Adenovirus

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ABSTRACT

Adenoviruses (AdV) are DNA viruses that typically cause mild infections involving the upper or lower respiratory tract, gastrointestinal (GI) tract, or conjunctiva. Rare manifestations of AdV infections include hemorrhagic cystitis, hepatitis, hemorrhagic colitis, pancreatitis, nephritis, or encephalitis. Adenovirus infections are more common in young children, owing to lack of humoral immunity. Epidemics of AdV infections 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 (eg, organ transplant recipients, human immunodeficiency virus infection, congenital immunodeficiency syndromes). 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 trophisms and correlate with clinical manifestations of infection. The predominant serotypes differ among countries or regions and change over time. Transmission of novel strains between countries or across continents and replacement of dominant serotypes by new strains may occur. Treatment of AdV infections is controversial because prospective, randomized therapeutic trials have not been done. Cidofovir is considered the drug of choice for severe AdV infections, but not all patients require treatment. Vaccines have been shown to be highly efficacious in reducing the risk of respiratory AdV infection but are currently not available.

KEYWORDS: Adenovirus, respiratory viral infection, serotypes, cidofovir

ADENOVIRUS (AdV)

Adenovirus (AdV) infections most often involve the upper or lower respiratory tract, pharynx, conjunctiva, or gastrointestinal (GI) tract.[1,2] More than 80% of AdV infections occur in children <4 years old (due to lack of humoral immunity).[1–5] Immunosuppressed persons[1,3,6,7] are also more susceptible.[2,8–11] High baseline immunity against AdV (titer of ≥1:32) confers substantial protection.[12] Epidemics of AdV infections may occur in healthy children[2,8–11] or adults in closed or crowded settings (particularly military recruits).[13–17] The vast majority of cases are self-limited. However, the clinical spectrum is broad, and dissemination or pneumonia can be fatal, in both immunocompetent[18,19] and immunocompromised patients.[1,3,20–24]

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Virology

Human AdV is a family of double-stranded, nonenveloped DNA viruses belonging to the genus *Mastadenovirus* of the Adenoviridae family.[25,26] Fifty-two serotypes and seven species (A through G) are recognized.[27–29] New candidates are recognized,[30] but their classification is still under discussion. The use of phylogenetic analysis as the sole means of classifying a new serotype is controversial. Species A, B, C, D, and E circulate globally and have been implicated in outbreaks of infections in humans.[20] However, more than half of AdV serotypes are infrequently detected,[20] and only one third of serotypes are associated with human disease.[22,25,27,30–33] Different serotypes display different tissue trophisms and correlate with clinical manifestations of infection[1,22,27,29] (discussed in detail later).

Epidemiology

AdVs may cause epidemics of febrile respiratory infections (FRIs), pharyngoconjunctival fever,[34] keratoconjunctivitis (KC),[35–38] or gastroenteritis and diarrheal illness.[39–50] Severe or disseminated AdV infections may occur in patients with impaired immunity[6] [eg, organ transplant recipients[3]; human immunodeficiency virus (HIV) infection[51]; congenital or combined immunodeficiency syndromes[52,53]] and rarely in immunocompetent patients.[19,54]

Infection can be by reactivation, exposure to infected individuals, or new acquisition from exogenous sources.[1,22] Infections occur throughout the year,[1] but most epidemics occur in the winter or early spring.[5] Latent AdV may reside in lymphoid tissue,[6,55] renal parenchyma,[56] or other tissues after childhood inoculation; reactivation may occur in severely immunosuppressed patients.[6,55,56] Importantly, *asymptomatic* carriage of AdV may persist for weeks or months.[27,57,58] Transmission of AdV can occur via inhalation of aerosolized droplets, direct conjunctival inoculation, fecal–oral spread, exposure to infected tissue or blood,[1,59,60] or environmental surfaces (eg, linen, pillows, lockers, guns).[61,62] The incubation period ranges from 2 to 14 days and depends upon viral serotype and mechanism of transmission.[1] Epidemics may spread rapidly among closed populations, for example, among military recruits[12,13,16,29,33,61,63–65] and in hospitals,[5,60,66,67] neonatal nurseries,[66] psychiatric[67,68] or long-term care facilities (LTCFs),[37,59,69] job training centers,[17] boarding schools or dormitories,[70] a children's home,[71] orphanages,[72] public swimming pools,[73,74] and so forth. Crowding and poor hygienic behaviors may facilitate spread.[67] In institutionalized settings, infection control measures and cohorting may be essential to limit spread.[59,60,75] AdV lacks an envelope and is thus resistant to many disinfectants.[76] Alcoholic (95% ethanol) solution is an effective disinfectant.[58]

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).[1,27] In immunocompetent patients (children or adults), symptoms abate spontaneously (within 2 weeks) and induce type-specific immunity.[1] Fever, pharyngitis, tonsillitis, cough, and sore throat are common symptoms in children and young adults with AdV RTI.[2,15] GI symptoms may manifest concomitantly.[2,15] In a study of 317 hospitalized children with acute AdV RTI in Taiwan, GI symptoms included diarrhea (25%), vomiting (22%), and abdominal pain (19%).[11] Another study in Korean children with RTIs cited the following GI symptoms: diarrhea (31%), vomiting (20%), and abdominal pain (4%).[77] Pneumonia occurs in up to 20% of young children (particularly in newborns and infants)[2,8,10,77] but is uncommon in immunocompetent adults.[1,12,13,67,68,78] However, fatalities due to AdV pneumonia (sometimes associated with septic shock) have been described in previously healthy children[8] or adults.[15,19,54,68] Meningitis is a rare complication of AdV pneumonia.[78] In immunocompromised persons, dissemination and/or severe respiratory failure may develop in 10 to 30% of cases.[1,3,23,79] Fatality rates for severe AdV pneumonia may exceed 50%[1,3,78] (Fig. 1). In children, long-term respiratory sequelae of AdV RTI include bronchiectasis, bronchiolitis obliterans, and hyperlucent lung.[80,81]

Keratoconjunctivitis

Adenoviral keratoconjunctivitis is a major cause of ocular morbidity and can lead to visual loss.[82,83] Manifestations of ocular AdV infection include epidemic keratoconjunctivitis (EKC), pharyngoconjunctival fever, and nonspecific conjunctivitis.[38,84–86] The most common serotypes associated with EKC are AdV-8, 19, 37, and 5,[38,82,83,85,87–90] but other serotypes (eg, AdV-3, 4, 7, 11, and 14) can cause conjunctivitis.[35,36,82,83,88,91,92] In Taiwan, AdV-8, 19, and 37 were the predominant causes of AdV EKC.[87] AdV-8 predominated from 1980 to 1994; after 1995, AdV-37 and AdV-19 predominated and AdV-8 disappeared.[87] Outbreaks of EKC can occur in chronic care facilities,[59,93] hospitals or outpatient clinics,[84,85,94] and closed settings.[95] In one chronic care facility, 47 of 95 residents developed EKC due to AdV-37 between September 14 and December 1990 (attack rate 49%).[59] The outbreak was successfully interrupted following strict infection control, cohorting, suspension of new admissions, and changing to a disinfectant that inactivated AdV. Nosocomial transmission has been noted in eye clinics or hospitals via environmental contamination (ophthalmic instruments, eyedrops).[85,94]

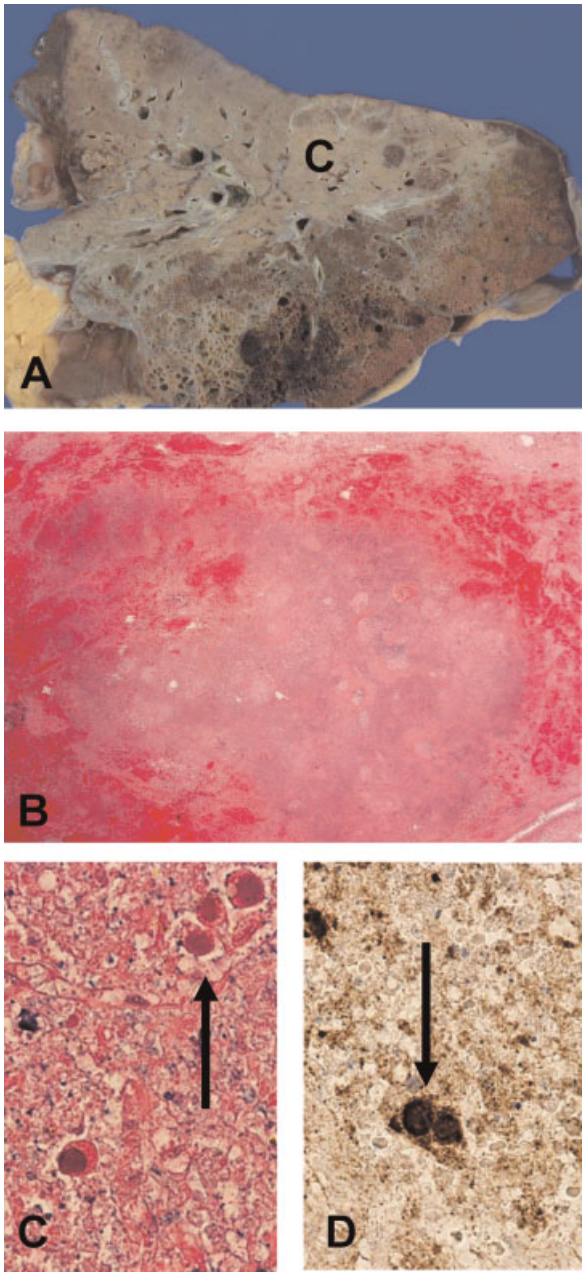

Figure 1 Fatal case of adenovirus pneumonia. (A) Gross lung with pale, consolidated region, C. (B) Histopathology showing hemorrhagic necrotic lung tissue [hematoxylin and eosin (H&E) stain, × 40]; (C) High magnification showing three cells with intranuclear inclusions (arrow) (H&E, × 400). (D) Immunohistochemical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

Rigorous sterilization of instruments and infection control were essential to curb epidemics.[85,94]

Gastrointestinal Manifestations

AdV infections can cause GI symptoms even when the primary site of involvement is the respiratory tract (particularly in young children).[2,11,77] However, some serotypes (notably AdV-40 and 41) have an affinity for the GI tract,[39,42,43,46] with predominant symptoms of gastroenteritis or diarrhea.[96] Rare complications include hemorrhagic colitis,[1,23] hepatitis,[23,97,98] cholecystitis,[99] and pancreatitis.[100]

Urinary Tract Involvement

AdV may cause urinary tract infections (UTIs),[101] particularly among hematopoietic stem cell transplant (HSCT)[56,102–105] and solid organ transplant (SOT) recipients.[106–109] Typical manifestations include dysuria, hematuria, hemorrhagic cystitis (HC), and renal allograft dysfunction.[107,108,110] Renal biopsies may reveal viral nephropathy[111,112] or (in the context of renal transplant recipients) allograft rejection.[108] Most AdV UTIs (including HC) are self-limiting.[32,56,106,110] However, necrotizing tubulointerstitial nephritis,[112,113] fatal or dialysis-dependent renal failure,[111,112,114] obstructive uropathy,[113] and fatal dissemination[115,116] may occur. Most common serotypes associated with HC include AdV-11, 34, 35, 3, 7, and 21.[1,108,110,112] The diagnosis is often made by culture, or polymerase chain reaction (PCR) in urine, or serology.[1,103,108] Renal biopsy may demonstrate viral infection of tubular epithelial cells with "smudge cells" and intranuclear inclusions.[111,112]

Disseminated Disease

Disseminated AdV infections are rare among immunocompetent hosts, but dissemination occurs in 10 to 30% of HSCT recipients with AdV infection.[1,3,21,22,79,117–119] Diagnosis is made by PCR in blood[116] or recovery of AdV from more than one site. Among HSCT recipients with *symptomatic* AdV disease, fatality rates range from 12 to 70%[1,3,21,117,120–122]. Case fatality rates for AdV pneumonia may exceed 50%.[1,3,23,78]

Rare Manifestations

Rare manifestations of AdV infections include myocarditis and cardiomyopathy,[123] encephalitis,[124–126] mononucleosis-like syndromes,[127] pulmonary dysplasia,[128] intestinal intussusception in children,[129] and sudden infant death.[130]

SPECIFIC PATIENT POPULATIONS AT RISK

Adenovirus Infections in Immunocompetent Persons

Epidemics of AdV respiratory infections may occur in healthy children (particularly <4 years old)[2,8–11] or adults in closed settings (particularly the military).[13,15–17] The vast majority of cases are self-limited;

disseminated and fatal infections are rare in immunocompetent hosts.[15,78]

Adenovirus Infections in Military Recruits

Outbreaks of AdV FRIs among military recruits elucidated the molecular epidemiology and dynamics of transmission of AdV.[12,13,29,61,62] Acute FRI due to AdV is a major cause of morbidity in the military, not only in the United States[15,63,64] but globally.[33,65] Military recruits are especially vulnerable, owing to crowding and stresses associated with the basic training environment.[15] The affected (military) population is highly mobile. Following completion of basic training, recruits are dispersed to secondary sites for advanced training, paving the way for epidemic spread.[75] Peak illness rates occur during weeks 3 through 5 of training.[16] AdV accounts for >50% of FRIs and 90% of pneumonia cases among healthy military recruits.[12,13,15,16] 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 titer of <1:4.[62] Serum antibodies to AdV-4 were present in 34% at enrollment and climbed to 97% by 6 weeks.[62] Historically, serotypes AdV-7 and 4 predominated as a cause of FRIs in the U.S. military.[12,13,63] Beginning in 1971, all recruits in the U.S. military were vaccinated with live enteric-coated AdV-4 and AdV-7 vaccines.[131] Following this strategy, the incidence of AdV infections in the military setting fell substantially.[131] Unfortunately, in 1995 the sole manufacturer of the AdV vaccines ceased production; existing supplies were completely depleted by 1999.[15] The lack of availability of vaccines led to reemergence of epidemics of AdV infections in military facilities (all services).[15,16,63,64,132–134] Surveillance of U.S. recruits in training from 1999 to 2004 cited >73,000 AdV infections; during that time frame, serotype 4 accounted for >95% of AdV infections.[16] The epidemic of infections resulted from spread of AdV-4 from an army basic training site to secondary sites.[64] In 1997, an epidemic (>500 cases) of AdV FRIs in the navy's sole basic training center in the United States was attributed to serotypes AdV-7 (70%) and AdV-3 (24%), respectively.[15] 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[29] and has become the predominant strain in the military.

Hematopoietic Stem Cell Transplant Recipients

The reported incidence of AdV infections is highly variable (3 to 47%) among HSCT recipients.[1,3,21–24,31,117–120,135–137] The lower range (3%) was observed when systematic screening was not performed,[137] whereas higher rates reflect prospective studies with regular sampling of plasma for AdV DNA (by PCR).[117,138] The incidence is 2 to 3.5 times higher in children (>20%) compared with <10% in adults.[79,136,137,139,140] Additional risk factors for AdV infections among HSCT recipients include allogeneic HSCT,[79,137] HLA (human leukocyte antigen) mismatch,[79,141] severe T cell depletion,[24,79] and graft versus host disease (GVHD).[1,21,23,24,117,118,120,137] Infection can reflect primary infection (eg, community or nosocomial acquisition)[58] or reactivation of latent infection.[3,55,58] Serotypes most commonly cited among organ transplant recipients include species C (AdV-1, 2, 5), species A (AdV- 31), and species B (AdV-11, 34, 35).[40,116,135]

AdV in HSCT recipients is usually detected within 100 days of the transplant.[79] Clinical manifestations range from mild, self-limited disease to fatal dissemination.[79] In most patients, the disease is localized (eg, urinary tract, gastroenteritis, upper or lower respiratory tract infections) but dissemination occurs in 10 to 30% of cases.[24,79,136,139] In this context, mortality rates are high.[79] Among 76 adult HSCT recipients with *symptomatic* AdV infections the mortality rate was 26%.[137] Mortality rates were higher among patients with pneumonia (73%) and disseminated disease (61%). Severe lymphopenia,[1,79] severe GVHD,[24,137] isolation from more than one site,[79] and high AdV viral loads in plasma[142,143] correlate with higher mortality. However, the 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 seven (63%) without antiviral therapy.[32] Quantification of AdV DNA load by real-time PCR in plasma of HSCT recipients may identify patients at high risk for dissemination[139,142] or assess response to therapy.[139,142] Although indications and efficacy of therapy are controversial, cidofovir (CDV) was associated with a low mortality rate (2%) in pediatric HSCT recipients with AdV infections.[138] In that study, clinical and microbiological cure was achieved in 56/57 patients.[138]

Solid Organ Transplant Recipients

The incidence of AdV infections is 5 to 22% among SOT recipients.[1,79,120,144] AdV infections have been noted in liver,[145,146] renal,[108,114,147] intestinal,[148] heart,[144] and lung[149] transplant recipients (primarily in children). Among SOT recipients, risk factors for AdV include pediatric age,[79,145] receipt of antilymphocyte antibodies,[79] and donor-positive/recipient-negative AdV status.[79] In a prospective study, PCR detected AdV viremia within 12 months of transplant in 19/263 (7.3%) SOT recipients, including liver 10/121 (8.3%), kidney 6/92 (6.5%), and heart 3/45 (6.7%).[144] 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; nine died of invasive AdV infection.[145] In another retrospective review of 191 adult liver transplant recipients, 11 (5.8%) had AdV infection associated with two deaths.[146] Clinical manifestations of AdV infection are protean, but the primary site of disease in SOT recipients is often related to the transplanted organ.[79] In liver transplant recipients, AdV typically causes jaundice, hepatomegaly, and hepatitis.[79] In renal transplant patients, the principal symptom is HC; further, AdV may target the renal allograft, leading to graft failure.[108,114,147] In pediatric heart transplant recipients, the presence of AdV in posttransplant endomyocardial biopsies increased the risk for graft loss and posttransplant coronary artery disease.[150–152] Only four cases of AdV infections were identified in a cohort of 383 lung transplant recipients (LTRs) (1.3%); incidence was 3/40 (8%) among pediatric LTRs and 1/268 (0.4%) among adult LTRs. However, all four developed severe hemorrhagic, necrotizing AdV pneumonia; all died within 45 days of the transplant.[149] In a study of 19 pediatric LTRs, AdV was detected in eight, resulting in two early deaths as well as late graft loss and obliterative bronchiolitis.[147] A case of fatal AdV pneumonia in an adult LTR 4 years posttransplant was described.[153] Although these studies underscore the potential for AdV to cause severe, even fatal, infections in SOT recipients, routine PCR surveillance in adult SOT recipients is not recommended. Further, the need for therapy for mild or asymptomatic cases is not clear. Prospective studies have shown that AdV viremia may be asymptomatic and may clear spontaneously.[144] We reserve treatment (with cidofovir) for symptomatic patients or those with dissemination. AdV infections in organ transplant recipients are discussed elsewhere in this issue by Dr. Weigt et al and will not be further discussed here.

Human Immunodeficiency Virus Infection

The risk for AdV infection in patients with acquired immunodeficiency syndrome (AIDS) is 28% at 1 year (17% if the CD4 count is $>200/mm^3$ vs 38% if the CD4 count is $<200/mm^3$).[154] The GI tract is involved in >90%, but most patients are asymptomatic or have mild symptoms (eg, diarrhea).[154] UTIs may occur in up to 20% of AIDS patients, but bladder inflammation or bleeding is rare.[79] Serotype D is associated with GI infection, whereas UTIs are usually caused by serotype B or D.[154] AdV (particularly serotypes 1, 2, 3) may cause fatal cases in HIV-infected patients.[79] Since the advent of highly active antiretroviral therapy (HAART), AdV disease is uncommon in HIV/AIDS patients until immune system deterioration occurs.[79]

Congenital Immunodeficiency Syndromes

AdV may complicate congenital immunodeficiency disorders such as severe combined immunodeficiency (SCID) syndrome, agammaglobulinemia, common variable immunodeficiency, immunoglobulin A deficiency, and others.[53,79,155] Patients with SCID are most susceptible. In these patients, AdV tends to cause severe and recurrent pulmonary infections, disseminated disease, and even death.[79] Incidence data for AdV in patients with congenital immunodeficiencies are limited.[79] A review of 201 patients with Bruton X-linked agammaglobulinemia cited only one death due to AdV infection.[155]

IMPORTANCE OF SEROTYPES

Globally, serotypes 1 through 5, 7, 21, and 41 are most commonly associated with human disease (Table 1). Different serotypes display different tissue trophisms and correlate with clinical manifestations of infection.[1,22,27,29] Among children, the most common AdV serotypes associated with RTIs are types 1 through 7 and 11.[27,156] In adults (particularly military recruits), serotypes implicated in FRIs include subspecies B1 (AdV-3, 7, 11, 16, and 21), species C (AdV-1, 2, 5, and 6), and species E (AdV-4).[8,20,30,63] Historically, most infections among U.S. military recruits were due to AdV strains 4 and 7.[12,13,65] Recently, AdV-14 (a subspecies B2 serotype) was implicated as a cause of severe FRI in

Table 1 Adenovirus Serotype According to Geographic Region

Country	1 (%)	2 (%)	3 (%)	4 (%)	7 (%)	21 (%)	41 (%)
United States (2004–07) (civilians)[126]	17.7	24.3	34.6	4.8	3.0	2.0	1.7
United States (2004–07) (military)[126]	NA	NA	2.6	92.8	NA	2.4	NA
Toronto (2007–08)[4]	18	26	46	4.8	NA	5.5	NA
Korea (1991–2007)[27]	9.2	11.2	37	3.9	23.3	NA	NA
Taiwan (1981–1989)[9]	NA	6	68	0	3	NA	NA
Taiwan (2000)[9]	NA	6	36	28	21	NA	NA
Taiwan (2001)[9]	NA	15	2	52	1	NA	NA
Taiwan (2004–05)[2]	4.1	6.4	87.2	0.6	NA	NA	NA
United Kingdom (1982–1996)[180]	12.1	18.6	14.9	NA	NA	NA	10.9

NA, not available.

both military and civilian populations in the United States.[14,20,29,157,158] Other B2 subspecies rarely cause FRIs but AdV-11 (a B2 subspecies) was implicated in outbreaks of FRIs in China,[70] Singapore,[33] the Middle East,[159] the United States,[17] and Latin America.[160] AdV-11 may also cause UTIs or HC in children or transplant recipients.[3,29,79] Other serotypes associated with HC include AdV-33, 34, and 35.[3,29] AdV-35 was also implicated in an epidemic of pneumonia in a chronic psychiatric facility.[67] Species D (AdV-8, 19, and 37) usually cause conjunctivitis,[27,82,161] but more common serotypes (eg, AdV-3, 4, 7, and 11) can also cause conjunctivitis.[9,57] Gastroenteritis is associated with enteric AdV strains 40 and 41 (species F)[3,162]; AdV-12, 18, and 31 (species A)[3]; and AdV-52 (species G).[28] Serotypes AdV-5, 31, 34, 35, and 39 have been implicated in outbreaks in immunocompromised patients,[32,40,135,156,163] particularly HSCT[1,32,97,164,165] or SOT[108,166] recipients. In some patients, multiple serotypes or species were isolated concomitantly.[167]

Molecular Characterization of AdV

Different genome types *within serotypes* have been identified by restriction enzyme analysis,[63] multiplex PCR techniques targeting fiber genes[168] or hypervariable regions of the hexon genes, and sequencing of the fiber genes[25,169] and hexon genes.[25,27,170] The widely used genotyping system was proposed and modified by Li et al.[10,171] The prototype AdV strain is designated "p"; other genome types within the serotype are designated "a" through "k." Genome types may be further distinguished by restriction pattern with selected enzymes (eg, AdV-7p, AdV-7p1, etc.).[10,63] Using this system, at least 27 genome types of AdV-7 were identified.[69] This system has been used to correlate genomic types with geographic distribution and pathogenic potential.[63] New serotype(s) may emerge as the dominant pathogen(s), and may exhibit heightened virulence or transmissibility from earlier strains.

The fiber gene mediates attachment of AdV to the host cell.[172,173] Different fiber types display different tissue trophisms. For example, AdV-11p causes mostly UTIs, whereas AdV-11p1, AdV-11a, and AdV-14p exhibit a trophism for the respiratory tract.[30] Most AdVs utilize the coxsackie-AdV receptor (CAR), except for species B viruses that use CD46, a complement protein, as a receptor.[173] A secondary interaction with specific integrins is required for viral entry.

Global Epidemiology

The predominant serotypes differ among different countries or regions, and they change over time.[2,10,27,63,75,174–177] Transmission of novel strains between countries or across continents and replacement of dominant serotypes by new strains may occur.[29,178]

Serotypes 1 through 7 account for >80% of AdV infections in infants and children.[27,179] In the United States from 2004 to 2006, the most common serotypes among respiratory isolates from civilians (children or adults) were AdV-3 (34.6%), AdV-2 (24.3%), AdV-1 (17.7%), AdV-5 (5.3%), AdV-4 (4.8%), AdV-7 (3.0%), AdV-21 (2.0%), and AdV-41 (1.7%)[126] (Table 1). In Toronto, Ontario, Canada, the most common serotypes (2007–08) (respiratory isolates) were AdV-3 (46%), AdV-2 (26%), AdV-1 (18%), and AdV-21 (5.5%)[4] (Table 1). In a survey in the United Kingdom (1982 to 1996), most common serotypes implicated in AdV infections (all sites) were AdV-2 (18.6%), AdV-3 (14.9%), AdV-1 (12.1%), and AdV-41 (10.9%).[180]

In Latin America, AdV-7 has been the predominant strain associated with RTI in many countries.[8,160] In Argentina and Uruguay, AdV-7 accounted for 62.4% of AdV RTI in children from 1991 to 1994, followed by species C serotypes (AdV-1, 2, and 5).[160] Notably, AdV-4 was isolated in only one patient (0.6%).[160] In Brazil, AdV-7 was the predominant serotype for decades, but an outbreak of AdV-3 was noted in 2000.[8]

In Asia, AdV-3 and AdV-7 have been the predominant serotypes associated with RTI in children.[9,10,181] A survey of isolates from children with RTIs in South Korea from 1991 to 2007 implicated the following serotypes: AdV-3 (37.0%), AdV-7 (23.3%), AdV-2 (11.2%), AdV-1 (9.2%), AdV-5 (5.9%), AdV-4 (3.9%), AdV-11 (3.4%), and AdV-6 (1.8%)[27] (Table 1). In southern Taiwan, AdV-3 accounted for 68% of AdV RTIs from 1981 to 1989, 44% from 1990 to 1998, 36% in 2000, and 46% in 2002.[2,9,11] In Beijing, China, AdV-3 was the predominant cause of AdV RTIs from 1962 to 1985.[10]

Striking differences in distribution of serotypes have been noted in civilian and military populations. In the United States from 2004 to 2006, AdV-3 was implicated in 34.6% of respiratory AdV infections among civilians, AdV-4 in 4.8%, and AdV-21 in 2.0%[126] (Table 1). By contrast, during that same time frame, AdV-4 accounted for 92.8% of AdV RTIs among military recruits, AdV-3 for 2.6%, and AdV-21 for 2.4%.[126] A previous survey in the United States from 1999 to 2002 implicated AdV-4 in >95% of AdV RTIs among military recruits.[182] Interestingly, between 2002 and 2006, diverse B serotypes (AdV-3, 7, 21, and 14) emerged among U.S. military recruits.[182] After 2006–07, AdV-14 emerged as the predominant serotype in U.S. military recruits.[29]

Changes in serotypes and genome types among geographic regions underscore the potential for new strains to evolve and replace existing strains. Globally, AdV-7c and 7b were the predominant AdV-7 genotypes in North America, Europe, and Australia from the 1960s

to the 1980s.[9,176] In Beijing, China, AdV-7d predominated from 1980 to 1990[10] and was responsible for outbreaks in Japan in 1995[183] and Korea in the 1990s.[181] In Latin America, AdV-7b had been the predominant AdV-7 subtype,[8] but in the mid-1980s a new strain (AdV-7h) emerged in Argentina,[178,184] Brazil,[8] and Chile[178] and largely replaced AdV-7b.[8] In Taiwan, all isolates of AdV-7 during the 1999 to 2001 outbreaks were AdV-7b.[9] In the United States, the AdV-7 prototype strain (Ad7p) accounted for two thirds of AdV-7 isolates from 1966 to 2000.[63] AdV-7d2 first appeared in the United States in 1993 and since 1996 was implicated in several civilian and military outbreaks in the United States and Canada.[63] AdV-7h was first identified in the United States in 1998.[63] The appearance of AdV-7d2 and AdV-7h in North America represents recent introduction of these viruses and may herald a shift in predominant genome types circulating in the United States.

Among AdV-3 strains, AdV-3a, 3b, and p have predominated in the United States and globally since the 1960s.[54,185,186] In the 1980s, three major clusters of AdV-3, comprising 17 genomic types, were noted among six continents.[185] Cluster 1 occurred in Africa, Europe, South America, and North America. Genomic cluster 2 was identified in Africa; genomic cluster 3 was identified in Africa, Asia, Australia, Europe (a few), and North America. In Europe, AdV-3p1 and AdV-3b predominated from 1961 to 1980, whereas AdV-3p and AdV-3p1 predominated in the United States.[185] In Korea, epidemics of AdV-3 in children from 1991 to 1999 were due to AdV-3a and included six novel genotypes.[181] In the People's Republic of China, AdV-3a2 genotype was the predominant AdV-3 genome type from 1962 to 1985.[10] Since 1983, AdV-3a4, 3a5, and 3a6 have occurred in parallel with AdV-3a2 in China.[185] In Taiwan, all AdV-3 isolates during an outbreak (2004–05) were AdV-3a2.[2] In 2006–07, an outbreak of AdV-3 infections due to a novel strain (AdV-3a51) was reported in New Haven, Connecticut.[187]

Epidemiology and Characteristics of Specific Serotype

Given the large number of AdV serotypes ($n = 53$), a discussion of each serotype is beyond the scope of this review. However, the following sections discuss a few of the common serotypes (eg, AdV-1, 2, 3, 4, 7, 21), additional serotypes associated with specific clinical syndromes (eg, AdV-8, 37, 40, 41), 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 epidemic FRIs worldwide but appear to be less virulent than AdV-7[9,160,178] or AdV-3.[77,160] The prevalence of AdV-1 and AdV-2 varies among different geographic regions and populations. In the United States (2004–06), AdV-1 and AdV-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.[126] The prevalence of these serotypes at other sites is variable: Toronto, Ontario, Canada (2007–08), AdV-1 (18%), AdV-2 (26%)[4]; United Kingdom (1982 to 1996), AdV-1 (12.1%), AdV-2 (18.6%)[180]; Buenos Aires (1984 to 1988), AdV-1 (10%), AdV-2 (20%)[178]; Seoul, South Korea (1990 to 1998), AdV-1 (9.2%), AdV-2 (11.2%)[77]; Taiwan (2004–05), AdV-1 (4.1%), AdV-2 (6.4%).

ADENOVIRUS SEROTYPE 3

Globally, AdV-3 is among the most common serotypes implicated in AdV infections in children and adults.[2,73,126,185] AdV accounted for 13% of AdV respiratory isolates reported to the World Health Organization from 1967 to 1976[73] and continues to be a cause of endemic and epidemic infections[2,4,15,126,180] (Table 1). In the United States and southern Ontario from 2004 to 2006, AdV-3 accounted for 34.6% of AdV RTI in civilians and 2.6% among military trainees.[126] The prevalence of AdV-3 at other sites is variable: Toronto, Ontario, Canada (2007–08), 46%[4]; United Kingdom (1982 to 1996), 14.9%[180]; Seoul, South Korea (1990 to 1998), 15%[77]; Seoul, South Korea (1991 to 2007), 37.0%.[27] AdV-3 (along with AdV-7) was the most common cause of AdV RTIs in South Korea,[77,181] Taiwan,[9] and China.[10] In Taiwan, during an outbreak of respiratory AdV infections in children from November 2004 to February 2005, AdV-3 was implicated in 87.5% of cases.[2] However, changes in serotype distribution may occur. In Taiwan, AdV-3 was the predominant serotype from 1981 to 1989 (68%) and 1990–98 (44%) but decreased to 2% of respiratory isolates in 2001 (largely replaced by AdV-4 and AdV-7).[9]

Importantly, AdV-3 may cause fatal pneumonias in immunocompetent children[181,188] and adults.[54] 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.[188]

ADENOVIRUS SEROTYPE 4

AdV-4 is a cause of sporadic infections in civilians[4] and has been implicated in epidemics of FRI or pneumonia in civilian[9,189] and military[14,16,64,133] populations. In civilian populations, AdV-4 was implicated in 4.8% of AdV RTI in the United States (2004 to 2006[126]; 1% in Toronto, Ontario, Canada (2007–08)[4]; 3.9% (pediatric isolates) in South Korea (1991 to 1997).[27] In Taiwan, AdV-4 accounted for 29% of pediatric respiratory isolates from 1981 to 2001, and became the predominant serotype (52%) in 2001.[9] Until recently, AdV-4 was the most common serotype associated with FRI in U.S.

military recruits.[14,69,133,190] The strategy of vaccinating all military recruits against AdV-4 and AdV-7 beginning in 1971[131,191] eliminated both serotypes as causes of epidemic of FRI in the military for more than 2 decades.[69] After the vaccine was depleted, an outbreak of AdV-4 occurred at an army basic training site in 1997.[64] Over the next several years, AdV-4 spread to multiple secondary sites.[16] From 1999 to 2004, AdV-4 accounted for >95% of AdV FRIs among U.S. military recruits.[16] By 2006–07 the novel strain AdV-14 largely replaced AdV-4 as a cause of AdV FRI among U.S. military recruits.[29]

ADENOVIRUS SEROTYPE 7

Globally, AdV-7 was the third most common serotype reported to the World Health Organization (WHO) from 1967 through 1976, following AdV-1 and AdV-2,[73] and remains one of the leading serotypes worldwide.[27,63,192] AdV-7 infections manifest as FRI, pharyngoconjunctival fever, bronchitis, necrotizing bronchiolitis, or pneumonia.[63,160,183] Importantly, AdV-7 appears to be more virulent than other serotypes.[9,77,160,174,181,193] Fatal pneumonias may occur in immunocompetent children[5,160,184,194,195] and adults.[19]

Epidemic AdV-7 infections have been reported in the United States,[5,195,196] Canada,[194] Latin America,[160,197] Australia,[198] Israel,[175] South Korea,[65,77] Japan,[174,183] China,[10] and globally.[126,175] Outbreaks typically occur in closed settings, such as military barracks,[15] chronic care facilities,[69] hospitals,[5] and neonatal[66] and pediatric[5,199,200] units. In the late 1960s, AdV-7 and AdV-4 accounted for most cases of FRI among U.S. military recruits.[69,190] Following routine vaccination of U.S. military recruits beginning in 1971,[131,191] no epidemics of FRI were attributed to AdV-7 or AdV-4 from 1984 through 1994.[69] 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%).[15] Since 2007, AdV-7 has largely disappeared as a cause of FRI in U.S. military settings (replaced by AdV-14).[29]

The prevalence of AdV-7 varies according to geographic regions and over time and depends on strain type, herd immunity in the region, and epidemiological settings.[5,69,126,195] 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 48/1653 (2.9%) isolates in civilian settings.[126] In Toronto, Ontario, Canada, AdV-7 was not detected among 96 AdV respiratory isolates from 2007 to 2008.[4] By contrast, AdV-7 has been a prominent cause of FRI in Latin America[160,197] and Asia.[27,77,192] AdV-7 was the leading cause of death due to AdV pneumonia in Latin America in the 1980s and 1990s.[160,197] 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.[160] The prevalence of AdV-7 as a cause of AdV FRI in Asia is variable, ranging from <1%[174] to >60%.[65] In Seoul, South Korea, from 1990 to 1998, AdV-7 accounted for 41% of RTIs, followed by AdV-3 (15%) and AdV-2 (15%).[77] From 1991 to 2007 in Seoul, AdV-7 accounted for 23.3% of pediatric respiratory AdV isolates, second only to AdV-3 (37.0%)[27] (Table 1). Outbreaks of AdV-7 infections in Korea from 1995 to 2000 were due to diverse genome types; one genome type (AdV7d) may have been introduced from Japan.[192] In a survey of 200 military recruits in South Korea in 2006, 122 recruits (61%) developed AdV FRIs.[65] All 122 isolates were caused by AdV-7. By contrast, in Taiwan, AdV-7 was implicated in only 2% of AdV RTIs in children in 2001, but 19% in 2002.[11] In Taiwan, AdV-7 emerged as the predominant serotype (45%) in 1999–2000 but fell drastically to 1% in 2001 (replaced by AdV-4).[9] In Beijing, China, AdV-7 and AdV-3 were the most common serotypes causing pneumonia from 1958 to 1990.[10] In Japan, AdV-7 constituted <1% of AdV infections from 1981 to 1992 (one to four cases per year), but increased to >100 cases/year from 1995 to 1997.[174]

At least 27 genome types of Ad-7 have been identified by enzyme restriction fragment analysis[69]; shifts or replacement of predominant genome types may occur.[63,126,175,176] Globally, AdV-7c and 7b were the predominant subtypes in the 1960s and 1970s.[176] A shift from AdV-7c to AdV-7b was noted in Europe in 1969, and in 1975 in Australia.[176] During the 1970s, AdV-7b was the predominant subtype in the United States, Europe, and Australia.[176] During that decade, AdV-7c was detected in South Africa, AdV-7d in China, AdV-7e in Brazil, and AdV-7f in Australia.[176] A new subtype (AdV-7d)[175] was associated with sporadic[175] and epidemic FRIs in children[69] and military recruits.[15] Sporadic and epidemic spread of AdV-7a was noted in hospitals[5,66] and other closed community settings.[71] In Buenos Aires from 1984 to 1988, 29 cases of FRI due to a new strain (AdV-7h) were reported; 84% were children <1 year old; more than half ($n = 16$) required intensive care unit (ICU) care: 10 patients with multifocal pneumonia or necrotizing bronchiolitis died.[184] In a review of 73 pediatric cases of AdV FRI in Buenos Aires between 1984 and 1988, AdV-7h was implicated in 25 and was responsible in all six deaths.[178] A similar strain had been circulating in Chile from 1984 to 1987.[178] Pediatric respiratory AdV-7 isolates from Uruguay, Chile, and Argentina from 1984 to 1990 included AdV-7b, 7c, and 7h.[197] AdV-7c predominated in 1984, but AdV-7h emerged as the predominant strain in 1986. AdV-7b cocirculated during this period but was of lower virulence.[197] AdV-7h accounted for 61.2% of AdV RTIs in children in Argentina and Uruguay from 1991 to 1994 and was responsible for 17 of 18 fatalities.[160] In São

Paulo, Brazil, in 1995, AdV-7h replaced AdV-7b, which had been the predominant AdV-7 subtype for more than a decade.[8] In the United States and eastern Ontario from 1966 to 2000, AdV-7b accounted for 65% of clinical respiratory isolates of AdV-7, followed by AdV-7c (28%), and AdV-7h (2%).[63] AdV-7d2 was first detected in the United States in 1993; ADV-7h was first detected in the U.S. Southwest in 1998.[63] Since 1996, AdV-7d was responsible for several civilian and military epidemics in the United States.[63] In Beijing, China, AdV-7d was the predominant AdV-7 subtype responsible for AdV pneumonia from 1980 to 1990.[10] In Taiwan, AdV-7a was detected in 1983 but all clinical isolates from 1999 to 2001 were AdV-7b.[9] In Israel, four genotypes (AdV-7a1, 7b, 7d2, and 7k) were detected among clinical isolates from 1968 to 1995.[175] These various studies emphasize that new serotypes may emerge as the dominant pathogen and may exhibit heightened virulence or transmissibility from earlier strains.

ADENOVIRUS SEROTYPE 8

AdV-8 accounts for <1% of AdV infections[4,27,77,126] but is a well-recognized cause of EKC.[77,82,87,93] In four studies in Asia and the Middle East, AdV-8 accounted for 64 to 79% of EKC due to AdV.[82,83,89,95] Conjunctival hemorrhage, corneal involvement, and preauricular lymphadenopathy were noted in most cases.[82]

ADENOVIRUS SEROTYPE 11

AdV-11 is relatively uncommon, but may cause hemorrhagic conjunctivitis[34–36,70] and FRI (including pneumonia) in immunocompetent patients and hemorrhagic cystitis in immunocompromised patients.[17,70] In the United States from 2004 to 2006, AdV-11 accounted for <1% of AdV RTI in military recruits and civilians[126]; in Toronto, Ontario, Canada, AdV-11 was not detected among 96 clinical respiratory AdV isolates (Table 1). By contrast, AdV-11 represented 3.4% of 741 pediatric respiratory isolates from South Korea from 1991 to 2007.[27] Outbreaks of AdV-11 FRIs were described in Asia,[33,70] South America,[160] the United States,[17,182] the Middle East,[159] and globally. AdV-11 may cause UTI, including hemorrhagic cystitis, in organ transplant recipients (particularly children).[1,56,105,201] AdV may remain dormant in the renal parenchyma until it is reactivated by an impaired immune system.[56]

EMERGENCE OF ADENOVIRUS SEROTYPE 14 IN THE UNITED STATES

AdV-14 was first isolated in the Netherlands in 1955 during an outbreak of acute respiratory disease (ARD) among military recruits,[29] AdV-14 was subsequently isolated during similar outbreaks of ARD in Great Britain in 1955,[202] Uzbekistan in 1962,[29] and Czechoslovakia in 1963.[29] Interestingly, apart from sporadic isolations in the Netherlands in the early 1970s, no cases of AdV-14 infections were reported globally between the 1960s and 2004.[11,29] A retrospective study of children hospitalized in Taiwan during 2001–02 with ARD implicated AdV-14 in 2 to 11% of isolates.[11] However, AdV-14 had never been identified in North America before its emergence in 2006.[30] Beginning in March 2006, outbreaks of FRI due to AdV-14 (several hundred cases) were noted in several U.S. military bases.[61,75,182,203] Subsequent cases among health care workers suggested nosocomial infection.[61] Surveillance cultures from patients with FRIs from 21 military training sites in 2007 detected AdV-14 at multiple sites in California, Florida, Mississippi, Texas, and South Korea.[75] By 2007, several outbreaks in civilian populations were documented in Washington,[157] Oregon,[204] Alaska,[158] Wisconsin,[29] Pennsylvania,[29] and at least 15 states.[20,29] The severity of FRIs was variable, but fatal pneumonias were described.[20,29,61,157,204] Reconstruction of the history of circulation of AdV-14 in the United States traced the earliest detected case of infection to California in December 2003.[29] In Oregon, AdV-14 emerged in October 2005 and become the predominant circulating serotype by 2007.[204] By 2007, AdV-14 had replaced AdV-4 as the dominant serotype on U.S. military bases.[30,182] 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.[29] These isolates represented a new genomic type designated AdV-14p1 (formerly known as 14a).[29] The complete genetic sequence of AdV-14p1 indicates a close relationship to AdV-11a, suggesting recombination between AdV-14 and AdV-11 strains.[30] Enhanced surveillance and identification of early cases, infection control measures, cohorting, and restricting travel curbed epidemics at several sites,[75] but endemic and epidemic cases have continued in some locales.[29] As a recently emerged virus, AdV-14p1 has an increased potential for high attack rates and rates of transmission, owing to the lack of herd immunity.[30]

ADENOVIRUS SEROTYPE 21

AdV-21 was associated with epidemics of FRIs in military recruits in the Netherlands in the 1960s,[205] but only sporadic cases were noted over the next 2 decades.[206] In 1984 and 1985, outbreaks of AdV-21 infections in children in the Netherlands and Germany reflected the emergence of closely related variants of the original AdV-21 in the 1960s.[206] AdV-21 has been associated with pharyngitis and conjunctivitis,[207] FRI,[163] and pulmonary complications (eg, bronchiectasis, bronchiolitis obliterans) in children[208] but is uncommon.[27] 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.[126] In Toronto, Ontario, Canada (2007–08), 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.[27] Interestingly, Adv-21 may be less transmissible than other AdV serotypes. In an isolated station in Antarctica, only 15% of individuals developed clinical infections over a 5-week period, despite contact with infected individuals and low baseline humoral immunity (neutralizing antibody titer >1:3 in only 11%).[209]

ADENOVIRUS SEROTYPE 31

AdV- 31 may cause gastroenteritis in healthy children and has been associated with severe (sometimes) fatal infections in HSCT recipients.[24,121,210–212] Nosocomial transmission (seven cases) in a pediatric HSCT unit was described[212]

ADENOVIRUS SEROTYPE 37

AdV-37 accounts for <1% of AdV infections[4,27,77,126] but may cause epidemic keratoconjunctivitis.[77,82,83,85,87–89]

ADENOVIRUS SPECIES F (SEROTYPES 40 AND 41)

Globally, AdV species F (serotypes 40 and 41) are endemic and typically cause gastroenteritis and diarrheal illness in children.[39–50] Fatalities may occur as a result of dehydration in infants.[39,40] In immunocompromised hosts (particularly HSCT recipients), fatal dissemination may occur[58,213] but is rare. Epidemics have been cited in schools[45] and hospitals.[58] Endogenous reactivation (probably originating from AdV persistent in mucosal lymphoid cells)[55] may occur. Nosocomial transmission may occur due to high AdV levels in feces during diarrheal illnesses.[58] Importantly, shedding of these viruses may be prolonged in immunosuppressed patients.[58] In one pediatric HSCT unit, six children developed AdV-41 infection within 2 weeks (principal manifestation gastroenteritis and mild hepatitis).[58] The outbreak was curtailed following strict infection control procedures.

Diagnosis of Adenovirus Infection

AdV can be detected in affected sites [eg, nasopharyngeal aspirates, swabs, washings, bronchoalveolar lavage (BAL), urine, stool, blood] by virus-specific direct or indirect immunofluorescent stains, conventional or shell vial cultures, or PCR.[3,27] Viral cultures by conventional techniques are the gold standard but could be insensitive for certain samples (eg, blood) and may take up to 21 days to detect the cytopathic effect.[1,3,27] Biopsy of involved tissues may reveal AdV nuclear inclusions[1]; immunohistochemical stains may identify the AdV hexon antigen.[114] PCR of AdV DNA in plasma, urine, or infected sites may establish the diagnosis[1,142] and is highly sensitive for disseminated disease.[214,215] Quantification of the viral load using real-time PCR is a useful marker to assess response to therapy.[139,214] Among transplant recipients, serial PCR assays of blood and stool weekly may detect AdV disease prior to the onset of symptoms and facilitate early, preemptive therapy.[22,117,138,144] The role of routine surveillance is controversial, although it has been increasingly used, especially in high-risk patients.[1] Quantitative viral loads may not correlate with clinical presentation or disease severity.[32] The study of the viral kinetics may be more useful to determine prognosis of disease.

Determination of serotype with the neutralization test is laborious and time consuming. Multiplex PCR-based techniques targeting the fiber genes[168] or hypervariable regions of the hexon[170] and/or sequencing of hexon genes allows definitive identification of the serotype/species.[25,27] Serological tests may be useful in epidemiological investigations but are of limited practical value in individual patients.[79]

THERAPY

No antiviral drug has been approved to treat AdV.[79] Prospective randomized, controlled trials are lacking. Ganciclovir displays in vitro activity against AdV but has no role to treat AdV infections.[1] Ribavirin, a guanoside analogue, has antiviral activity against both DNA and RNA viruses.[216] More importantly, in small clinical studies, ribavirin has not been shown to be efficacious.[137,215] Cidofovir (CDV), a cytosine nucleotide analogue that inhibits DNA polymerase, has the greatest in vitro activity against AdV[216–218] and is the preferred therapeutic agent.[1] CDV is available only intravenously.[1] Regimens (dosing, frequency, duration) are variable. The standard dose is 5 mg/kg every 1 to 2 weeks[79,138] or 1 mg/kg twice weekly.[79,122,138] Duration of therapy is variable (weeks to months) and depends upon clinical response and persistence or eradication of AdV.[122,138] Although CDV is generally well tolerated,[117,138] adverse effects include nephrotoxicity, myelosuppression, and uveitis.[1,79] Hydration and probenacid may minimize nephrotoxicity.[1,109,117,219] Careful monitoring of renal function (serum creatinine, proteinuria) is critical.

Numerous nonrandomized studies in HSCT and SOT recipients documented favorable responses to CDV.[21,22,24,117,122,138,141,166,219–221] In a multicenter trial in allogeneic HSCT recipients, CDV eradicated AdV infection in 20/29 patients (69%) with various clinical manifestations.[220] Another study cited improvement with CDV in 10/14 (77%) HSCT recipients with AdV hemorrhagic cystitis.[222] Intravesicular CDV was beneficial in an HSCT recipient with intractable hemorrhagic cystitis.[105] In a cohort of pediatric HSCT recipients, CDV led to clinical improvement in eight of 10 with severe AdV infection and to viral clearance in

nine patients.[141] However, given the lack of controlled trials, indications for and efficacy of CDV remain controversial.[23] Interpretation of these studies is confounded by heterogeneous patient populations, differing extent and sites of disease, and degree of immunosuppression or immune reconstitution.[79]

Immune reconstitution plays a critical role in controlling AdV infection.[79] Increases in lymphocyte counts or CD4 counts were associated with clearance of AdV infection[223,224] and improved survival.[224,225] Further, serotypic-specific neutralizing antibodies correlate with clearance of AdV.[79,224] Patients whose viremia cleared exhibited an increased humoral response, with an eight- to 16-fold increase in serotype-specific antibodies.[224] In light of these observations, reduction of immunosuppression,[114,117] immune reconstitution of HSCT recipients,[21,79] or donor leukocyte infusions[24] may have adjunctive roles. Intravenous immunoglobulin (IVIg) has been used (together with CDV), but data are insufficient to assess efficacy.[21]

Importantly, not all patients with AdV infections or viremia require treatment.[1,32] High mortality rates in retrospective studies in part reflect that virtually all patients had symptoms attributable to AdV infection. Prospective studies in SOT[144] or HSCT[32] 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.[144] Similarly, in a study of pediatric HSCT recipients, AdV viremia was detected in 42% and cleared without therapy in 64%.[32] We believe antiviral treatment should be considered for the following indications: disseminated ($\geq$ two sites) disease, severe pneumonia, high viral loads in blood, virulence or trophism 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. In one study, CDV was administered to 18 pediatric HSCT recipients with asymptomatic viremia; viremia resolved in 13 (81%). 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[16] were depleted by 1999.[16] A new vaccine for AdV-4 and AdV-7 has been developed; phase 3 has been completed and hopefully vaccination of military populations can be accomplished soon.[16,75] Importantly, antibodies to AdV-4 and AdV-7 may cross protect against other serotypes (eg, AdV-3[75,182] and AdV-14).[75,182,226]

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