Adenovirus: Epidemiology, Global Spread of Novel Serotypes, and Advances in Treatment and Prevention

Joseph P. Lynch III, MD1 Adriana E. Kajon, PhD2

1Division of Pulmonary, Critical Care Medicine, Allergy, and Clinical Immunology, Department of Internal Medicine, The David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California
2Department of Infectious Disease, Lovelace Respiratory Research Institute, Albuquerque, New Mexico

Address for correspondence Joseph P. Lynch, III, MD, Division of Pulmonary, Critical Care Medicine, Allergy, and Clinical Immunology, Department of Clinical Medicine, Step VIII, The David Geffen School of Medicine at University of California, Los Angeles, 10833 Le Conte Avenue, Room CHS 37-131, Los Angeles, CA 90095 (e-mail: jplynch@mednet.ucla.edu).


Abstract

Adenoviruses (AdVs) are DNA viruses that typically cause mild infections involving the upper or lower respiratory tract, gastrointestinal tract, or conjunctiva. Rare manifestations of AdV infections include hemorrhagic cystitis, hepatitis, hemorrhagic colitis, pancreatitis, nephritis, or meningoencephalitis. AdV infections are more common in young children, due to lack of humoral immunity. Epidemics of AdV infection may occur in healthy children or adults in closed or crowded settings (particularly military recruits). The disease is more severe and dissemination is more likely in patients with impaired immunity (e.g., organ transplant recipients, human immunodeficiency virus infection). Fatality rates for untreated severe AdV pneumonia or disseminated disease may exceed 50%. More than 50 serotypes of AdV have been identified. Different serotypes display different tissue tropisms that correlate with clinical manifestations of infection. The predominant serotypes circulating at a given time differ among countries or regions, and change over time. Transmission of novel strains between countries or across continents and replacement of dominant viruses by new strains may occur. 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. Live oral vaccines are highly efficacious in reducing the risk of respiratory AdV infection and are in routine use in the military in the United States, but currently are not available to civilians.

Keywords
► adenovirus
► respiratory viral infections
► serotypes
► cidofovir

Adenoviruses (AdVs) are DNA viruses that typically cause mild infections involving the upper or lower respiratory tract, gastrointestinal tract, or conjunctiva. Rare manifestations of AdV infections include hemorrhagic cystitis, hepatitis, hemorrhagic colitis, pancreatitis, nephritis, or meningoencephalitis. AdV infections are more common in young children, due to lack of humoral immunity. Epidemics of AdV infection may occur in healthy children or adults in closed or crowded settings (particularly military recruits). The disease is more severe and dissemination is more likely in patients with impaired immunity (e.g., organ transplant recipients, human immunodeficiency virus infection). Fatality rates for untreated severe AdV pneumonia or disseminated disease may exceed 50%. More than 50 serotypes of AdV have been identified. Different serotypes display different tissue tropisms that correlate with clinical manifestations of infection. The predominant serotypes circulating at a given time differ among countries or regions, and change over time. Transmission of novel strains between countries or across continents and replacement of dominant viruses by new strains may occur. 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. Live oral vaccines are highly efficacious in reducing the risk of respiratory AdV infection and are in routine use in the military in the United States, but currently are not available to civilians.

Immunosuppressed persons2,7–9 are more susceptible.3,10–15 High baseline immunity against AdV (IgG titer of ≥ 1:32) confers substantial protection.16 AdV infections may occur in healthy children3,10–13 or adults in closed or crowded settings (particularly military recruits).17–21 The vast majority of cases are self-limited. However, the clinical spectrum is broad, and dissemination or pneumonia can be fatal, both in immunocompetent22,23 and immunocompromised patients.2,9,24–28
Virology

Human AdVs are a group of double-stranded nonenveloped DNA viruses belonging to the genus Mastadenovirus of the Adenoviridae family.\textsuperscript{29,30} Currently, 51 serotypes, and over 70 genotypes defined by bioinformatics analysis of complete genomic sequences and designated with consecutive numbers (52, 53, 54, etc.) have been described and classified within 7 species (HAdV-A through HAdV-G).\textsuperscript{31–37} Species A, B, C, D, E, and F circulate globally, and have been implicated in outbreaks of infection in humans.\textsuperscript{1} Different genome types (or genomic variants) can be distinguished within the same serotype by restriction enzyme analysis of genomic DNA.\textsuperscript{38–40} Approximately one-third of the described serotypes are associated with human disease.\textsuperscript{24,26,29,31,41–44} Different serotypes display different tissue tropisms that correlate with clinical manifestations of infection\textsuperscript{2,26,31,33} (discussed in detail in the next sections).

Epidemiology

AdVs may cause epidemics of febrile respiratory illness (FRI), pharyngoconjunctival fever,\textsuperscript{45} keratoconjunctivitis (KC),\textsuperscript{46–49} or gastroenteritis and diarrheal illness.\textsuperscript{50–61} Severe or disseminated AdV infections may occur in immunocompromised hosts\textsuperscript{7,9,62–64} and rarely in immunocompetent patients.\textsuperscript{23,65}

Most epidemics occur in the winter or early spring,\textsuperscript{6} but infections occur throughout the year with no clear seasonality.\textsuperscript{2} Infection can result from exposure to infected individuals (inhalation of aerosolized droplets, conjunctival inoculation, fecal oral spread),\textsuperscript{1,2,66,67} acquisition from exogenous sources (e.g., pillows, linens, lockers, guns),\textsuperscript{58,69} or reactivation.\textsuperscript{2,26} Incubation period ranges from 2 to 14 days.\textsuperscript{2} Importantly, latent AdV may reside in lymphoid tissue,\textsuperscript{7,70} renal parenchyma,\textsuperscript{71} or other tissues for years; reactivation may occur in severely immunosuppressed patients.\textsuperscript{7,70,71} Asymptomatic carriage of AdV may persist for weeks or months.\textsuperscript{31,72,73} Epidemics may spread rapidly among closed populations\textsuperscript{16,17,20,33,40,44,68,74–76} (e.g., hospitals,\textsuperscript{6,67,77} neonatal nurseries,\textsuperscript{78} psychiatric\textsuperscript{77,79} or long-term care facilities,\textsuperscript{48,66,80} job training centers,\textsuperscript{21} boarding schools or dormitories,\textsuperscript{81} a children’s home,\textsuperscript{82} orphanages,\textsuperscript{83} public swimming pools\textsuperscript{84,85}). In institutionalized settings, infection control measures and cohorting may be essential to limit spread.\textsuperscript{66,67,86} AdV is resistant to many disinfectants\textsuperscript{87} but 95% ethanol solution is an effective disinfectant.\textsuperscript{73}

Clinical Features of Adenovirus Infection

Respiratory Tract Involvement

AdV accounts for at least 5 to 10% of pediatric and 1 to 7% of adult respiratory tract infections (RTIs).\textsuperscript{2,31} Typical symptoms of AdV RTI include fever, pharyngitis, tonsillitis, cough, and sore throat.\textsuperscript{3,19} GI symptoms may be present concomitantly, particularly in children.\textsuperscript{3,13,19,88} In immunocompetent patients, symptoms usually abate spontaneously (within 2 weeks) and infection induces type-specific immunity.\textsuperscript{2} Pneumonia occurs in up to 20% of newborns and infants\textsuperscript{3,10,12,88,89} but is uncommon in immunocompetent adults.\textsuperscript{2,16,17,77,79,90,91} However, fatalities due to AdV pneumonia have been described in previously healthy children\textsuperscript{10} or adults.\textsuperscript{19,23,65,79,90} In immunocompromised persons, dissemination and/or severe respiratory failure develop in 10 to 30% of cases\textsuperscript{2,9,27,38} and fatality rates for severe AdV pneumonia may exceed 50%.\textsuperscript{2,9,90} (\textsuperscript{\textcopyright}Fig. 1). In children, long-term respiratory sequelae of AdV RTI include bronchiectasis, bronchiolitis obliterans, and hyperlucent lungs.\textsuperscript{92–94} AdVs have a propensity to establish latent or
persistent infection within the upper
tissues, and lower respiratory
tracts. Persistent AdV infection in children may elicit chronic
neutrophilic inflammation within the airways, protracted bacterial
bronchiolitis and bronchietasis. AdVs (particularly
types 1–5, 7, 14, and 21) have been associated with small airs
dysfunction and bronchiectasis in children and chronic
obstructive pulmonary disease in adults. These various
studies suggest that HAdV is not an innocent bystander in the
predominant symptoms of gastroenteritis or diarrhea.

Keratoconjunctivitis

Manifestations of ocular AdV infection include: epidemic KC
(EKC), pharyngoconjunctival fever, and nonspecific conjunctivi-
tis. The most common serotypes associated with EKC are
AdV-8, -19, and -37,9,105,112 but other serotypes (e.g.,
AdV-3, -4, -7, -11, and -14) can also cause conjunctivi-
tis.66,74 Outbreaks of EKC can occur in hospitals or outpatient
clinics; chronic care facilities; and closed settings.117 Nosocomial transmission has been noted in
eye clinics or hospitals via environmental contamination (oph-
thalmic instruments, eyewears).103,115,118 Rigorous sterilization of
instruments and strict infection control were essential to curb
epidemics.103,115 The recently described genotypes 53, 54, and
56 of species HAdV-D have been reported in association with
outbreaks of EKC.119–124

Gastrointestinal Manifestations

AdV infections can cause GI symptoms even when the primary
site of involvement is the respiratory tract (particularly in
young children).3,13,88,125 Some serotypes (notably AdV-40
and -41) have an affinity for the GI tract,50,53,54,57 with
predominant symptoms of gastroenteritis or diarrhea.126 Rare complications include hemorrhagic colitis,2,7,127 hepatici-
tis,27,128–131 cholecystitis,132 and pancreatitis.133,134

Urinary Tract Involvement

AdV may cause urinary tract infections (UTIs),135 particularly
among hematopoietic stem cell transplant (HSCT)131,136–139
and solid organ transplant (SOT) recipients.140–143 Typical
manifestations include dysuria, hematuria, hemorrhagic cyst-
itis (HC), and renal allograft dysfunction.141,142,144,145 Most
AdV UTIs (including HC) are self-limiting13,71,140,144 but fatal
or dialysis-dependent renal failure.146–148 fatal dissemina-
tion,149,150 necrotizing tubulointerstitial nephritis,148,151 or
obstructive uropathy151 have been described. Most common
serotypes associated with HC include: AdV-11, -34, -35, -3, -7,
and -21.2,142,144,148 The diagnosis may be confirmed by
culture or polymerase chain reaction (PCR) in urine, or
serology.2,137 Renal biopsy may demonstrate viral infection
of tubular epithelial cells, with “smudge cells” and
intranuclear inclusions.147,148 AdV urethritis has also been
described.152

Disseminated Disease

Disseminated AdV infections are rare among immunocom-
petent hosts, but dissemination occurs in 10 to 30% of HSCT
recipients with AdV infection.2,25,26,38,153–155 Diagnosis is
made by PCR in blood and/or detection (or recovery) of
AdV from more than one site. Among HSCT recipients with
symptomatic AdV disease, fatality rates range from 12 to
70%,25,153,156–158 Case fatality rates for AdV pneumonia may exceed 50%.27,90

Rare Manifestations

Rare manifestations of AdV infections include: encephali-
tis, meningitis, myocarditis and cardiomy-
opathy, mononucleosis-like syndrome, pulmonary
dysplasia, intestinal intussusception in children; sudden
infant death.171

Specific Patient Populations at Risk

Adenovirus Infections in Immunocompetent Persons

Epidemics of AdV respiratory infection may occur in healthy
children (particularly < 4 years old)1,10–13,172 or adults in
closed settings (particularly the military).17,19–21,173 The vast
majority of cases are self-limited; disseminated and fatal
infections are rare in immunocompetent hosts.19,90

Adenovirus Infections in Military Recruits

AdV accounts for > 50% of FRI and pneumonia cases among
unvaccinated military recruits;16,17,20,33,68,69,173 not only in
the United States19,40,74 but globally.44,75 Military recruits are
especially vulnerable during basic training, owing to crowding
and stresses.19 In a survey of eight military training sites in the
United States from 2004 to 2009, > 21,000 cases of FRI or
pneumonia were detected; AdV was implicated in 63.6%;
influenza, in only 6.6%.76 Peak illness rates occur during
weeks 3 to 5 of training.20 In a prospective study of 271 new
military recruits in training, 25% developed an acute FRI due to
AdV-4 over a 6-week period; all FRIs occurred among recruits
with an initial AdV antibody titer of < 1:4.69 Serum antibodies to
AdV-4 were present in 34% at enrollment, and 97% by
6 weeks.69 Following completion of basic training, recruits
are dispersed to secondary sites, paving the way for epidemic
spread.86 Historically, serotypes AdV-7 and -4 predominated
as a cause of FRIs in the military in the United States.16,17,40
Beginning in 1971, all recruits in the United States military
were vaccinated with live enteric-coated AdV-4 and -7
vaccines.174 Following this strategy, the incidence of AdV
infections in the military setting plummeted.174 In 1995, the
sole manufacturer of the AdV vaccines ceased production;
existing supplies were completely depleted by 1999.19 In 1996,
the last year AdV vaccines were given to recruits year round,
AdV-21 was the most prevalent type, implicated in 58% of AdV
infections; AdV-4 and -7 were each implicated in only 4%.175
The lack of availability of vaccines led to re-emergence of
epidemics of AdV infections in military facilities in the
United States.19,20,40,74,176–178 Surveillance of U. S. recruits in
training cited > 73,000 AdV infections from 1999 to 2004;
serotype 4 accounted for > 95% of AdV infections.20 In a large
surveillance study of eight military recruit training centers in
the United States from 2000 to 2011, AdV-4 was implicated in
80% of AdV infections; the remaining 20% comprised AdV-14,
-21, -3, and -7.175 In 2006 and 2007, a novel strain of AdV-14
emerged as a cause of FRIs in recruits at a U. S. Air Force base, and became the predominant strain in the military.

Beginning in October 2011, after a 12-year hiatus, the administration of live nonattenuated oral vaccines against AdV-4 and -7 to U. S. military recruits was resumed. From 1996 to 2013, FRI surveillance was performed at eight military training centers in the United States. During the 2 years after reintroduction of the vaccine, AdV burden declined 100-fold (from 5.8 to 0.02 cases per 1,000 person weeks, p < 0.001). Although the percentage of type 14 increased following reintroduction of the vaccine, the mean annual number of AdV-14 infections decreased (from 610 in 2000 to 2011 to 44 in 2013). Continuing to vaccinate all incoming recruits will reduce cases among trainees, and may reduce transmission to other geographical locations and to civilians. Future surveillance studies will monitor AdV infection rates and pay attention to emergence of AdV types not targeted by the vaccines.

Hematopoietic Stem Cell Transplant Recipients

The incidence of AdV infections among HSCT recipients is highly variable (range, 3–47%). The incidence is much higher among allogeneic (range, 5–47%) compared with autologous (range, 2.5–14%) HSCT recipients. Higher rates of AdV infections reflect prospective studies with regular (often weekly) sampling of plasma for AdV DNA (by PCR). The incidence is 2 to 3.5 times higher in children (≥20%) compared with <10% in adults. Additional risk factors for AdV infections among HSCT recipients include: allogeneic HSCT; 

Solid Organ Transplant Recipients

The incidence of AdV infections among SOT recipients is 5 to 22%, usually within the first 6 months posttransplantation. AdV infections have been noted in liver, renal, intestinal, and lung transplant recipients. Among SOT recipients, risk factors for AdV include: pediatric age, donor-positive/recipient-negative AdV status, receipt of antilymphocyte antibodies. In a prospective study, AdV viremia (by PCR) was detected within 12 months of transplant in 19/263 (7.3%) SOT recipients including: liver, 10/121 (8.3%); kidney, 6/92 (6.5%); heart, 3/45 (6.7%). At the time of viremia, 11 (58%) were asymptomatic. All recovered spontaneously without sequelae. In a retrospective review of 484 pediatric liver transplant recipients, 49 (10%) developed AdV infections; 9 died of invasive AdV infection. In another retrospective review of 191 adult liver transplant recipients, 11 (5.8%) had AdV infection, and 2 AdV-associated deaths were documented. Clinical manifestations of AdV infection are protean, but the primary site of disease in SOT recipients is often related to the transplanted organ.

In liver transplant recipients, AdV typically causes hepatitis, jaundice, and hepatomegaly. In renal transplant patients, HC is the principal symptom; further, AdV may target the renal allograft, leading to graft failure. In pediatric heart transplant recipients, the presence of AdV in posttransplant endomyocardial biopsies increased the risk for graft loss and posttransplant coronary artery disease. In a cohort of 383 lung transplant recipients, only 4 AdV infections were identified; incidence was 3/40 (8%) among pediatric LTR and 1/268 (0.4%) among adult LTR. However, all four developed severe hemorrhagic, necrotizing AdV pneumonia; all died within 45 days of transplant. In another study of 19 pediatric LTR, 8 developed AdV, resulting in 2 early deaths, as well as late graft loss and obliterator bronchiolitis. A case of fatal AdV pneumonia in an adult LTR 4 years posttransplant was described. Although AdV can cause fatal infections in SOT recipients, indications for treatment with CDV for mild infections have not been established. AdV viremia may be asymptomatic, and may clear spontaneously. Routine PCR surveillance is not recommended in adult SOT recipients. Further, treatment (with CDV) should be reserved for symptomatic patients or those with pneumonia or disseminated infection.
Human Immunodeficiency Virus Infection

AdV infections occur in 12 to 28% of human immunodeficiency virus (HIV)-infected patients. In one prospective study of 63 HIV+ patients, 18 (28%) developed AdV infections within 1 year (17% if CD4 count was >200/mm3 vs. 38% if the CD4 count was <200/mm3). In Nigeria, 30% of 184 HIV-infected patients had serological evidence for AdV infection. The GI tract is involved in >90%, but most patients are asymptomatic or have mild symptoms (e.g., diarrhea). UTIs occur in up to 20% of AIDS patients but HC is rare. Serotype D is associated with GI infection whereas UTIs are usually caused by serotypes B or D. AdV (particularly serotypes 1 to 3) may cause fatal cases in HIV-infected patients. Since the availability of highly active antiretroviral therapy, AdV disease is uncommon in HIV/AIDS patients until immune system deterioration occurs.

Congenital Immunodeficiency Syndromes

AdV infection may complicate congenital immunodeficiency disorders such as severe combined immunodeficiency syndrome, common variable immunodeficiency, agammaglobulinemia, immunoglobulin A deficiency, and others. In patients with severe immunodeficiency, AdV tends to cause severe and recurrent pulmonary infections, disseminated disease, and even death.

Importance of Serotypes

Globally, serotypes 1 to 5, 7, 21, and 41 are most commonly associated with human disease (Table 1). Different serotypes display different tissue tropisms and clinical manifestations of infection. Among children, the most common AdV serotypes associated with RTI are types 1 to 7 and an intertypic recombinant H11F14 designated as genotype 55. In adults, serotypes most often implicated in FRI include: AdV-1 to 7, -21, and -14. The GI tract is involved in >90%, but most patients are asymptomatic or have mild symptoms (e.g., diarrhea). UTIs occur in up to 20% of AIDS patients but HC is rare. Serotype D is associated with GI infection whereas UTIs are usually caused by serotypes B or D. AdV (particularly serotypes 1 to 3) may cause fatal cases in HIV-infected patients. Since the availability of highly active antiretroviral therapy, AdV disease is uncommon in HIV/AIDS patients until immune system deterioration occurs.

Molecular Characterization of Adenovirus

Different genome types within serotypes have been identified by restriction enzyme analysis, multiplex PCR techniques targeting fiber genes or hexon genes or sequencing of the fiber genes and hexon genes. The widely used genome typing system was proposed and modified by Li et al. The prototype AdV strain is designated "p"; other genome types within the serotype are designated "a" through "k" based on their distinct BamHI digestion profiles. Genome types may be further distinguished by restriction pattern with additional selected enzymes (e.g., AdV-7p, AdV-7p1, etc.). This system has been used to correlate intraserotypic genetic variability with geographic distribution and pathogenic potential.

Whole Genome Sequencing and Designation of Viruses Described by Bioinformatics Analysis of Complete Genomic Sequences

Rapidly advancing sequencing technologies at affordable costs have allowed relatively easy access to complete genomic sequence data for human AdV strains expanding the information on the genetic makeup of several viruses of medical importance and contributing to a better understanding of AdV evolution.

Novel genomes representing cases of intertypic recombination or viruses with truly novel hexon, penton base or fiber genes have been under consideration as candidate new types and designated with numbers consecutive to the original set.

Table 1: Adenovirus serotype according to geographic region

<table>
<thead>
<tr>
<th>Country</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>7</th>
<th>21</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States (2004–2007) (civilians)</td>
<td>17.7%</td>
<td>24.3%</td>
<td>34.6%</td>
<td>4.8%</td>
<td>3.0%</td>
<td>2.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>United States (2004–2007) (military)</td>
<td>NA</td>
<td>NA</td>
<td>2.6%</td>
<td>92.8%</td>
<td>NA</td>
<td>2.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Toronto (2007–2008)</td>
<td>18%</td>
<td>26%</td>
<td>46%</td>
<td>4.8%</td>
<td>NA</td>
<td>5.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Korea (1991–2007)</td>
<td>9.2%</td>
<td>11.2%</td>
<td>37%</td>
<td>3.9%</td>
<td>23.3%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Taiwan (1981–1989)</td>
<td>NA</td>
<td>6%</td>
<td>68%</td>
<td>0%</td>
<td>3%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Taiwan (2000)</td>
<td>NA</td>
<td>6%</td>
<td>36%</td>
<td>28%</td>
<td>21%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Taiwan (2001)</td>
<td>NA</td>
<td>15%</td>
<td>2%</td>
<td>52%</td>
<td>1%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Taiwan (2004–2005)</td>
<td>4.1%</td>
<td>6.4%</td>
<td>87.2%</td>
<td>0.6%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>United Kingdom (1982–1996)</td>
<td>12.1%</td>
<td>18.6%</td>
<td>14.9%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
Source: Reproduced with permission from Lynch et al.
of 51 used to designate HAdV serotypes. The criteria for designation remain a matter of active debate.241

Global Epidemiology

The predominant serotypes detected in association with disease differ among different countries or regions, and change over time.3,12,31,40,86,242–245 Transmission of novel strains between countries or across continents and replacement of dominant serotypes by new strains may occur.33,246

Serotypes 1 to 7 account for > 80% of AdV infections in infants and children.31,247 The most common serotypes reported in the United States,161 Canada,5 the United Kingdom,248 Taiwan,11 and South Korea31 are displayed in Table 1. Striking differences in distribution of serotypes have been noted in civilian and military populations161 (Table 1).

In South America, AdV-7 has been a predominant strain associated with RTI requiring hospitalization in many countries.10,224 In Brazil, AdV-7 was the predominant serotype for decades, but an outbreak of AdV-3 occurred in 2000.10 In Asia, AdV-3 and -7 have been the predominant serotypes associated with RTI in children.3,11–13,249

Documented changes in relative prevalence of serotypes and genomic variants among geographic regions underscore the potential for new strains to emerge and replace existing strains.10–12,40,65,244,246,250–252 For interested readers, we discussed the epidemiology and temporal changes in circulating genomic variants globally in greater detail in a review in 2011.1

Epidemiology and Characteristics of Specific Serotypes

Given the large number of AdV serotypes, a discussion of each serotype is beyond the scope of this review. However, we will discuss a few of the commonly detected serotypes (e.g., AdV-1, -2, -3, -4, -7, and -21), additional serotypes associated with specific clinical syndromes (e.g., AdV-8, -37, -40, -41, and -55) and the recent emergence of AdV-14 in the United States.

Adenovirus Serotypes 1 and 2

Serotypes AdV-1 and -2 (both species C) are common causes of acute FRI worldwide, but appear to be less virulent than AdV-7.111,224,246 or -3.88,224 However, a nosocomial outbreak of severe pneumonia in immunocompetent hosts due to AdV-1 was recently described in France.253 The prevalence of AdV-1 and -2 varies among different geographic regions and populations. In the United States (2004–2006), AdV-1 and -2 accounted for 17.6 and 24.3% of AdV clinical respiratory isolates among civilians (children or adults), respectively, but only 0.4 and 0.4% among military recruits.161 The prevalence of these serotypes at other sites is variable: that is, Toronto, Canada (2007–2008), AdV-1 (18%); AdV-2 (26%); United Kingdom (1982–1996), AdV-1 (12.1%); AdV-2 (18.6%); Buenos Aires (1984–1988); AdV-1 (10%); AdV-2 (20%); Seoul, Korea (1990–98); AdV-1 (9.2%); AdV-2 (11.2%).88

Adenovirus Serotype 3

Globally, AdV-3 is among the most common serotypes implicated in AdV infections in children and adults.3,84,161,251 AdV accounted for 13% of AdV respiratory isolates reported to the World Health Organization from 1967 to 1976 and remains a cause of endemic and epidemic infections3,5,19,161,248 (Table 1). In the United States and southern Ontario from 2004 to 2006, AdV-3 accounted for 34.6% of AdV RTI in civilians but only 2.6% among military trainees.161 The prevalence of AdV-3 at other sites is variable: that is, Toronto, Canada (2007–2008), (46%); United Kingdom (1982–1996), (14.9%); Seoul, Korea (1990–1998), (15%); Seoul, Korea (1991–2007), (37.0%).31 In Taiwan, AdV-3 was the predominant serotype in 1981–1989 (68%) and 1990–1998 (44%) but decreased to 2% of respiratory isolates in 2001 (largely replaced by AdV-4 and -7). During an outbreak of respiratory AdV infections in children from November 2004 to February 2005 in Taiwan, AdV-3 was implicated in 87.5% of the cases.3 AdV-3 may cause fatal pneumonias in immunocompetent children249,254 and adults.65 AdV-3 and a recombinant strain of AdV-3/7 were responsible for an outbreak of FRIs (including two fatalities) in children in Portugal in 2004.254

Adenovirus Serotype 4

AdV-4 is a cause of sporadic infections in civilians25 and has been implicated in epidemic outbreaks of FRI or pneumonia in civilian11,255 and military18,20,74,177 populations. In civilian populations, AdV-4 was implicated in 4.8% of AdV RTI in the United States (2004–2006)31; 1% in Toronto, Canada (2007–2008)5; 3.9% (pediatric isolates) in South Korea (1991–1997).31 In Taiwan, AdV-4 accounted for 29% of pediatric respiratory isolates from 1981–2001, and became the predominant serotype (52%) in 2001.11 Until recently, AdV-4 was the most common serotype associated with FRI in military recruits in the United States.18,80,177,256 The strategy of vaccinating all military recruits against AdV-4 and -7 beginning in 197174,257 eliminated both serotypes as causes of epidemic of FRI in the military for more than two decades.80 After the vaccine was depleted, an outbreak of AdV-4 occurred at an Army basic training site in 1997.74 Over the next several years, AdV-4 spread to multiple secondary sites.50 From 1999 to 2004, AdV-4 accounted for > 95% of AdV FRI among military recruits in the United States.20 By 2006 to 2007 the emerging AdV-14 largely replaced AdV-4 as a cause of AdV FRI among military recruits in the United States.33 After a 12-year interruption in vaccination the original vaccine formulation was reintroduced in October of 2011 resulting in a dramatic decline in the rates of AdV-associated febrile illness among recruits in training.175

Adenovirus Serotype 7

Globally, AdV-7 was the third most common serotype reported to the World Health Organization from 1967 through 1976, following AdV-1 and -2.84 and remains one of the leading serotypes detected in association with disease globally.31,40,258 AdV-7 infections manifest as FRI,
Adenovirus Serotype 8

AdV-8 accounts for <1% of AdV infections, but is a common cause of EKC in Asia and the Middle East. In four studies, AdV-8 accounted for 64 to 79% of EKC due to AdV. In a neonatal intensive care unit in Turkey, cases of conjunctivitis due to AdV-8 were linked to a contaminated eyelid speculum.

Adenovirus Serotype 11

AdV-11 is relatively uncommon, but may cause hemorrhagic conjunctivitis and FRI (including pneumonia) in immunocompetent patients and HC in immunocompromised patients. In the United States from 2004 to 2006, AdV-11 accounted for <1% of AdV RTIs in military recruits and civilians; in Toronto, Canada, AdV-11 was not detected among 96 clinical respiratory AdV isolates. AdV-11 comprised 3.4% of 741 pediatric respiratory isolates from Korea from 1991 to 2007. Outbreaks of AdV-11 FRIs were described in South America, United States, Asia, the Middle East, and globally. AdV-11 may cause UTI, including HC, in organ transplant recipients (particularly children).

Adenovirus Serotype 14

AdV-14 was first isolated in the Netherlands in 1955 during an outbreak of acute respiratory disease (ARD) among military recruits. Subsequent outbreaks of ARD were described in Great Britain in 1955, Uzbekistan in 1962, and Czechoslovakia in 1963. Apart from sporadic cases in the Netherlands in the early 1970s, no cases of AdV-14 infections were reported globally between the 1960s and 2004. AdV-14 had never been identified in North America before 2006. Beginning in March 2006, outbreaks of FRI due to AdV-14 (several hundred cases) were noted in several military bases in the United States and among health care workers. By 2007, outbreaks in civilian populations were documented in at least 15 states. The severity of FRIs was variable, but fatal pneumonias were reported. Analysis of 99 isolates recovered from patients (military and civilian) with AdV FRI between December 2003 and June 2009 from different geographic locations confirmed that all isolates were identical. These isolates represented a new genomic type designated AdV-14p1 (formerly known as 14a). The complete genetic sequence of AdV-14p1 indicates a close relationship to AdV-11a, suggesting recombination between AdV-14 and -11 strains. AdV-14p1 was implicated in outbreaks of severe pneumonias in the United States and Ireland. AdV-14p1 has an increased potential for high attack rates and rates of transmission, owing to the lack of herd immunity.

Adenovirus Serotype 21

AdV-21 was associated with epidemics of FRIs in military recruits in the Netherlands in the 1960s, but only sporadic
cases were reported over the next two decades.\textsuperscript{281} In 1984 and 1985, outbreaks of AdV-21 infections in children in the Netherlands and Germany were published.\textsuperscript{281} AdV-21 has been associated with pharyngitis and conjunctivitis\textsuperscript{282} and FRF\textsuperscript{228} but is uncommon.\textsuperscript{31} In the United States from 2004 to 2006, AdV-21 accounted for 2.0 and 2.4\% of AdV RTI in civilians and military recruits, respectively.\textsuperscript{161} In Toronto, Canada (2007–2008), AdV-21 accounted for 5.5\% of clinical respiratory AdV isolates. By contrast, AdV-21 was never isolated in 741 pediatric respiratory isolates from Korea from 1991 to 2007.\textsuperscript{31} Interestingly, AdV-21 may be less transmissible than other AdV serotypes.\textsuperscript{283} However, a highly virulent strain of AdV-21 was associated with severe pneumonia cases in Germany\textsuperscript{24} and neurological\textsuperscript{284} and cardiac\textsuperscript{285} manifestations in Malaysia. Similar strains were found to circulate in the United States over the last 3 decades\textsuperscript{39} with no apparent association with severe disease among the infected young adults.

**Adenovirus Serotype 31**

AdV-31 may cause gastroenteritis in healthy children, and has been associated with severe (sometimes) fatal infections in HSCT recipients.\textsuperscript{28,157,286–288} Nosocomial transmission (seven cases) in a pediatric SCT unit was described.\textsuperscript{288}

**Adenovirus Serotype 37**

AdV-37 accounts for < 1\% of AdV infections\textsuperscript{5,31,88,161} but may cause EKC.\textsuperscript{88,103,105–109}

**Adenovirus of Species F (Serotypes 40 and 41)**

AdV of species F (serotypes 40 and 41) typically cause gastroenteritis and diarrheal illness in children.\textsuperscript{50–61} Fatalities may occur as a result of dehydration in infants.\textsuperscript{50,51} In immunocompromised hosts, fatal dissemination may occur.\textsuperscript{73,289} Epidemics have been cited in schools\textsuperscript{56} and hospitals.\textsuperscript{73} Endogenous reactivation originating from AdV persistent in mucosal lymphoid cells may occur.\textsuperscript{70} Nosocomial transmission may occur due to high AdV levels in feces.\textsuperscript{73} Shedding of these viruses may be prolonged in immunosuppressed patients.\textsuperscript{74}

**Adenovirus Genotype 55**

Infections due to AdV-55 of species B are rare, but this virus has been implicated in outbreaks of severe pneumonia and acute respiratory distress syndrome in China since 2006.\textsuperscript{89,91,200,291} This type is an intertypic recombinant with an AdV-11-like hexon gene and an AdV-14-like fiber gene.\textsuperscript{240} Several reports describing cases of respiratory infection by this unique AdV under other designations (AdV-11, 14–11 or genome type 11a, depending on the typing approach) can be found in the literature.\textsuperscript{44,292–294}

**Diagnosis of Adenovirus Infection**

AdV can be detected in affected sites (e.g., nasopharyngeal aspirates, swabs, washings, bronchoalveolar lavage, urine, stool, blood) by direct or indirect immunofluorescence, conventional or shell vial cultures, or PCR.\textsuperscript{31} Viral cultures by conventional techniques are the gold standard, but could be insensitive for certain samples (e.g., blood) and may take up to 21 days to develop the cytopathic effect.\textsuperscript{2,31} Biopsy of involved tissues may reveal AdV nuclear inclusions;\textsuperscript{2} immunohistochemical stains may identify the AdV hexon antigen in tissue.\textsuperscript{146} PCR of AdV DNA in plasma, urine, or other clinical specimens is currently the most frequently used approach to establish the diagnosis,\textsuperscript{2,194} and is highly sensitive for disseminated disease.\textsuperscript{295,296} Quantification of the viral load using real-time PCR is a useful marker to assess response to therapy.\textsuperscript{189,299} Among transplant recipients, serial PCR assays of blood and stool weekly may detect AdV disease before the onset of symptoms, and facilitate early “preemptive” therapy.\textsuperscript{26,153,188,196} In one study of 138 pediatric allogeneic SCT recipients, AdV was detected in stool samples at median of 11 days before AdV viremia.\textsuperscript{297} The role of routine surveillance is controversial although it has been increasingly used in high-risk patients (particularly HSCT recipients\textsuperscript{2}). Quantitative viral loads may not correlate with clinical presentation or disease severity.\textsuperscript{43}

Molecular typing is not routinely performed on AdV-positive clinical specimens in clinical diagnostic laboratories but has been the focus of several recently reported studies investigating the epidemiology of AdV-associated disease. Serological tests may be useful in epidemiological investigations, but are of limited practical value in individual patients.\textsuperscript{38} Determination of serotype by seroneutralization with reference sera is laborious and time-consuming and currently only performed at a few reference public health laboratories around the world. PCR-based techniques targeting the fiber genes\textsuperscript{231} or hypervariable regions of the hexon\textsuperscript{235,298} and/or sequencing of hexon genes allow definitive identification of the type/species.\textsuperscript{29,31} Molecular typing by PCR amplification and sequencing of both hexon and fiber genes has proved to be extremely valuable for the identification of intertypic recombinants.\textsuperscript{299,300}

**Therapy**

No antiviral drug has been approved to treat AdV.\textsuperscript{38} Prospective randomized controlled trials are lacking.\textsuperscript{14} CDV, a cytosine nucleotide analogue that inhibits DNA polymerase, has the greatest in vitro activity against AdV among currently available antiviral agents\textsuperscript{301–303} and is the preferred therapeutic agent.\textsuperscript{2} CDV is available only intravenously.\textsuperscript{2} Regimens (dosing, frequency, and duration) are variable. Standard doses include 5 mg/kg every 1 to 2 weeks\textsuperscript{38,188} or 1 mg/kg twice weekly.\textsuperscript{38,138,188} Duration of therapy is variable (weeks to months) and depends upon clinical response and persistence or eradication of AdV.\textsuperscript{158,188} CDV is generally well tolerated\textsuperscript{153,186,304} but adverse effects include nephrotoxicity, myelosuppression, and uveitis.\textsuperscript{2,38} Hydration and probenecid may minimize nephrotoxicity.\textsuperscript{2,143,153,201,209} Careful monitoring of renal function (serum creatinine, proteinuria) is critical. Hexadecyloxy propyl-CDV or brincidofovir (CMX001), an orally active lipophilic form of CDV, has potent activity against AdV in vitro\textsuperscript{305} and in animal models,\textsuperscript{306,307} with anecdotal successes in small clinical
series.\textsuperscript{308,309} Compared with CDV, CMX001 appears to be less nephrotoxic.\textsuperscript{310} An open-label phase 3 trial to assess safety and efficacy of CMX001 for treating AdV infections in immuno-suppressed patients is in progress (ClinicalTrials.gov identifier: NCT02087306).

Numerous nonrandomized studies in HSCT and SOT recipients documented favorable responses to CDV.\textsuperscript{25,26,28,153,158,188,192,209,231,311–317} Three studies of allelogetic HSCT recipients with AdV infections cited improved survival.\textsuperscript{22,23,317} In one study, 20/29 (69\%) of HSCT recipients with AdV infections cited improvement following indications: disseminated (\textsuperscript{22}) or extrapulmonary (\textsuperscript{23,317}) disease; 

Interpretation of these studies is confounded by heterogeneous patient populations, differing extent and sites of disease, and degree of immunosuppression or immune reconstitution.\textsuperscript{38} Intravenous immunoglobulin has been used (together with CDV), but data are insufficient to assess efficacy.\textsuperscript{25,316}

Immune reconstitution plays a critical role in controlling AdV infection.\textsuperscript{38} Increases in lymphocyte counts or CD4 counts were associated with clearance of AdV infection\textsuperscript{319,320} and improved survival.\textsuperscript{320,321} Serotype-specific neutralizing antibodies correlate with clearance of AdV.\textsuperscript{38,320} Reduction of immunosuppression,\textsuperscript{146,153} immune reconstitution of HSCT recipients,\textsuperscript{25,38} or donor leukocyte infusions\textsuperscript{28} may have adjunctive roles to treat serious or recalcitrant AdV infections. T cells are important to eradicate AdV. Adoptive transfer of AdV antigen-specific T cells may reconstitute immunity against AdV.\textsuperscript{322,323} In a recent clinical trial of HSCT recipients with AdV disease refractory to therapy, ex vivo adoptive T-cell transfer with predominately TH-1 phenotype was highly effective in clearing viremia and markedly reduced mortality.\textsuperscript{324}

Importantly, not all patients with AdV infections or viremia require treatment.\textsuperscript{2,14,43,201} High-mortality rates in retrospective studies in part reflect that virtually all patients had symptomatic AdV infections. Prospective studies in SOT\textsuperscript{196} or HSCT\textsuperscript{43} recipients using plasma PCR at regular intervals noted that up to 58\% were asymptomatic at the time of viremia, and spontaneous resolution without sequelae was common. In a cohort of SOT recipients with AdV viremia, all 19 recovered spontaneously without sequelae.\textsuperscript{196} Similarly, in a cohort of 26 pediatric HSCT recipients, 11 (42\%) developed AdV viremia that cleared without therapy in 7 (64\%).\textsuperscript{43} Two children died as a result of AdV infections. Antiviral treatment should be considered for the following indications: disseminated (\geq 2 sites) disease; pneumonia; high viral loads in blood; virulence or tropism of the viral strain; persistent severe lymphopenia or immune deficits. Further, “preemptive” therapy may have a role in viremic but asymptomatic organ transplant recipients at high risk for dissemination. Prospective, randomized trials are needed to elucidate indications for therapy in both symptomatic and asymptomatic patients with AdV infections.

**Vaccines**

Oral vaccines against AdV types 4 and 7 developed for the U.S. military in 1971\textsuperscript{20} were depleted by 1999.\textsuperscript{20} Produced by a new manufacturer, and after a new round of clinical trials\textsuperscript{179} the same live nonattenuated vaccine formulation for AdV-4 and -7 was successfully reintroduced for military use in the United States in October 2011.\textsuperscript{19} Importantly, antibodies to AdV-4 and -7 may cross-protect against other serotypes (e.g., AdV-3 and -14).\textsuperscript{86,274,325}

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