

Adenoviruses

Joanne M. Langley, MD,
MSc*

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Objectives After completing this article, readers should be able to:

1. Describe clinical manifestations of adenovirus infection.
2. Explain how adenovirus is transmitted and how this risk can be reduced.
3. Delineate who should be tested for adenovirus infection and the laboratory tests available.
4. Describe treatment options for immunocompromised patients who have adenovirus infection.

Case Report

A 4-year-old previously well boy presents with fever, bilateral conjunctivitis, and a rash. Five days ago, while at child care, he began to complain of a sore throat. He developed a nonproductive, nonparoxysmal cough and clear rhinorrhea. Throughout the illness, he was anorexic and “not himself” according to his mother. On physical examination, he appears quiet and unwell and has a fever. His temperature is 104°F (40°C), heart rate is 120 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 114/86 mm Hg. There is bilateral mild, nonpitting periorbital edema; mild conjunctival injection; and some greenish discharge from the eyes. One soft, tender, enlarged 1.5-cm diameter cervical node can be palpated. A 2/6 vibratory systolic ejection murmur is audible at the left sternal border. A blanching pink maculopapular rash is visible on the face, limbs, trunk, and lateral borders of the feet.

The clinical impression suggests a viral illness, but because Kawasaki disease is part of the differential diagnosis, some investigations are performed. The white blood cell count is $8.5 \times 10^3/\text{mcL}$ ($8.5 \times 10^9/\text{L}$), hemoglobin is 10.2 mg/dL (102 g/L), and platelet count is $251 \times 10^3/\text{mcL}$ ($251 \times 10^9/\text{L}$). A few atypical and reactive lymphocytes are seen on the peripheral smear. Bacterial cultures of the throat and blood are negative.

Defervescence occurs on day 7 of the illness; the other symptoms resolve over the ensuing 3 days. A culture of the posterior pharynx taken on admission grows adenovirus.

Introduction

In 1953, Rowe and associates described an infectious agent that disrupted tissue cultures of adenoidectomy specimens from children. This agent later came to be known as adenovirus because of its frequent isolation from adenoidal and other lymphatic tissue. Some 51 serotypes now are identified.

Our understanding of the spectrum of clinical manifestations of adenovirus infection has deepened because of population-based community studies of febrile illness in families, national viral surveillance systems, investigation of outbreaks of respiratory illness in close-quartered young military recruits, and hospital-based case reports of serious or unusual disease presentations. Adenovirus is perhaps best known as a cause of acute respiratory and conjunctival infection, but it can infect many human tissues, cause illness through childhood and beyond, and establish latency with later recrudescence. Many infections are asymptomatic. In recent years, adenovirus has been explored as a potential vector for introducing new genes into human cells as treatment for genetic diseases.

Virology and Pathogenesis

Adenovirus is a DNA virus. The adenoviral coat, or capsid, is composed of subunits called capsomeres, which are arranged morphologically as an icosahedral structure. There are

* Division of Infectious Diseases, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada.

surface structural proteins in the capsid, which are common among adenoviral serotypes, and proteins that show type specificity. Adenovirus does not have a lipid envelope.

All viruses are obligate intracellular parasites and cannot multiply outside the host cell. Adenoviruses are highly stable outside the host cell and can maintain infectivity at room temperature for 2 weeks, after freezing at 39°F (4°C), and at a pH ranging from 5 to 9. They can be destroyed by heating to 129°F (54°C) for 30 minutes, standard disinfectants and detergents used for cleaning noncritical environmental surfaces, or hand hygiene agents.

Adenoviruses infect the host cell by attachment, using a capsid protein, and subsequently are internalized by receptor-mediated endocytosis. The endosome is disrupted by the virion, allowing the DNA to enter the nucleus of the host cell, where replication occurs. Replication begins as early as 5 hours after infection and is associated with inhibition of cellular and protein synthesis. In permissive cells, about 10⁴ virions per cell may be produced over the next 48 hours. Ultimately, host cell protein synthesis comes to a halt and cell death occurs.

Adenoviral infection may become latent and has been identified in the host genome and in cells of the lymphatic system. Reactivation of latent infection may be asymptomatic in the healthy host or cause serious illness in the immunocompromised patient.

Immunity to adenovirus has been correlated with the serum type-specific antibody and susceptibility with seronegativity. Cell-mediated immune responses also are important in the containment and resolution of infection. The importance of cell-mediated immunity has been illustrated in animal models and infection in immunocompromised hosts, where the degree of T-cell depletion can be correlated with the incidence and severity of infection.

Epidemiology

Adenovirus spreads between persons by droplets from the respiratory tract and eye or, in the case of enteric adenoviruses, in feces.

Direct-contact transmission occurs when there is physical contact with the infected person (eg, kissing, touching). Transmission occurs indirectly when a susceptible person encounters secretions of an infected person through an intermediate vehicle such as a contaminated medical device or toy, contaminated water, or the unclean hands of a health care worker. Droplet transmission occurs when secretions from a cough or sneeze or during a procedure (eg, suctioning) are generated. Because of

their size and weight, droplets are propelled only a short distance (1 meter or 3 ft) before they are pulled downward by gravity. A susceptible host is infected when infectious respiratory droplets are deposited on the conjunctivae, nasal mucosa, or mouth. Adenovirus is not transmitted by the airborne route.

The incubation period for adenovirus infection is about 5 to 10 days. In the normal host, illness usually lasts about 1 week, but asymptomatic shedding of virus can occur for months to years. Adenovirus has been isolated from up to 50% of surgically removed tonsils. Infection is more common in winter and spring but occurs throughout the year. It is uncommon in the first 6 postnatal months, suggesting that maternal antibody confers protection. Neutralizing antibodies develop in early childhood after asymptomatic and symptomatic infection, which occur with equal frequency. By age 5 years, as many as 75% of children have serologic evidence of adenovirus exposure.

About 50% of all adenoviral serotypes have been linked to human infection. For example, serotypes 41 and 42 are associated with diarrheal illness; types 1 through 7 with acute respiratory illness; and types 3, 7, and 14 with pharyngoconjunctival fever.

Clinical Manifestations

Although adenoviruses possibly are known best as agents of acute respiratory illness, diarrhea, and eye infections, they have been recovered from many organ systems (Table). Clinical illness usually is localized to one system in the immunocompetent host, but may become disseminated and life-threatening in the recipient of a transplant or the patient undergoing immunosuppressive chemotherapy. Signs and symptoms of adenoviral illness are not specific or diagnostic, but outbreaks of pharyngoconjunctival fever almost always are due to adenovirus.

Respiratory

Adenoviruses cause respiratory illness throughout the lifespan, but most commonly in young or school-age children and in settings where crowding or close contact occurs, such as in residential institutions or child care settings. About 2% to 3% of all acute infectious respiratory illnesses are believed to be caused by adenovirus, as are up to 8% of acute respiratory illnesses presenting in infants younger than 2 years of age. Upper respiratory tract infection presents as nonspecific nasal congestion, coryza, and cough. Up to 25% of exudative pharyngitis in pediatric patients is due to adenovirus. In military recruits, 75% of nonstreptococcal pharyngitis can be adenoviral and is associated with malaise, fever, chills, my-

Table. Clinical Syndromes Caused by Adenoviruses

System	Clinical Presentation
Respiratory	<ul style="list-style-type: none"> • Upper respiratory tract <ul style="list-style-type: none"> – Pharyngitis – Coryza • Lower respiratory tract <ul style="list-style-type: none"> – Croup/Laryngotracheobronchitis – Cough illness – Bronchiolitis – Pneumonia
Eye	<ul style="list-style-type: none"> • Conjunctivitis with respiratory illness • Acute follicular conjunctivitis • Epidemic keratoconjunctivitis • Pharyngoconjunctival fever
Gastrointestinal	<ul style="list-style-type: none"> • Diarrhea • Hepatitis in immunocompromised host
Urinary	<ul style="list-style-type: none"> • Hemorrhagic cystitis
Nervous system	<ul style="list-style-type: none"> • Aseptic meningitis • Encephalitis, meningoencephalitis • Myelitis, acute flaccid paralysis • Myositis
Cutaneous	<ul style="list-style-type: none"> • Exanthemata
Disseminated infection (newborns, immunocompromised)	<ul style="list-style-type: none"> • Multiorgan failure

algia, and headache. Lower respiratory tract infection such as pneumonia, bronchiolitis, laryngotracheobronchitis (croup), or a cough illness similar to pertussis may occur. Adenoviral respiratory illness may be associated with signs of conjunctival inflammation.

In neonates, a syndrome of adenoviral pneumonia and sepsis has been reported as well as fatal disseminated infection. Adenoviral pneumonia in infancy has been associated with chronic lung damage leading to restrictive lung disease and with intraluminal fibrosis leading to irreversible narrowing of small airways. Adenoviral pneumonia in the immunocompromised host has been associated with bronchial necrosis and high mortality rates (up to 45% in acquired immunodeficiency syndrome patients).

Ophthalmologic

Adenovirus is the most common cause of acute conjunctival infection. It is associated with four ophthalmologic syndromes: acute follicular conjunctivitis, epidemic keratoconjunctivitis, pharyngoconjunctival fever, and conjunctivitis occurring in association with respiratory illness.

Acute follicular conjunctivitis, known as “pink eye,” presents with itching, burning, lacrimation, and conjunc-

tival injection, which resolves spontaneously in days to weeks. By contrast, epidemic keratoconjunctivitis (EKC) begins with the relatively mild symptoms of follicular conjunctivitis but progresses to a diffuse keratitis associated with a foreign body sensation. In addition to the signs and symptoms of acute follicular conjunctivitis, EKC may cause swelling or redness of the eyelid, discharge from the eyes, the sticking together of eyelids, and photophobia. Chronic and painful superficial epithelial opacities of the cornea may result in prolonged visual impairment. Outbreaks have been reported from neonatal intensive care units and from patients attending the same ophthalmology office. In these outbreaks, inadequately disinfected equipment contaminated with adenovirus has been identified. Of note, newborns may not have signs of systemic illness with EKC or, unlike adults, persistent visual

abnormality or subepithelial corneal infiltrates.

Pharyngoconjunctival fever describes a syndrome of fever, sore throat, and conjunctivitis. Rhinitis and cervical adenitis may be present. Onset may be monocular, and a granular appearance may be seen on the palpebral conjunctivae. Outbreaks of pharyngoconjunctival fever, with attack rates of up to 60%, have been reported after exposure to contaminated ponds and inadequately chlorinated swimming pools.

Gastrointestinal

Children may shed adenovirus in feces for months to years after infection, and in the child care setting, enteric adenoviruses are detected in equal percentages of children who have and do not have diarrhea. However, adenovirus can be identified in 5% to 12% of acute diarrhea in infants. In one large study of infants hospitalized with acute diarrhea, adenovirus was found in 15% of all fecal isolates. In these children, 94% of whom were younger than 4 years of age, vomiting and diarrhea were prominent symptoms. Illness resolves in about 1 week. Adenovirus also has been identified in up to 40% of children who have intussusception.

Acute Hemorrhagic Cystitis

Acute onset of hematuria, dysuria, and polyuria has been associated with adenovirus in studies in Japanese and American children. Gross hematuria lasts about 3 days, with microscopic hematuria persisting for a few more days before spontaneous resolution. Children who have this illness are otherwise healthy and have no structural abnormalities of the urinary tract. Hemorrhagic cystitis, tubulointerstitial nephritis, and adenoviruria have been reported in patients who have had bone marrow and kidney transplants.

Neurologic

A variety of central nervous system presentations have been described in which adenovirus has been identified in cerebrospinal fluid. These symptoms occur with or without concomitant respiratory infection. Encephalitis, meningoencephalitis, encephalomyelitis, and a Reye-like syndrome have been described. Except for chronic meningoencephalitis in patients who have hypogammaglobulinemia or immunocompromise of cell-mediated immunity, these illnesses generally resolve spontaneously.

Immunocompromised Host

Adenoviral infection in the child who has no normal host defenses can be life-threatening. Disease may be localized and severe, as in pneumonitis, colitis, hemorrhagic cystitis, hepatitis, nephritis, or encephalitis. Case fatality rates may be as high as 60% to 80% in the period after bone marrow transplantation, before immunoreconstitution, or in the child who has severe combined immunodeficiency syndrome. Disseminated disease with multiorgan failure also occurs in the immunocompromised child and has been observed in neonates. A high concentration of adenovirus DNA in serum correlates with fatal outcomes of adenovirus infection in children in some studies.

Cutaneous

A nonspecific erythematous maculopapular skin eruption can occur in association with adenoviral respiratory illness. Less commonly, morbilliform eruptions with confluence of erythema are found.

Laboratory Tests

In most instances, infection caused by adenovirus is self-limiting, short-lived, and not life-threatening. In such clinical settings, specific viral diagnosis is not sought routinely because it will not change clinical management. However, a diagnosis may be required during the inves-

tigation of an outbreak, for appropriate placement of a hospitalized patient, or for an immunocompromised or severely ill person in whom antiviral therapy may be warranted or the investigational plan altered.

Adenovirus has been identified in patient specimens from the respiratory tract, cerebrospinal fluid, and stool and in biopsy specimens. The available methods include viral culture, detection of adenoviral antigen or of viral DNA, histopathology, and serology. In all cases, consultation with the microbiology laboratory is advised to ensure that appropriate patient specimens are obtained in adequate quantity and that they arrive in the laboratory in a timely manner and in the correct containers.

Adenovirus can be identified in specimens from the respiratory tract, eye, cerebrospinal fluid, or tissue biopsy in culture by using cells of human origin. This may take 3 to 7 days. Adenovirus can be identified rapidly via antigen detection by using enzyme immunoassay, immunofluorescence, or antibody agglutination or by using more recently available molecular techniques such as polymerase chain reaction (PCR). DNA amplification and hybridization techniques can be used for in situ diagnosis from biopsied tissue. Serum samples taken at the time of the acute illness and 2 to 3 weeks later can be tested for rising antibody titers by various methods (eg, complement-fixation, enzyme-linked immunosorbent antigen assay, hemagglutination-inhibition, neutralization). Antibody production may be poor in infants or immunocompromised hosts, leading to falsely negative serology. Antibody production following infection generally is long-lasting. Serum samples also can be submitted for viral DNA detection by PCR or dot hybridization.

Cytohistopathology or electron microscopic analysis of tissue usually is not helpful, although indistinct nuclear eosinophilic inclusions without cytoplasmic inclusions have been seen in alveoli.

Because prolonged viral shedding from the respiratory or gastrointestinal tract may occur after adenovirus infection, identification of adenovirus may not indicate that it is causing the child's current illness.

Enteric adenoviruses do not grow in routinely available tissue culture and are detected through use of specialized cell cultures, electron microscopy, or antigen detection assays. Rapid diagnostic kits combining detection of rotavirus and enteric adenovirus are available.

Treatment

Antiviral therapy has not been used routinely for adenovirus infection, and few well-designed studies have evaluated efficacy and adverse effects adequately. The use of

intravenous cidofovir or aerosolized or intravenous ribavirin has been reported in case reports and case series of severely ill patients who have received allogeneic stem-cell transplants and those who have received anti-T-cell immunosuppressive regimens following transplant or for cancer therapy. Cidofovir is associated with nephrotoxicity, and intravenously administered ribavirin with anemia. Vidarabine has been used for treatment of adenovirus-associated hemorrhagic cystitis. To enhance the ability of the immunosuppressed host to respond to adenoviral infection, clinicians have reported use of intravenous immunoglobulin, lymphocyte transfusion, and reduction or withdrawal of therapy in stem-cell transplants.

Prevention

The only currently available means to prevent adenoviral infection is through infection control measures. Although a vaccine was used for a time in the United States to prevent outbreaks of respiratory illness associated with adenovirus in military recruits, it has not been manufactured since 1996.

The practice of Standard Precautions (www.cdc.gov), in which all body fluids, secretions, or excretions are assumed to be potentially infectious regardless of whether they contain visible blood, can interrupt transmission of adenovirus in health care settings. Briefly, Standard Precautions involve the use of appropriate hand hygiene, gloves, and other barrier precautions. When a child has a laboratory-diagnosed adenoviral infection or a clinical syndrome characterized by rash, respiratory infection, or diarrhea, empiric use of Transmission-based Precautions should be implemented in addition to Standard Precautions. For example, Contact Precautions would be used empirically for patients who have diarrhea and contact and droplet precautions for those who have respiratory infections. To prevent transmission between uninfected and infected children, contact between them should be minimized where possible. Waiting room toys and inanimate surfaces in the office that are touched frequently should be cleaned and decontaminated regularly.

Outbreaks of adenovirus have occurred in crowded settings such as in military training, summer camps, child care, and institutions. Children who have symptoms of active adenoviral illness, such as diarrhea or conjunctivi-

tis, should be excluded from child care until the symptoms have resolved.

Most outbreaks of pharyngoconjunctival fever can be prevented by adequate chlorination of swimming pools or avoidance of contaminated lakes.

Adenovirus as a Gene Delivery Vector

Adenovirus has been explored as a means to deliver genes to the nucleus of human cells. Components of the adenoviral genome are deleted and replaced with therapeutic genes. Among the potential uses of such vectors are supplementation of functional genes to cells with defective genes and delivery of therapeutic genes to cancer cells or to infected cells. Adenovirus is appealing as a vector because it can infect a variety of cell types, the genome has the potential to be manipulated to avoid producing infectious pathogenic virions, and gene expression occurs in large quantities. Large-scale human studies have not been conducted to date. Death following use of an attenuated adenovirus gene delivery vector occurred in a teenage boy and was attributed to a massive inflammatory response to the adenovirus. To solve the problem of the immunogenicity of the adenovirus vector, scientists have attempted to create “gutless” vectors in which all nonessential viral genes are deleted. Another challenge of using adenovirus as a vector is the high frequency of pre-existing antibody in the general population because infection is so common.

Suggested Reading

- Chaberny IR, 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;124:514–519
- Enders JF, Bell JA, Dingle JH, et al. “Adenoviruses”: group name proposed for new respiratory tract viruses. *Science*. 1956;124:119–120
- Erdman DE, Xu W, Gerber SI, et al. Molecular epidemiology of adenovirus type 7 in the United States, 1966–2000. *Emerg Infect Dis*. 2003;8:269–277
- Ljungman P. Treatment of adenovirus infections in the immunocompromised host. *Eur J Clin Microbiol Infect Dis*. 2004;23:583–588
- Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. *Clin Infect Dis*. 1998;27:1194–2000
- Teper AM, Kofman CD, Maffey AF, Vidaurreta SM. Lung function in infants with chronic pulmonary disease after severe adenoviral illness. *J Pediatr*. 1999;134:730–733

PIR Quiz

Quiz also available online at www.pedsinreview.org.

9. You are evaluating a 2-year-old boy who has conjunctivitis, rhinitis, cough, and fever. Enzyme immunoassay for adenovirus is positive. He is not in child care, and his mother asks you how he could have caught this infection. Of the following, the *least* likely mode of transmission for this virus is:
 - A. Airborne.
 - B. Direct contact.
 - C. Droplet.
 - D. Fecal-oral.
 - E. Indirect contact.
10. Which of the following statements regarding the clinical manifestations of adenovirus is true?
 - A. Adenovirus infection is very unlikely in the absence of conjunctivitis.
 - B. Adenovirus is the etiologic agent in more than 50% of cases of exudative pharyngitis in childhood.
 - C. Gastrointestinal adenovirus infection typically causes vomiting in the absence of diarrhea.
 - D. Hemorrhagic cystitis is seen primarily in children who have abnormalities of the urinary tract.
 - E. Neurologic manifestations of adenovirus infections can occur without any evidence of respiratory symptoms.
11. A 15-month-old girl is admitted to the hospital with gastroenteritis and dehydration. Rapid antigen detection confirms the diagnosis of adenovirus. Which of the following precautions should be implemented for this patient?
 - A. Airborne precautions and standard precautions.
 - B. Contact precautions and droplet precautions.
 - C. Contact precautions and standard precautions.
 - D. Droplet precautions and standard precautions.
 - E. Standard precautions only.
12. Which of the following statements regarding the treatment and prevention of adenovirus infections is true?
 - A. A child may return to child care at anytime after adenoviral gastroenteritis is diagnosed.
 - B. Antiviral agents used for the treatment of adenoviral infections are not associated with serious adverse effects.
 - C. Children who have pneumonitis caused by adenovirus should receive treatment with antiviral agents regardless of immunologic status.
 - D. Child care contacts of a child who is known to have adenovirus infection should be given adenovirus vaccine to prevent the spread of the infection.
 - E. Immunocompetent children who have pharyngoconjunctival fever can be treated symptomatically without antiviral agents.