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Adenoviruses in the Immunocompromised Host

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INTRODUCTION

Infections in the immunocompromised host constitute a relatively new and severe problem magnified by the current AIDS epidemic and by the escalation in organ and tissue transplantations. Adenoviruses and herpesviruses are among the many agents that take advantage of an impaired or destroyed immune system to set up persistent and generalized infections in the immunocompromised host. Such infections are difficult to treat, tend to be long-term, add to the burden of debilitation in the patient, and sometimes rapidly overwhelm the patient and result in death (5, 7, 13, 20, 34, 37, 43, 52, 54, 55, 59, 75, 77, 81, 82, 86, 97, 101, 105, 114, 130, 141).

The immunocompromised host is a patient with one of the immunodeficiency diseases or a patient being treated with cytotoxic and immunosuppressive drugs. The principal primary immunodeficiency diseases are classified into humoral immunodeficiencies, cell-mediated immunodeficiencies, combined immunodeficiencies, and partial immunodeficiencies; these are inherited diseases but are rare. Much more common are the secondary states of immunodeficiency, which result from underlying conditions such as AIDS, neoplasms in the immune system, nephrotic syndrome, severe burns and other sources of major protein loss, and immunosuppressive therapy. Any infectious agent causing additional illness in such an immunocompromised host is loosely said to be causing immunocompromised host disease (ICHD). A great variety of protozoans, fungi, bacteria, and viruses are poised to become opportunistic pathogens in the immunocompromised host, who, depending on the nature of the immunosuppression at the moment of infection, can do little to overcome the infection. More complete descriptions of the congenital and secondary immunodeficiency states and the role of pathogenic organisms in such patients can be found elsewhere (37, 55, 86).

This review is concerned with the role of adenoviruses in patients with ICHD; adenovirus infections are associated with case fatality rates as high as 60% in those with pneumonia and 50% in those with hepatitis, compared with 15% in immunocompetent patients with pneumonia and 10% in immunocompetent patients with hepatitis. The review excludes adenovirus infection in immunocompetent patients with temporary immunosuppressions that result from infection with various parasites and viruses. It also excludes infection in patients with autoimmune and other diseases of immune regulation or with lowered host resistance due to general health status (diabetes, stress, etc.), breaks in the mechanical barriers to infection, or temporary fluctuations in complement, interleukin, or interferon levels.

ADENOVIRUSES IN HUMAN DISEASE

General Description of Adenoviruses

Adenoviruses are nonenveloped viruses 70 to 90 nm in diameter, with 10 structural proteins. The capsid proteins are arranged in an icosahedron having 20 triangular faces and 12 vertices, with 240 hexon components and 12 pentons per virus particle. Each penton consists of a base (or vertex capsomere) and a fiber, which is a rodlike outward projection of variable length with a terminal knob. The hexon contains group-specific antigenic determinants plus some subgroup-specific determinants and type-specific neutralizing epitopes; the vertex capsomere is a toxic factor that detaches cells in culture; and the fiber possesses hemagglutinins and major neutralizing epitopes that are type specific (43, 52, 90, 127). Inside the capsid is a single molecule of linear, double-stranded DNA with a molecular weight of 20 $\times 10^6$ to 24 $\times 10^6$ (or ~35 kb). The G+C base composition of the genome for the different adenoviruses ranges from 48 to 58%. The human adenoviruses presently number 47 serotypes, which are conveniently divided into six subgroups (subgenera A to F) on the basis of their oncogenic potential in rodents, their differential hemagglutination with erythrocytes from a variety of species, the lengths of their fibers, the percent homology and G+C ratios of their DNAs, and the sizes of two of their internal polypeptides (Table 1) (43, 52, 127, 135).

The adenoviruses replicate well and produce obvious cytopathology in continuous human cell lines of epithelial origin (HeLa, HEp-2, KB) and primary human embryonic or neonatal kidney (HEK, HNK); other cell lines such as A549, Graham-293, and HLF are sometimes used with good results (43, 52, 69). Details of the routine inoculation of clinical

TABLE 1. Subdivision of human adenoviruses by oncogenic, hemagglutinating, and morphologic properties[a]

Subgroup	Serotypes	Oncogenicity	HA[b] subgroup	Species giving HA titers	Fiber length (nm)	% DNA homology[c]	*Sma*I fragments (at CCC/GGG)[d]
A	12, 18, 31	High	3B[e]	Rat (incomplete)	28–31	48–69 (8–20)	4–5
B	3, 7, 11, 16, 34, 35	Weak	1A	Monkey	9–11	89–94 (9–20)	8–10
	14, 21	Weak	1B[f]	Monkey			
C	1, 2, 5, 6	None	3A	Rat (incomplete)	23–31	99–100 (10–16)	10–12
D	8, 9, 37	None	2A	Rat, mouse, human, guinea pig, dog	12–13	94–99 (4–17)	14–18
	10, 19, 26, 27, 36, 38, 39	None	2B	Rat, mouse, human			
	13, 43	None	2C	Rat, mouse, human, monkey			
	15, 22, 23, 30, 44–47	None	2D	Rat, mouse, monkey			
	17, 24, 32, 33, 42	None	2E	Rat, mouse			
	20, 25, 28, 29	None	2F[f]	Rat (atypical), monkey			
E	4	None	3A	Rat (incomplete)	17	(4–23)	16–19
F	40, 41	None	3A[f]	Rat (atypical)	~29	62–69 (15–22)	9–12

[a] Data are adapted from references 43, 126, 127, and 135.
[b] HA, hemagglutination.
[c] Range of percent DNA homology among serotypes of the same subgroup (first listed) and between serotypes of different subgroups (in parentheses).
[d] Although *Sma*I from *Serratia marcescens* is only one of many restriction enzymes that can be used to subdivide the human adenoviruses, it conveniently cuts the DNA in the middle of every CCC/GGG base sequence and gives the tabulated number of fragments (127).
[e] Very low HA titers.
[f] Moderate-range HA titers.

specimens and culturing of adenoviruses are given elsewhere (43, 44, 52, 127).

Adenovirus Detection and Identification

Adenoviruses can be detected directly in clinical specimens by rapid tests that measure their common, group-specific hexon antigen. Fluorescent-antibody tests are fast, convenient, and qualitative; enzyme immunoassays, radioimmunoassays, and time-resolved fluoroimmunoassays are somewhat less convenient but are quantitative measures of the hexon component (43, 44). All can be performed within a half day provided that the laboratory is routinely set up to do the tests or commercial kits are used. The rapid tests thus detect adenovirus in a specimen but cannot yield the serotype. For serotyping, the virus must be grown out in cell culture and typed by hemagglutination inhibition and neutralization tests with hyperimmune type-specific animal antisera (43, 44, 47, 127).

Another important measure of adenovirus interrelationships is restriction enzyme analysis. In this procedure, viruses grown in cell culture are disrupted and the DNA is crudely extracted and precipitated. The DNA is then cut into fragments that are 4 to 7 nucleotides long, depending on the endonuclease used, and the fragments are separated by gel electrophoresis, stained with ethidium bromide, and visualized under UV light. A large selection of endonucleases derived from various bacteria and fungi are now available, and most studies employ 6 to 10 enzymes to show genome variant groupings and relationships among strains (2, 13, 25, 27, 36, 43, 45, 49, 52, 53, 60, 103, 120, 121, 126, 127, 132).

Adenoviruses Causing Human Disease

Adenoviruses have been recovered from virtually every organ system of humans and have been associated with many clinical syndromes. About one-half of the known serotypes are documented as causing illness; the others are rarely encountered and may or may not act as pathogens in recognizable disease (2, 43, 52, 104, 127, 134, 135). Most illnesses are self-limiting within 2 weeks and induce type-specific immunity. Adenoviruses are endemic in pediatric populations, but outbreaks can occur in association with certain body systems and in selected populations (13, 15, 43, 48, 103, 104, 126, 129, 134). These are summarized in Table 2.

ADENOVIRUSES IN PRIMARY IMMUNODEFICIENCIES

All inherited forms of immunodeficiency disease are rare. The most commonly recognized of these diseases is severe combined immunodeficiency disease (SCID), which usually becomes apparent between the first and second years of life, when the child does not mount the normal response to the usual childhood infections. In patients with either SCID or more focal types of congenital immunodeficiencies, adenovirus infections that are normally not severe tend to cause generalized illness and sometimes death (6, 8, 10, 21, 30, 40, 60, 75, 84, 93, 109, 111, 112, 118, 137). The subgenera and serotypes involved are indicative of the exposure of these patients to the common childhood serotypes in their environment (Table 3).

In subgenus A, type 31 has been found in SCID patients with pneumonia, hepatitis, diarrhea, and acute hemorrhagic cystitis (AHC) (42, 60). In subgenus B, types 3, 7, and 11 are common agents of pneumonia and generalized disease in patients with SCID and other underlying congenital immunosuppressions; types 34 and 35 are less common (6, 10, 21, 42, 109, 118). In subgenus C, types 1, 2, and 5 cause respiratory, hepatic, and gastrointestinal illness in children with SCID (8, 42, 111, 112, 137). In subgenus F, adenovirus 41 has been found in four SCID infants with gastroenteritis

TABLE 2. Association of adenoviruses with human disease

Syndrome	Principal serotypes involved in subgenus:					
	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, 21			4	
Pharyngoconjunctival fever		3, 7			4	
Epidemic keratoconjunctivitis				8, 19, 37		
Acute hemorrhagic conjunctivitis		11				
Acute hemorrhagic cystitis		7, 11, 21, 35				
Immunocompromised host disease	31	All	All	29, 30, 37, 43, 45		
Infant gastroenteritis[a]	31		2			40, 41
Central nervous system disease		3, 7				
Sexually transmitted disease[b]			2	19, 37		

[a] Gastroenteritis is due predominantly to types 40 and 41 and to a lesser extent to types 2 and 31 (35, 36, 42, 43, 60, 69).
[b] Penile and labial ulcers and urethritis (reviewed in reference 43).

(42). Because of the ease with which adenoviruses can cause disseminated disease in such immunocompromised children, isolation of the virus from multiple sites was the rule rather than the exception when multiple sites were studied (6, 10, 42, 60, 111, 137).

Types 1, 2, 3, 5, 7, and 41 are the most common adenoviruses found in normal children, but these serotypes account for just 53% of the adenovirus infections reported for congenitally immunocompromised children. The spectrum of symptoms differs also. In normal children, these viruses cause mild to moderately severe upper respiratory illness (URI), some lower respiratory illness (LRI) (particularly type 7), and some gastroenteritis (particularly type 41). In children with adenovirus-related ICHD, however, lung, liver, and kidney involvement is common and often has a fatal outcome. The mean age of patients detailed in Table 3 is 4.4 years, and the case fatality rate is 55.3%.

ADENOVIRUSES IN SECONDARY IMMUNODEFICIENCIES

The three major categories of patients with secondary immunodeficiencies are tissue or organ transplant recipients, who are immunologically impaired by high doses of cytotoxic and immunosuppressive drugs and for whom careful surveillance for infections is routinely performed; cancer patients undergoing chemotherapy and radiation treatments; and AIDS patients. The kinds of illness and the adenovirus serotypes involved vary with the organs affected in the underlying disease and the patient's age. These are outlined below.

TABLE 3. Adenoviruses in primary immunodeficiencies

Subgroup	Serotype	Age and sex	Clinical presentation[a]	Site(s) of virus detection	No. fatal[b]	Reference(s)
A	31	1–4 yr	4 patients: SCID; pneumonia, hepatitis	Stool, urine, throat, liver	3+	42
	31	1–5 yr, M	8 patients: SCID; pneumonia, hepatitis	Liver, stool, urine, throat	7+	60
B	3	5 yr, M	IgG3 deficiency; tonsillitis, URI, other	Throat	–	42
	3	1 yr, F	DiGeorge syndrome; hepatosplenomegaly	Urine	–	118
	7	7 days, F	Undetermined; hepatosplenomegaly, hemorrhage	Urine, lung, liver, kidney	+	6
	7	5 mo, F	SCID; pneumonia, rash	Blood, lung, liver, kidney	+	10, 111
	7	5 yr, F	SCID; pneumonia, leukopenia	Lung, pleural effusions	–	21
	11	1 mo, M	SCID; pneumonitis	Lung, throat	+	42
	11	26 yr, M	Agammaglobulinemia; pneumonia, headache	Lung	+	109
	34	1 yr, 3 yr	2 patients: SCID; fever, URI	Urine	1+	42
	35	5 yr, F	SCID; pneumonia	Stool	–	42
	35	25 yr, F	Stevens-Johnson syndrome; pneumonitis	Throat	–	42
C	1	1–4 yr	3 patients: SCID; hepatitis, URI, anemia	Urine, throat, liver, CSF[c]	1+	42
	1	37 yr, M	Humoral antibody deficiency; bronchitis	Sinuses	–	112
	2	2 mo, F	SCID; hepatic necrosis	Liver	+	8
	2	1–3 yr	3 patients: SCID; pneumonia, hepatitis	Stool, throat, liver	2+	42
	2	10 mo, M	SCID; hepatitis, bronchiolitis	Blood, brain, lung, liver	+	137
	5	2 yr, M	SCID; URI, rash	Urine	–	42
	5	1 mo, F	SCID; hepatic necrosis, diarrhea	Liver, blood	+	111
F	41	1–4 yr	4 patients: SCID; gastroenteritis	Stool	–	42

[a] Only major findings are listed.
[b] Number of patients in each line entry who died of adenovirus infection; if the line entry was for a single patient, + indicates a fatal outcome to the infection and – indicates recovery.
[c] CSF, cerebrospinal fluid.

TABLE 4. Adenoviruses in secondary immunodeficiencies: BMT recipients

Subgroup	Serotype	Age and sex	Clinical presentation[a]	Site(s) of virus detection	No. fatal[b]	Reference(s)
A	31	1–3 yr	6 patients: SCID; pneumonia, hepatitis, GI	Urine, liver, lung, stool	5+	35, 42
	31	4–45 yr	6 patients: various cancers; pneumonia, enteritis	Stool, urine	3+	42
	31	16 yr, M	AA; pneumonia	Ileum, bladder	+	106
B	7	12, 38 yr, M	2 patients: various cancers; pneumonia, hepatitis, GI	Liver, lung	2+	42
	7	8, 9 yr, M	2 patients: ALL; pneumonia, renal failure	Lung, kidney, stool, throat	2+	106
	11	25 yr, M	CGL; AHC, diarrhea, pneumonitis	Lung, liver, kidney, etc.	+	4
	11	13–33 yr	5 patients: various cancers; AHC	Urine, others	1+	4
	11	10 yr, M	AA; AHC, hepatitis, rash, chills	Urine	−	42
	11	19 yr, F	AML; AHC, bacterial pneumonia	Urine	+	50
	11	7 mo, F	Wilm's tumor; pancytopenia, hepatomegaly	Lung, liver, heart, etc.	+	79
	11	17 yr, M	AA; hematuria, CMV pneumonia	Kidney	+	106
	34	15–19 yr	3 patients: various cancers; hepatitis, pneumonia	Urine, throat	1+	42
	34	29 yr, M	ALL; AHC, nephritis, pneumonia	Lung	+	81
	35	17–30 yr, M	3 patients: various cancers; pneumonia, hepatitis	Urine, kidney, stool	2+	42
	35	31 yr, M	AML; renal failure, pneumonia, AHC	Lung, kidney	+	106
C	1	6, 12 yr, M	2 patients: AA/ALL; liver dysfunction	Throat, stool	−	27
	1	5, 6 yr	2 patients: ALL/CML; enteritis, fever	Stool, throat, urine	−	42
	1	24, 25 yr	2 patients: AML; pneumonia	Lung, liver, kidney, etc.	2+	106
	2	6 mo, 19 yr	2 patients: thalassemia/AML; GI, other	Throat, stool	−	27
	2	1 yr, M	SCID; pneumonia	Urine	+	35, 42
	2	5, 23 yr, M	2 patients: various cancers; hepatitis, hemorrhage, GI	Urine, stool, blood	−	42
	2	39 yr, M	CML; gastroenteritis, pneumonitis	Liver, lung, blood, stool	+	73
	5	2 yr, M	Lymphoma; hepatitis, enteritis, PCF	Urine, stool	−	42
	5	34 yr, M	Lymphoma; hepatitis, AHC	Urine, liver	+	62
	5	19 yr, M	XLS; liver failure, rash	Liver	+	95
	5	13–19 yr	3 patients: AA/AML; pneumonia, renal failure	Lung, liver, spleen, etc.	3+	106, 132
	6	13 yr, M	AA; pneumonia, hepatomegaly, other	Lung	+	141
E	4	13 yr, M	AML; hepatitis, rash	Throat	−	42

[a] Abbreviations: AA, aplastic anemia; ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CGL, chronic granulocytic leukemia; CML, chronic myelocytic leukemia; CMV, cytomegalovirus; GI, gastrointestinal illness; PCF, pharyngoconjunctival fever; XLS, X-linked lymphoproliferative syndrome.

[b] See Table 3, footnote *b*.

Transplant Recipients

Bone marrow transplant (BMT) recipients are children or young adults with aplastic anemia, leukemia, other cancers, or congenital immunodeficiencies as their underlying illness, and their adenovirus infections reflect their exposure to the more common serotypes (Table 4). Thus, type 31 in subgenus A, type 11 in subgenus B, and types 1, 2, and 5 in subgenus C tend to predominate (4, 27, 35, 42, 50, 62, 73, 79, 95, 105, 106, 130, 132, 141). Types 12 (subgenus A); types 3, 7, 34, and 35 (subgenus B); type 6 (subgenus C); types 15 and 30 and untyped (subgenus D); and type 4 (subgenus E) occurred less often (4, 22, 30, 35, 42, 54, 81, 106, 130, 140, 141). Lung, liver, and gastrointestinal diseases are the most common. In addition, types 11, 34, and 35 have been associated with cystitis and nephritis in adults following BMT (4, 81, 106). As in other immunocompromised groups, adenovirus infections in BMT recipients often become disseminated and have a fatal outcome, with virus being recovered from multiple sites (4, 22, 35, 42, 62, 73, 79, 106, 132). The mean age of BMT patients in this review is 15.6 years, with a case fatality rate of 60.0%. Fatal cases were not evenly distributed among all subgenera, with 69% of subgenus A cases resulting in death compared with 64% of subgenus B cases and 53% of subgenus C cases.

Liver transplant (LT) recipients are young children with various severe underlying conditions; their posttransplant adenovirus infections are caused by common childhood serotypes that are frequently disseminated (Table 5) (12, 42, 67, 68, 82, 85, 98, 102, 110, 122, 138). Infection of the transplanted liver, particularly by adenovirus types 1, 2, and 5, is evidenced by clinical signs of jaundice, hepatomegaly, and hepatitis (42, 67, 68, 85, 122). Pneumonia and diarrhea also occur in some patients, and the virus is found in multiple organs and secretions (42, 68, 85, 98, 102, 122, 138). In one patient who had no serologic evidence of prior infection before transplantation, type 5 was introduced with the first transplanted liver and set up an overwhelming infection that resulted in graft failure. The residual adenovirus infection then lingered to reinfect the second transplanted liver, and the child died (122). Another patient in whom type 7 apparently persisted through two liver transplants also died (138). The mean age of LT recipients in this review was 2.0 years, with a case fatality rate of 53.1%; 91% of the LT cases involved subgenus C types.

Adenovirus infections in renal transplant (RT) patients are often seen as AHC and, to a lesser extent, pneumonia (Table 6). The patients are older (mean age, 35.6 years) and less susceptible to generalized infection, and thus their prognoses are much better than those of other groups (5, 14, 26, 30, 36, 39, 42, 46, 64, 76, 77, 87, 91, 103, 107, 108, 113, 139, 141). The predominant subgenus is B, and the prevalent serotypes, 7, 11, 34, and 35, account for 88% of the cases

TABLE 5. Adenoviruses in secondary immunodeficiencies: LT recipients

Subgroup	Serotype	Age and sex	Clinical presentation[a]	Sites of virus detection	No. fatal[b]	Reference
A	31	6 mo, M	SCID; hepatomegaly, jaundice, pneumonia	Liver, lung	+	98
B	7	2 yr, F	Biliary atresia; URI, pneumonia	Liver, lung, spleen, kidney	+	138
C	1	Children	3 patients: various cancers; hepatitis	Liver, urine, bile, respiratory tract	2+	85
	2	1–3 yr	4 patients: various cancers; hepatitis, diarrhea	Stool, liver, blood	2+	42
	2	Children	6 patients: various cancers; hepatitis, pneumonia	Liver, urine, blood, etc.	3+	85
	5	Children	5 patients: various cancers; hepatitis	Liver, blood, urine, throat	2+	68
	5	Children	10 patients: various cancers; hepatitis, pneumonia	Liver, blood, urine, etc.	4+	85
	5	8 mo, M	Biliary atresia; jaundice, other	Liver, abdominal organs	+	122
E	4	Child	Atresia?; pneumonia, disseminated disease	Blood, respiratory tract	+	85

[a] "Various cancers" includes other underlying diseases.
[b] See Table 3, footnote *b*.

shown (Table 6). The subgenus B viruses are easily found in the urine both because these serotypes have a general predilection for the urinary tract and because adenoviruses in transplant recipients tend to target the transplanted organ (14, 26, 30, 36, 39, 42, 46, 64, 76, 103, 107, 139). During disseminated disease, the viruses are found in respiratory specimens, blood, and many internal organs (39, 42, 87, 91, 141).

Cancer Patients

Cancer patients undergo intensive chemotherapy with cytotoxic and immunosuppressive drugs and often radiation treatment in attempts to destroy the neoplastic growth. These measures also attack the immune system, leaving the patient with little defense against opportunistic pathogens. Many cases of fulminant adenovirus infection in these patients have been described (11, 16, 18, 30, 38, 42, 61, 65, 80, 83, 100, 117, 141). The variety of adenovirus serotypes isolated reflects the range of ages and diseased organs in this group of patients, with subgenera B and C predominating (Table 7). The mean age of well-documented patients is 25.0 years; 53.3% of these infections were fatal.

AIDS Patients

Recently, adenovirus infections have been found to afflict AIDS patients, usually in cohort with multiple other opportunistic infections (7, 17, 19, 20, 25, 30, 42, 45, 49, 51, 53, 57–59, 63, 70, 71, 97, 99, 116, 119, 133). Adenovirus pneumonia, meningoencephalitis, and hepatitis occur in these patients, sometimes as generalized infections with a rapidly fatal course (17, 25, 49, 51, 53, 57, 71, 119, 133). In other patients, gastroenteritis or colitis is the major clinical presentation (20, 58, 59, 63, 99, 116). Almost all patients are coinfected with up to six other pathogens in addition to the adenovirus. In our studies, the prevalent pathogens, in decreasing order of prevalence, were cytomegalovirus, herpes simplex virus type 2, *Pneumocystis carinii*, hepatitis B virus, hepatitis A virus, Epstein-Barr virus, *Neisseria gonorrhoeae*, *Candida albicans*, *Mycobacterium avium*, *Cryptosporidium parvum*, *Cryptococcus neoformans*, varicella-

TABLE 6. Adenoviruses in secondary immunodeficiencies: RT recipients

Subgroup	Serotype	Age (yr) and sex	Clinical presentation[a]	Site(s) of virus detection	No. fatal[b]	Reference(s)
B	7	15–40	3 patients: various; URI, fever, chills	Throat, blood	1+	42
	11	54, F	Polycystic disease; dysuria, AHC	Urine	–	26
	11	26, F	Not given; fever, AHC, trigonitis	Urine, throat	–	39
	11	4–59	5 patients: various; AHC, pneumonia, nephritis	Urine	1+	42
	11	29, M	Glomerulonephritis; AHC, fever	Urine	–	107
	11	29, F	Not given; AHC	(Serology only)	–	108
	11	32, 36, M	2 patients: various; AHC, nephropathy	Urine	–	139
	34	17, M	Glomerulonephritis; fever	Urine	–	46
	34	18, M	Glomerulonephritis; pneumonia	Urine	–	64
	35	46, F	Polycystic disease; AHC, urethritis	Urine, urethra, other	–	14
	35	Adults	2 patients: various; asymptomatic	Urine	–	36
	35	26–58	9 patients: various; AHC, LRI, CNS, GI, fever	Urine	2+	42
	35	61, F	Pyelonephritis; pneumonia, other	Lung, kidney, pancreas, etc.	+	87, 113
C	2	45, M	Not given; URI, pharyngitis, cough	Throat	–	42
	5	56, F	Glomerulosclerosis; AHC, other	Lung, liver	+	91
	1 and 5	35, F	Glomerulonephritis; LRI, HA, other	Sputum (Ad5), CSF (Ad1)[c]	–	141
E	4	31, F	Not given; LRI, headache, nausea and vomiting, diarrhea	Blood	–	141

[a] Abbreviations: CNS, central nervous system disease; GI, gastrointestinal illness; various, various underlying diseases.
[b] See Table 3, footnote *b*.
[c] Abbreviations: Ad1, Ad5, adenovirus types 1 and 5, respectively; CSF, cerebrospinal fluid.

TABLE 7. Adenoviruses in secondary immunodeficiencies: cancer immunosuppression patients

Subgroup	Serotype	Age and sex	Clinical presentation[a]	Site(s) of virus detection	No. fatal[b]	Reference(s)
A	12	10 mo, M	Astrocytoma; fever	CSF[c]	–	65
	31	20, 28 yr	2 patients: various cancers; URI, diarrhea	Stool, throat	–	42
B	7	9 yr, M	Leukemia; disseminated CMV disease	Urine (+CMV)	+	38
	7	6 yr, M	ALL; fever, vomiting, abdominal pain	CSF, urine, stool	+	65
	11	Adult	T-cell leukemia; AHC	Urine	–	117
	21	5, 57 yr	2 patients: neuroblastoma/CLL; pneumonia, GI	Stool, lung	–	42
	35	40–59 yr	3 patients: various cancers; URI, LRI, rash	Urine	1+	42
C	1	6, 26 yr, F	2 patients: various cancers; pneumonia, hepatitis	Lung, throat	1+	42
	1	45 yr, F	CLL; hepatitis, renal failure	Lung, liver, blood, urine	+	80
	1	Children	3 patients: various cancers; pneumonitis, other	Brain, tumor tissues	2+	83
	1	6 yr, M	AML; PCF, AHC, hepatomegaly, pneumonia	Eye, lung	+	141
	2	4 yr, M	ALL; pneumonia	Throat	–	141
	5	34 yr, M	Hodgkin's disease; hepatitis, other	Liver, blood	+	11
	5	18 yr, F	ALL; hepatitis, disseminated disease	Liver, mouth, bone marrow	+	16
	5	3 yr, F	ALL; hepatomegaly, gastroenteritis	Blood, urine, stool	–	61
	5	19 yr, F	ALL; hepatic necrosis, headache, DIC	Liver, urine, bone marrow	+	141
D	32	42 yr, M	Lymphoma; hepatosplenomegaly, encephalitis	Brain, CSF	+	18, 100
	37	66 yr, F	Cancer; keratoconjunctivitis	Eye	–	42
E	4	6 yr, M	CML; pneumonia, URI, chills, diarrhea	Blood	–	141
	4	51–65 yr, F	3 patients: various cancers; pneumonia, other	Urine, lung	3+	141
F	41	4 yr, F	ALL; gastroenteritis, pneumonia, rash	Stool	+	42

[a] Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; PCF, pharyngoconjunctival fever.
[b] See Table 3, footnote *b*.
[c] CSF, cerebrospinal fluid.

zoster virus, *Mycobacterium tuberculosis*, enteroviruses, other respiratory viruses, *Treponema pallidum*, molluscum contagiosum virus, and *Histoplasma capsulatum* (42, 49). Because of this prevalence of multiple opportunistic infections, we cannot ascribe particular symptoms, clinical findings, or death to adenovirus infection alone. The subgroups and serotypes involved in infection in AIDS patients are quite diverse and can be divided according to the site of isolation (Table 8). Isolates from serum or leukocytes are usually of subgenus C, type 5; isolates from urine are usually of subgenus B, types 11, 21, 34, and 35 and intermediate strains of these; and isolates from stool are of subgenus D and are often untypeable, being intermediate strains of diverse combinations (45, 49, 53, 116).

COMMENTARY

The human adenoviruses presently comprise 47 serotypes grouped into six subgenera, which roughly parallel the hemagglutination and oncogenic subgroups (43, 90, 126, 127, 135). Within these serotypes are a multitude of atypical and intermediate strains and DNA variants that complicate the precise identification of newly isolated strains (2, 3, 13, 22, 25, 27, 30, 36, 43, 45, 47–49, 52, 53, 100, 103, 120, 121, 126, 132, 136).

Adenoviruses are among the many pathogens that contribute to debilitating and often fatal illnesses in immunosuppressed patients. These viruses are not unexpected in such patients, because they have biological properties that facilitate their spread under conditions of immunosuppression. Specific properties are as follows. (i) Adenoviruses are pathogenic for diverse tissues and normally cause a wide variety of clinical syndromes in humans. (ii) New serotypes and intermediate strains are frequently described, including two new adenoviruses isolated from RT recipients and associated with cystitis, pneumonia, or generalized disease (46, 113). Most recently, types 43 to 47 have been found to contribute to generalized disease in AIDS patients (45, 49). (iii) Some serotypes can produce tumors in laboratory animals. (iv) Many are known to readily become latent in lymphoid tissue and kidneys and are assumed to reactivate in immunosuppressed patients. (v) Adenoviruses can be excreted in the stool for weeks or months after initial infection (52, 127). All of these features are compatible with the apparent long-term presence of adenoviruses in the intestinal and urinary tracts and with their possible contribution to disease in immunocompromised hosts. At the same time, adenovirus infections in the immunosuppressed patient are often different from those in the normal host in terms of persistence and severity of disease and the association with a different spectrum of serotypes (43, 45, 49, 53, 104, 134).

Immunosuppression also probably contributes to the diversity of serotypes. The immunocompromised patient can develop chronic adenovirus disease as a result of persistent infection and an altered or ineffective immune system. This combination increases the likelihood that the patient will become infected with a second serotype while still infected with the first, thus making it possible for the two serotypes to recombine to form an intermediate type. Recombination may explain the unusual frequency and variety of intermediate strains in the gastrointestinal tracts of AIDS patients. An alternative explanation for the number of different adenovirus serotypes and intermediate strains is that the immunosuppressed patient may be more likely to manifest symptoms with a severe virus infection and therefore have the infection detected in standard laboratory workups.

TABLE 8. Adenoviruses in secondary immunodeficiencies: AIDS patients

Subgroup	Serotype	Age and sex	Clinical presentation[a]	Site(s) of virus detection	No. fatal[b]	Reference(s)
A	31	28–50 yr, M	6 patients: AIDS; diarrhea, URI, fever	Stool, urine, blood, throat	3+	42, 45, 49
	31	35 yr, M	AIDS; dementia, encephalitis	CSF	+	51
B	3	24 yr, F	AIDS; hepatosplenomegaly, pneumonia	Brain, lung, liver, bronchus	+	71
	11[c]	22–40 yr	10 patients: AIDS; pneumonia, rash, AHC	Urine, kidney	4+	45, 49
	16	23 yr, M	AIDS; pneumonia, hepatitis	Stool	–	45, 49
	21[c]	52 yr, M	AIDS; URI, pneumonia, AHC	Stool	–	45, 49
	34[c]	19, 34 yr, M	2 patients: pneumonia, diarrhea	Urine	1+	45, 49
	35[c]	Adults	36 patients: AIDS or ARC; AHC, other	Urine, stool, throat	NG	25, 30, 53
	35[c]	25–34 yr	3 patients: AIDS; pneumonia, hepatitis	Urine, stool	1+	45, 49
C	1	27 yr, M	ARC; erythematous papules, nodules	Skin lesion	+	19
	1	7 yr, M	AIDS; hepatitis, pneumonia, DIC	Lung, kidney, marrow, liver	+	71
	1	58 yr, M	AIDS; diarrhea	Colon	–	42
	2	6 mo, M	AIDS; pneumonia, diarrhea, hepatitis	Lung, liver, kidney, throat	+	71
	2	30 yr, M	Early ARC; encephalitis	Brain	–	133
	5	29–37 yr, M	3 patients: AIDS; pneumonia, diarrhea	Blood, liver, lung	2+	45, 49
	5	7 mo, F	AIDS; hepatosplenomegaly, pneumonia	Liver	+	57
D	8	26, 31 yr, M	2 patients: AIDS/PGL; pneumonia, GI	Throat, stool, urine, eye	–	42, 45, 49
	20[c]	25 yr, M	AIDS; diarrhea	Stool	–	45, 49
	22[c]	27–30 yr	3 patients: AIDS; pneumonia, diarrhea	Stool, lung, throat	2+	42, 45, 49
	26	29 yr, M	AIDS; diarrhea	Stool	+	45, 49
	28	33 yr, M	AIDS; hepatitis, diarrhea	Urine	–	45, 49
	29	26 yr, F	AIDS; URI, diarrhea	Stool	–	45,49
	29	32 yr, M	AIDS; pneumonitis, diarrhea	Lung	+	119
	30[c]	27–35 yr, M	3 patients: AIDS; pneumonia, diarrhea	Stool	1+	45, 49
	32[c]	35 yr, M	AIDS; gastroenteritis	Colon	+	45, 49
	37	22 yr, M	AIDS; pneumonia	Bronchoalveolar lavage	NG	17
	37[c]	33, 37 yr, M	2 patients; AIDS; pneumonia, diarrhea	Stool	–	45, 49
	43	22–39 yr	5 patients; AIDS; pneumonia, diarrhea	Stool, urine	2+	42, 45, 49
	44[c]	35, 37 yr, M	2 patients; AIDS; pneumonia, diarrhea	Stool	1+	45, 49
	45[c]	33–40 yr, M	4 patients; AIDS; pneumonia, diarrhea	Stool	1+	42, 45, 49
	46[c]	33, 64 yr, M	2 patients; AIDS; pneumonia, diarrhea	Stool, bronchial brush	1+	45, 49
	47	54 yr, M	AIDS; pneumonia	Stool	+	45, 49
	Untyped	21–47 yr	12 patients; AIDS; pneumonia, diarrhea	Stool, lung, throat	5+	42

[a] Abbreviations: ARC, AIDS-related complex; PGL, persistent generalized lymphadenopathy. Because of the prevalence of multiple opportunistic infections in most AIDS patients, it is impossible to ascribe particular symptoms, clinical findings, or death to adenovirus infection alone.
[b] Death within 2 months of the date of the first specimen containing adenovirus. NG, information not given.
[c] This serotype includes one or more antigenically intermediate strains, which are listed here according to their neutralization activity.

A comparison of ICHD patient groups shows that both the nature of the immunosuppression and the age of the patient affect the serotype of adenovirus likely to infect the patient (Table 9) and that all three parameters—type of immunosuppression, age, and serotype—are related to fatal outcome (Table 10). Congenital immunodeficiencies had a high case fatality rate (55% overall), owing to the young age of the patients (mean, 4 years) and the drastic nature of SCID. In this category, type 31 was the largest contributor to fatal outcome (83% of subgenus A cases) but not to infection (32% of primary immunodeficiency cases). Type 31 appeared to be particularly severe in cases of hepatitis, gastroenteritis, and generalized disease in these patients. Subgenera A (type 31), B (types 3, 7, 11, 34, and 35), and C (types 1, 2, and 5) were equally represented in the primary immunodeficiency category.

In the BMT category, type 31 again had the highest case fatality rate (69%) while causing only 24% of the infections. Hepatitis and gastroenteritis were severe complications of infection in these patients. Subgenera B (types 7, 11, 34, and

TABLE 9. Adenovirus serotypes associated with ICHD

Patient group	Table	Serotypes involved in subgenus[a]:					
		A	B	C	D	E	F
Primary	3	31	3, 7, 11, 34, 35	1, 2, 5			41
BMT recipients	4	31	7, 11, 34, 35	1, 2, 5, 6		4	
LT recipients	5	31	7	1, 2, 5		4	
RT recipients	6		7, 11, 34, 35	1, 2, 5		4	
Cancer patients	7	12, 31	7, 11, 21, 35	1, 2, 5	32, 37	4	41
AIDS patients	8	31	3, 11, 16, 21, 34, 35	1, 2, 5	8, 20, 22, 26, 28, 29, 30, 32, 37, 43–47		

[a] Serotypes reported in the literature and from my laboratory, as shown in the individual tables.

TABLE 10. Case fatality rates among immunocompromised patients infected with different adenovirus subgenera

Patient group	Table	Case fatality rate (%) in subgenus:						Overall % fatality	Mean age of patients (yr)
		A	B	C	D	E	F		
Primary	3	83	45	54			0	55	4.4
BMT recipients	4	69	64	53		0[a]		60	15.6
LT recipients	5	100[a]	100[a]	48		100[a]		53	2.0
RT recipients	6		17	33[a]		0[a]		18	35.6
Cancer patients	7	0[a]	38	67	50[a]	75	100[a]	53	25.0
AIDS patients	8	57	39	67	40			45[b]	31.1

[a] Fewer than four cases, therefore insufficient denominator for accurate assessment.
[b] Association of adenovirus infection with death not accurately calculable because of the presence of multiple other pathogens.

35) and C (types 1, 2, and 5) were about equal in the number of cases (22 and 19, respectively) but not in fatal outcome, having a 64 and 53% fatal outcome rate, respectively; the numbers were insufficient to reveal any one serotype as more pathogenic than another. Overall, the BMT recipients suffered a 60% fatal outcome rate, which was the highest in this survey.

Adenovirus infection in LT recipients was mostly associated with subgenus C serotypes (types 1, 2, and 5), which caused 91% of adenovirus infections in this category and which had a fatality rate of 48%. Hepatitis was the predominant clinical presentation. The single case associated with each of types 31, 7, and 4 was a fatal pneumonia. These cases and the pneumonias in other groups of ICHD patients exemplify the broader serotype association of adenoviruses with LRI seen in ICHD patients compared with immunocompetent hosts (89, 92). The mean age of 2 years, coupled with the high incidence of liver damage, was undoubtedly related to the overall case fatality rate of 53% in this group.

By contrast, adenovirus infection in RT patients was largely caused by subgenus B serotypes, namely types 7, 11, 34, and 35, which caused 88% of the adenovirus infections in this category and had a fatality rate of 17%. Fatal outcome was not significantly associated with any particular serotype, but, interestingly, neither case involving infection with type 34 resulted in death. Just as hepatitis was the major problem in LT recipients, kidney infection was the predominant problem in RT patients. Thus, the major clinical finding was hemorrhagic cystitis and the most important specimen was urine. The overall case fatality rate for RT patients was 18%, the lowest in this review, which is due to the older age (mean, 36 years) and the less severe clinical findings (milder respiratory illness, diarrhea, cystitis).

Because of the diverse types of cancer and the diverse ages of patients involved, adenovirus infections in cancer patients were associated with all six subgenera, with B, C, and E being most common. Three cases were associated with subgenus A, types 12 and 31; these were febrile respiratory illnesses that were not fatal. Three (38%) of 8 subgenus B cases (types 7, 11, 21, and 35) had fatal outcomes, compared with 8 (67%) of 12 subgenus C cases (types 1, 2, and 5) and 3 (75%) of 4 subgenus E cases (type 4). The presenting illnesses were quite diverse, with an overall case fatality rate of 53%, reflecting the various types of cancer, diverse adenovirus serotypes involved, and wide range of ages (<1 to 66 years).

Finally, Tables 9 and 10 summarize the serotypes and subgenus-related case fatality rate for AIDS patients, who constitute a special category because of their gradually diminishing immune systems and their unusually intense exposure to multiple opportunistic pathogens. With subgenus A, four (57%) of seven patients died within 2 months of the first recognition of type 31 infection. With subgenus B, 7 (39%) of 18 patients whose complete history was known died in this time; fatal cases were associated with types 3, 11, 34, and 35 but not with types 16 and 21. With subgenus C, six (67%) of nine patients with type 1, 2, or 5 infection died, the highest percentage in this clinical category. With subgenus D, 17 (40%) of 42 patients died; these were associated with types 22, 26, 29, 30, 32, and 43 to 47 and untyped subgenus D viruses but not with type 8, 20, 28, or 37. Overall, 45% of AIDS patients died within 2 months of the time when their first adenovirus-containing specimen was collected; their mean age at the time of known adenovirus infection was 31 years.

The large number of subgenus B and D antigenically intermediate strains found in the urine and stool, respectively, of AIDS patients has greatly complicated the identification of adenoviruses from these patients. In one study, 67 adenovirus isolates were identified from 48 AIDS patients (49). The isolates included 5 of subgenus A (all type 31), 23 of subgenus B, 4 of subgenus C (all type 5), and 35 of subgenus D. The subgenus A and C strains were from the liver, lungs, blood, urine, and stool and were unremarkable in their antigenic characteristics. The subgenus B strains were mostly from urine and were serotyped as type 11 (12 isolates), type 16 (1 isolate), type 35 (3 isolates), strain 21/H21+35 (1 isolate), plus new intermediate strains 34/H11 (3 isolates), 35/H11 (1 isolate), and 11+35/H11 (2 isolates). The subgroup D adenoviruses were isolated from 24 patients; 30 isolates were from rectal specimens, 4 were from urine, and 1 was from a bronchial brush biopsy. Eight isolates (types 8, 22, 26, 28, 29, and 30) were typical serotypes by serum neutralization and hemagglutination inhibition tests. Types 8 and 28 were recovered from urine specimens, a highly unusual source of these viruses. The isolates from 12 patients were not neutralized by type 1 to 42 prototype antisera and clustered into five groups, becoming serotypes 43 to 47. Many new intermediate strains were found among these isolates as well (45, 49), including strain 32/H27, which was previously found in brain tissue from an immunosuppressed man with subacute encephalitis (18, 100).

The most unusual aspects of the adenoviruses isolated from AIDS patients are this diversity of serotypes and the frequency of antigenically intermediate strains. Patients who are therapeutically immunosuppressed to receive BMT, LT, or RT or who are undergoing cancer chemotherapy can have generalized adenovirus infections with multisystem symptoms or localized infections of the respiratory tract, urinary tract, or abdominal organs; in this review, 15 different adenoviruses of subgenera A (35, 42, 65, 98, 106), B (4, 14,

26, 36, 38, 39, 42, 46, 50, 64, 65, 79, 81, 87, 106–108, 113, 117, 138, 139), C (11, 16, 27, 35, 42, 61, 62, 68, 73, 80, 83, 85, 91, 95, 106, 122, 132, 141), D (18, 42, 100), E (42, 85, 141), and F (42) were isolated from appropriate specimens from these non-AIDS patients and were readily identifiable. This is in marked contrast to the 23 serotypes and 14 different intermediate strains reported from AIDS patients (17, 19, 25, 30, 42, 45, 49, 51, 53, 57, 71, 119, 133).

Also in contrast to serotypes obtained from other immunosuppressed groups of patients, adenoviruses from AIDS patients have proven unusually difficult to serotype. This is because intermediate strains require extensive cross-testing by neutralization and hemagglutination inhibition tests, preferably with strain-specific hyperimmune antisera, and because most laboratories have no experience in serotyping the subgenus D viruses from stool, which are rarely encountered in non-AIDS patients (3, 42–45, 47, 49, 52, 53, 104, 134). The reasons for the differences in associated serotypes noted in Tables 3 to 8 must lie in the adult ages and sexual life-styles of AIDS patients, whose practices expose them to many uncommon viruses. Of particular note is the etiology of adenovirus-related gastroenteritis, which is nearly always due to types 31 (subgenus A), 2 (subgenus C), and 40 or 41 (subgenus F) in other immunocompromised patients but is usually due to serotypes of subgenus D in AIDS patients (42, 49).

The antigenically intermediate strains are particularly interesting because they may derive from the length of time that adenoviruses are in an infectious state in AIDS patients, which presumably extends from the time of onset of adenovirus infection to the death of the patient. Long-term infection may provide the opportunity for mutations to occur within a strain or for recombinational events between coinfecting serotypes to take place, resulting in the generation of viruses with new antigenic makeups.

The observation that 45% of AIDS patients die within 2 months of the first evidence of adenovirus infection suggests a role for adenovirus in AIDS pathogenesis. This is particularly intriguing because adenovirus E1A antigens, as well as herpesvirus ICPO proteins, are known to transactivate transcription in both human T-cell leukemia virus type I and human immunodeficiency virus (66, 74, 88, 124, 125). Another role of adenoviruses in AIDS pathogenesis was suggested by Horwitz and coworkers (25, 53), who found an unusually high prevalence of type 35 in the New York area during the early years of the AIDS epidemic. Their studies showed that several antigenic intermediates were made in vivo in the fiber protein, apparently the result of recombination in the fiber gene. The suggestion that these fiber changes might be related to functional mechanisms in the nonstructural E3 polypeptide (which associates with the class I major histocompatibility antigens of human cells) was drawn from the fact that the E3 and fiber genes are adjacent on the type 35 genome (28–30, 45, 53, 120). The role of adenoviruses or other viruses in advancing the stages of human immunodeficiency virus disease is quite unclear at present, and considerable effort must be devoted to this area of research.

The case fatality rates in Table 10 may be biased upward by (i) the fact that only the most serious cases tend to be studied in detail and reported and (ii) the proven or suspected presence of other pathogens that may contribute to death. On the other hand, the rates may be biased downward by incomplete laboratory studies and/or reporting. Some 300 adenovirus infections in immunocompromised patients are covered in this review; they had an overall case fatality rate of 48%.

Several studies have provided data on the adenovirus infection rate in immunocompromised patients. Adenoviruses have been found in different studies to infect 3.8, 4.9, or 17.7% of patients receiving BMT (4, 106, 130); specifically, they have been isolated from the respiratory tract in 6.4% and the gastrointestinal tract in 15.4% of BMT patients (81, 140). Survey studies have also shown adenoviruses infecting 8.4, 10.1, or 17.5% of LT recipients (68, 85, 102) and 11.5% of RT patients (77). Considering that all adenoviruses isolated from stool are probably not causing clinical disease but that adenoviruses from any other site are causing disease, we estimate that 11% of transplant recipients become infected with adenoviruses and show clinical signs of the infection. Case fatality rates vary from 44 to 60% of BMT patients with adenovirus (140, 141) to 18.4% of LT patients with adenovirus (85); these agree with the 60 to 18% rates derived from the expanded sets of data and summarized in Table 10.

Studies indicate that the adenovirus infection rate in AIDS patients is even higher than that in organ recipients. A comprehensive study of Australian men showed that 54% of diarrheal illnesses in AIDS patients were caused by viruses and that 37% of the viral diarrheas were adenovirus related; thus, 20% of these AIDS patients had adenovirus-related diarrhea (20). Other studies found adenoviruses in 10% of AIDS patients generally (42, 49); in stools of 7.4, 5.2, or 21.2% of AIDS patients with diarrhea (58, 63, 99); and in urine specimens of 12.6% of AIDS patients in one hospital and 6.7% in another (53). Thus, adenoviruses cause active infection in an estimated 12% of patients with clinical AIDS; Table 10 shows that 45% of these cases end in death within 2 months of the initial detection of adenovirus. This can be interpreted two ways: that AIDS patients acquire their adenovirus infection late in the course of AIDS when they are already debilitated by other infections, or that adenoviruses are unusually severe in AIDS patients and contribute significantly to their demise, perhaps by advancing the stages of HIV disease as discussed above. The evidence at hand suggests the latter interpretation; further work in progress should provide a clearer answer.

The source of the virus in adenovirus-related ICHD is unclear in most cases because appropriate laboratory studies have not been done. The presence of type-specific antibody in organ recipients before transplantation indicates that the patients have been infected with the virus at some time in their life, with the virus presumably becoming latent in renal and lymphoid tissues and therefore spontaneously reactivating in the face of massive therapeutic immunosuppression. This situation has been shown in BMT recipients (4, 50, 62, 106, 130, 132) and LT patients (67). Similarly, the presence of type-specific antibody before initiation of immunosuppressive therapy indicated reactivation of the virus in a cancer patient (61). Results of serologic studies are particularly suggestive of reactivation if the donor did not possess that same type-specific antibody at the time of organ donation. Conversely, if the recipient had no antibody to the infecting virus but the donor did, the serologic data suggest that the virus was latent in the donor organ and proceeded to set up a new infection in the recipient. In LT (67, 122) and RT (39, 46, 64, 76, 87, 91, 107, 113) recipients, this has been the case more often than infection from reactivated endogenous virus.

In all of the reactivated-virus cases mentioned above, the adenovirus infections were of subgenus B or C serotypes. Indeed, latent adenovirus infections of adenoid tissue in children are known to be caused by subgenus C serotypes,

and kidney tissues in children and adults have been documented as containing subgenus B types (reviewed in references 43 and 52). Latent infections by subgenus D serotypes have not been documented before, and none were found in this review. Hence, infections with subgenus D viruses are likely to be new infections rather than reactivations.

The exogenous sources of infecting adenovirus for other immunocompromised patients have been community outbreaks (30), family illness (6, 49, 75), or nosocomial outbreaks (13, 80, 85, 95, 103, 140). The incidence of nosocomial spread of adenoviruses among immunosuppressed patients has actually been remarkably low, considering the severity of adenovirus-related ICHD and the presence of virus in multiple sites for extended periods.

Treatment regimens and the clinical management of these patients are reviewed elsewhere (5, 26, 37, 55, 81, 86). Although no specific treatment for adenovirus infection is available, many natural and synthetic products have been tried. Thymic humoral factor was successfully used on a disseminated type 3 infection in a child who probably had a temporary immunosuppression due to the adenovirus infection (123). Pooled immunoglobulin G, given in the hope that it would contain the correct type-specific antibody, has been tried with both positive (21) and negative (75, 137) results. Interferon given topically to reduce adenovirus eye infection has had little success because adenoviruses inhibit the mode of action of interferon (1, 33, 56, 65a, 96). Corticosteroids also have been given to ameliorate eye infections and have generally not been useful (31, 32, 72). Live, oral enteric-coated vaccines against types 4 and 7, which have been effectively used in the military to prevent epidemics of acute respiratory disease (115), have not been approved for use in civilian populations because of the multitude of other serotypes that can cause equally severe illness; no other adenovirus vaccines are planned at present. More recently, purine and pyrimidine base analogs, such as ganciclovir, have been studied as both topical and internal medications and may show some promise (9, 11, 23, 24, 41, 78, 94, 116, 128, 131, 138). Otherwise, the best strategies are those of prevention, which have been successfully applied to curtail adenovirus outbreaks in ophthalmologic clinics, hospitals, and nurseries (15, 96, 129).

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