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## Review Article: Special Edition

# Human adenovirus infections in pediatric population - An update on clinico–pathologic correlation



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## ABSTRACT

Human adenoviruses can cause infections at any age but most commonly in pediatric population, especially in young children and infants. By the time of 10 years old, most children have had at least one episode of adenovirus infection. Adenoviruses can cause many symptoms similar to common cold, including rhinorrhea, fever, cough, and sore throat. Lower respiratory infections such as bronchitis, bronchiolitis, and pneumonia can be severe and even fatal. Other diseases such as conjunctivitis, gastroenteritis, cystitis, myocarditis, cardiomyopathy, and meningoencephalitis can also be associated with adenovirus infections. A variety of recent advancement of structural and molecular biology methods have revamped the taxonomy of adenoviruses and furthered our understanding of the diversity of related clinical diseases. Because of the wide spectrum and complexity of diseases associated with human adenovirus infections, the scope of this review is limited to basic virology and epidemiology of adenoviruses with a main focus on the clinico–pathologic correlation. Clinical manifestations and pathology of any infectious disease are always related; therefore, it is logical to review clinico–pathologic correlation within the specific disease entity caused by adenoviruses to better understand this common viral infection in pediatric population.

## Virology

Human adenoviruses (HAdVs) are members of the Adenoviridae family. The name derives from the initial isolation of the virus from human adenoids in 1953 [1]. Adenoviruses are

medium-sized (70–100 nm), nonenveloped viruses with an icosahedral nucleocapsid containing a double-stranded linear DNA genome 34–36 kbp length [Fig. 1A]. The icosahedral shell is composed primarily of 240 capsomeres of hexon trimers, 12 pentameric penton capsomeres at each vertex of the icosahedron, and 12 fibers extending from the pentons [Fig. 1B]. The

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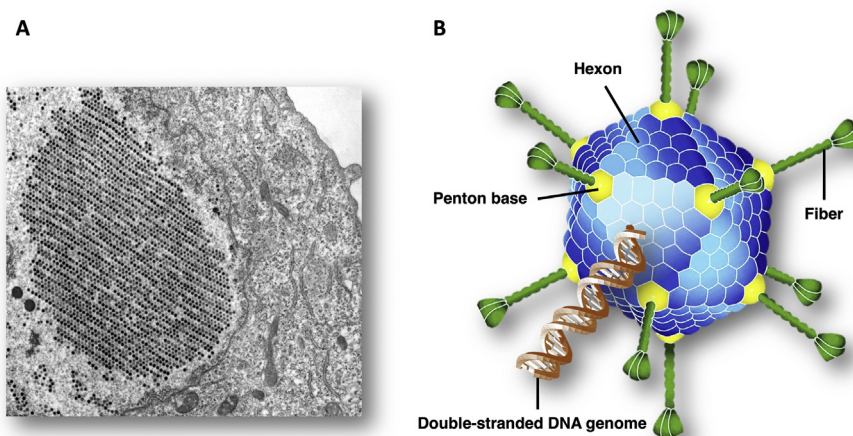


Fig. 1 (A) Transmission electron micrograph with an ultra-thin section of an adenovirus-infected cell showing adenoviruses replicate in the nucleus of cells and form intranuclear paracrystalline arrays of 70–90 nm adenovirus particles. (B) Structure of adenovirus virion. Non-enveloped capsid with an icosahedral symmetry and nucleocapsid containing a double-stranded linear DNA genome. The icosahedral shell is composed of 240 capsomeres of hexon trimers (12 per triangular facet of the icosahedron), 12 pentameric penton capsomeres at each vertex, and 12 fibers extending from the pentons.

hexon has been established to carry the antigen specificity markers  $\alpha$  and  $\epsilon$  with group, subgroup and type-specific immunogenicity and neutralization [2]. The penton base carries  $\beta$  epitope and reacts as a minor group-specific antigen. It has been associated with cellular toxicity and interacts with the inner surface of endosomes during disruption of internalized vesicles [3]. The fiber contains a major antigen,  $\gamma$ , and is responsible for type specificity, cell attachment, and hemagglutination [2]. Because of their important roles in cell entry and establishment of host infection, these structural proteins are crucial in the pathogenesis of HAdV infections. HAdVs bind to cell surface receptors and trigger internalization by endocytosis [4]. Viral messenger RNA transcription, genomic replication, and progeny virion particles assemble all occur in the nucleus [5]. The infected cells will subsequently lyse and release viral particles. The replication process and cellular lysis of HAdV infection produce unique cytopathologic features, which will be described later.

Advances in structural biology methods (such as cryo-electron microscopy), availability of novel techniques (such as atomic force microscopy), and discovery of new viruses have resulted in notable advances in our understanding of the adenovirus particle organization and its variations throughout the different species and genera [6,7]. Currently, there are 104 different HAdV types known, which have been classified into seven species A to G based on the percentage of guanine plus cytosine in their DNA and other biochemical and biophysical criteria [8] [Table 1]. Types were exclusively defined as serotypes up to Ad51. A genotype definition was mostly used for newer types, which requires either novel sequences or recombinant phylogeny in genes coding for major capsid proteins [9]. The majority of HAdV types belong to species D (73 types) followed by species B (16 types), and new adenovirus types continue to emerge.

HAdVs use distinct cellular receptors for attachment and internalization. Initial attachment of HAdVs in species A, C, D, E, and F (but not species B) is mediated by high-affinity binding

of the fiber knob domain to the host-cell transmembrane CAR protein (coxsackie B, adenovirus receptor), which is abundantly expressed in a variety of tissues [10]. In contrast to other HAdV species, fiber knobs in the B species and species D Ad37 bind CD46, a regulator of the complement cascade present on the plasma membrane of most cell types, including hematopoietic cells [11,12].

HAdV species C is known for its ability to establish persistence and latent infections in lymphoid organs such as tonsils and adenoids [13]. Ad5 is a member in species C and has been widely used as a recombinant, non-replicative vector for vaccine development [14,15], including the recent COVID-19 vaccine formulations [16,17]. Adenoviruses are considered excellent vectors for vaccine development or cancer therapy because they can deliver target antigens to mammalian hosts efficiently with the following properties: 1) They contain a relatively large-sized and well-defined genome for genetic manipulation; 2) The risk of insertion mutagenesis is much less than other viral vectors, such as retrovirus, because adenoviruses do not integrate the viral genome within the host genome; 3) They can grow to high titers with higher thermostability, and can be easily applied through systemic or respiratory routes; 4) They are capable of infecting a wide range of cells due to their broad tissue and cellular tropism; 5) They induce strong and sustained innate and adaptive immune responses, including both CD4<sup>+</sup> T cell and CD8<sup>+</sup> T cell-mediated immune responses; 6) Certain types, such as Ad5, cause asymptomatic or mild infections in humans and their replication can be inhibited by genetic modifications.

AdV-based vaccines are generally safe with very few adverse effects. However, there are still possible side effects associated with AdV-based vaccines. For example, the capability of Ad5 vectors to sequester platelets has been previously demonstrated, which can cause temporary thrombocytopenia [18]. Recombinant Ad5 can activate platelets via binding the platelets CD62 and increases D-dimer for at least 6 h following Ad5 introduction. Despite such evidence, the rate of

**Table 1 Human adenovirus classification, associated clinical diseases, epidemiologic features, seroprevalence and distribution.**

Species	Types	Clinical Diseases	Epidemiologic Features	Seroprevalence and Distribution <sup>a</sup>
A	12, 18, 31, 61	Gastroenteritis	Rare cause of gastroenteritis in children	<b>Ad31:</b> 73% in Belgium
B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66, 68, 76-79	*Conjunctivitis §Acute respiratory diseases Common cold Bronchitis Bronchiolitis Pneumonia †Hemorrhagic cystitis †Meningoencephalitis †Myocarditis †Gastroenteritis	*Outbreaks of conjunctivitis due to inadequate chlorination of swimming pools; transmission via swimming or swallowing water §Third most common cause of viral respiratory infection in children under the age of 4 years; transmitted via aerosols or direct contact †Relatively rare and sporadic occurrence	<b>Ad3:</b> 90–100% in the USA; 69% in Belgium; 18% in Germany; 80% in Southern China; 40–73% in Singapore; 42–62% in Japan <b>Ad7:</b> 26–78% in the USA; 38% in Belgium; 13–86% in China; 3–13% in Japan; 7–31% in Singapore <b>Ad11:</b> 3–18% in the USA; 6–22% in Europe; 16–40% in Sub-Saharan Africa; 18–30% in Japan <b>Ad14:</b> 25% in China; 51–56% in North and South America; 17% in Belgium <b>Ad35:</b> 7–22% in the USA; <10% in Europe; 2% in Japan; 17% in Thailand, 19–41% in South America; 3–22% in Sub-Saharan Africa <b>Ad50:</b> 4% in Belgium; 19% in Sub-Saharan Africa <b>Ad55:</b> 22% in China; 19–49% in South Korea
C	1, 2, 5, 6, 57, 89, 104	* Respiratory infections §Intussusception in infants †Symptomatic respiratory infections and hepatitis in immunosuppressed patients	*Endemic respiratory infections in early childhood; usually mild §Sporadic intussusception in infants; equivocal association with oral vaccines †Relatively rare and sporadic occurrence	<b>Ad1:</b> 15–55% in the USA; 75% in Belgium <b>Ad2:</b> 36–61% in the USA; 63% in Belgium; 45% in Germany; 60–92% in China <b>Ad5:</b> 30–70% in the USA; 50–60% in Europe; 48–66% in Japan; 64–80% in China; 70–80% in Brazil; nearly 100% in northern India; 82–94% in Thailand <b>Ad6:</b> 36–46% in the USA; 38–52% in Europe; 67–78% in Sub-Saharan Africa; 79% in Thailand; 12–28% in China
D	8-10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51, 53, 54, 56, 58–60, 62–65, 67, 69–75, 80–88, 90-103	*Epidemic keratoconjunctivitis Gastroenteritis in AIDS patients	*Outbreak of epidemic keratoconjunctivitis in children; transmitted via direct contact, fomites, tonometry, instruments and solutions used in ophthalmology	<b>Ad26:</b> 8–15% in the USA; 3–7% in Europe; 44% in Brazil; 55–61% in Thailand; 35% in China; 21–88% in Sub-Saharan Africa <b>Ad28:</b> 2–17% in the USA; 6% in Belgium <b>Ad36:</b> 5% in the USA; 48–92% in Sub-Saharan Africa; 35% in Thailand <b>Ad48:</b> 3–12% in the USA; 5% in Belgium; 3–50% in Sub-Saharan Africa; 13% in Thailand <b>Ad49:</b> 6% in the USA; 9% in UK; 8% in Belgium; 22% in Sub-Saharan Africa; 9% in Japan
E	4	Acute respiratory disease and conjunctivitis in military recruits	Military recruits from various background in an overcrowded environment; transmission via close contact and air filters in barracks	<b>Ad4:</b> 34–79% in the USA military recruit; 46% in Belgium; 58.4% in China
F	40, 41	Gastroenteritis and diarrhea in children	Second most common cause of gastroenteritis in children under the age of 2 years; fecal–oral transmission	<b>Ad41:</b> 94% in North America; 73–95% in Southern China
G	52	Gastroenteritis	Rare cause of gastroenteritis in children	

<sup>a</sup> The seroprevalence and distribution of HAdVs are based on various studies of selected types with published data.

thrombogenic adverse effects is minimal regarding Ad5 vaccine-based safety [19].

## Epidemiology

Adenoviruses are a diverse group found naturally in the upper respiratory tracts and gastrointestinal systems of humans, other mammals, and avian species. In humans, transmission of adenovirus infection and associated clinical diseases can be sporadic or epidemic. The pattern often correlates with the HAdV type and the age of the susceptible population. Serologic surveys have provided estimates of the prevalence of HAdV infections. Early surveys indicated that antibodies to Ad1, 2, and 5 are most common and are present in 40%–60% of children [20]. The incidence of HAdV infection peaks in infants and children between 6 months and 5 years of age. By 5 years of age, 70%–80% of children have neutralizing antibody to Ad1 and 2, and 50% have antibody to adenovirus type Ad5. The incidence of antibodies to Ad3, 4, and 7 is low at the same age groups. The survey data also suggested that neonates acquire maternal antibody, which then declines following birth, but the children acquire new infections as they grow up. The seroprevalence and worldwide distribution of HAdVs are too broad to describe in detail. A review of 65 years of HAdV seroprevalence was reported by Mennechet et al. and the results based on various studies of selected types are summarized in Table 1 [21].

From global collections of epidemiological data, different types of HAdV appear to manifest different pathogenic properties and cause diverse diseases, suggesting tissue tropism

varies among HAdVs [Table 1, Fig. 2]. HAdVs have a predilection for pediatric population younger than 5 years because they spend a significant portion of their days in closed environments, such as daycare centers, orphanages, or other institutions. Respiratory infections are the most common disease caused by HAdVs in children. HAdVs are estimated to account for 7%–8% of viral respiratory illnesses in children less than 5 years [20,22]. In addition to respiratory system, HAdVs have been associated with clinical diseases in other systems, as illustrated in Fig. 2.

## Clinico-pathologic correlation

### Overview

HAdV infection causes inhibition of cellular DNA, mRNA, and protein synthesis. The infected cell degenerates in specific ways with unique morphologic features that can assist pathologic diagnosis if biopsy or autopsy tissue samples are available for examination. Production of host DNA stops abruptly 8–10 h after HAdV infection, and host protein synthesis ceases 6–10 h later. Since the process of virion assembly is quite inefficient, only about 10%–15% of newly synthesized viral nucleic acids and proteins is incorporated into virions; other products will accumulate in the nucleus [23,24]. These excess unassembled viral components can develop characteristic nuclear lesions that have become the hallmark of cytologic changes in HAdV infections. The nuclear lesions mainly show two types of inclusion bodies: 1) a large amorphous basophilic crystal in “smudge cells”; 2) a bar-

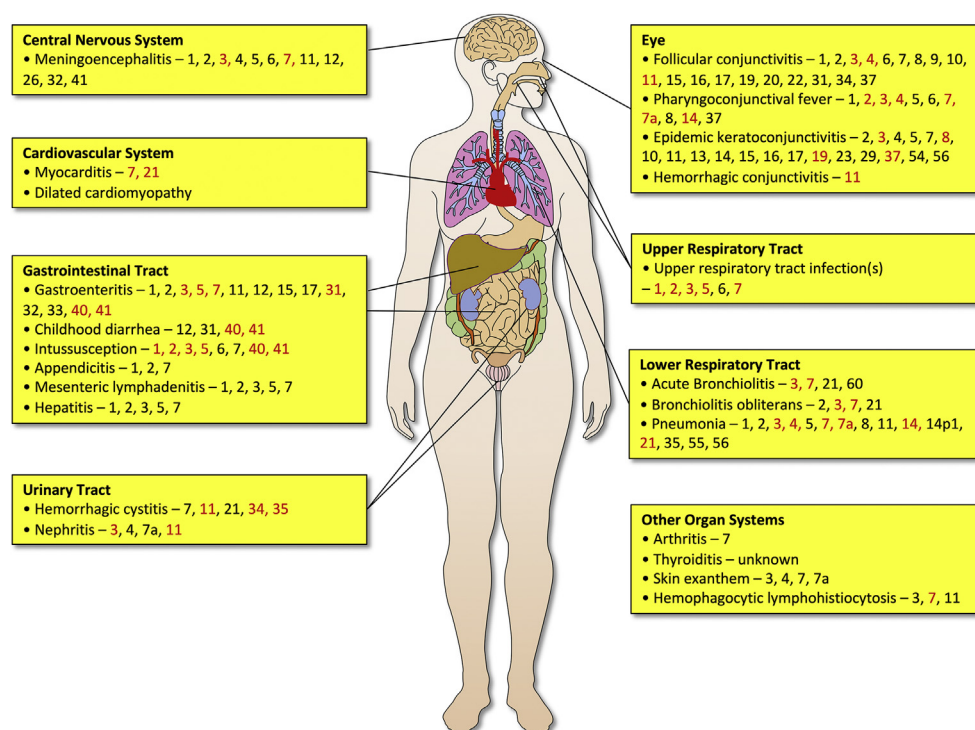


Fig. 2 Tropism of human adenoviruses with associated clinical diseases in various organ systems. The numbers indicate HAdV types; the numbers in red are the more common types.

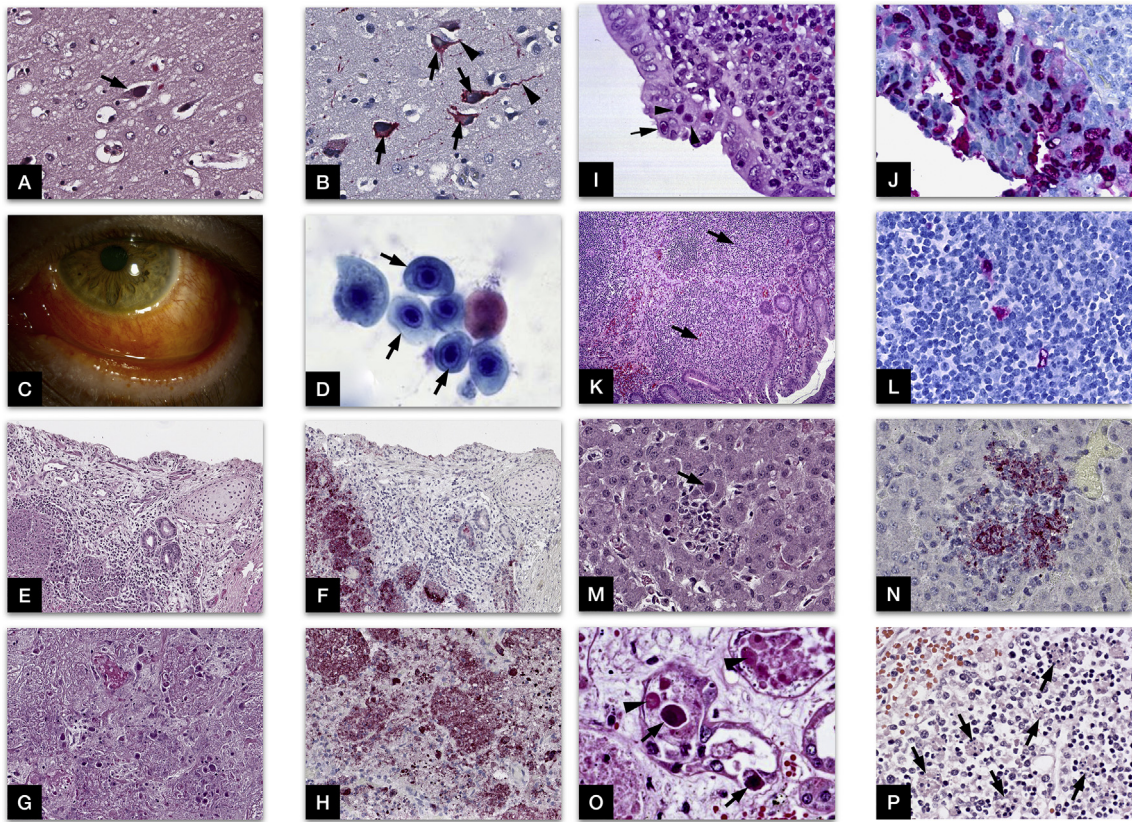


Fig. 3 (A) Adenoviral encephalitis with characteristic smudge cells in infected neurons (arrow). (B) Immunostaining showing HAdV antigens within neurons (arrows) and neuronal processes (arrow heads). (C) Chemosis and diffuse erythema of the bulbar and palpebral conjunctiva in a child with epidemic keratoconjunctivitis. (D) Cytology of conjunctival scraping showing Cowdry type A intranuclear inclusion (arrows) of early HAdV infections in epidemic keratoconjunctivitis. (E) Necrotizing bronchitis in a fatal case of infant showing extensive denudation of the surface epithelium, edematous lamina propria, necrosis, and mononuclear inflammatory cells infiltrate. (F) Immunostaining of HAdV antigens in the denuded surface epithelium and necrotic areas in the same patient with necrotizing bronchitis. (G) Adenoviral necrotizing pneumonia with abundant smudge cells, fibrinous exudate, mixed inflammatory cells, and karyorrhectic debris in alveoli. (H) Immunostaining showing abundant HAdV antigens in smudge cells and lung parenchyma with necrotizing inflammation. (I) Basophilic intranuclear inclusions (arrow) and smudge cells (arrow heads) in surface intestinal epithelium in a child with intussusception. (J) Immunostaining showing abundant HAdV antigens in intestinal epithelial cells in the same child with intussusception. (K) Hyperplasia of submucosal lymphoid follicles (arrows) in an infant with intussusception. (L) Scattered immunostaining of HAdV antigens in the submucosal lymphoid follicle in the same infant with intussusception. (M) Adenoviral hepatitis with focal necrotizing inflammation showing karyorrhectic debris, smudge cells, and large basophilic intranuclear inclusions (arrow) in hepatocytes. (N) Immunostaining showing abundant HAdV antigens in necrotic foci in the liver. (O) Higher-power magnification of adenoviral necrotizing nephritis showing characteristic smudge cells (arrows) and eosinophilic necrotic material (arrow heads) in HAdV infected renal tubular cells. (P) Lymph node biopsy from a hemophagocytic lymphohistiocytosis patient showing effacement of nodal structure and increased number of histiocytes with hemophagocytosis (arrows). Hematoxylin and Eosin stain, A, E, G, I, K, M, O, P. Original magnifications:  $\times 400$  (A);  $\times 100$  (E, G);  $\times 200$  (I, M, P);  $\times 50$  (K);  $\times 630$  (O). Immunoalkaline phosphatase with naphthol fast red substrate and hematoxylin counterstain, B, F, H, J, L, N. Original magnifications:  $\times 400$  (B);  $\times 100$  (F, H);  $\times 200$  (J, L, N). Papanicolaou stain, D. Original magnification:  $\times 1,000$ .

shaped eosinophilic crystal with the arginine-rich viral proteins in “Cowdry type A inclusions” [25]. After lysis, the cell releases new infectious particles and causes damage to epithelial mucosa and tissue parenchyma, showing a pattern of necrotizing inflammation with karyorrhectic debris, fibrinous exudate, and mixed inflammatory cells. Host responses to HAdV infection include the recruitment of neutrophils, lymphocytes, macrophages, and natural killer cells to the site of infection and the elaboration of various cytokines and

chemokines [26,27]. This host immune response is likely to contribute to the symptoms of HAdV infection, but specific mechanisms of pathogenesis still need further studies to elucidate.

#### Central nervous system

Meningoencephalitis is a rare complication of HAdV infection, and it is usually seen in immunocompromised patients

when it occurs, such as patients with AIDS or lymphoma [28]. Although not a common finding, several reports have directly demonstrated HAdVs in CSF [29]. Neurological manifestations range from mild aseptic meningitis to potentially fatal acute necrotizing encephalopathy [30]. There are cases of encephalopathy using viral isolation from extraneural sites or increased antibody titer to establish a diagnosis, especially associated with epidemic Ad7 pneumonia in children [31]. However, whether the neurologic symptoms were caused by direct viral infection in the brain remains unknown. In rare fatal cases, typical smudge cells can be seen within neurons in the brain [Fig. 3A] and infection can be confirmed by using immunohistochemical (IHC) assay with a specific anti-AdV antibody [Fig. 3B].

## Eye

HAdV is the most common cause of infectious conjunctivitis and “red eye” worldwide, accounting for up to 75% of all conjunctivitis cases and affecting people of all ages and demographics [32]. The majority of adenoviral ocular infections are subclinical, with some being mildly symptomatic and self-limiting. Incidence is higher in the pediatric population than the adults with immunocompromised status [33]. The ocular manifestations of HAdV infections are widely variable and can present as acute follicular conjunctivitis, pharyngoconjunctival fever, and epidemic keratoconjunctivitis [34]. Virus can be recovered from the eye for a usual period of approximately 2 weeks but has been detected for 2–3 years in patients with chronic papillary conjunctivitis [35]. Adenoviral conjunctivitis is primarily a clinical diagnosis. Laboratory diagnosis, such as viral cultures, immunofluorescence studies, serologic examinations, and molecular techniques can be employed although rarely used [36]. Conjunctival biopsy is seldom obtained for pathologic diagnosis.

### *Acute follicular conjunctivitis*

Acute follicular conjunctivitis is the most common form of adenoviral ocular infections. The infection is usually confined to one eye and appears as follicular lesions on the palpebral conjunctival surface. Symptoms usually occur after an incubation period of 5–7 days and include itching, burning, lacrimation, discharge, foreign body sensation, and prominent conjunctival congestion [37]. Physical examination shows erythema and lymphoid follicular hyperplasia in the conjunctiva in association with serous drainage and increased lacrimation. Occasionally, adenopathy of the preauricular lymph nodes is seen. Symptoms usually resolve in 10 days to 3 weeks with complete recovery.

### *Pharyngoconjunctival fever*

Pharyngoconjunctival fever (PCF) is a syndrome characterized by pharyngitis, conjunctivitis, and fever [38]. Not all patients have the complete syndrome triad during epidemics. The usual onset of illness is abrupt, with sore throat, eye irritation or pain, fever, and generalized soreness. Photophobia and lacrimation are unusual. Many patients develop cough from catarrhal inflammation of the nasal mucosa and posterior nasal discharge. On examination, the palpebral conjunctiva usually appears granular, and

hemorrhages occasionally are noted on the bulbar surface. The tonsils, adenoids, and pharyngeal lymphoid tissue are often enlarged with various degrees of pharyngeal congestion, which may result in nasal blockage. Approximately one-third of affected patients show follicular exudative lesions that is similar to streptococcal disease on clinical presentations. Involvement frequently starts in one eye and does not involve the other eye until 2 or 3 days later. The fever is sustained or remittent for 3–4 days in most patients. Throat and eye findings usually are improved considerably by the seventh day of illness, but some constitutional symptoms may persist for two weeks or longer.

### *Epidemic keratoconjunctivitis*

Epidemic keratoconjunctivitis (EKC) is caused most commonly by Ad8 and Ad37 [39,40]. It occurs more commonly in adults than children. The usual mode of viral spread is by contaminated ophthalmic instruments and eye solutions, hand-to-eye contact by infected personnel, swimming pools, or fomites in close-contact situations. The incubation period typically is 5–10 days. The initial symptom generally is unilateral follicular conjunctivitis with a foreign body sensation. Photophobia, lacrimation, discharge, hyperemia, and edema of the conjunctiva are notable [Fig. 3C]. Preauricular adenopathy is frequently present and many of those afflicted also have pharyngitis and rhinitis. The conjunctivitis resolves 7–10 days after onset of the disease. In severe cases, blurred vision may continue for a long period of time. An infantile form of EKC has been described that usually affects children younger than 2 years old [41]. High fever, pharyngitis, otitis media, diarrhea, and vomiting usually accompany this form of pseudomembranous or membranous conjunctivitis. In acute illness, conjunctival scrapings obtained during the first 10 days of infection reveal characteristic inclusion bodies when stained with Giemsa or Papanicolaou stain. Intranuclear inclusions with a ground-glass nuclear appearance can be demonstrated [Fig. 3D]. The conjunctival smears usually show inflammation with predominantly lymphocytes and little fibrinous discharge. Virus-specific fluorescent antibody staining is diagnostic in EKC [42]. Preparations of corneal and conjunctival epithelia reveal adenoviral particles when examined with the electron microscope.

## *Respiratory tract*

### *Upper respiratory infections*

Although HAdVs have been frequently implicated as an etiologic agent in common colds, only 3%–6% of common colds in children were attributed to HAdVs [22,43]. Adenoviral pharyngitis is an acute illness characterized by fever, sore throat, extensive exudative tonsillitis, and frequently, cervical adenopathy [22,44]. Other associated symptoms include headache, myalgia, chills, malaise, and cough. In infants and preschool children, nasal congestion and discharge are more prominent, and abdominal pain is a common complaint [45]. Acute febrile pharyngitis is the most common adenoviral illness in children and is particularly important as an epidemic illness in closed environments [46]. On occasion, HAdVs have been associated with acute laryngotracheitis. In general, the symptoms caused are not severe and usually

only presents with a barking and harsh cough. Laryngotracheitis frequently is seen in association with febrile pharyngitis, bronchiolitis, and pneumonia [47].

Recently, a 3-year cross-sectional hospital-based study showed HAdV species B, C, and E were detectable in adenoid and palatine tonsil tissues and nasopharyngeal secretions from nearly 85% of children with adenotonsillar hyperplasia or recurrent tonsillitis [48]. There is no association with the severity of airway obstruction, nor with the presence of recurrent tonsillitis, sleep apnea or otitis media. The histopathology shows follicular hyperplasia with increased lymphocytes and macrophages. No characteristic viral inclusions are observed. Epithelial and subepithelial cells in tonsils seem to be crucial for HAdV species C production and shedding in such persistent HAdV infection.

#### *Acute bronchitis and bronchiolitis*

HAdVs account for approximately 5%–11% of bronchitis [49] and 5%–18% of bronchiolitis in infants [50]. The bronchiolitis caused by HAdVs is usually sporadic and similar to illness associated with other viral agents. Many cases of bronchiolitis eventually progress to pneumonia. Adenoviral bronchiolitis that occurs early in infancy can be fatal or results in serious residual lung damage and chronic disease [51].

#### *Bronchiolitis obliterans*

Bronchiolitis obliterans (BO) is an uncommon and severe sequela of chronic obstructive lung disease in children that results from a damage to the lower respiratory tract. It typically occurs after a severe respiratory infection in previously healthy pre-school children. HAdV infection may be a major cause of post-infectious bronchiectasis and BO in childhood [52,53]. Children with severe adenoviral pneumonia who have a longer duration of fever (especially more than 10.5 days), develop dyspnea, or require invasive mechanical ventilation in the acute phase are more likely to develop BO [53]. Symptoms and signs of air trapping, such as hyperinflated chest or expiratory wheeze with persistent oxygen requirement are characteristic findings in BO. The histopathologic features usually show necrotizing inflammation in bronchi, bronchioles, alveoli, bronchial mucous glands, with the presence of intranuclear inclusions [54].

#### *Pneumonia*

HAdVs are common isolates in young children with pneumonia. The overall frequency of HAdVs as a cause of nonbacterial pneumonia in children is less than that of respiratory syncytial virus and parainfluenza virus type 3, but an alarming number of fatal illnesses have been reported. Adenoviral pneumonia is probably responsible for about 10% of the pneumonias of childhood and can occur in epidemic or sporadic pattern [55,56]. Ad3, 7, and 21 are the most common etiologic types of adenoviral pneumonia between 6 months and 5 years of age [55,57]. Ad3 and Ad7 are particularly pathogenic types that can disseminate and often cause fatal disease in previously healthy children. Periodic epidemics of adenoviral pneumonia in young adults have also been identified, particularly Ad4 among military recruits [58].

Severe pneumonia occurs most commonly in neonates and young children from 3 to 18 months old [52,59,60]. The onset of illness is usually acute, with persistent cough and high fever (>39 °C). On physical examination, moderate to severe dyspnea with associated tachypnea is apparent. Auscultation reveals inspiratory and expiratory wheezes and rales. Chest radiographs usually demonstrate bilateral diffuse infiltrates, which may be bronchial, peribronchial, or interstitial [61,62]. Pleural effusion or mediastinal lymphadenopathy has rarely been described. Other clinical manifestations include lethargy, sore throat, diarrhea, anorexia, vomiting, and occasionally conjunctivitis. Extrapulmonary complications that have been reported include meningitis, encephalitis, hepatitis, myocarditis, nephritis, disseminated intravascular coagulopathy, and skin rashes [55,59,63–65]. However, many of these disease entities are observed based on clinical manifestations or laboratory tests without histopathologic correlation. In surviving infants, symptoms may persist for 2–4 weeks, and radiographic changes resolve slowly at the 3-week follow-up examination. Recovery often is gradual, and exacerbations occur commonly [66].

The histopathologic findings in fatal cases of adenoviral pneumonia usually show necrotizing bronchitis and bronchiolitis with extensive denudation of the surface epithelium, particularly in medium-sized intrapulmonary bronchi. The lamina propria of bronchi and bronchioles is typically congested, edematous, and infiltrated with predominantly mononuclear inflammatory cells [Fig. 3E]. Amorphous eosinophilic material, mixed inflammatory cells, sloughed epithelium, and cellular debris may occlude affected airways. Serous and mucous glands in bronchi are often involved with necrotizing inflammation as well. The pulmonary parenchyma usually shows bronchocentric necrosis with hemorrhage, mixed inflammatory infiltrates, and abundant karyorrhectic debris [Fig. 3G]. These findings generally occur on a background of exudative diffuse alveolar damage (DAD), which shows macrophages, fibrin, and detached pneumocytes in alveoli. Hyaline membrane formation may be observed at early stage of DAD. Disseminated intravascular coagulopathy and fibrin thrombi in vessels may be present in lung and other organs, such as kidney, heart, adrenals, and central nervous system. Typical intranuclear inclusions can be seen in respiratory epithelial cells of the trachea, bronchi, and bronchioles, as well as in the acinar cells of bronchial glands and in alveolar pneumocytes [Fig. 3G]. They are usually more abundant around the necrotic foci. On routine hematoxylin and eosin stain, early inclusions appear as “Cowdry type A inclusions” with small, dense, amphophilic structures surrounded by a clear zone and peripherally margined chromatin. Unlike herpetic or paramyxoviral infections, no multinucleated giant cells or syncytial cells are seen. As the infection progresses, the characteristic “smudge cells” become more apparent and abundant with larger and more basophilic inclusions, and the margins of the nuclear membrane become less distinct [Fig. 3G]. This is due to the inefficient assembly of viral particles and accumulation of large number of nucleic acids and peptides in the infected cells, as previously described. The

presence of HAdV inclusions can be highlighted by using IHC with specific antibodies [Fig. 3F and H]. The pathologic features of necrotizing inflammation in bronchi, bronchioles, and lung parenchyma correlate well with the clinical manifestations of bronchitis, bronchiolitis, and pneumonia.

## Heart

### Myocarditis

Enterovirus infections, such as coxsackieviruses have been considered as the most common etiologic pathogens of viral myocarditis in pediatric population. However, there is evidence that HAdVs may be a significant cause as well [67,68]. Such evidence mainly comes from utilization of PCR assays to detect the presence of nucleic acids in clinical samples. In an extensive study of myocarditis, HAdV DNA was identified by PCR in 23% of the endomyocardial biopsy [68]. The results suggest that HAdVs may play an important role in viral myocarditis. In children, myocarditis has been noted in association with severe pneumonia and disseminated disease caused by several types of HAdVs [68,69]. However, the etiologic role of HAdVs in myocarditis remains controversial. Viral particles have not been observed by EM and the characteristic cytopathic features, such as smudge cells or intranuclear inclusions are usually not observed in tissue samples of myocarditis cases.

### Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common type of nonischemic cardiomyopathy, and most cases of DCM are idiopathic. Recently, the human coxsackievirus and adenovirus receptor (CAR) was discovered, and its increased expression has been reported in patients with DCM and myocarditis [70,71]. A previous study showed 12% had HAdV DNA demonstrated by PCR in the endomyocardial biopsy specimen from patients with DCM [68]. A more recent study shows that myocardial infection with HAdV may play an important role in the pathogenesis of severe DCM [72]. Further studies are needed to elucidate the pathogenesis of DCM caused by HAdV infection.

### Pericarditis

Pericarditis associated with severe adenoviral pneumonia has been reported [73,74], albeit rare. A report described a 10-month-old boy with fatal pericarditis caused by Ad7. Interleukin-6, tumor necrosis factor- $\alpha$ , and adenovirus-specific immune complexes were identified in serum and pericardial fluid from this child [74]. In another report, electrocardiographic changes were consistent with pericarditis in a child with Ad7 pneumonia and the virus was isolated in high titer from pericardial fluid at postmortem examination [75].

## Gastrointestinal tract

### Gastroenteritis

The widespread use of electron microscopy for the study of rotaviral diarrhea led to the finding of previously unrecognized HAdVs that were fastidious and could not be grown in routine cell cultures [76]. These HAdVs, now identified as Ad40 and Ad41, subsequently were shown to be important causes of

gastroenteritis in children [77,78]. The incidence of adenoviral gastroenteritis differs considerably in various studies and geographic locations reported by many authors. In general, HAdV infections are the cause of 2%–15% of acute diarrheal illnesses in children. It is less prevalent than rotavirus infection, occurs most often in children younger than 4 years of age, and is not easily distinguishable from other infectious gastroenteritis based on clinical manifestations. Outbreaks associated with Ad3 and Ad7 infections have been reported with acute abdominal pain followed by diarrhea, nausea and vomiting, fever, headache, and pharyngitis [79,80]. Other symptoms that may occur in patients with adenoviral diarrhea include conjunctivitis, rhinitis, pharyngotonsillitis, and cervical adenitis. Adenoviral gastroenteritis is usually self-limiting and lasts approximately 2–3 days. Microscopic findings in biopsy samples from patients with adenoviral diarrhea shows non-specific inflammation and infected epithelial cells with characteristic nuclear and cellular changes [81].

### Intussusception

HAdV infections have been well documented to be associated with intussusception [82,83]. Previous studies have suggested that bowel wall hypermotility caused by direct viral involvement or by hyperplasia of lymphatic tissue is the lead point for the intussusception. Many HAdV types have been implicated and species C represent the largest proportion in identification [84]. Most children with intussusception were younger than 2 years old and some had preceding respiratory symptoms. In these cases, viral inclusions can be seen in surface or desquamated gastrointestinal epithelium [Fig. 3I] and can be confirmed by using IHC assay [Fig. 3J]. Mesenteric lymph nodes often are enlarged at surgery. The lymphoid follicles adjacent to the intussusception areas are usually hyperplastic [Fig. 3K] and viral antigens can be demonstrated by IHC staining [Fig. 3L]. Typical adenoviral intranuclear inclusions can also be demonstrated in cells in stool, intestinal epithelium, and the appendix by electron microscopy [85].

### Appendicitis and mesenteric lymphadenitis

HAdVs have been reported in both acute and chronic appendicitis [86]. Right iliac fossa abdominal pain in conjunction with sore throat is a common finding. The virus has been isolated from the appendix and mesenteric lymph nodes at surgery. During acute infection, evidence of HAdVs can be discerned with characteristic intranuclear inclusions and positive IHC staining in lymphoid follicles of the ileum, appendix, and mesenteric lymph nodes. In chronic infection, only mild non-specific inflammation is seen in the appendix. Several types of HAdVs have been recovered from lymph nodes and the appendix in cases of mesenteric lymphadenitis [82,87]. Patients with mesenteric lymphadenitis often have abdominal pain and other symptoms similar to those of acute appendicitis. Mesenteric adenitis may be associated with concurrent or recent adenoviral illness, such as pharyngitis.

### Hepatitis

Hepatitis in association with HAdV infection has been reported in small infants, mainly in children with overwhelming disseminated disease or in immunocompromised patients [88,89]. Few cases of HAdV hepatitis in immunocompetent



pediatric patients have been documented. Adenoviral hepatitis can occur secondary to hepatic transplants or by the spread of virus to the liver hematogenously in sporadic cases. In transplants, it may be directly related to infection of the transplanted liver or reactivation of the virus from a latent source. Focal inflammatory infiltrates with hepatocellular necrosis and typical smudgy cells can be seen [Fig. 3M]. Pathologic diagnosis can be confirmed by PCR, IHC [Fig. 3N], and thin section transmission EM.

### Genitourinary tract

#### Acute hemorrhagic cystitis

Acute hemorrhagic cystitis is an uncommon manifestation of HAdV infection in immunocompetent children and is characterized by a sudden onset of dysuria and frequency, with hematuria developing 12–24 h later [90,91]. It occurs more frequently in boys and usually is associated with Ad11. Occasionally, fever, suprapubic pain, and enuresis may occur. Symptoms can persist for a few days to 2 weeks, with average duration being approximately 5 days. HAdV antigen has been identified by immunofluorescence in exfoliated bladder cells. Although no sequelae have been reported, the long-term prognosis is unknown.

#### Nephritis

Hematuria occasionally has been reported in infants with severe pneumonia and disseminated HAdV infection. Some children with upper respiratory illnesses caused by HAdV, specifically in patients with PCF have also been noted to manifest with hematuria [92]. A series of autopsy cases of necrotizing tubulointerstitial nephritis caused by HAdV infection showed hemorrhagic, necrotizing tubulitis with intranuclear inclusion bodies in the kidney [93]. The presence of hemorrhagic cystitis and localization of invasive infection in urogenital organs suggested that renal infection might occur by ascending route from the bladder. Histopathologically, typical smudge cells or Cowdry type A intranuclear inclusions are present in necrotic tubular epithelial cells surrounded by inflammatory cells [Fig. 3O]. Immunofluorescent or IHC examination with anti-HAdV antibody can demonstrate viral antigens in the affected tubular cells. Electron microscopic examination on biopsy or autopsy kidney tissue samples may reveal intranuclear crystalline arrays of viral particles. Extrarenal involvement, if present, is usually confined to bladder or prostate. To date, most of the reported cases of acute necrotizing tubulointerstitial nephritis caused by HAdV infection have occurred in individuals with primary or secondary immunodeficiency and have resulted in renal failure and death.

### Infections in immunocompromised hosts

In addition to the infections described above, HAdVs take advantage of impaired immune systems to establish persistent and disseminated infections in immunocompromised hosts [94]. They can cause prolonged fever with elevated inflammatory markers and may mimic certain systemic illnesses, such as bacterial sepsis or Kawasaki disease [95].

Immunocompromised patients are also susceptible to a broader range of different HAdV infections. HAdV infection has been a common complication in bone marrow/hematopoietic stem cell transplant and solid organ transplant recipients [96,97]. Because some HAdVs establish latency in lymphoid tissues and the kidneys of their host, it is believed that many cases of clinical disease caused by HAdVs in immunocompromised patients are actually reactivated infections [98].

A rare but fulminant form of adenovirus-associated hemophagocytic lymphohistiocytosis (HLH) has been reported in children. Most of these HLH cases were associated with severe HAdV pneumonia or bone marrow transplant recipients [99,100]. Bone marrow aspiration or lymph node biopsy from HLH patients typically reveals increased numbers of histiocytes with hemophagocytosis [Fig. 3P]. The evidence of HAdV infection in such cases is usually confirmed by serology or PCR assays.

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## Conclusions

The tissue tropism, cytologic features, and histopathologic changes of HAdV infections correlate well with the biologic properties of the virus. The clinical manifestations correspond to the organ systems involved in HAdV infection and the degree of tissue damage with host immune responses. There is still a need to conduct further studies to elucidate the pathogenesis of this common viral infection in pediatric population.

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## Conflicts of interest

The author declares no conflicts of interest. Some of the work described in this manuscript was done when the author was working as a medical officer at Infectious Diseases Pathology Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

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