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

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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

Adenovirus

In 2011, we published a comprehensive review of adenovirus (AdV) infections in this journal[1]; this article updates new developments since that review. AdVs most often infect the upper or lower respiratory tracts, conjunctiva, or gastrointestinal (GI) tract.[1–4] More than 80% of diagnosed AdV infections occur in children < 4 years old (due to lack of humoral immunity).[2,3,5,6]

Immunosuppressed persons[2,7–9] are more susceptible.[3,10–15] High baseline immunity against AdV (IgG titer of $\geq$ 1:32) confers substantial protection.[16] AdV infections may occur in healthy children[3,10–13] 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 immunocompetent[22,23] 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.[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).[31–37] Species A, B, C, D, E, and F circulate globally, and have been implicated in outbreaks of infection in humans.[1] Different genome types (or genomic variants) can be distinguished within the same serotype by restriction enzyme analysis of genomic DNA.[38–40] Approximately one-third of the described serotypes are associated with human disease.[24,26,29,31,41–44] Different serotypes display different tissue tropisms that correlate with clinical manifestations of infection[2,26,31,33] (discussed in detail in the next sections).

Epidemiology

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

Most epidemics occur in the winter or early spring,[6] but infections occur throughout the year with no clear seasonality.[2] Infection can result from exposure to infected individuals (inhalation of aerosolized droplets, conjunctival inoculation, fecal oral spread),[1,2,66,67] acquisition from exogenous sources (e.g., pillows, linens, lockers, guns),[68,69] or reactivation.[2,26] Incubation period ranges from 2 to 14 days.[2] Importantly, latent AdV may reside in lymphoid tissue,[7,70] renal parenchyma,[71] or other tissues for years; reactivation may occur in severely immunosuppressed patients.[7,70,71] Asymptomatic carriage of AdV may persist for weeks or months.[31,72,73] Epidemics may spread rapidly among closed populations[16,17,20,33,40,44,68,74–76] (e.g., hospitals,[6,67,77] neonatal nurseries,[78] psychiatric[77,79] or long-term care facilities,[48,66,80] job training centers,[21] boarding schools or dormitories,[81] a children's home,[82] orphanages,[83] public swimming pools[84,85]). In institutionalized settings, infection control measures and cohorting may be essential to limit spread.[66,67,86] AdV is resistant to many disinfectants[87] but 95% ethanol solution is an effective disinfectant.[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).[2,31] Typical symptoms of AdV RTI include fever, pharyngitis, tonsillitis, cough, and sore throat.[3,19] GI symptoms may be present concomitantly, particularly in children.[3,13,19,88] In immunocompetent patients, symptoms usually abate spontaneously (within 2 weeks) and infection induces type-specific immunity.[2] Pneumonia occurs in up to 20% of newborns and infants,[3,10,12,88,89] but is uncommon in immunocompetent adults.[2,16,17,77,79,90,91] However, fatalities due to

AdV pneumonia have been described in previously healthy children[10] or adults.[19,23,65,79,90] In immunocompromised persons, dissemination and/or severe respiratory failure develop in 10 to 30% of cases[2,9,27,38] and fatality rates for severe AdV pneumonia may exceed 50%[2,9,90] (►**Fig. 1**).

In children, long-term respiratory sequela of AdV RTI include bronchiectasis, bronchiolitis obliterans, and hyperlucent lung.[92–94] AdVs have a propensity to establish latent or
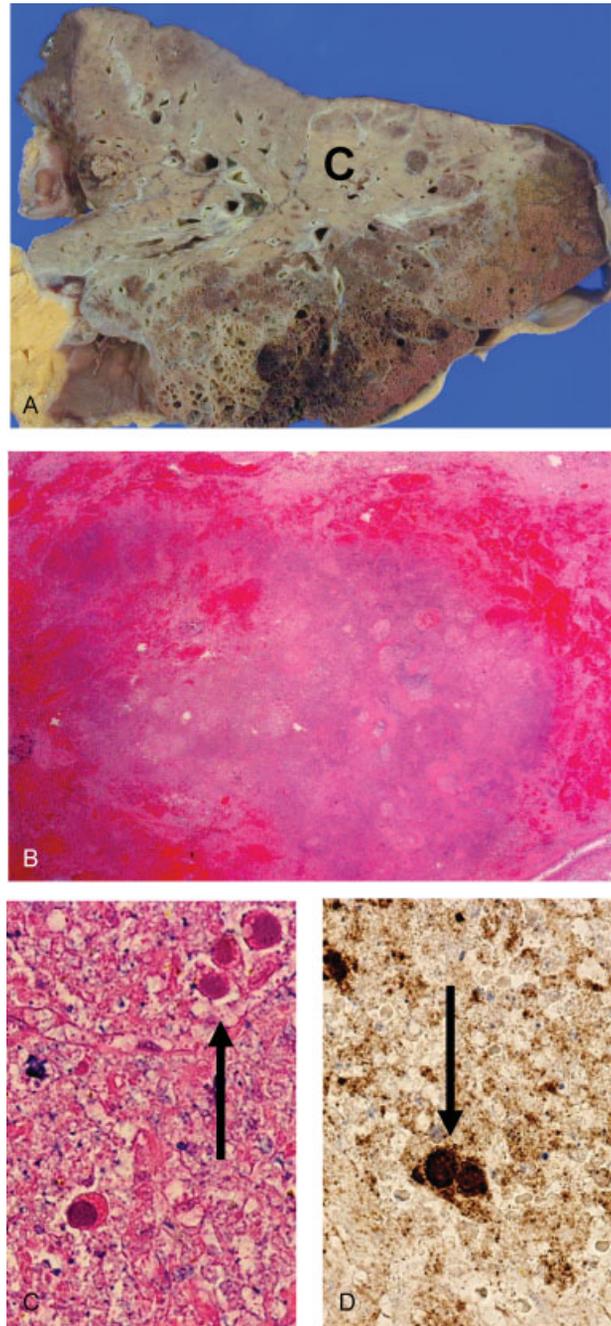

Fig. 1 Fatal case of adenovirus pneumonia. (**A**) Gross lung with pale, consolidated region, C. (**B**) Histopathology showing hemorrhagic necrotic lung tissue (hematoxylin and eosin [H & E] stain ×40. (**C**) High magnification showing three cells with intranuclear inclusions (arrow) (H & E) stain ×400. (**D**) Immunohistochemical staining for adenovirus showing positive staining of the intranuclear inclusions in two cells (arrow) (immunoperoxidase ×400). (Reproduced with permission from Lynch et al.[1])

persistent infection within the upper[95] and lower respiratory tracts.[96] Persistent AdV infection in children may elicit chronic neutrophilic inflammation within the airways, protracted bacterial bronchitis and bronchiectasis.[97–99] HAdVs (particularly types 1–5, 7, 14, and 21) have been associated with small airways dysfunction[96] and bronchiectasis in children[94,98] and chronic obstructive pulmonary disease in adults.[100,101] These various studies suggest that HAdV is not an innocent bystander in the lower airways, but may play a role in the pathogenesis of chronic suppurative endobronchial and lung disease.

Keratoconjunctivitis

Manifestations of ocular AdV infection include: epidemic KC (EKC), pharyngoconjunctival fever, and nonspecific conjunctivitis.[49,102–106] The most common serotypes associated with EKC are AdV-8, -19, and -37,[49,103,105–112] but other serotypes (e.g., AdV-3, -4, -7, -11, and -14) can also cause conjunctivitis.[46,47,105,106,108,113,114] Outbreaks of EKC can occur in hospitals or outpatient clinics,[102,103,115] chronic care facilities,[66,116] and closed settings.[117] Nosocomial transmission has been noted in eye clinics or hospitals via environmental contamination (ophthalmic instruments, eyedrops).[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,[2,27,127] hepatitis,[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)[71,136–139] and solid organ transplant (SOT) recipients.[140–143] Typical manifestations include dysuria, hematuria, hemorrhagic cystitis (HC), and renal allograft dysfunction.[141,142,144,145] Most AdV UTIs (including HC) are self-limiting[43,71,140,144] but fatal or dialysis-dependent renal failure,[146–148] fatal dissemination,[149,150] necrotizing tubulointerstitial nephritis,[148,151] or obstructive uropathy[151] 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.[2,137,142] 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 immunocompetent 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[150] 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: encephalitis[159–163]; meningitis[162,164,165]; myocarditis and cardiomyopathy[166,167];mononucleosis-like syndromes[168]; pulmonary dysplasia[169]; intestinal intussusception in children[170]; 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)[3,10–13,172] 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 States[19,40,74] 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,[33] 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.[179] From 1996 to 2013, FRI surveillance was performed at eight military training centers in the United States.[175] 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, $p < 0.001$).[175] 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).[175] Continuing to vaccinate all incoming recruits will reduce cases among trainees, and may reduce transmission to other geographical locations and to civilians.[175] 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%).[2,4,25–28,42,153–156,180–184] The incidence is much higher among allogeneic (range, 5–47%)[4] compared with autologous (range, 2.5–14%)[185–187] HSCT recipients. Higher rates of AdV infections reflect prospective studies with regular (often weekly) sampling of plasma for AdV DNA (by PCR).[153,188] The incidence is 2 to 3.5 times higher in children ($> 20\%$) compared with $< 10\%$ in adults.[38,181,182,189,190] Additional risk factors for AdV infections among HSCT recipients include: allogeneic HSCT[4,38,182]; graft versus host disease (GVHD)[2,25,27,28,153,154,156,182,191]; severe T-cell depletion[28,38,191]; human leukocyte antigen (HLA) mismatch.[38,192] Infection can reflect primary infection (e.g., community or nosocomial acquisition)[73] or reactivation of latent infection.[70,73]

AdV in HSCT recipients is usually detected within 100 days of transplant.[38,193] The disease is usually localized (e.g., urinary tract, gastroenteritis, upper or lower respiratory tract) but dissemination occurs in 10 to 30% of cases.[28,38,181,189] In this context, mortality rates are high.[38] Among 76 adult HSCT recipients with symptomatic AdV infections, mortality rate was 26%.[182] Mortality rates were higher among patients with pneumonia (73%) and disseminated disease (61%).[182] Severe lymphopenia,[2,38] severe GVHD,[28,182] isolation from more than one site,[38] and high AdV viral loads in plasma[194,195] correlate with higher mortality. In one study of 123 consecutive pediatric allogeneic HSCT recipients, 12.3% developed symptomatic AdV infections.[183] Overall survival was much worse in patients with AdV infections (15.4%) compared with noninfected subjects (50%; $p < 0.03$). In multivariate analysis, the most important risk factor for mortality was AdV infection (hazard ratio, 3.15; $p < 0.001$).[183] However, prognosis may be good, particularly when the viral load is low. A retrospective study in pediatric HSCT recipients detected AdV in blood (by PCR) in 11/26 (42%); viremia cleared in 7 (63%) without antiviral therapy.[43] In another study of 116 adult HSCT recipients who had weekly screening for AdV in blood by PCR, 14 (12.1%) developed AdV

viremia.[193] Only five were treated with cidofovir (CDV); only one died as a result of AdV infection. In another study of pediatric HSCT recipients, weekly sampling of plasma PCR identified 57 patients with AdV infections; 8 (14%) patients had disseminated disease. All 57 patients were treated with intravenous CDV; clinical and microbiological cure was achieved in 56 (98%). One patient died of AdV pneumonia.[188] Quantification of AdV DNA load by real-time PCR in plasma of HSCT recipients may identify patients at high risk for dissemination[189,194] or assess response to therapy.[189,194] However, indications for, and duration of therapy, with CDV are controversial.

Solid Organ Transplant Recipients

The incidence of AdV infections among SOT recipients is 5 to 22%, usually within the first 6 months posttransplantation.[2,4,38,156,196,197] AdV infections have been noted in liver,[198,199] renal,[140,142,146,200–202] heart,[196,203,204] intestinal,[205,206] and lung[207–209] transplant recipients. Among SOT recipients, risk factors for AdV include: pediatric age[4,38,198]; donor-positive/recipient-negative AdV status[38]; receipt of antilymphocyte antibodies.[38] 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%).[196] At the time of viremia, 11 (58%) were asymptomatic. All recovered spontaneously without sequela. In a retrospective review of 484 pediatric liver transplant recipients, 49 (10%) developed AdV infections; 9 died of invasive AdV infection.[198] In another retrospective review of 191 adult liver transplant recipients, 11 (5.8%) had AdV infection, and 2 AdV-associated deaths were documented.[199] Clinical manifestations of AdV infection are protean, but the primary site of disease in SOT recipients is often related to the transplanted organ.[38,210] In liver transplant recipients, AdV typically causes hepatitis, jaundice, and hepatomegaly.[38] In renal transplant patients, HC is the principal symptom; further, AdV may target the renal allograft, leading to graft failure.[142,146,200] In pediatric heart transplant recipients, the presence of AdV in posttransplant endomyocardial biopsies increased the risk for graft loss and posttransplant coronary artery disease.[211–213] In a cohort of 383 lung transplant recipients (LTRs), only 4 AdV infections were identified; incidence was 3/40 (8%) among pediatric LTR and 1/268 (0.4%) among adult LTR.[207] 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 obliterative bronchiolitis.[200] A case of fatal AdV pneumonia in an adult LTR 4 years posttransplant was described.[214] 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.[196] 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.[215,216] In one prospective study of 63 HIV+ patients, 18 (28%) developed AdV infections within 1 year (17% if CD_4 count was $> 200/mm^3$ vs. 38% if the CD_4 count was $< 200/mm^3$).[216] In Nigeria, 39% of 184 HIV-infected patients had serological evidence for AdV infection.[217] The GI tract is involved in $> 90\%$, but most patients are asymptomatic or have mild symptoms (e.g., diarrhea).[216] UTIs occur in up to 20% of AIDS patients,[218] but HC is rare.[38] Serotype D is associated with GI infection whereas UTIs are usually caused by serotypes B or D.[216] AdV (particularly serotypes 1 to 3) may cause fatal cases in HIV-infected patients.[38,197] Since the availability of highly active antiretroviral therapy, AdV disease is uncommon in HIV/AIDS patients until immune system deterioration occurs.[38]

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.[38,64,197,219] In patients with severe immunodeficiency, AdV tends to cause severe and recurrent pulmonary infections, disseminated disease, and even death.[38]

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.[2,26,31,33] Among children, the most common AdV serotypes associated with RTI are types 1 to 7 and an intertypic recombinant H11F14 designated as genotype 55.[31,220] In adults, serotypes most often implicated in FRI include: AdV-1 to 7, -21, and -14.[10,16–18,24,33,40,41,75,221,222] AdV-55 was implicated in outbreaks of FRI in China,[81] Singapore,[44] the Middle East,[223] United States,[21] and South America.[224] AdV-11 may cause UTIs or HC in children or transplant recipients.[33,38] Other serotypes associated with HC include: AdV-7, -33, -34, and -35.[33,225]

AdV-8, -19, and -37 are frequent causative agents of KC.[31,105,226] Gastroenteritis is most frequently associated with infection by enteric AdV-40 and -41,[9,227] but has also been reported in association with AdV-12, -18, and -31,[9] and AdV-52[32] infection. AdV-5, -31, -34, -35, and -39 have been implicated in infections in immunocompromised patients[43,51,180,220,228] (particularly HSCT[2,43,128,229,230] or SOT[142,231] recipients). Hepatitis has been reported associated with infection by serotypes 1 to 3, 5, and 7.[38,225]

Molecular Characterization of Adenovirus

Different genome types within serotypes have been identified by restriction enzyme analysis,[39,40,232] multiplex PCR techniques targeting fiber genes or hexon genes[233] or sequencing of the fiber genes[29,234] and hexon genes.[29,31,235] The widely used genome typing system was proposed and modified by Li et al.[12,236] 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.).[12,40,80] This system has been used to correlate intraserotypic genetic variability with geographic distribution and pathogenic potential.[40]

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.[35,237–240]

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

Country	1	2	3	4	7	21	41
United States (2004–2007) (civilians)[161]	17.7%	24.3%	34.6%	4.8%	3.0%	2.0%	1.7%
United States (2004–2007) (military)[161]	NA	NA	2.6%	92.8%	NA	2.4%	NA
Toronto (2007–2008)[5]	18%	26%	46%	4.8%	NA	5.5%	NA
Korea (1991–2007)[31]	9.2%	11.2%	37%	3.9%	23.3%	NA	NA
Taiwan (1981–1989)[11]	NA	6%	68%	0%	3%	NA	NA
Taiwan (2000)[11]	NA	6%	36%	28%	21%	NA	NA
Taiwan (2001)[11]	NA	15%	2%	52%	1%	NA	NA
Taiwan (2004–2005)[3]	4.1%	6.4%	87.2%	0.6%	NA	NA	NA
United Kingdom (1982–1996)[248]	12.1%	18.6%	14.9%	NA	NA	NA	10.9%

Abbreviation: NA, not applicable.
Source: Reproduced with permission from Lynch et al.[1]

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 Korea[31] are displayed in ►Table 1. Striking differences in distribution of serotypes have been noted in civilian and military populations[161] (►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[11,224,246] 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%)[5]; United Kingdom (1982–1996), AdV-1 (12.1%); AdV-2 (18.6%)[248]; Buenos Aires (1984–1988); AdV-1 (10%); AdV-2 (20%)[246]; 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[84] and remains a cause of endemic and epidemic infections[3,5,19,161,248] (►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%)[5]; United Kingdom (1982–1996), (14.9%)[248]; Seoul, Korea (1990–1998), (15%)[88]; 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[11]). 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 children[249,254] 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 civilians[5] and has been implicated in epidemic outbreaks of FRI or pneumonia in civilian[11,255] and military[18,20,74,177] populations. In civilian populations, AdV-4 was implicated in 4.8% of AdV RTI in the United States (2004–2006)[161]; 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 1971[174,257] 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.[20] 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,

pharyngoconjunctival fever, bronchitis, necrotizing bronchiolitis, or pneumonia.[40,224,259] AdV-7 appears to be more virulent than other serotypes.[11,88,224,242,249,260–262] Fatal pneumonias may occur in immunocompetent children[6,224,250,263,264] and adults.[23,265]

Epidemic AdV-7 infections have been reported in the United States,[6,264,266] Canada,[263] Latin America,[224,267] Australia,[268] Israel,[243] Korea,[75,88] Japan,[242,259] China,[12,262] the Philippines,[261] and globally.[161,243] Outbreaks typically occur in closed settings (e.g., military barracks[18,39]; chronic care facilities[80]; hospitals[6,78,269,270]). In the late 1960s, AdV-7 and -4 accounted for most cases of FRI among military recruits in the United States.[80,256] Following routine vaccination of military recruits in the United States beginning in 1971,[174,257] no epidemics of FRI were attributed to AdV-7 or -4 from 1984 through 1994.[80] However, in 1997 (after the vaccine supply was depleted), an epidemic (> 500 cases) of AdV FRI in a U. S. Navy training site was attributed to serotypes AdV-7 (70%) and AdV-3 (24%), respectively.[19] Since 2007, AdV-7 has largely disappeared as a cause of FRI in U. S. military settings (possibly replaced by AdV-14).[33]

The prevalence of AdV-7 varies according to geographic regions and over time, and depends on strain genome type, herd immunity in the region, and epidemiological settings.[6,80,161,264] In the United States from 2004 to 2006, AdV-7 accounted for only 5/581 (0.9%) of clinical AdV respiratory isolates in military facilities and 48/1,653 (2.9%) isolates in civilian settings.[161] By contrast, AdV-7 was a prominent cause of FRI in South America in the 1990s[224,267] and Asia.[12,13,31,88,242,258] AdV-7 has been recently reported in association with severe disease in several provinces of China.[262,265,271] AdV-7 was the leading cause of death due to AdV pneumonia in South America in the 1980s and 1990s.[224,267] In a study of 165 AdV RTIs in children in Argentina and Uruguay, AdV-7 accounted for 62.2% of isolates and was responsible for 17 of 18 fatalities.[224] The prevalence of AdV-7 as a cause of AdV FRI is Asia is variable, ranging from < 1[242] to > 60%.[75] In Seoul, Korea from 1990 to 1998, AdV-7 accounted for 41% of RTI (followed by AdV-3 [15%] and AdV-2 [15%]).[88] From 1991 to 2007 in Seoul, AdV-7 accounted for 23.3% of pediatric respiratory AdV isolates, second only to AdV-3 (37.0%) (►Table 1).[31] In a survey of 200 military recruits in South Korea in 2006, 122 recruits (61%) developed AdV infections; all 122 isolates were AdV-7.[75] In Taiwan, AdV-7 emerged as the predominant serotype (45%) in 1999 to 2000, but fell drastically to 1% in 2001 (replaced by AdV-4).[11] In Beijing, China, AdV-7 and -3 were the most common serotypes causing pneumonia from 1958 to 1990.[12]

At least 27 genome types of AdV-7 have been identified by restriction enzyme fragment analysis[80]; shifts or replacement of predominant genome types may occur.[40,161,243,244] In some cases, new genomic variants exhibit an apparent heightened virulence or transmissibility compared with earlier strains. For interested readers, the epidemiology, global shifts, and changing genotypes of AdV-7 were discussed in detail in our previous review.[1]

Adenovirus Serotype 8

AdV-8 accounts for < 1% of AdV infections,[5,31,88,161] but is a common cause of EKC.[88,105,107,111,116,272,273] In four studies in Asia and the Middle East, AdV-8 accounted for 64 to 79% of EKC due to AdV.[105,106,109,117] In a neonatal intensive care unit in Turkey, cases of conjunctivitis due to AdV-8 were linked to a contaminated eyelid speculum.[272]

Adenovirus Serotype 11

AdV-11 is relatively uncommon, but may cause hemorrhagic conjunctivitis[45–47,81] and FRI (including pneumonia) in immunocompetent patients and HC in immunocompromised patients.[21,81] In the United States from 2004 to 2006, AdV-11 accounted for < 1% of AdV RTI in military recruits and civilians[161]; in Toronto, Canada, AdV-11 was not detected among 96 clinical respiratory AdV isolates (►Table 1). AdV-11 comprised 3.4% of 741 pediatric respiratory isolates from Korea from 1991 to 2007.[31] Outbreaks of AdV-11 FRIs were described in South America,[224] United States,[21,274] Asia,[44,81] the Middle East,[223] and globally. AdV-11 may cause UTI, including HC, in organ transplant recipients (particularly children).[2,71,139,275]

Adenovirus Serotype 14

AdV-14 was first isolated in the Netherlands in 1955 during an outbreak of acute respiratory disease (ARD) among military recruits.[33] Subsequent outbreaks of ARD were described in Great Britain in 1955,[276] Uzbekistan in 1962,[33] and Czechoslovakia in 1963.[33] 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.[13,33] AdV-14 had never been identified in North America before 2006.[41] Beginning in March 2006, outbreaks of FRI due to AdV-14 (several hundred cases) were noted in several military bases in the United States[68,86,274,277] and among health care workers.[68] By 2007, outbreaks in civilian populations were documented in at least 15 states.[24,33,221,222,278] The severity of FRIs was variable, but fatal pneumonias were reported.[24,33,68,221,278] By 2007, AdV-14 had replaced AdV-4 as the dominant serotype on U. S. military bases.[41,274] 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.[33] These isolates represented a new genomic type designated AdV-14p1 (formerly known as 14a).[33] The complete genetic sequence of AdV-14p1 indicates a close relationship to AdV-11a, suggesting recombination between AdV-14 and -11 strains.[41] AdV-14p1 was implicated in outbreaks of severe pneumonias in the United States[33] and Ireland.[279] AdV-14p1 has an increased potential for high attack rates and rates of transmission, owing to the lack of herd immunity.[41]

Adenovirus Serotype 21

AdV-21 was associated with epidemics of FRIs in military recruits in the Netherlands in the 1960s,[280] but only sporadic

cases were reported over the next two decades.[281] In 1984 and 1985, outbreaks of AdV-21 infections in children in the Netherlands and Germany were published.[281] AdV-21 has been associated with pharyngitis and conjunctivitis[282] and FRI[228] but is uncommon.[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.[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.[31] Interestingly, Adv-21 may be less transmissible than other AdV serotypes.[283] However, a highly virulent strain of AdV-21 was associated with severe pneumonia cases in Germany[34] and neurological[284] and cardiac[285] manifestations in Malaysia. Similar strains were found to circulate in the United States over the last 3 decades[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.[28,157,286–288] Nosocomial transmission (seven cases) in a pediatric SCT unit was described.[288]

Adenovirus Serotype 37

AdV-37 accounts for < 1% of AdV infections,[5,31,88,161] but may cause EKC.[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.[50–61] Fatalities may occur as a result of dehydration in infants.[50,51] In immunocompromised hosts, fatal dissemination may occur.[73,289] Epidemics have been cited in schools[56] and hospitals.[73] Endogenous reactivation originating from AdV persistent in mucosal lymphoid cells may occur.[70] Nosocomial transmission may occur due to high AdV levels in feces.[73] Shedding of these viruses may be prolonged in immunosuppressed patients.[73]

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.[89,91,290,291] This type is an intertypic recombinant with an AdV-11-like hexon gene and an AdV-14-like fiber gene.[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.[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.[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.[2,31] Biopsy of involved tissues may reveal AdV nuclear inclusions[2]; immunohistochemical stains may identify the AdV hexon antigen in tissue.[146] PCR of AdV DNA in plasma, urine, or other clinical specimens is currently the most frequently used approach to establish the diagnosis,[2,194] and is highly sensitive for disseminated disease.[295,296] Quantification of the viral load using real-time PCR is a useful marker to assess response to therapy.[189,295] 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.[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.[297] The role of routine surveillance is controversial although it has been increasingly used in high-risk patients (particularly HSCT recipients[2]). Quantitative viral loads may not correlate with clinical presentation or disease severity.[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.[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[233] or hypervariable regions of the hexon[235,298] and/or sequencing of hexon genes allow definitive identification of the type/species.[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.[299,300]

Therapy

No antiviral drug has been approved to treat AdV.[38] Prospective randomized controlled trials are lacking.[14] CDV, a cytosine nucleotide analogue that inhibits DNA polymerase, has the greatest in vitro activity against AdV among currently available antiviral agents[301–303] and is the preferred therapeutic agent.[2] CDV is available only intravenously.[2] Regimens (dosing, frequency, and duration) are variable. Standard doses include 5 mg/kg every 1 to 2 weeks[38,188] or 1 mg/kg twice weekly.[38,158,188] Duration of therapy is variable (weeks to months) and depends upon clinical response and persistence or eradication of AdV.[158,188] CDV is generally well tolerated,[153,188,304] but adverse effects include nephrotoxicity, myelosuppression, and uveitis.[2,38] Hydration and probenecid may minimize nephrotoxicity.[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[305] and in animal models,[306,307] with anecdotal successes in small clinical

series.[308,309] Compared with CDV, CMX001 appears be less nephrotoxic.[310] An open-label phase 3 trial to assess safety and efficacy of CMX001 for treating AdV infections in immunosuppressed patients is in progress (Clinical Trials.gov identifier: NCT02087306).

Numerous nonrandomized studies in HSCT and SOT recipients documented favorable responses to CDV.[25,26,28,153,158,188,192,209,231,311–317] Three studies of allogeneic HSCT recipients with AdV infections cited improvement with CDV in 20/29 (69%),[311] 10/14 (77%),[318] and 8/10 (80%) patients, respectively.[192] However, given the lack of controlled trials, indications for, and efficacy of CDV remain controversial.[27] Interpretation of these studies is confounded by heterogeneous patient populations, differing extent and sites of disease, and degree of immunosuppression or immune reconstitution.[38] Intravenous immunoglobulin has been used (together with CDV), but data are insufficient to assess efficacy.[25,316]

Immune reconstitution plays a critical role in controlling AdV infection.[38] Increases in lymphocyte counts or CD_4 counts were associated with clearance of AdV infection[319,320] and improved survival.[320,321] Serotypic-specific neutralizing antibodies correlate with clearance of AdV.[38,320] Reduction of immunosuppression,[146,153] immune reconstitution of HSCT recipients,[25,38] or donor leukocyte infusions[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.[322,323] In a recent clinical trial of HSCT recipients with AdV disease refractory to therapy, ex vivo adoptive T-cell transfer with predominantly TH-1 phenotype was highly effective in clearing viremia and markedly reduced mortality.[324]

Importantly, not all patients with AdV infections or viremia require treatment.[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[196] or HSCT[43] recipients using plasma PCR at regular intervals noted that up to 58% were asymptomatic at the time of viremia, and spontaneous resolution without sequela was common. In a cohort of SOT recipients with AdV viremia, all 19 recovered spontaneously without sequela.[196] Similarly, in a cohort of 26 pediatric HSCT recipients, 11 (42%) developed AdV viremia that cleared without therapy in 7 (64%).[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[20] were depleted by 1999.[20] Produced by a new manufacturer, and after a new round of clinical trials[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.[39] Importantly, antibodies to AdV-4 and -7 may cross protect against other serotypes (e.g., AdV-3 and -14).[86,274,325]

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