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Adenoviruses in Immunocompromised Hosts

Marcela Echavarría*

Clinical Virology Laboratory, Centro de Educación Médica e Investigaciones Clínicas (CEMIC) University Hospital, Buenos Aires, Argentina

INTRODUCTION

Adenovirus infections were traditionally associated with respiratory, ocular, or gastrointestinal disease, occurring mainly in children and U.S. military recruits as endemic infections or during outbreaks. Over the last years, adenoviruses have increasingly been recognized as significant viral pathogens, with high morbidity and mortality, among immunocompromised patients. This phenomenon may be associated with the growth of the immunocompromised population, especially of patients with acquired immunodeficiencies and more aggressive interventions, with the development of more sensitive diagnostic methods, and with the increased awareness of this virus as a pathogen.

The immunocompromised host is a patient incapable of developing a normal immune response. Immunodeficiencies occur when one or more components of the immune system are defective. Congenital immunodeficiencies are caused by gene defects, are rarely observed, and can be classified into humoral, cellular, or combined immunodeficiency. Acquired immunodeficiencies are more frequent and are not caused by

intrinsic abnormalities in the development or function of T and B cells. They result from underlying conditions, such as immunosuppressive therapy with cytotoxic drugs, use of corticosteroids, radiation therapy, AIDS, malnutrition, or severe burns. Protozoans, fungi, bacteria, and viruses can become opportunistic pathogens, causing a variety of illnesses in immunocompromised patients.

Adenoviruses take advantage of the impaired immunological response. Thus, acute or persistent infections are developed, which lead to high morbidity or even mortality in these patients.

At least seven human adenoviruses species, including 52 serotypes, have been described. They have different organ tropisms, causing a wide variety of clinical manifestations.

This review focuses on adenovirus infections in patients with acquired immunodeficiencies, with a major emphasis on hematopoietic stem cell transplant (HSCT) recipients, and on the recent advances in diagnosis, mostly due to the development of molecular methods. Therapeutic interventions in this population are discussed.

GENERAL DESCRIPTION OF HUMAN ADENOVIRUSES

Human adenoviruses belong to the *Adenoviridae* family and the *Mastadenovirus* genus. They are divided into seven species, from A through G, based on immunologic, biologic, and bio-

* Mailing address: Clinical Virology Laboratory, Centro de Educación Médica e Investigaciones Clínicas (CEMIC) University Hospital, Galvan 4102 (C1431FWO), Buenos Aires, Argentina. Phone: (5411) 4546-8228. Fax: (5411) 4541-3790. E-mail: mechavarria@cemic.edu.ar.

TABLE 1. Properties of human adenovirus serotypes by species characteristics[a]

Species	Serotype(s)	Oncogenic potential	% G+C	Hemagglutination		Fiber length (nm)
				Rhesus monkey	Rat	
A	12, 18, 31	High	48–49	−	±	28–31
B1	3, 7, 16, 21, 50	Weak	50–52	+	−	9–11
B2	11, 14, 34, 35	Weak	50–52	+	−	9–11
C	1, 2, 5, 6	None	57–59	−	±	23–31
D	8–10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51	None	58	±	+	12–13
E	4	None	57–61	−	±	17
F	40, 41	None	57–59	−	±	~29
G (proposed)	52	ND	ND	ND	ND	ND

[a] ND, not determined; ±, equivocal.

chemical characteristics (Table 1). Species B is further subdivided into subspecies B1 and B2. Different adenovirus serotypes are described within a species. A serotype is defined on the basis of its neutralization by specific animal antisera. To date, 52 serotypes have been described (25, 58), and different genotypes can be distinguished within the same serotype. The genotypes are named with letters. The letter "p" is assigned to the prototype strain, while other letters, such as a, b, c, d, h, i, etc., are assigned to the rest. These genotypes represent changes of the genomic DNA, which are not always associated with serological changes (21). Genotypes can be determined by restriction enzyme analysis or by sequencing.

Adenoviruses are medium-sized, nonenveloped, icosahedral viruses of 70 to 90 nm in diameter. Each particle contains a single linear, double-stranded DNA molecule of about 36 kb carrying approximately 40 genes. The protein capsid is formed by 252 capsomeres, including 240 hexons and 12 pentons. Each penton consists of a base and the fiber with a terminal knob that interacts with cellular receptors. Cross-reacting antibodies are directed against the hexons, which contain the generic antigenic component common to all mammalian adenoviruses. Hexons also contain serotype-specific sites which induce neutralizing antibodies. Fibers have serotype-specific and some species-specific antigenic determinants that are responsible for hemagglutination in vitro. Expect for species B, all other adenoviruses use the coxsackie-adenovirus receptor (88). Secondary receptors include $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, which bind to the penton base.

As nonenveloped viruses, adenoviruses are highly resistant to physical and chemical agents. They remain infectious at room temperature for prolonged periods (up to 3 weeks) in certain fomites, giving them a high potential for spread. Transmission is person to person, through water, fomites, and instruments. Nosocomial infections and severe outbreaks have been reported. There is no animal reservoir, and few animal models can reproduce the human disease (38).

Adenoviruses are stable at low pH and are resistant to gastric and biliary secretions, thus allowing the virus to replicate and achieve a high viral load in the gut. Sodium hypochlorite (500 ppm) for 10 min or 70% ethanol for at least 1 minute can be used to inactivate them (90).

PATHOGENESIS

Pathophysiology studies are limited due to the lack of animal models that faithfully reproduce the diseases seen in humans. Pathogenesis studies have been conducted with cotton rats (*Sigmodon hispidus*), as they are susceptible to intranasal infection with adenovirus serotype 5. They further develop a pulmonary histopathology similar to that in humans (38). Whether the cell-damaging effects of adenovirus infection or the host immune responses are responsible for the tissue pathology and clinical manifestations remain unclear. On the other hand, emphasis must be laid on the fact that severe clinical manifestations in humans can be observed in extremely immunosuppressed patients, and immune reconstitution in these patients has always been beneficial.

Adenoviruses have mechanisms for evading host immune responses, such as inhibition of interferon functions by virally associated RNA and E1A, inhibition of intrinsic cellular apoptosis in infected cells, and the prevention of major histocompatibility complex class I expression on the cell surface (81).

T-cell-mediated immunity is important for recovery after an acute infection. Immunocompromised patients who lack effective cellular immunity are at higher risk of adenovirus infection. Studies on adenovirus pathogenesis in children with fatal adenovirus disease have shown that tumor necrosis factor alpha, interleukin-6, and interleukin-8 were detected in the serum, while these cytokines were not found in those patients with moderate diseases (83).

The humoral response also plays an important role in controlling adenovirus infection. HSCT recipients with adenovirus viremia showed an increase in the level of serotype-specific antibodies when they cleared the infection (45).

The reasons for the different organ tropisms and the production of such diverse diseases by the different serotypes have not been elucidated completely. It has been shown that different fiber specificities demonstrate different receptor attachments.

Latency/Persistence

Adenoviruses devote a significant portion of their genomes to gene products whose sole function seems to be the modulation of the host immune responses. These mechanisms might

TABLE 2. Association of adenoviral diseases and principal serotypes in immunocompetent and immunocompromised individuals

Syndrome	Principal serotype(s) in species					
	A	B	C	D	E	F
Upper respiratory illness		All	All			
Lower respiratory illness		3, 7, 21			4	
Pertussis syndrome			5			
Acute respiratory disease		7, 14, 21			4	
Acute conjunctivitis		7	1, 2, 3		4	
Acute hemorrhagic conjunctivitis		11				
Pharyngoconjunctival fever		3, 7				
Epidemic keratoconjunctivitis				8, 19, 37		
Gastroenteritis						40, 41
Hemorrhagic cystitis		7, 11, 34, 35				
Hepatitis		3, 7	1, 2, 5			
Myocarditis		7, 21				
Meningoencephalitis		7	2, 5			
Venereal disease			2			
Disseminated disease	31	11, 34, 35	1, 2, 5			40

play a role in maintaining the virus in a persistent state. This is particularly observed for species C. Serotypes 1, 2, and 5 persist in tonsils for years through low-grade replication. Specifically, T lymphocytes in tonsils and adenoids may harbor adenovirus DNA (37). This condition may represent specific characteristics of virus pathogenesis, such as the mode of infection and reactivation. Endogenous reactivation may also occur during periods of immunosuppression.

Persistence of adenovirus species C, demonstrated by the presence of DNA in T lymphocytes from tonsils, is higher for members of younger age groups, in whom most primary infections with species C tend to occur. There is an age-related decrease in the quantity of adenovirus DNA, either from immune elimination or from depletion of latent stores. On the other hand, PCR studies have demonstrated the absence or low (1.7%) presence of adenovirus DNA in peripheral blood from healthy adult volunteers (35, 107). Thus, the virus may be associated strictly with the mucosa-lymphocyte compartment and rarely found in circulation. Whether adenoviruses from species other than species C are also capable of inducing a persistent or latent infection is still unknown.

The gp19 protein and 14.7-kDa protein play a key role in the ability of species C to produce persistent infections. gp19 prevents transport of class I major histocompatibility complex molecules to the surfaces of infected cells, thus reducing cytotoxic T-cell attack of the infected cells (74).

CLINICAL MANIFESTATIONS

Adenovirus infections are common, have a worldwide distribution, and occur throughout the year. These infections are frequent during childhood, when they tend to be self-limited and to induce serotype-specific immunity. Adenoviruses are endemic in the pediatric population; epidemics and outbreaks with higher morbidity and mortality can also occur. There is a broad spectrum of adenovirus-associated diseases due to the various serotypes and different tissue tropisms (Table 2). About one-half of the known 52 serotypes have been recognized as causing illnesses. The others (mostly from species D) are found rarely, were obtained mostly from AIDS patients, and may not cause disease. A recent study evaluated adenovi-

rus serotype prevalence rates from 2004 to 2006 in civilians and military trainees from the United States (42). The most prevalent serotypes were 3, 2, 1, and 5 among civilians and 4, 3, and 21 among military trainees. In immunocompromised patients, adenovirus infections tend to be more prolonged, more severe, and sometimes fatal. They may occur due to endogenous reactivation or primary infection. Coinfection with more than one adenovirus serotype per clinical event was more frequent in immunocompromised patients (30%) than in immunocompetent patients (5%) (42). Clinical manifestations in immunocompromised patients include pneumonia, hepatitis, hemorrhagic cystitis, colitis, pancreatitis, meningoencephalitis, and disseminated disease, depending on the underlying disease, affected organ system, patient age, and virus serotype (4, 8, 24, 56, 63, 77, 97, 108) (Table 2).

DIAGNOSIS

The diagnostic method depends on the type of disease and the sample obtained. Detection of the virus without clinical manifestations represents adenovirus infection and does not necessarily imply clinical disease. The diagnosis of adenovirus infections is primarily performed using direct methods. These include virus isolation in cell culture, antigen detection, and genome detection, with or without amplification. Electron microscopy is not routinely used in clinical laboratories. Indirect diagnosis using serology is limited due to a lack of sensitivity, heterotypic responses, or inadequate antibody production, especially in immunocompromised patients. Serology should therefore be restricted to epidemiologic investigations or used to confirm associations between virus detection and unusual clinical outcomes.

Conventional and molecular methods are used for direct detection of the virus. Some of the limitations of conventional methods are that culture may be prolonged and can be inhibited by neutralizing antibody or other interfering substances, while electron microscopy and antigen detection methods may be insensitive. In recent years, the development and application of molecular methods using DNA amplification by PCR have increased the sensitivity and rapidity of diagnosis.

Conventional Methods

Virus isolation. Cell line cultures of human origin, such as A549, Hep-2, and HeLa, can be used for the recovery of adenoviruses from all clinical specimens (48, 53). All adenovirus serotypes, except for serotypes 40 and 41, grow well in human epithelial cell lines and produce a cytopathic effect characterized by clumping and cell rounding with refractile intranuclear inclusion bodies (76). Cytopathic effect is usually visible in 2 to 7 days, although it may take up to 28 days. Although cell culture remains the gold standard, it can be insensitive with many clinical samples (i.e., blood), may be slow, and may be noninterpretable because of bacterial or fungal contamination.

Direct antigen detection. Direct antigen detection is widely used for diagnosis of respiratory and gastrointestinal infections because it is rapid and reasonably sensitive. Immunofluorescence (especially useful for respiratory specimens, swabs, or biopsies) and enzyme immunoassays (especially useful for fecal samples) are common approaches (7, 39). The sensitivities of adenovirus immunofluorescence assays with respiratory specimens are 40 to 60% compared to culture (96).

Other rapid antigen detection methods include immunochromatography and latex agglutination (36, 40). These approaches are especially useful for stool samples, with which immunofluorescence cannot be performed, and a small number of specimens may be tested at one time. One study evaluating an immunochromatography kit with respiratory samples showed 90% sensitivity compared to culture (36).

Electron microscopy. The characteristic morphology of adenovirus particles permits detection by electron microscopy without need for further identification. This method is restricted to a few institutions and is used mainly for the diagnosis of acute gastroenteritis, based on the large number of viral particles excreted in stools (10^6 to 10^8 particles/ml).

Histopathology. Histopathologic findings in the lung are characterized by diffuse interstitial pneumonitis, necrosis of bronchial epithelial cells, bronchiolitis with mononuclear cell infiltrates, and hyaline membrane formation. Adenovirus-infected cells have enlarged nuclei with basophilic inclusions surrounded by a thin rim of cytoplasm. These cells are referred to as "smudge" cells (66). In situ hybridization, immunohistochemistry, or PCR can further identify adenovirus in fixed tissue.

Molecular Methods

Amplification and detection of the viral genome are highly sensitive and are especially applicable when noninfectious virus is present, when the viral load is too low to be detected by culture, or when results are needed rapidly.

The usefulness and application of molecular methods in the clinical setting have increased significantly in the last years. Until 1997, only a few PCR methods for stools and ocular swabs were available for clinical diagnosis (2, 85). Later, different generic and species-specific conventional PCR assays were developed and tested with different clinical samples (3, 30, 112). PCR primers for the hexon gene, fiber gene, or virally associated RNA I and II regions are usually chosen because they have some areas that are highly conserved among serotypes. Nevertheless, one of the major challenges for the development of a sensitive generic PCR capable of detecting all strains is the high degree of heterogeneity among the various serotypes.

Since adenovirus DNA has been detected in virtually all clinical samples, specimen selection depends largely on the associated disease. In patients with disseminated disease, PCR proved able to detect the virus in the bloodstream, while other methods failed to do so (31).

Two types of PCR methods can be used, including conventional PCR, which is a qualitative assay and usually takes 1 to 2 days, and real-time PCR, which can be a qualitative or quantitative assay with results available within hours, since amplification and detection of amplified products occur simultaneously. Several real-time adenovirus home-brew PCRs have been developed, initially for bone marrow transplant (BMT) patients and recently for other patient populations (20, 29, 46, 73, 98). A commercial real-time PCR assay (adenovirus r-gene PCR) was recently developed and validated for the generic detection of all adenovirus serotypes. In general, more than one set of primers and several probes are necessary to detect all serotypes by a real-time PCR approach. Many specimen types have been assessed, but blood is frequently obtained to determine the viral load in plasma or serum. There is no clear viral load cutoff value that predicts disease or outcome. Therefore, it may be preferable to analyze the viral kinetics for each patient, considering the adenoviral load over time rather than the absolute value (71).

Detection of adenovirus DNA by PCR in specimens from healthy adult asymptomatic immunocompetent individuals is unusual (30, 33, 107). The clinical specificity of the PCR for urine was 96% in an evaluation of 23 healthy volunteers (30). PCR yielded a 100% specificity when 42 throat swab samples from asymptomatic adults were studied and when 15 leukocyte samples from adult volunteers were included (33, 107). Different considerations apply for analyzing blood from transplant recipients, especially solid organ recipients, in whom asymptomatic reactivation of the virus may occur and may not be associated with disease.

Typing. Typing is primarily used for epidemiologic investigations, for studies on pathogenesis, for unusual or especially severe infections, or for treatment approaches.

Species identification can initially be obtained by determining the agglutination patterns of the isolate with human and animal erythrocytes. It can also be performed by molecular methods, such as multiplex PCRs and amplicon size visualization, or by utilizing amplified products followed by hybridization with different species-specific probes (103, 112).

Serotyping is performed by neutralization or hemagglutination inhibition with the strain already amplified by culture and the animal antisera prepared for each adenovirus serotype (25). This methodology can take several weeks. Serotyping can also be performed using molecular methods such as multiplex PCRs (112). Sequencing can also be used for serotype determination or confirmation. This method is increasingly performed because it is rapid, utilizes molecular equipment and expertise now available in many laboratories, and does not require expensive or difficult-to-obtain antisera.

Genotyping can be performed with genomic adenovirus DNA followed by restriction enzyme analysis (REA) (1, 57). The REA method can be applied to purified virus, to virus-

infected cells, or directly to stools from children with diarrhea (1, 12). The starting material is first lysed and digested with restriction endonucleases (e.g., SmaI). Serotype- and/or genotype-specific band patterns are then visualized after agarose gel electrophoresis. Since the strains that defined the initial REA patterns are no longer circulating, patterns of currently obtained adenoviruses may be noninterpretable. Coinfections can also cause ambiguous results. REA is still useful for presumptive identification of new serotypes, for identification of genotypes (e.g., 7h or 7d2) associated with severe disease, or to confirm results obtained by other means (25, 41). Other molecular typing methods include single-stranded confirmation polymorphism and heteroduplex mobility analysis (99).

In general, molecular methods are now preferred by many laboratories. These methods consist of the amplification of extracted DNA from an isolate or purified virus, using a generic or multiplex species-specific PCR and hexon gene or fiber gene primers (80). The serotype is then indicated by measurement of the product length, size, or DNA sequence for fragments generated after cleavage with restriction enzymes or DNA sequencing (15). Some schemes detect only a limited number of serotypes, whereas others are more comprehensive and can demonstrate coinfections (82, 92). The correlation between hexon gene sequence typing methods and the classic serologic typing method varies from 71% to 97% (42, 65).

ADENOVIRUSES IN CONGENITAL IMMUNODEFICIENCY

A wide variety of congenital immunodeficiencies have been described (89). Congenital immunodeficiency disorders reflect abnormalities in the development and maturation of cells of the immune system, thus leading to an increased susceptibility to infections. Defective development of B cells results in abnormal humoral immunity, while defects in the development of T cells result in abnormal cellular immunity. Some congenital immunodeficiencies are very rare and include disorders such as severe combined immunodeficiency syndrome (SCID), agammaglobulinemia, common variable immunodeficiency, hyperimmunoglobulin M syndrome, immunoglobulin A deficiency, and others. Although adenoviral infections have mostly been reported for patients with SCID, there are a few reports of patients with agammaglobulinemia and DiGeorge syndrome as well as a variety of more unusual immunodeficiency syndromes (23, 57, 102). A recent review of outcomes for 201 patients with Bruton's X-linked agammaglobulinemia reported 1 patient with fatal adenovirus infection (111). In addition, a fatal case of disseminated adenovirus serotype 1 infection has been reported for a child with CD40 ligand deficiency, a condition that involves failure of antibody class switching, also associated with predisposition to infection with *Pneumocystis jirovecii* (22). Since both arms of the immune system are affected, patients with SCID are very vulnerable to severe adenovirus infection, as they are to infection with a number of other microbial agents. Usually, infants with SCID become ill by 3 months of age, and this immunodeficiency can be rapidly fatal if BMT is not performed in a timely manner. SCID is three times more common in boys than in girls because the most common form of the disorder is X linked. Death from varicella virus, herpesvirus, adenovirus, or cytomegalovirus infection may occur rapidly after infection. Adenovirus infections in these patients

tend to cause severe and recurrent respiratory infections, disseminated disease, and sometimes death. Incidence data for adenovirus disease in patients with congenital immunodeficiencies are limited, and most information refers to case reports. The fatality rate could be as high as 55% (47, 100). In SCID patients, adenovirus may produce infection in the lungs, liver, and kidneys, causing pneumonia, bronchiolitis, hepatitis, or gastroenteritis, with a fatal outcome. The most frequent adenovirus serotypes recovered from immunocompetent children are serotypes 1, 2, 3, 5, 7, and 41. In patients with congenital immunodeficiencies, these serotypes are seen in only 50% of cases. Other infections are related to adenovirus serotypes 11, 31, 34, and 35.

ADENOVIRUSES IN ACQUIRED IMMUNODEFICIENCY

BMT and HSCT Recipients

BMT or HSCT is frequently performed in patients with congenital immunodeficiencies, aplastic anemia, hematological malignancies, or other cancers. Transplant success depends largely on controlling complications, including infections, in the posttransplant period. The incidence of adenovirus infection in these patients has increased in the last years due to a variety of factors, such as greater awareness of this pathogen, aggressiveness of conditioning regimens, greater sensitivity of diagnostic methods, and systematic screening (34, 108). The rate of adenovirus infection varies from 5% to 47% depending on patient age, conditioning regimen, type of diagnostic method, and clinical sample analyzed (Table 3). Lower ranges of infection (3%) were observed when systematic screening was not performed (68). Most of the studies reported were retrospective and evaluated patients up to day 100 after transplantation. In addition, studies performed in the 1980s and 1990s were based only on culture methods, which are less sensitive than the molecular methods used in more recent studies.

The risk factors for adenovirus infection include younger age (pediatric recipients are 2 to 3.5 times more likely than adults to become infected), allogeneic transplantation, T-cell depletion, unrelated or HLA-mismatched grafts, total body irradiation, and low T-cell count after transplantation (104). The pediatric population may be more vulnerable because they are more likely to experience either primary infections or reactivation. Larger quantities of adenovirus DNA from species C were detected in tonsils from children of less than 9 years old than in those from older children (37). The higher occurrence of adenovirus reactivation could be due to the discontinuation of the once widespread practice of tonsillectomy and adenotomy in young children. However, no proven evidence is yet available.

The risk factors for adenovirus disease include the number of sites where adenoviruses can be detected, immunosuppressive therapy, lymphocytopenia, detection of adenovirus in blood, and detection of a rising viral load in blood. Severe lymphopenia (<300 cells/mm^3) is a risk factor for progression to disseminated disease and is often fatal (18).

Clinical manifestations in these patients comprise upper or lower respiratory disease, such as interstitial pneumonitis; hepatitis, including ascending cholangiohepatitis (11) disease of the genitourinary tract, including hemorrhagic cystitis or ne-

TABLE 3. Frequencies of adenovirus infection, disease, and mortality in BMT or SCT recipients, methods for adenovirus infection diagnosis, and serotypes involved[a]

Study authors (yr of publication)	Population (period)	% Adenovirus infection (no. of adenovirus-infected patients/total no. of patients)	% Adenovirus disease (no. of symptomatic patients/no. of infected patients)	% Adenovirus-related mortality (no. of deaths/no. of infected patients)	Types of specimens positive for adenovirus (methods)	Species or serotype(s)
Shields et al. (1985) (97)	BMT (1976–1982)	5 (51/1,051)	20 (10/51)	10 (5/51)	U, S, TH, BS (culture, histopathology)	1, 2, 5, 7, 11, 34, 35
Wasserman et al. (1988) (110)	BMT (allo and auto), C, TBI (1979–1986)	18 (17/96)	ND	6 (1/17)	U, S, TH, B (culture)	1, 2, 3, 4, 11, 12, 15
Ljungman et al. (1989) (77)	BMT (1987)	6 (5/78)	ND	20 (1/5)	TH (culture, IIF, histopathology)	34
Flomenberg et al. (1994) (34)	BMT (allo and auto), TCD, TBI (1987–1990)	21 (42/201); A, 14 (16/118); C, 31 (26/83)	31 (13/42)	17 (7/42)	S, TH, U, B (culture)	1, 2, 4, 5, 29, 35
Blanke et al. (1995) (8)	BMT (allo), TCD (1990–1992)	14 (10/74)	10 (1/10)	50 (5/10)	U, L, S, TH (culture)	1, 11, 12
Hale et al. (1999) (43)	BMT (auto and allo), C, TBI (1990–1994)	6 (13/206)	46 (6/13)	50 (7/13)	U, TH, S, L, B, LI (culture)	5, 7, 11
Howard et al. (1999) (51)	HSCT (allo and auto), TCD, TBI (1986–1997)	12 (64/532); A, 9 (35/405); C, 23 (29/127)	64 (41/64)	17 (11/64)	U, S, L, LI, BM, B, BR, NP (culture, histopathology)	ND
Venard et al. (2000) (105)	BMT (allo and auto), C, TCD (1995–1996)	20 (13/65)	61 (8/13)	70 (9/13)	U, S, TH, BAL, CO, SA (culture)	1, 2, 3
Hoffman et al. (2001) (49)	HSCT C(allo) (1998)	47 (17/36)	82 (14/17)	12 (2/17)	U, TH, CSF, B ND (culture)	
Bordigoni et al. (2001) (9)	HSCT C(allo), TCD (1985–1999)	12 (35/303)	60 (21/35)	68 (15/22)	U, S, TH, CO (culture, EIA)	1, 2, 3, 5, 8, 31
Echavarria et al. (2001) (32)	HSCT (allo) (1985–1999)	12 (38/328)	45 (17/38)	18 (7/38)	U, TH, S (culture), serum (PCR)	1, 2, 5, 12/31
La Rosa et al. (2001) (68)	BMT, HSCT A(allo and auto) (1990–1998)	3 (85/2889)	89 (76/85)	23 (20/85)	U, NP, S, BAL, BM, CO (culture)	ND
Leruez-Ville et al. (2004) (71)	BMT, other immunocompromised A, C (2002)	18 (8/44)	ND	25 (2/8)	B, BM, NP, BAL, U, BS (IIF, culture, RT-PCR)	2, 5, 6, 12
Kampmann et al. (2005) (61)	HSCT C(allo), TCD (1999–2002)	41 (63/155)	ND	19 (5/26)	B, S (culture, PCR, EM, histopathology)	A, B, C
van Tol et al. (2005) (104)	HSCT C(allo) (1985–1999)	11 (37/328)	46 (17/37)	19 (7/37)	S, U, B, TH (culture, PCR)	ND
Yusuf et al. (2006) (114)	HSCT C (2001–2004)	32 (57/177)	75 (43/57)	2 (1/57)	PBMC (RT-PCR)	ND
Kroes et al. (2007) (65)	HSCT C (2001–2004)	40 (33/83)	29 (8/28)	30 (10–33)	S, U, TH (culture)	1, 2, 3, 5, 6, 7, 11, 21, 31 (36% multiple infection)
Kalpoe et al. (2007) (60)	HSCT A and C (2001–2005)	A, 5 (5/107); C, 14 (8/58)	A, 20 (1/5); C, 50 (4/8)	A, 20 (1/5); C, 38 (3/8)	B (RT-PCR)	ND

[a] A, adults; allo, allogeneic; auto, autologous; B, blood; BAL, bronchoalveolar lavage; BM, bone marrow; BMT, bone marrow transplantation; BR, brain; BS, biopsy specimens; C, children; CO, conjunctiva; CSF, cerebrospinal fluid; EM, electron microscopy; HSCT, hematopoietic stem cell transplantation; IIF, indirect immuno-fluorescence; L, lung; LI, liver; NP, nasopharynx; ND, not determined/done; PBMC, peripheral blood mononuclear cells; RT-PCR, real-time PCR; S, stool; SA, saliva; TBI, total body irradiation; TCD, T-cell depletion; TH, throat; U, urine.

phritis; gastrointestinal disease, including hemorrhagic colitis; and central nervous system disease or disseminated disease (4, 61, 110, 113). Diarrhea is the commonest manifestation (27). Hemorrhagic cystitis can be especially severe and may predict the onset of dissemination (31).

Adenovirus in BMT or HSCT patients is usually detected within 100 days posttransplant. The mean time is 58 days, ranging from −44 to 333 days. Some patients have shown prolonged viral excretion (63).

The disease can either be localized to a single organ or be disseminated. Definitions have varied depending on the study and can sometimes be confusing. Therefore, it may be difficult to compare studies given the wide variations in the definitions used. Although there is no consensus, the following definitions have been widely used. Asymptomatic infection applies to any detection of adenovirus from stool, blood, urine, or upper respiratory samples (by culture, PCR, or antigen detection) without signs and symptoms. Probable adenovirus disease is defined as the presence of symptoms and signs in addition to adenovirus detection (by culture, PCR, or antigen detection) from the corresponding body site (78). Definite adenovirus disease is defined as the presence of symptoms and signs from the appropriate organ combined with histopathological documentation of adenovirus and/or adenovirus detection (by culture, PCR, or antigen detection) from biopsy specimens, bronchoalveolar lavage fluid, or cerebrospinal fluid, in the absence of any other identified cause. Disseminated disease is defined as documented disease in two or more organs (19). When adenovirus disease is considered, blood specimens should be tested by PCR, since detection of adenovirus DNA from blood is usually predictive of disseminated disease (32). Surveillance of blood samples is currently a common practice among HSCT recipients, especially in the pediatric population. The virus can be detected in blood 2 to 3 weeks before development of clinical symptoms, which offers the opportunity for intervention (75). Follow-up and prognosis are better assessed with

quantitative PCR methods. Increased viral load measurements are associated with increased risk of death (93).

The rate of disease occurrence is hard to assess due to the variation in the inclusion criteria used in different studies. Disease prevalence may vary from 10% to 89%, even among adult patients (Table 3). Mortality rates of 6 to 70% are reported for pediatric and adult transplant patients (Table 3). A lower mortality rate (2%) was reported when a program of preemptive therapy with cidofovir was implemented (114). The range varies depending on the studied populations, stage of disease, interventions, and treatment.

Different adenovirus serotypes have been isolated from these patients, most commonly belonging to species A, B, and C (63). Since most of these studies identified the serotypes by neutralization, growth of the virus in culture was required to achieve serotyping. Lack of detection of species F from these patients may be associated with poor recovery of this species in culture. In general, different clinical manifestations were associated with different serotypes. Respiratory manifestations were mostly associated with species A (serotype 31), B (serotypes 7, 11, 34, and 35), and C (serotypes 1, 2, 5, and 6). Hemorrhagic cystitis was mostly associated with species B (serotypes 11, 34, and 35), while hepatitis was mostly associated with species C (serotypes 1, 2, and 5) (Table 2). Gastrointestinal disease was mainly associated with species A (serotype 31), B (serotype 7), and C (serotype 2). Adenovirus serotype 31 has increasingly been reported in recent years. Moreover, a nosocomial outbreak of adenovirus 31 occurred in a pediatric hematology unit (72). Coinfection with different serotypes, even from different species, has been documented, especially in evaluating different body sites (105). A recent study demonstrated that 36% of pediatric SCT recipients had sequential multiple serotypes after transplantation (65). This observation may sustain the hypothesis of viral reactivation as opposed to primary infection. Patients with multiple serotypes showed a longer duration of excretion than that for patients with only one serotype. Interestingly, the initial occurrence of adenovirus serotype 31 was frequently observed in patients with multiple infections (65).

Solid Organ Transplant Recipients

In the solid organ transplant recipient, the primary site of adenovirus disease is usually related to the transplanted organ. Some of the clinical manifestations described for lung, liver, renal, and small bowel transplantations include pneumonia, hepatitis, nephritis, hemorrhagic cystitis, enteritis, and disseminated disease (56). Incidence data for adenovirus disease in solid organ transplant recipients are more limited than those for SCT recipients. The most symptomatic and severe infections have been reported for pediatric transplant populations, for liver and lung allograft recipients, for patients who receive antilymphocyte antibodies, and for patients with donor-positive/recipient-negative adenovirus status.

In liver transplant recipients, adenovirus typically causes jaundice, hepatomegaly, and hepatitis. The incidence of infection in pediatric liver transplant recipients ranges from 4 to 10%, with mortality rates as high as 53% (63). Infections in these patients are usually associated with adenovirus species C, serotypes 1, 2, and 5. In renal transplant recipients, the pre-

dominant symptom is acute hemorrhagic cystitis and, to a lesser extent, pneumonia, with a 17% fatality rate. The predominant species among these patients is adenovirus species B, serotypes 7, 11, 34, and 35. Adenovirus infections in lung transplant recipients can be associated with respiratory failure leading to death or graft loss. Adenovirus was identified in the transplanted lung in 50% of pediatric lung or heart-lung transplant recipients with bronchiolitis or graft loss (10). Surveillance of adenovirus infection in pediatric transplant recipients by qualitative PCR and serial monitoring by quantitative PCR in blood may provide useful information about when antiviral therapy should be started. This may be effective in preventing fatal disease (95). Significant rises in viral load detected by serial monitoring have preceded clinical diseases in many cases.

On the other hand, a prospective surveillance study evaluating detection of adenovirus DNA in blood by PCR for all adult solid organ transplant recipients, including liver, kidney, and heart transplant recipients, showed that viremia occurred in 7% of the cases. However, 58% were asymptomatic and showed transient and self-limited viremia (54). Therefore, routine PCR surveillance of adult lung transplant recipients is not indicated (55).

AIDS Patients

Adenovirus infection in AIDS patients may cause pneumonia, hepatitis, meningoencephalitis, nephritis, and gastrointestinal and disseminated disease, which may be fatal (62, 94). Some of the fatal cases were caused by serotypes 1, 2, and 3. Since coinfection with other microorganisms, including bacteria and fungi, is common in these patients, a direct association with adenovirus infection is sometimes difficult to establish. Most of the adenovirus serotypes infecting the gastrointestinal tracts of human immunodeficiency virus (HIV)-infected patients belong to species D, including serotypes 9, 17, 20, 22, 23, 26, 27, and 42 to 51. The risk for adenovirus infection in patients with AIDS at 1 year is 28% (17% if the CD4 count is >200/mm^3 versus 38% if the CD4 count is <200/mm^3) (62).

Adenovirus is infrequently found in the urine of immunocompetent patients. In contrast, the presence of adenovirus in the urine of AIDS patients, especially in the era before highly active antiretroviral therapy, was observed in 20% of cases. However, bladder inflammation and bleeding are rarely evidenced (26). Persistence in urine can be as long as 12 months (50). The most frequent serotypes in these patients are 11, 34, and 35. One study showed that patients with parenteral exposure to HIV were more likely to be adenovirus positive in urine than those with sexual exposure. In addition, in that study, the median time to death was shorter for adenovirus-positive AIDS patients than for adenovirus-negative AIDS patients.

Most of the serotypes of species D have been detected in AIDS patients. Furthermore, the last nine described adenovirus serotypes were identified from HIV-infected individuals (25). It has been suggested that the long-term infection seen in AIDS patients and potential coinfection with more than one serotype may provide the opportunity for mutations within a strain or for recombination between coinfecting serotypes.

In the post-highly active antiretroviral therapy era, adenovirus disease is uncommon in HIV/AIDS patients until immune system deterioration occurs. The pathogenic significance of these infections in AIDS patients is unclear, and many infections remain asymptomatic.

Malnutrition

Severe acute lower respiratory adenovirus infections have been documented for hospitalized children of less than 2 years of age (59, 106). Fatality rates as high as 17% have been reported for this population. None of them were transplant recipients or AIDS patients, but malnutrition had been documented for 40 to 45% of them (13, 86). Increased severity was observed in children with adenovirus serotype 7, genotype h (14, 86). It is not clear whether severity in these cases was related to a deficient host response or to a higher level of virulence of the genotype involved. Further studies are needed to better understand these associations.

TREATMENT AND PREVENTION

At present, there is no specific antiviral treatment for adenovirus, although drugs such as ganciclovir, vidarabine, ribavirin, and cidofovir have been used (6, 9, 49). Both successes and failures have been reported. Clinical studies with immunocompromised patients have so far focused on cidofovir and ribavirin, but prospective randomized controlled trials are missing. Ribavirin is a purine nucleoside analogue with in vitro activity against RNA and DNA viruses. Different mechanisms of action have been proposed, including the inhibition of RNA capping activity, direct inhibition of viral polymerases, and increased mutation in newly synthesized DNA. It has not been established which one is the possible mechanism of action against adenoviruses. The most common adverse effect is reversible mild anemia. Successful use was described for the treatment of adenovirus-induced hemorrhagic cystitis, pneumonia, enteritis after BMT, and hepatitis in a liver transplant recipient (6, 51). Other authors, however, have described its therapeutic failure (16, 43). Success seems to be related to early treatment and the serotype involved. In addition, a recent study evaluating in vitro drug susceptibilities of clinical adenovirus isolates found that only strains from species C (serotypes 1, 2, 5, and 6) were sensitive to ribavirin (84).

Cidofovir is an acyclic nucleoside phosphonate analogue used as a broad-spectrum antiviral agent. Incorporation of diphosphate cidofovir results in termination of DNA chain elongation. All adenovirus serotypes are susceptible in vitro. Despite its significant side effects (nephrotoxicity, myelosuppression, and uveitis), cidofovir is currently used among BMT recipients and solid organ transplant recipients. Typically, one of the following two regimens is used: 5 mg/kg of body weight every 1 to 2 weeks or 1 mg/kg three times a week (49, 56, 68). Strict monitoring of renal function should be performed for treated patients. Treatment success, defined as the disappearance of signs and symptoms and the clearance of adenovirus infection, was noted in 20/29 patients (69%) in a multicenter study of patients with various clinical manifestations, including gastrointestinal disease,

pneumonia, encephalitis, and hepatitis (78). Improvements were noted in 10 of 14 (71%) BMT patients with hemorrhagic cystitis (87). Clinical improvement of diarrhea, cystitis, and fever and clearance of the virus were observed in 5/7 (71%) children who received cidofovir treatment, despite the persistence of their immunodeficiency, as measured by CD4 counts (70). An apparent increased effectiveness in 56/57 (98%) patients was observed when patients were aggressively screened and treated regardless of symptoms or viral load in blood (114).

A drawback of most of these studies is the lack of data regarding immune recovery after transplantation and its relationship to adenovirus infection. Immune reconstitution plays a significant role in the course of adenovirus infection. A strong association between immune reconstitution (measured by the absolute lymphocyte count and CD4 count) and clearance of adenovirus infection was observed (18). An increase in lymphocyte count was associated with a decrease in plasma viral load and survival of the host (45, 104).

In addition, specific immune recovery measured by serotype-specific neutralizing antibodies showed a correlation with adenovirus clearance. Patients with adenovirus viremia who cleared the infection showed an increased humoral response, as titers of serotype-specific antibodies increased 8- to 16-fold (45).

Antiviral treatment should be considered for patients with a positive sample for adenovirus at two or more sites if immunosuppression cannot be reduced or if the patient has severe lymphocytopenia (19). High viral loads in blood may be an indication for starting treatment. Prospective studies on drug efficacy, including active surveillance and evaluation of the immune recovery of the patient, are strongly needed.

Preemptive Therapy

The rationale behind the use of preemptive therapy is to apply it before clinical symptoms are installed. It was noted that disseminated adenovirus disease may be preceded by a period of asymptomatic viremia (75). Progression to disease or mortality is probably determined by the host immune response and the virulence or tropism of the virus strain. Therefore, the early initiation of preemptive therapy may be useful in controlling viral replication before the inflammatory response and disease have been triggered. Some investigators have suggested that surveillance of high-risk HSCT recipients and early preemptive therapy with cidofovir will be more effective than treatment after symptoms develop. One study showed that 13/16 (81%) asymptomatic patients resolved the infection when cidofovir was given as preemptive therapy (78). These children were at higher risk for developing adenovirus disease, as they received transplants from unrelated or HLA-mismatched donors and mostly received T-cell-depleted grafts.

Some investigators have proposed an algorithm for adenovirus surveillance and preemptive therapy (19). They propose that on the first detection of adenovirus isolate in a surveillance sample from urine, stool, or the throat, immunosuppression should be reduced. Preemptive antiviral therapy should be initiated if there is a positive PCR for blood, the patient has severe lymphocytopenia, or immunosuppression cannot be reduced or withdrawn.

Although no controlled clinical trials have been done with

the use of cidofovir and the numbers of patients were low in published studies, the use of preemptive therapy is common in some hospitals.

Immunotherapy

Since lymphocyte reconstitution seems to play a significant role in clearance of adenovirus infection and survival of the host, the use of therapeutic interventions that improve immune recovery is warranted. Manipulation of the immunocompetence of these patients can be achieved by decreasing the immunosuppression (sometimes impossible to achieve due to graft-versus-host disease or because of the concern for allograft rejection), by donor lymphocyte infusion, or both. Exogenous lymphocyte therapy has been successful in a few cases, although it is limited by the risk of exacerbation of graft-versus-host disease. van Tol et al. have proposed to initiate immunotherapy in patients with a plasma load of 1,000 copies/ml or an increase in the viral load within a week and a lymphocyte count of <300 mm^3 (104). One approach describes the generation of adenovirus-specific T-cell lines from donors, diluting out alloreactive T cells (44). Several groups are developing methods to produce adenovirus-specific cytotoxic lymphocytes efficiently (5, 69).

Although clinical reports on immunotherapy are still scarce, recovery from symptoms and clearance of the virus have occurred in some patients (17, 52). This field seems promising for further investigation.

The use of intravenous immunoglobulin has been associated with successful recovery, but data are limited (23).

Vaccine

No vaccine is currently available for nonmilitary populations. Adenovirus-induced acute respiratory disease has caused large epidemics and fatal pneumonia among U.S. military recruits (28, 64). Live adenovirus vaccines directed against serotypes 4 and 7, the most common serotypes involved in acute respiratory disease among these individuals, were introduced in 1980 and significantly reduced morbidity and mortality (101). In 1996, vaccine production was discontinued and respiratory outbreaks recurred. Reintroduction of the vaccine to the military population is planned. Interestingly, adenovirus serotype 4 is not as frequent among civilians (91).

CONCLUSIONS AND PERSPECTIVES

The number of immunosuppressed patients has grown steadily as a result of both a larger number of patients receiving solid organ transplants and HSCT and their longer times of survival. In addition, the use of newer, more potent immunosuppressive regimens has increased the frequency of severe adenovirus infections documented in major medical centers. In addition, improvements in the control of cytomegalovirus infections after transplantation have changed the focus to other opportunistic viral infections, including adenovirus infection. On the other hand, the development of more sensitive and rapid diagnostic methods has also improved adenovirus detection.

Human adenoviruses are a wide group of viruses, represented by at least 52 serotypes with various genotypes divided into genomic clusters, which may cause a broad variety of clinical manifestations. The genetic diversity among them should be considered for diagnosis, typing, and therapeutic interventions.

A significantly higher incidence of adenovirus infections is observed mainly in pediatric SCT recipients. This condition may well represent specific characteristics of virus pathogenesis regarding the mode of infection and reactivation. The persistence of adenovirus species C, demonstrated by the presence of DNA in T lymphocytes from tonsils, is higher in younger age groups (37).

The development and implementation of molecular methods, especially the application of PCR assays to test blood samples, have significantly contributed to the identification of patients with disseminated adenovirus disease. Dissemination has been recognized more widely among transplant patients, especially among HSCT recipients, who are at higher risk of developing a severe or fatal disease. This manifestation has been underestimated in the past, since conventional methods failed to detect viremia. In 1999, Echavarría et al. reported the utility of PCR methods for serum or plasma for detection of adenovirus disease among BMT recipients (31). Furthermore, a subsequent study demonstrated that the presence of adenoviral DNA in serum was associated with severe or fatal disease (32). Nowadays, PCR in blood is broadly used for screening of adenovirus infection in SCT recipients, who are at higher risk for developing disease. Since proper management of these patients depends on early diagnosis and differentiation from other conditions, PCR can offer a valuable tool as an early marker for disease (67).

More recently, the development of real-time PCR assays has permitted the quantification of the virus. The determination and blood monitoring of adenovirus viral load for the treatment and prognosis of these infections are gaining wide acceptance, especially for the pediatric population. Most real-time PCR assays are home-brew approaches, and currently there is only one commercial assay available. Interlaboratory comparisons are limited due to the lack of an international standard and FDA-cleared or -approved assays. No absolute viral load threshold in blood has yet been determined for adenoviruses, due to the lack of standardization and to assay performance at different centers as well as to individual variations in viral replication. Adenovirus DNA can be detected in peripheral cells, whole blood, plasma, or serum, with some different results. Therefore, determination of the changes in the viral load over time by regular monitoring (i.e., weekly) of the same specimen type performed at the same institution may be more useful than determination of the absolute viral load.

The clinical interpretation of adenovirus viral load determinations is still controversial. In one study, the viral load was significantly higher in peripheral blood mononuclear cells from symptomatic than from asymptomatic patients (114). However, another study showed no significant correlation between clinical presentation, disease severity, and quantitation of viral load in blood (109). The same study also showed that lower viral loads were cleared earlier than higher viral loads (109). Not all children with adenovirus viremia will develop symptoms, and in fact, some are able to clear the virus spontaneously.

In some cases, asymptomatic adult allogeneic SCT recipients were able to clear the virus spontaneously (60). Therefore, host

immunity plays a significant role in controlling the infection. Patients who died with adenovirus viremia had continuously increasing viral loads without lymphocyte recovery (45). Close surveillance of patients at higher risk of developing disease is of utmost importance, since early interventions may contribute to clinical response and may avoid fatal outcomes. Boosting of immunity by decreasing immunosuppression or adoptive immunotherapy with adenovirus-specific T cells or infusion of donor cells seems to be a significant tool for patients at risk of adenovirus disease.

Although there is no specific treatment for adenovirus, different antiviral drugs have been used (79). Cidofovir is currently the most widely used drug among SCT recipients. Furthermore, the use of preemptive therapy with cidofovir is a common practice in many centers. Active surveillance for adenovirus and preemptive therapy should be strongly considered, particularly for pediatric SCT recipients at high risk of developing disease, until sufficient restoration of T-cell function occurs. Antiviral treatment should be considered for patients with adenovirus detected at two or more sites and for those with evidence of end organ disease or with severe lymphopenia, in which case reduction of immunosuppression is not feasible (19).

The presence of coinfections with various adenovirus strains and the finding of sequential emergence of multiple adenovirus serotypes after pediatric SCT are characteristic features of adenovirus infection compared to other viral diseases. This observation is relevant for diagnostic purposes and therapeutic interventions, including antiviral treatment or immunotherapy (65).

Sensitive diagnostic tests for adenovirus can contribute to the early detection and successful treatment of life-threatening adenovirus infections, especially in complex immunocompromised patients who may be thought to have other diagnoses, such as graft-versus-host disease. The wider availability of these tests has led to a better understanding of the frequency and potential severity of adenovirus infection in immunocompromised hosts. Diagnostic accuracy is essential to minimize immunosuppression in patients with adenoviral infections. In addition, improved adenovirus diagnosis should greatly facilitate the evaluation of more effective and less toxic adenovirus therapies. Large prospective multicenter controlled clinical trials with different patient populations will be needed and are likely to rely on the improved molecular diagnostic tests that are now becoming available.

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