after lytic infection.(15-17) In the latent mode of infection, human adenoviruses generally remain in lymphoid organs, such as adenoids, tonsils, or Peyer's patches.(12,15,18) The virus-mediated tissue damage results from direct cytotoxicity of the virus, but it can also occur due to the inflammatory cell infiltrate.(19) These latent virus particles can eventually "re-activate, re-infect", and replicate in epithelial cells, causing disease symptoms again.(15)

**Clinical Presentation**

Earlier it is mentioned that, some serotypes and subgroups have been linked to different clinical presentations and vary by their age. Most of the primary infections with adenovirus generally occur during infancy and early childhood (8,20). Serotypes 1, 2, 5, and 6 have been isolated from the lymphoepitheial and nasopharyngeal tissue of children, and have been linked to very low-grade infection (likely from latent replication) (20). Serotypes 3, 4, and 7 mainly and many more serotypes have been linked to acute upper and lower respiratory tract infections in children as well as adults (8,20).

The usual clinical presentation includes upper respiratory symptoms, rhinorrhea, pharyngitis, fevers, conjunctivitis, and cough, with lower respiratory tract symptoms (8). The severity and extent of the clinical symptoms depend on the both of the serotype and clinical syndrome (8,20). The usual incubation period ranges from 5 to 6 days, but can

take as long as 10 days (8,20). The usual complications associated with lower respiratory tract symptoms are bacterial pneumonia, effusion, and superinfected bacterial empyema (8).

More recently, reports have been published of severe adenoviral respiratory infections associated with acute respiratory distress syndrome (ARDS) in immunocompetent adults (21). Table 1 lists the most common respiratory clinical syndromes and their associated serotypes in different age groups.

**Table 1:-** Adenovirus serotypes associated with clinical syndromes in different age groups.

| GROUP AFFECTED | DISEASE | ADENOVIRUS SEROTYPES |
|---|---|---|
| Neonates | Fatal disseminated infection | 3,7,21,30 |
| Infants | Coryza,pharyngitis (most asymptomatic) | 1,2,5 |
| Children | Upper respiratory disease | 1,2,4-6 |
| | Lower respiratory tract infection | 3, 4, 7, 14, 21, 35 |
| | Pharyngoconjunctival fever | 3,7 |
| | Haemorrhagic cystitis | 11,21 |
| | Diarrhoea | 2,3,5,40,41 |
| | Intussuception | 1,2,4,5 |
| | Meningoencephalitis | 2,6,7,12 |
| Young Adults | Acute respiratory disease and pneumonia | 3,4,7 |
| Adults | Epidemic keritoconjunctivitis | 8,19,37 |
| Immunocompromised | Pneumonia with dissemination, urinary tract infection | 5,31,34,35,39,42-47 |
| | CNS disease including encephalitis | 7,12,32 |

**Upper and Lower Respiratory Tract Infections**

Acute lower respiratory tract infections (ALRTIs) are the leading cause of morbidity and mortality worldwide, particularly in developing countries. Human adenovirus (HAdV), plays a significant role in respiratory tract infections, accounting for 2–5 % of the overall respiratory illnesses and 4–10 % of the pneumonias (22,23). Although most of the cases are mild and indistinguishable from other viral causes, ALRTIs caused by HAdV can be severe, or even fatal, and all are associated with the highest risk of long term respiratory sequelae (24). Thus, HAdV-associated ALRTIs are of particular interest to both of the clinicians and the researchers.

HAdV are responsible for a wide spectrum of clinical diseases, including respiratory illness (both upper and lower respiratory tract), pharyngoconjunctival fever, conjunctivitis, cystitis, gastroenteritis, and neurologic and venereal disease (25). HAdV were first isolated in 1953 as respiratory pathogens.(26,27)

**Pharyngoconjunctival fever**

Pharyngoconjunctival fever (PCF) is an acute and highly infectious illness that is characterized by fever, pharyngitis, acute follicular conjunctivitis, and also regional lymphoid hyperplasia with tender, enlarged preauricular adenopathy.

Adenoviruses are the most common cause of acute viral infections of the conjunctiva, occurring epidemically or sporadically throughout all seasons. Clinically, 4 syndromes of adenoviral ocular infection have been recognized, as follows: epidemic keratoconjunctivitis, pharyngoconjunctival fever (PCF), nonspecific sporadic follicular conjunctivitis, and chronic papillary conjunctivitis.(28,29)

A condition that caused by a virus, pharyngoconjunctival fever is highly contagious, especially during the first few days. After 10 or 15 days the communicability is almost zero. The incubation period of this virus is 5-12 days and people suffering from it can have a fever for up to ten days. Children between the ages of 5 and 18 are most susceptible to the condition.(28,29) Kids attending summer camps often pass it around, and it is especially rampant during the spring and fall seasons in schools. It is often spread by kids swimming in public swimming pools.

The conjunctivitis associated with this syndrome is usually self-limited, resolving within a few days. It rarely leads to keratitis or other ophthalmologic sequela (29).

**Epidemic Keratoconjunctivitis**

Epidemic keratoconjunctivitis (EKC) is a viral conjunctivitis that is caused by a group of adenoviruses. (30) This family of adenoviruses contains different types of serotypes, can also cause pharyngoconjunctival fever and nonspecific follicular conjunctivitis. EKC is highly contagious and has a tendency to occur in epidemics. It has been reported worldwide. (30)

Infants and neonates tend to present with conjunctival injection, increased lacrimation, and periorbital edema. The most common serotypes those are associated with EKC are 8, 19, and 37 (30-33). More recently, the adenovirus 22/H8, a new hybrid adenovirus, that is associated with EKC among patients who were examined with contaminated ophthalmologic equipment (30-33).

As a result, there has been greater focus on the early identification of those infections via polymerase chain reaction (PCR) and/or direct florescent antigen testing, and early and effective isolation and infection-control methods for all identified patients . The incubation period for EKC is almost 4 to 24 days, and the usual course is a self-limited illness (31-34). In some cases, it may progress to a deeply established keratitis, which can persist for months and that can lead to visual disturbances or significant corneal damage (34).

**Diagnosis**

Laboratory diagnosis is available for detection of adenovirus. These are particularly useful for detecting and preventing large outbreaks.

Some of the laboratory diagnostic techniques include:-

**Antigen detection**

The adenovirus, like other viruses, contains numerous proteins on its surface. Within the body these act as antigens against which several antibodies are formed. This helps the body to fight off an adenovirus infection. For example, the core of the particle contains at least 4 proteins called the TP (Terminal Protein), V, VII and Mu, a small protein.

**Polymerase chain reaction assay**

These can be used to identify the viral nuclear material or the viral DNA. Adenovirus has a double stranded linear DNA genome of length 36-40 kilo basepairs (kbp).

**Virus isolation**

The intact adenovirus particles may be isolated from samples of mucous, stool, blood and urine of an infected person. Once isolated the virus is usually types into subgroups and types. Virus isolation may also require virus cell cultures. Adenovirus typing is usually done by hemagglutination-inhibition and neutralization with type-specific antisera or by molecular methods.

**Serology tests**

These tests utilize measures to assess the levels of the antibodies that have been generated against an active infection with adenovirus.

However in real-time PCR has a much higher sensitivity and provides results within 1 to 2 days maximum(35,36). The rapidity of real-time PCR is extremely helpful in the clinical setting, especially in outbreaks and epidemics. Recently, Metzgar et al. (37) described that the increased utility of real-time PCR, especially in detection of pathogenic serotype 14. Their study showed that PCR had a higher sensitivity and specificity for serotype 14, with no known cross-reactivity with the other respiratory viral pathogens (37).

**Treatment**

There aren't any specific treatments for adenovirus infections. Most of the infections are mild and require only symptom relief. You can relieve most symptoms with over-the-counter fever reducers and pain relievers. In addition, make sure to drink plenty of water and get plenty of rest.

Antiviral medications aren't useful for treatment in people with healthy immune systems. Antibiotics won't work on an adenovirus.

Currently, cidofovir is the only recognized and well-studied antiviral agent that has shown some success in adenoviral respiratory tract infections. It is commonly used, with moderate success, in immunocompromised patients with acute adenoviral infection (39). In a previous outbreak of serotype 14cidofovir was tried in some patients and resulted in variable success. Not all patients who were hospitalized received cidofovir; however, of the six who did, four survived their infection (38). The major limitation of cidofovir therapy is the high risk of nephrotoxicity, which limits its use and duration of therapy, especially in high-risk or immunocompromised patients (39).

**Prevention**

Prevention of adenovirus infection relies on healthy habits applicable for prevention of most viral infections. These measures include:-

1. Hand washing before and after eating or handling material used by an infected person. Alcohol-based hand sanitizers may be used frequently if hands are not visibly dirty.
2. Eyes, nose or mouth should not be touched using contaminated hands or fingers.
3. Covering mouth and nose with a tissue when coughing or sneezing helps prevent spread of the virus.
4. Isolation and avoidance of work or school when ill with a cold or viral infection.
5. Keeping swimming pools adequately chlorinated.
6. Avoiding sharing towels and utensils etc. with an infected person. Avoidance of close contact with a person ill with adenovirus infection.

## Conclusion:-

The impact of these outbreaks led to the development of the first oral live-attenuated adenovirus vaccine. This vaccine resulted in a significant decrease in both epidemics and outbreaks, especially among military recruits (7,42,44). However, since production of the vaccine ceased in the late 1990s, we have seen an increase of more serotypes in this population, resulting in high levels of morbidity and mortality (43). Adenovirus has also been implicated as a major pathogen in immunocompromised individuals and is notorious for causing outbreaks in hospital and clinical settings (38,40,41). The impact of this virus on the population, in particular among military recruits, has led to recent efforts to produce a new live-oral adenovirus vaccine, which is currently completing clinical trials (45).

## Reference:-

1. Rubin BA. Clinical picture and epidemiology of adenovirus infections a review. Acta Microbiol Hung 1993; 40(4): 303-23.
2. Hage E, Gerd Liebert U, Bergs S, Ganzenmueller T, Heim A. Human mastadenovirus type 70: A novel, multiple recombinant species D mastadenovirus isolated from diarrhoeal faeces of a haematopoietic stem cell transplantation recipient. J Gen Virol 2015; 96(9): 2734-42.
3. Espínola EE, Barrios JC, Russomando G, Mirazo S, Arbiza J. Computational analysis of a species D human adenovirus provides evidence of a novel virus. J Gen Virol 2017; 98(11): 2810-20.
4. Sambrook J, Sleigh M, Engler JA, Broker TR. The evolution of the adenoviral genome. Ann N Y Acad Sci 1980; 354: 426-52.
5. Lin LH. Adenovirus pneumonia complicated with acute respiratory distress syndrome: A case report. Medicine (Baltimore) 2015; 94(20)e776
6. Scott MK, Chommanard C, Lu X, et al. Human adenovirus associated with severe respiratory infection, Oregon, USA, 2013-2014. Emerg Infect Dis 2016; 22(6): 1044-51.
7. Woodward TE: The Armed Forces Epidemiological Board: Its First Fifty Years. Falls Church, VA: Center of Excellence in Military Medical Research and Education, Office of the Surgeon General, Department of the Army; 1994.
8. Mandell GL, Bennett JE, Dolin R: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, edn 7. Philadelphia: Elsevier; 2009.
9. Rowe WP, Huebner RJ, Gillmore LK, et al.: Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. Proc Soc Exp Biol Med 1953, 84:570–573.
10. Radke, J R, Yong, S L & Cook, J L . 2015. Low-level expression of the E1B 20-kilodalton protein by adenovirus 14p1 enhances viral immunopathogenesis. J Virol 90(1):497–505.
11. Echavarría, M . 2008. Adenoviruses in immunocompromised hosts. Clin Microbiol Rev 21(4):704–715.
12. Kuss, S K, Best, G T & Etheredge, C A . 2011. Intestinal microbiota promote enteric virus replication and

systemic pathogenesis. Science 334(6053):249–252.
13. Ghebremedhin, B . 2014. Human adenovirus: Viral pathogen with increasing importance. Eur J Microbiol Immunol (Bp) 4(1):26–33.
14. Murali, V K, Ornelles, D A, Gooding, L R, Wilms, H T, Huang, W, Tollefson, A E, Wold, W S & Garnett-Benson, C . 2013. Adenovirus death protein (ADP) is required for lytic infection of human lymphocytes. J Virol 88(2):3911668.
15. Crenshaw, B J, Jones, L B, Bell, C R, Kumar, S & Matthews, Q L . 2019. Perspective on adenoviruses: Epidemiology, pathogenicity, and gene therapy. Biomedicines 7(3):61.
16. Kamel, W, Segerman, B, Öberg, D, Punga, T & Akusjärvi, G . 2013. The adenovirus VA RNA-derived miRNAs are not essential for lytic virus growth in tissue culture cells. Nucleic Acids Res 41(9):4802–4812.
17. Lion, T . 2014. Adenovirus infections in immunocompetent and immunocompromised patients. Clin Microbiol Rev 27(3):441–462.
18. Furuse, Y, Ornelles, D A & Cullen, B R . 2013. Persistently adenovirus-infected lymphoid cells express microRNAs derived from the viral VAI and especially VAII RNA. Virology 447(1-2):140–145.
19. Ruuskanen, O, Metcalf, J P, Meurman, O & Akusjärvi, G . 2009. Adenoviruses. In: D.D. Richman, Whitley, R.J. & Hayden, F.J. , eds. Clinical Virology. (pp. 559-574) Washington, DC: American Society for Microbiology
20. Brandt CD, Kim HW, Vargosko AJ, et al. Infections in 18,000 infants and children in a controlled study of respiratory tract disease. I. Adenovirus pathogenicity in relation to serologic type and illness syndrome. Am J Epidemol. 1969;90:484–500
21. Hakim FA, Tleyjeh IM. Severe adenovirus pneumonia in immunocompetent adults: a case report and review of the literature. Eur J Clin Microbiol Infect Dis. 2008;27:153–158. doi: 10.1007/s10096-007-0416-z.
22. Cherry JD: Textbook of pediatric infectious diseases. 1988, Philadelphia: WB Saunders, 4
23. Robinson CM, Singh G, Henquell C, Walsh MP, Peigue-Lafeuille H, Seto D, Jones MS, Dyer DW, Chodosh J: Computational analysis and identification of an emergent human adenovirus pathogen implicated in a respiratory fatality. Virology. 2010, 409 (2): 141-147.
24. Jones MS, Harrach B, Ganac RD, Gozum MM, Dela Cruz WP, Riedel B, Pan C, Delwart EL, Schnurr DP: New adenovirus species found in a patient presenting with gastroenteritis. J Virol. 2007, 81 (11): 5978-5984. 10.1128/JVI.02650-06.
25. Kaneko H, Iida T, Ishiko H, Ohguchi T, Ariga T, Tagawa Y, Aoki K, Ohno S, Suzutani T: Analysis of the complete genome sequence of epidemic keratoconjunctivitis-related human adenovirus type 8, 19, 37 and a novel serotype. J Gen Virol. 2009, 90 (Pt 6): 1471-1476.
26. Walsh MP, Chintakuntlawar A, Robinson CM, Madisch I, Harrach B, Hudson NR, Schnurr D, Heim A, Chodosh J, Seto D, et al: Evidence of molecular evolution driven by recombination events influencing tropism in a novel human adenovirus that causes epidemic keratoconjunctivitis. PLoS One. 2009, 4 (6): e5635-10.1371/journal.pone.0005635.
27. Walsh MP, Seto J, Jones MS, Chodosh J, Xu W, Seto D: Computational analysis identifies human adenovirus type 55 as a re-emergent acute respiratory disease pathogen. J Clin Microbiol. 2010, 48 (3): 991-993. 10.1128/JCM.01694-09.
28. Aronson B, Aronson S, Sobel G, et al. Pharyngoconjunctival fevers; report of an epidemic outbreak. AMA J Dis Child. 1956;92:596–612.
29. Bell JA. Clinical manifestation of pharyngoconjunctival fever. Am J Opthalmol. 1957;43:11–14.
30. Chaberny IE, Schnitzler P, Geiss HK, Wendt C. An outbreak of epidemic keratoconjunctivitis in a pediatric unit due to adenovirus type 8. Infect Control Hosp Epidemiol. 2003;24:514–519.
31. Buffington J, Chapman LE, Stobierski MG, et al. Epidemic keratoconjunctivitis in a chronic care facility: risk factors and measures for control. J Am Geriatr Soc. 1993;41:1177–1181.
32. Usui N, Ookoshi H, Mori H, et al. Clinical features of epidemic keratoconjunctivitis in 41 patients. Nippon Ganka Gakkai Zasshi. 2001;105:183–188.
33. Engelmann I, Madisch I, Pommer H, Heim A. An outbreak of epidemic keratoconjuctivitis caused by a new intermediate adenovirus 22/H8 identified by molecular typing. Clin Infect Dis. 2006;43:e64–e66. doi: 10.1086/507533.
34. Murrah WF. Epidemic keratoconjunctivitis. Ann Ophthalmol. 1988;20:36–38.
35. Damen M, Minnaar R, Glasius P, et al. Real-time PCR with an internal control for detection of all known human adenovirus serotypes. J Clin Microbiol. 2008;46:3997–4003. doi: 10.1128/JCM.00563-08.
36. Wong S, Pabbaraju K, Pang XL, et al. Detection of a broad range of human adenoviruses in respiratory tract samples using a sensitive multiplex real-time PCR assay. J Med Virol. 2008;80:856–865. doi: 10.1002/jmv.21136.
37. Metzgar D, Skochko G, Gibbins C, et al. Evaluation and validation of a real-time PCR assay for detection and

quantitation of human adenovirus 14 from clinical samples. PLoS One. 2009;4:e7081.
38. Lewis PF. Schmidt MA, Lu X, et al.: A community-based outbreak of severe respiratory illness caused by human adenovirus serotype 14. J Infect Dis May. 2009;199:1427–1434. doi: 10.1086/598521
39. Legrand F, Berrebi D, Houhou N, et al. Early diagnosis of adenovirus infection and treatment with cidofovir after bone marrow transplantation in children. Bone Marrow Transplant. 2001;27:621–626. doi: 10.1038/sj.bmt.1702820
40. Leen AM, Rooney CM. Adenovirus as an emerging pathogen in immunocompromised patients. Br J Haematol. 2005;128:135–144. doi: 10.1111/j.1365-2141.2004.05218.x.
41. Kojaoghlanian T, Flomenberg P, Horwitz MS. The impact of adenovirus infection on the immunocompromised host. Rev Med Virol. 2003;13:155–171. doi: 10.1002/rmv.386.
42. Top FH, Dudding BA, Russell PK, et al. Control of respiratory disease in recruits with types 4 and 7 adenovirus vaccines. Am J Epidemiol. 1971;94:142–146.
43. Russell KL, Hawksworth AW, Ryan MAK, et al. Vaccine-preventable adenoviral respiratory illness in US military recruits, 1999–2004. Vaccine. 2006;24:2835–2842. doi: 10.1016/j.vaccine.2005.12.062.
44. Hilleman MR. Efficacy of and indications for use of adenovirus vaccine. Am J Public Health Nations Health. 1958;48:153–158. [PMC free article] [PubMed]
45. Lyons A, Longfield J, Kuschner R, et al. A double-blinded, placebo-controlled study of the safety and immunogenicity of live, oral type 4 and type 7 adenovirus vaccines in adults. Vaccine. 2008;26:2890–2898. doi: 10.1016/j.vaccine.2008.03.037.