

# Intravenous Ribavirin Treatment for Severe Adenovirus Disease in Immunocompromised Children

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**ABSTRACT.** *Background.* Adenovirus is an important cause of morbidity and mortality in the immunocompromised host. The incidence of severe adenovirus disease in pediatrics is increasing in association with growing numbers of immunocompromised children, where case fatality rates as high as 50% to 80% have been reported. There are no approved antiviral agents with proven efficacy for the treatment of severe adenovirus disease, nor are there any prospective randomized, controlled trials of potentially useful anti-adenovirus therapies. Apparent clinical success in the treatment of severe adenovirus disease is limited to a few case reports and small series. Experience is greatest with intravenous ribavirin and cidofovir. Ribavirin, a guanosine analogue, has broad antiviral activity against both RNA and DNA viruses, including documented activity against adenovirus in vitro. Ribavirin is licensed in aerosol form for the treatment of respiratory syncytial virus infection, and orally in combination with interferon to treat hepatitis C. Intravenous ribavirin is the treatment of choice for infection with hemorrhagic fever viruses. The most common adverse effect of intravenous ribavirin is reversible mild anemia. The use of cidofovir in severe adenovirus infection has been limited by adverse effects, the most significant of which is nephrotoxicity.

*Objective.* We report our experience with intravenous ribavirin therapy for severe adenovirus disease in a series of immunocompromised children and review the literature.

*Design/Methods.* We retrospectively reviewed the medical records of 5 children treated with intravenous ribavirin for documented severe adenovirus disease. Two patients developed adenovirus hemorrhagic cystitis after cardiac and bone marrow transplants, respectively. The bone marrow transplant patient also received intravenous cidofovir for progressive disseminated disease. An additional 3 children developed adenovirus pneumonia; 2 were neonates, 1 of whom had partial DiGeorge syndrome. The remaining infant had recently undergone a cardiac transplant. Intravenous ribavirin was administered on a compassionate-use protocol.

*Results.* Complete clinical recovery followed later by viral clearance was observed in 2 children: the cardiac transplant recipient with adenovirus hemorrhagic cystitis and the immunocompetent neonate with adenovirus pneumonia. The remaining 3 children died of adenovirus disease. Intravenous ribavirin therapy was well toler-

ated. Use of cidofovir in 1 child was associated with progressive renal failure and neutropenia.

*Discussion.* Our series of patients is representative of the spectrum of immunocompromised children at greatest risk for severe adenovirus disease, namely solid-organ and bone marrow transplant recipients, neonates, and children with immunodeficiency. Although intravenous ribavirin was not effective for all children with severe adenovirus disease in this series or in the literature, therapy is unlikely to be of benefit if begun late in the course of the infection. Early identification, eg by polymerase chain reaction of those patients at risk of disseminated adenovirus disease may permit earlier antiviral treatment and better evaluation of therapeutic response.

*Conclusions.* Two of 5 children with severe adenovirus disease treated with intravenous ribavirin recovered. The availability of newer rapid diagnostic techniques, such as polymerase chain reaction, may make earlier, more effective treatment of adenovirus infection possible. Given the seriousness and increasing prevalence of adenovirus disease in certain hosts, especially children, a large, multicenter clinical trial of potentially useful anti-adenoviral therapies, such as intravenous ribavirin, is clearly required to demonstrate the most effective and least toxic therapy. *Pediatrics* 2002;110(1). URL: <http://www.pediatrics.org/cgi/content/full/110/1/e9>; *adenovirus, immunocompromised host, pediatric, ribavirin.*

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ABBREVIATIONS. RSV, respiratory syncytial virus; IV, intravenous; CMH, Children's Memorial Hospital; IF, immunofluorescence; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; OHT, orthotopic heart transplant; CMV, cytomegalovirus; Ig, immunoglobulin; BMT, bone marrow transplant; GVHD, graft-versus-host-disease; SCT, stem-cell transplant; SCID, severe combined immunodeficiency; IVGG, intravenous gammaglobulin.

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Adenovirus infections are exceedingly common in childhood.<sup>1</sup> Adenoviruses have a predilection for the respiratory tract and account for up to 8% of respiratory infections in young children and an estimated 5% of all infections in infants.<sup>2-4</sup> Most of these infections are asymptomatic, mild, or self-limited; resolve within 2 weeks; and induce type-specific immunity.<sup>1,4</sup> In the immunocompromised host, however, adenovirus infection can cause severe localized disease including pneumonitis, colitis, hemorrhagic cystitis, hepatitis, nephritis, encephalitis, or disseminated disease with multiorgan failure.<sup>5,6</sup> The incidence of severe adenovirus disease in pediatrics is increasing in association with the growth in numbers of immunocompromised children.<sup>7-10</sup> Case fatality rates as high as 50% to 80% have been described.<sup>5,6,11,12</sup> There are no approved antiviral agents with proven efficacy for the

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treatment of severe adenovirus disease. Ribavirin, an antiviral agent licensed in aerosol form for the treatment of respiratory syncytial virus (RSV) infection and orally to treat hepatitis C in combination with interferon, has documented activity against adenovirus *in vitro*.<sup>13</sup> We report our experience in treating severe adenovirus disease with intravenous (IV) ribavirin among 5 children at Children's Memorial Hospital (CMH) from July 1997 through August 2001, and we review the literature on adenovirus treatment.

## METHODS

Five immunocompromised children (Table 1) diagnosed with severe adenovirus disease were treated with IV ribavirin after approval of compassionate use of an experimental agent by the CMH Institutional Review Board and the Food and Drug Administration and informed written consent was obtained.

An IV form of ribavirin was provided on a compassionate-case basis by the manufacturer (ICN Pharmaceuticals, Inc, Costa Mesa, CA). Cases 1, 3, and 5 received IV ribavirin 25 mg/kg in 3 divided doses on day 1 and 15 mg/kg/d divided q8 hourly on days 2 to 10. Case 4 received 1 day of therapy at 25 mg/kg, and case 2 received IV ribavirin 33 mg/kg on day 1, followed by 16 mg/kg/dose every 6 hours on days 2 to 4 and 8 mg/kg/dose every 8 hours on days 5 to 7.

Specimens for viral culture were grown on A549 human lung carcinoma, human embryonic lung fibroblast cells, and monkey kidney cell lines at the Virology Laboratory, Department of Microbiology, CMH. Adenovirus was identified by characteristic cytopathic effect and confirmed by immunofluorescence (IF) with an FITC-conjugated murine anti-adenovirus monoclonal antibody (Biowhittaker, Inc, Walkersville, MD). Secretions from nasopharyngeal aspirate and bronchoalveolar lavage (BAL) from case 4 were tested for adenovirus by an indirect IF method using murine monoclonal antibody (Bartels, Inc, Issaquah, WA). Biopsy specimens were processed for routine histologic studies; adenovirus was identified by characteristic histologic changes and by immunohistochemistry using an immunoperoxidase technique with a murine anti-adenovirus monoclonal antibody (Ventana Medical Systems, Tucson, AZ). Adenovirus was sought in biopsy specimens by cell culture from case 1 and by polymerase chain reaction (PCR) assay in blood from case 2. Adenovirus serotyping was performed on isolates from 3 children (cases 1–3) by neutralization using adenoviral antisera (Centers for Disease Control and Prevention, Atlanta, GA).

## CASE REPORTS

### Case 1

A 5-year-old girl was admitted with a 2-day history of abdominal pain, emesis, and low-grade fevers. Two months previously she had received an orthotopic heart transplant (OHT) for idiopathic restrictive cardiomyopathy. Both the patient and her donor were cytomegalovirus (CMV) immunoglobulin G (IgG)-positive but IgM-negative before transplantation. Posttransplant immuno-

suppression consisted of cyclosporin, azathioprine, and prednisolone; other medications included prophylactic acyclovir, nystatin, and trimethoprim-sulfamethoxazole.

Admission examination revealed a fever of 39.9°C, pulse of 160 beats per minute, and mild epigastric and suprapubic tenderness. Laboratory studies showed the following: hemoglobin, 9.1 g/dL; white blood cell count, 11 500/ $\mu$ L (41% neutrophils, 6% bands); platelet, 98 000/ $\mu$ L; and serum creatinine, 1.2 mg/dL. Urinalysis revealed 100 red blood cells and 80 white blood cells per high-power field with rare Gram-positive cocci in pairs. IV ceftriaxone and ampicillin were started for suspected pyelonephritis. Bacterial urine and blood cultures were negative, and antibiotics were discontinued after 3 days.

On the second hospital day, persistent gross hematuria with clots and profuse watery diarrhea developed. CMV IgM was positive, and viral cultures from urine and throat grew CMV. Cystoscopy revealed hemorrhagic mucosa, and IV ganciclovir (10 mg/kg/d) was started for presumed CMV hemorrhagic cystitis. Colonoscopy and biopsy were normal, and stool examination was persistently positive for rotavirus. Ganciclovir was stopped after 8 days because of lack of clinical response and negative CMV buffy coat culture. However, urine and bladder tissue viral cultures grew adenovirus. Serotyping of the adenovirus isolate was negative for types 1 through 11 and 19 through 24. Biopsy of the right kidney showed focal tubulitis and necrosis of tubular epithelium with "smudge cell" inclusions suggestive of adenovirus infection (Fig 1). Immunohistochemistry of renal tubular epithelial cells was positive for adenovirus, and renal tissue viral cultures subsequently grew adenovirus. No other bacteria, fungi, or viruses were demonstrated in special stains of the renal tissue. A revised diagnosis of adenovirus hemorrhagic cystitis and nephritis was made.

Despite reducing immunosuppressive medications, fever, diarrhea, and gross hematuria continued, and renal function progressively worsened (serum creatinine: 2.9 mg/dL). On the 19th hospital day, the patient was intubated and ventilated for worsening respiratory distress secondary to fluid overload. Multi-organ failure ensued rapidly, and the patient required inotropic support, hemodialysis, and blood product replacement for anemia and coagulopathy. Empiric vancomycin, cefotaxime, and stress doses of corticosteroid were started. On the 21st day of illness, 4 days after receipt of the renal histology report, IV ribavirin was started.

Over the next week hematuria resolved, and her condition stabilized. Renal function recovered slowly, intermittent hemodialysis was continued for 5 weeks, and the patient was discharged from the hospital after 3 months (serum creatinine: 0.8 mg/dL). Multiple myocardial biopsies failed to demonstrate evidence of adenovirus infection of the graft. Viral culture of urine 2 days after stopping ribavirin grew adenovirus; however, no additional therapy was instituted as the patient remained clinically stable and afebrile. Repeat urine viral culture was negative 6 weeks after stopping ribavirin. Three years later, the patient remains well and is culture-negative for adenovirus.

### Case 2

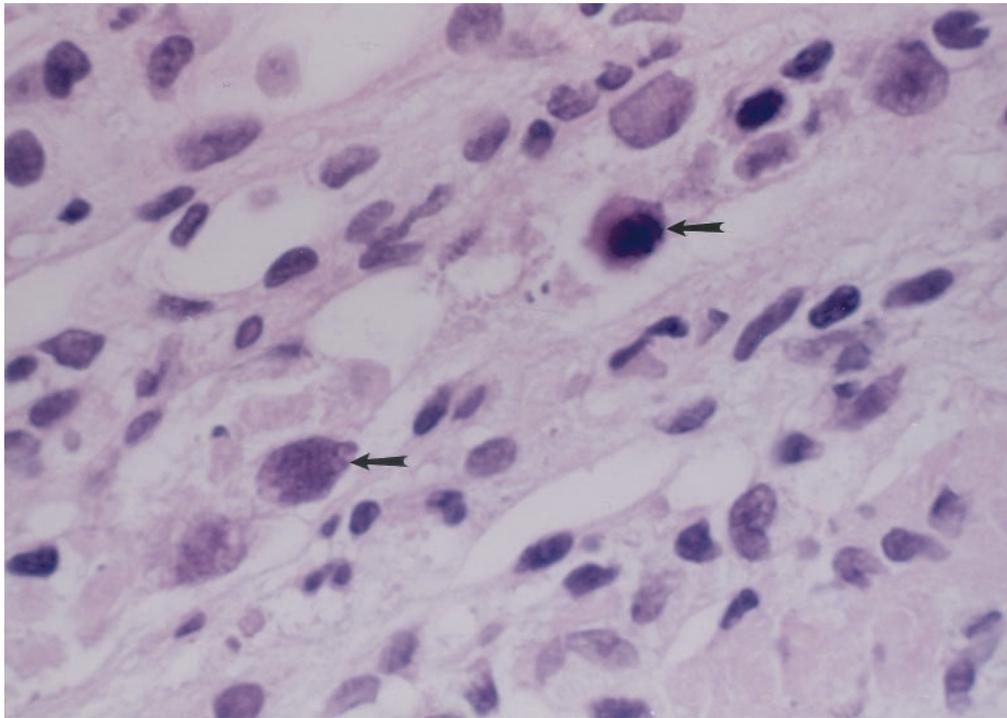
An 18-year-old boy underwent a matched unrelated allogeneic bone marrow transplant (BMT) for secondary acute myeloid leukemia in second complete remission. The conditioning regimen consisted of fractionated total body irradiation and chemotherapy,

**TABLE 1.** Pediatric Case Series of Severe Adenovirus Disease Treated With IV Ribavirin

Case	Age/ Sex	Risk Factor	Site of Adenovirus Disease	Adenovirus Serotype	Interval From Onset of Illness to Treatment	Treatment	Outcome of Adenovirus Disease	Cause of Death
1	5 y/F	OHT	Cystitis, nephritis	Nontypeable*	21 d	IV ribavirin	Cleared after 6 wk	Alive
2	18 y/M	AML/BMT/ GVHD	Cystitis, disseminated	34	6 d	IV ribavirin/ cidofovir	Persistent	AV disease
3	2 wk/F	Neonate	Pneumonia	2	6 d	IV ribavirin	Cleared after 3 wk	Alive
4	8 d/F	Neonate, DiGeorge	Pneumonia	NP	6 d	IV ribavirin	Persistent	AV disease
5	2 mo/M	OHT	Pneumonia	NP	12 d	IV ribavirin	Persistent	AV disease

AML indicates acute myeloid leukemia; AV, adenovirus; NP, not performed.

\* Nontypeable with antisera to adenovirus serotypes 1–11 and 19–24.

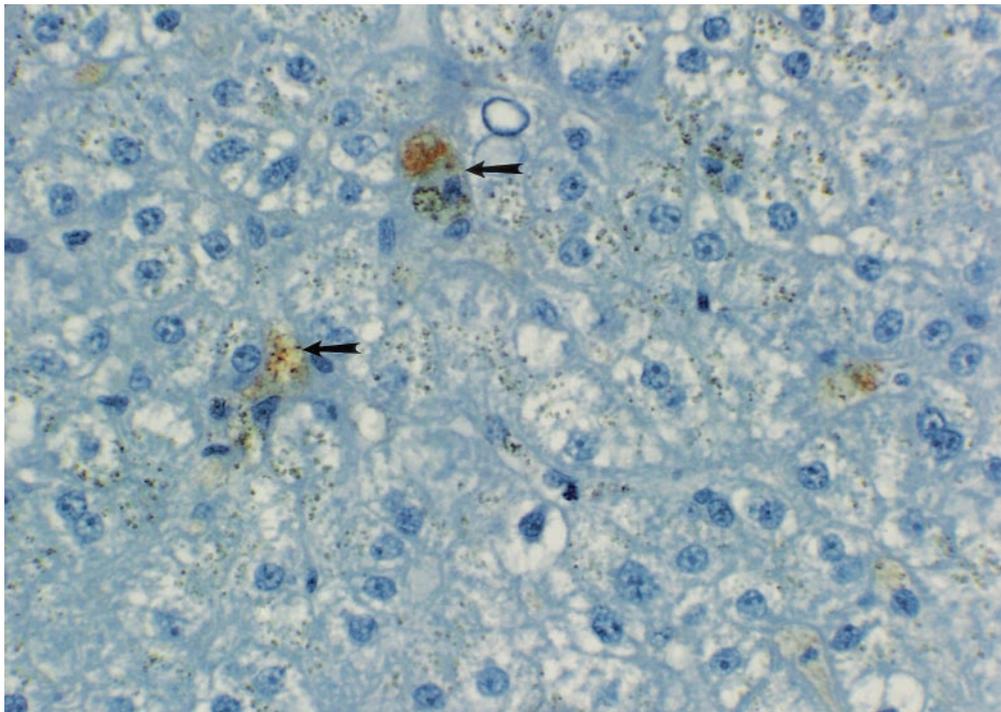


**Fig 1.** Case 1. Renal biopsy specimen demonstrates adenovirus “smudge cells” (renal tubular epithelial cells with deeply basophilic inclusion bodies that fill the nucleus and obliterate the nuclear membrane) (arrows) (hematoxylin-eosin stain, original magnification x 400).

and graft-versus-host disease (GVHD) prophylaxis with tacrolimus, solumedrol, and antithymocyte globulin. His early post-transplant course was complicated by acute GVHD of skin and intestine, and a *Bacillus subtilis* central venous catheter infection was treated by catheter removal and IV imipenem, and tobramycin.

Fever, dysuria, and gross hematuria with clots began on day 15 post-BMT, and 3 days later urine viral culture grew adenovirus.

Three days later, on day 21 post-BMT, IV ribavirin was started. Although fever improved, dysuria and gross hematuria persisted. Ribavirin therapy was discontinued after 7 days because of lack of response and the onset of hyperbilirubinemia (serum direct bilirubin: 11.8 mg/dL), hepatitis (alanine aminotransferase: 256 IU/L; aspartate aminotransferase: 102 IU/L), and mild renal dysfunction (blood urea nitrogen: 49 mg/dL; serum creatinine: 1.1 mg/dL). A liver biopsy demonstrated multifocal hepatocyte necrosis and pos-



**Fig 2.** Case 2. Immunohistochemistry of liver biopsy specimen demonstrates adenovirus in cytoplasm of scattered hepatocytes (positive cells stain brown) (arrows) (immunoperoxidase-based stain, original magnification x 160).

itive immunohistochemistry for adenovirus (Fig 2), and adenovirus PCR was positive in blood. Intravenous cidofovir (1 mg/kg/dose) was started with oral probenecid and IV saline hydration for disseminated adenovirus disease. However, cidofovir treatment was withheld after the second dose because of progression of renal dysfunction to acute failure (serum creatinine: 3.0 mg/dL) and the development of neutropenia. Gross hematuria, dysuria, and suprapubic pain remained unchanged. One week later (day 38 post-BMT), the patient developed acute mental status changes, respiratory distress, metabolic acidosis, and thrombocytopenia, suffered a cardiac arrest, and expired.

### Cases 3, 4, and 5

Three additional children were treated with IV ribavirin for severe adenovirus pneumonia. Two neonates were admitted separately to CMH from home: case 3, a 2-week-old infant girl, presented with fever and acute respiratory distress; case 4, an 8-day-old infant girl, presented with fever and hypocalcemic seizures (ionized calcium: 0.65 mM/L). Chest radiographs of both neonates demonstrated progressive diffuse bilateral pulmonary infiltrates (Fig 3). Additional investigations of case 4 were suggestive of partial DiGeorge syndrome: absence of radiographic evidence of a thymus and hyoid bone; ventricular septal defect on echocardiogram; and low activated T-lymphocyte count by flow cytometry (CD3 + T-cell count, 655/mm<sup>3</sup> [66%]; CD3+DR+ T-cell count, 20/mm<sup>3</sup> [2%]). A karyotype analysis was unsuccessful.

Both neonates developed rapidly worsening acute respiratory failure requiring intubation, high-frequency oscillatory ventilation and inotropic support. Bacterial cultures of blood, cerebrospinal fluid, urine, and stool were negative for pathogens, as were urine culture for CMV and viral serologic tests for herpes simplex virus, toxoplasma, CMV, and human immunodeficiency virus. Gram, acid fast, fungal, and silver stains and cultures of respiratory secretions for bacteria, ureaplasma, chlamydia, mycobacteria, and fungi were negative. However, viral cultures of secretions from nasopharyngeal aspirate and BAL from both neonates grew adenovirus.

Intravenous ribavirin was started in both neonates. After 48 hours of therapy, the condition of case 3 improved dramatically, permitting change to conventional mechanical ventilation, and the infant was discharged from the hospital without supplemental oxygen after 7 weeks. Respiratory cultures were negative for adenovirus 3 weeks after cessation of ribavirin. However, case 4 developed refractory hypoxemia, hypotension, progressive pancytopenia, hepatitis, and multiorgan failure and died within 24 hours of starting IV ribavirin.

Case 5, a 2-month-old boy, developed adenovirus pneumonia 5 weeks after OHT for idiopathic congenital cardiomyopathy and unstable ventricular arrhythmias. Immunosuppression consisted of cyclosporin A, solumedrol, and mycophenolate mofetil. The early postoperative course was complicated by *Klebsiella* pneumonia and bacteremia, which responded to IV cefuroxime, prolonged ileus and ascites, and failure to wean from ventilation. Subsequently, on day 34 post-OHT, the infant developed worsening respiratory failure necessitating a change to high-frequency oscillatory ventilation. Chest radiography showed new diffuse interstitial infiltrates, and BAL secretions were positive for adenovirus by IF. Intravenous ribavirin was started for severe adenovirus pneumonia. There was only minimal clinical improvement after a 10-day course of IV ribavirin, and the infant died 2 days after stopping therapy (7 weeks after OHT). Autopsy revealed bilateral necrotizing pneumonia and a massive unresectable mesenteric lymphangioma.

## DISCUSSION

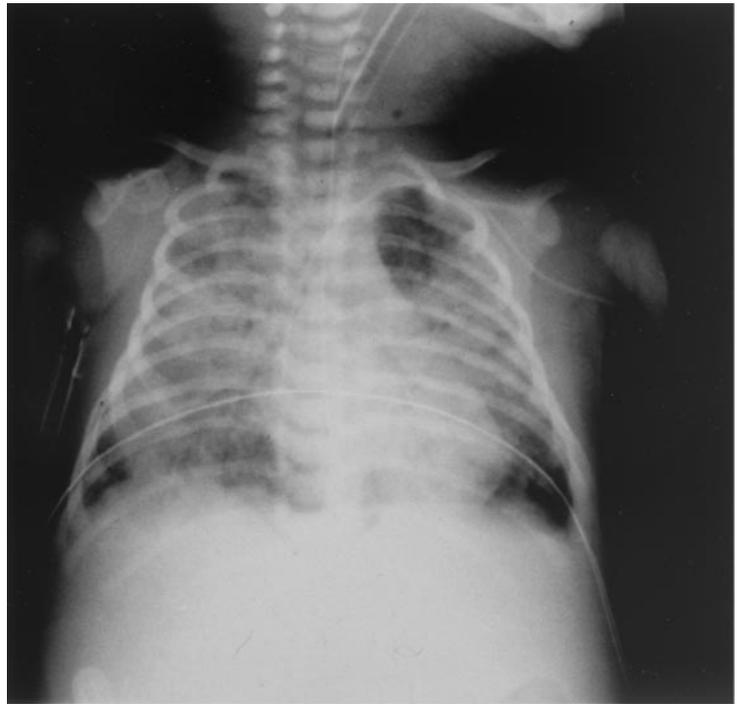
Immunocompetent children rarely develop severe adenovirus disease.<sup>1,3</sup> However, adenovirus is an important cause of morbidity and mortality in immunocompromised children and neonates, in whom both disseminated and severe focal disease are well described.<sup>6,11,12,14</sup> It has been estimated that 11% of all transplant recipients develop adenovirus disease at some time after transplantation.<sup>6</sup> Although adenovirus pneumonia is common in solid-organ transplant recipients, the transplanted organ is often also

the target for primary infection; this is especially true for recipients of liver or renal transplants.<sup>6,11</sup> Moreover, a strikingly higher incidence of adenovirus infection occurs in pediatric BMT recipients (21%–31%) compared with adult BMT recipients (9%–13%), with a higher proportion of pediatric infections leading to disease.<sup>7,8,15</sup> Case fatality rates as high as 60% are documented with adenovirus pneumonia in immunocompromised hosts compared with 15% in immunocompetent patients.<sup>6</sup> Adenovirus disease in infants with primary immunodeficiency has been reported to have a similarly high case fatality rate.<sup>6</sup> Our series of patients is representative of the spectrum of immunocompromised children at greatest risk for severe adenovirus disease, namely solid-organ and BMT recipients, neonates and children with immunodeficiency.

There are no approved antiviral agents with proven efficacy for the treatment of severe adenovirus disease. Nor are there any prospective randomized controlled trials of potentially useful anti-adenovirus therapies. Apparent clinical success in the treatment of severe adenovirus disease is limited to a few case reports and small series. Experience is greatest with intravenous ribavirin, which has had reported success in adenovirus disease in children such as: BMT recipients with hemorrhagic cystitis<sup>16,17</sup> or gastroenteritis<sup>18</sup>; a liver transplant recipient with hepatitis,<sup>19</sup> a leukemic child with disseminated disease,<sup>20</sup> stem cell transplant (SCT) recipients with pneumonia<sup>8</sup>; and in an infant with severe combined immunodeficiency (SCID).<sup>21</sup> However, even with this therapy many patients die (Table 2).<sup>8,9,12,22–25</sup>

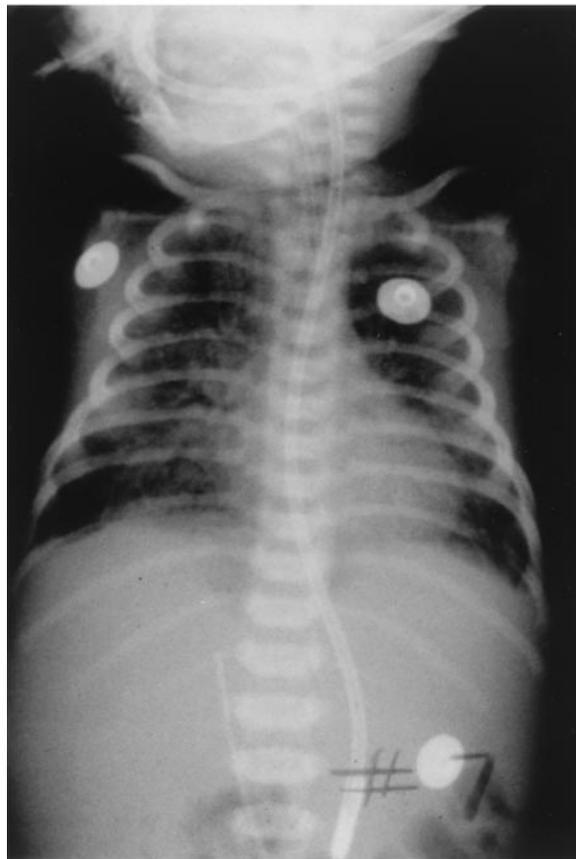
Cidofovir, a cytosine nucleotide analog, has shown apparent efficacy in eradicating both adenovirus infection and treating symptomatic disease in a number of immunocompromised patients, including children.<sup>23,25–31</sup> In a series of 22 SCT patients (age range: 1–19 years) with asymptomatic adenoviral infection or disease: 2 of 3 patients treated with cidofovir (both of whom had asymptomatic infection) recovered in contrast to 3 of 13 patients (2 asymptomatic infection and 1 probable disease) treated with ribavirin.<sup>25</sup> However, the toxicity profile of cidofovir, most notably nephrotoxicity, has limited its use. Reports of success with alternative strategies are less common and include an apparent beneficial effect of: donor leukocyte infusion in BMT recipients<sup>25,32</sup>; intravenous immunoglobulin (IVGG) in a child with SCID and adenovirus pneumonia<sup>33</sup> and IV ganciclovir in an adult OHT recipient with adenovirus pneumonia.<sup>34</sup> None of our patients received leukocyte transfusion or IVGG, and neither cidofovir nor ganciclovir were of any apparent clinical benefit in 2 of our 5 patients.

Ribavirin is a guanosine analog with broad antiviral activity against both DNA and RNA viruses.<sup>35,36</sup> In vitro and uncontrolled clinical experience has also shown possible benefit against adenovirus, RSV, influenza, parainfluenza, measles, and hantavirus.<sup>13,35</sup> It is licensed in aerosol form for the treatment of RSV infection and is of proven efficacy in chronic hepatitis C infection, when given orally, in combination with interferon.<sup>37</sup> Intravenous ribavirin is the treat-



**A**

**Fig 3.** A, Case 3. Chest radiograph obtained 6 days after hospital admission demonstrates diffuse bilateral alveolar and interstitial pulmonary infiltrates. B, Case 4. Chest radiograph obtained 3 days after hospital admission demonstrates bilateral interstitial pulmonary infiltrates and absence of a thymus.



**B**

ment of choice for infection with hemorrhagic fever viruses.<sup>38–40</sup> An IV loading dose (as recommended by the manufacturer and used in this series) ensures that therapeutic levels are achieved quickly.<sup>41</sup> Renal excretion, which accounts for approximately one

third of the drug's elimination, ensures high levels of ribavirin in renal and bladder tissues,<sup>41</sup> which may explain reports of therapeutic success in patients with adenovirus cystitis.<sup>25</sup>

The most common adverse effect of IV ribavirin is

**TABLE 2.** Published Reports of Adenovirus Infection Treated With IV Ribavirin

Report/ Reference	Age	Predisposing Condition	Site of Adenovirus Disease	Adenovirus Serotype	Interval From Onset of Symptoms to Treatment	Treatment	Outcome
Howard et al <sup>8†</sup>	Child	SCT	Enteritis		Early in course	RV	Recovered
	Child	SCT	Cystitis			RV	Recovered
	Child	SCT, GVHD	Pneumonia, disseminated	NR		RV	Recovered
Hale et al <sup>9</sup>	Adult	SCT	Cystitis		NR	RV, DLI	Recovered
	NR	SCT, GVHD	Cystitis, nephritis		NR	RV, cidofovir, IVGG	Failed to respond
	NR	AML, BMT, GVHD	Enteritis, cystitis	11	NR	RV	Died of AV
	18 y		Cystitis, pneumonia				Died of AV
Azbug and Levin <sup>12</sup>	7 y	ALL, BMT, GVHD	Cystitis, pneumonia	11		RV	Died of AV
Murphy et al <sup>16</sup>	5 d	Neonate	Pneumonia, disseminated	21	7 d	RV	Died of AV
Cassano <sup>17</sup>	8 y	AML, BMT, GVHD	Cystitis	NR	14 d	RV	Recovered
Kapelushnick et al <sup>18</sup>	9 y	AML, BMT, GVHD	Cystitis	NR	>7 d	RV	Recovered
Arav-Boger et al <sup>19</sup>	3 y	WAS, BMT, GVHD	Colitis	5	5 d	RV	Recovered
Arav-Boger et al <sup>19</sup>	13 mo	OLT	Hepatitis, disseminated	5	23 d	RV	Recovered
McCarthy et al <sup>20</sup>	14 mo	ALL	Disseminated	NR	33 d	RV	Recovered
Wulfrat et al <sup>21</sup>	8 mo	SCID, BMT	Pneumonia	31	11 d	RV	Recovered
Hromas et al <sup>22</sup>	7 y	ALL, BMT	Nephritis, enteritis	11	14 d*	RV	Died of AV
	20 y	MDS, BMT	Colitis	12	3 d*	RV	Alive; failed to respond
	24 y	ALL, BMT	Pneumonia	11	8 d*	RV	Died of AV
	45 y	NHL, BMT	Nephritis	11	3 d*	RV	Died; relapsed NHL
Ribaud et al <sup>23</sup>	17 y	ALL, SCT	Colitis, disseminated	7	1 d*	RV, cidofovir	Recovered after cidofovir
La Rosa et al <sup>24</sup>	Mean 36 y	AML, BMT, GVHD	Cystitis, pneumonia	NR	Mean 5 d	RV	Clinically improved
		CLL, BMT	Enteritis, disseminated	NR		RV	Clinically improved
		6 ALL, BMT patients	Disseminated	NR	Mean 35 d	RV	6 Failed to respond
Bordignon et al <sup>25</sup>	Median, 9.5 y	SCT	Asymptomatic infection	NR	4 d*	RV	Recovered
				NR	14 d*	RV	Recovered
			Probable/definite disease	NR		RV	Died of AV and GVHD
					18 d*	RV, cidofovir	Died of recurrent AV
					24 d*	RV, vidarabine	Died of recurrent AV and GVHD
					27 d*	RV	Recovered
					11 d*	RV + vidarabine	Died of recurrent AV
					9 d*	RV	Died of AV and GVHD
					68 d*	RV	Died of CMV pneumonitis
					26 d*	RV	Died of AV and GVHD
					1 d*	RV	Died of AV and GVHD
					22 d*	RV	Died of AV and GVHD
					1 d*	RV + vidarabine	Died of AV and graft failure
					49 d*	RV, vidarabine	Died of AV
						+ cidofovir/DLI	
Liles et al <sup>26</sup>	25 y	ALL, BMT	Cystitis, nephritis	11	16 d	RV	Recovered

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; AV, adenovirus; CLL, chronic lymphatic leukemia; DLI, donor leucocyte infusion; GCV, ganciclovir; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; NR, not recorded; OLT, orthotopic liver transplant; RV, intravenous ribavirin; WAS, Wiskott-Aldrich syndrome.

\* Interval from day of isolation of adenovirus to onset of treatment.

† Thirteen patients received IV ribavirin.

reversible mild anemia caused by a combination of transient suppression of erythropoiesis and extravascular hemolysis from accumulation of phosphorylated drug in red blood cells.<sup>41,42</sup> This anemia is rarely symptomatic, it reverses after cessation of treatment and is not associated with aplasia.<sup>36,38,42</sup> Anemia in excess of that attributable to documented blood losses did not occur in our series. In contrast, use of cidofovir in case 2 was associated with progressive renal failure and neutropenia.

It has been shown that the window of opportunity for successful treatment of hemorrhagic fever virus infection with IV ribavirin is narrow<sup>38,39</sup>; ribavirin started within 6 days of the onset of Lassa fever was significantly more effective than therapy begun later, as tissue damage and cell dysfunction are not reversible in later stages, despite inhibition of viral replication.<sup>38</sup> Similarly, in immunocompromised patients with adenovirus disease, a trend toward improved clinical and virological response has been reported in patients treated early and for a longer duration, or when infection was confined to a single site.<sup>8,15,24</sup> However, the use of newer rapid diagnostic tests, such as PCR, may permit earlier diagnosis and treatment.<sup>43–45</sup>

Although 2 of our 5 patients recovered coincident with IV ribavirin treatment, in critically ill patients receiving multiple treatment modalities it is difficult to attribute improvement to one specific intervention. Furthermore, in case 1 with adenovirus nephritis, the virus was only eradicated 6 weeks after completing ribavirin therapy. In addition, the tendency of adenovirus disease to spontaneously resolve in some cases makes the assessment of the impact of any experimental antiviral therapy difficult.<sup>24</sup> Based on this series and review of the literature, ribavirin does not appear particularly effective in severe adenovirus disease. As in other clinical settings, IV ribavirin is unlikely to be of benefit if begun late in the course of the infection. However, the ability to identify early by PCR those patients in a larger population who are at risk of disseminated adenovirus disease, as demonstrated recently by Echavarría et al,<sup>45</sup> may permit earlier antiviral treatment and better evaluation of therapeutic response.

## CONCLUSION

In the immunocompromised host, the need for effective and nontoxic anti-adenoviral therapy is readily apparent. Given the seriousness and increasing prevalence of adenovirus disease in certain hosts, especially children, a large multicenter clinical trial of potentially useful anti-adenoviral therapies, such as IV ribavirin, is clearly required to demonstrate the most effective and least toxic therapy.

## ACKNOWLEDGMENT

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## REFERENCES

- Cherry JD. Adenoviruses. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia, PA: WB Saunders Co; 1998:1666–1684

- Brandt CD, Kim HW, Vargosko AJ, et al. Adenovirus pathogenicity in relation to serologic type and illness syndrome. *Am J Epidemiol*. 1969; 90:484–500
- Edwards KM, Thompson J, Paolini J, Wright PF. Adenovirus infections in young children. *Pediatrics*. 1985;76:420–424
- Fox JP, Hall CE, Cooney MK. The Seattle virus watch VII. Observations of adenovirus infections. *Am J Epidemiol*. 1977;105:362–386
- Blanke C, Clark C, Broun R, et al. Evolving pathogens in allogeneic bone marrow transplantation: increased fatal adenovirus infections. *Am J Med*. 1995;99:326–328
- Hierholzler JC. Adenoviruses in the immunocompromised host. *Clin Microbiol Rev*. 1992;5:262–274
- Flomenburg P, Babbitt J, Drobyski WR, et al. Increasing incidence of adenovirus disease in bone marrow transplant recipients. *J Infect Dis*. 1994;169:775–781
- Howard DS, Phillips GL, Reece DE, et al. Adenovirus infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 1999;29: 1494–1501
- Hale G, Heslop H, Krance R, et al. Adenovirus infection after pediatric bone marrow transplantation. *Bone Marrow Transplant*. 1999;23:277–282
- Carrigan DR. Adenovirus infection in immunocompromised patients. *Am J Med*. 1997;102:71–74
- Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. *Clin Infect Dis*. 1997;27:1194–1200
- Azbug MJ, Levin MJ. Neonatal adenovirus infection: four patients and review of the literature. *Pediatrics*. 1991;87:890–896
- Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK. Broad spectrum antiviral activity of virazole. *Science*. 1972;177: 705–706
- Arditi M, Ostrove JM, Shulman ST. Acute measles complicated by fatal adenovirus pneumonia with bone marrow failure. *Pediatr Infect Dis J*. 1992;11:327–330
- Baldwin A, Kingman H, Darville M, et al. Outcome and clinical course of 100 patients with adenovirus infection following bone marrow transplantation. *Bone Marrow Transplant*. 2000;26:1333–1338
- Murphy GF, Wood DP, Roberts JWM, Henslee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. *J Urol*. 1993;149:565–566
- Cassano WF. Intravenous ribavirin therapy for adenovirus cystitis after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1991; 7:247–248
- Kapelushnick J, Or R, Delukina M, Nagler A, Livni N, Engelhard D. Intravenous ribavirin therapy for adenovirus gastroenteritis after bone marrow transplantation. *J Pediatr Gastroenterol Nutr*. 1995;21:110–112
- Arav-Boger R, Echavarría M, Forman M, Charache P, Persaud D. Clearance of adenoviral hepatitis with ribavirin therapy in a pediatric liver transplant recipient. *Pediatr Infect Dis J*. 2000;19:1097–1100
- McCarthy AJ, Bergin M, Silva LMD, Stevens M. Intravenous ribavirin therapy for disseminated adenovirus infection. *Pediatr Infect Dis J*. 1995; 4:1003–1004
- Wulffrat NM, Geelen SPM, van Dijken PJ, de Graeff-Meeder B, Kuis W, Boven K. Recovery from adenovirus pneumonia in a severe combined immunodeficiency patient treated with intravenous ribavirin. *Transplantation*. 1995;59:927
- Hromas R, Clark C, Blanke C, et al. Failure of ribavirin to clear adenovirus infections in T cell depleted allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1994;14:663–666
- Ribaud P, Scieux C, Freymuth F, Morinet F, Gluckman E. Successful treatment of adenovirus disease with intravenous cidofovir in an unrelated stem-cell transplant recipient. *Clin Infect Dis*. 1999;28:690–691
- La Rosa AM, Champlin RE, Mirza N, et al. Adenovirus infections in adult recipients of blood and marrow transplants. *Clin Infect Dis*. 2001; 32:871–876
- Bordigoni P, Carret A-S, Venard V, Witz F, Faou AL. Treatment of adenovirus infections in patients undergoing allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis*. 2001;32:1290–1297
- Liles WC, Cushing H, Holt S, Bryan C, Hackman RC. Severe adenoviral nephritis following bone marrow transplantation: successful treatment with intravenous ribavirin. *Bone Marrow Transplant*. 1993;12:409–412
- Kapoor N, Shah AJ, Hoffman J, et al. Cidofovir for treatment of adenoviral infections in pediatric hematopoietic stem cell transplant recipients. Proceedings of the 42nd Annual Meeting of the American Society of Hematology; December 1–5, 2000; San Francisco, CA
- Hedderwick SA, Greenon JK, McCaughey VR, Clark NM. Adenovirus cholecystitis in a patient with AIDS. *Clin Infect Dis*. 1998;26:997–998
- Hayashi M, Lee CK, deMagalhaes-Silverman M, Becker A, Scott S, Gingrich RD. Adenovirus infection in BMT patients successfully treated

- with cidofovir. Proceedings of the 42nd Annual Meeting of the American Society of Hematology; December 1–5, 2000; San Francisco, CA
30. Legrand F, Berrebi D, Houhou N, et al. Early diagnosis of adenovirus infection and treatment with cidofovir after bone marrow transplantation in children. *Bone Marrow Transplant.* 2001;27:621–626
  31. Ljungman P, Lambertenghi-Delilieri G, Platzbecker U, et al. Cidofovir in allogeneic stem cell transplant recipients; treatment of CMV and adenovirus infection and disease. A retrospective study from the Infectious Diseases Working Party of the EBMT. *Bone Marrow Transplant.* 2000;25(suppl 1):S47
  32. Hromas R, Cornetta K, Srouf E, Blanke C, Broun ER. Donor leukocyte infusion as therapy of life-threatening adenoviral infections after T-cell depleted bone marrow transplantation. *Blood.* 1994;84:1689–1690
  33. Dagan R, Schwartz RH, Insel RA, Menegus MA. Severe diffuse adenovirus 7a pneumonia in a child with combined immunodeficiency: possible therapeutic effect of human immune serum globulin containing specific neutralizing antibody. *Pediatr Infect Dis J.* 1984;3:246–251
  34. Duggan JM, Farrehi J, Duderstadt S, Turner NJ, Fekety R. Treatment with ganciclovir of adenovirus pneumonia in a cardiac transplant patient. *Am J Med.* 1997;103:439–440
  35. Balfour HH. Antiviral drugs. *N Engl J Med.* 1999;340:1255–1267
  36. Nelson CT, Eglund JA. New approaches to the use of ribavirin. *Semin Pediatr Infect Dis.* 1996;7:114–120
  37. Reichard O, Norkrans G, Fryden A, Braconier J-H, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon-alpha 2b with and without ribavirin for chronic hepatitis C. *Lancet.* 1998;351:83–87
  38. McCormick JB, King IJ, Webb PA, et al. Lassa fever: effective therapy with ribavirin. *N Engl J Med.* 1986;314:20–26
  39. Huggins JW, Hsiang CM, Cosgriff TM, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis.* 1991; 164:1119–1127
  40. Barry M, Russi M, Armstrong L, et al. Brief report: treatment of a laboratory-acquired Sabia virus infection. *N Engl J Med.* 1995;333: 294–296
  41. Laskin OL, Longstreth JA, Hart CC, et al. Ribavirin disposition in high-risk patients for acquired immunodeficiency syndrome. *Clin Pharmacol Ther.* 1987;41:546–555
  42. Canonico PG, Castello MD, Cosgriff TM, et al. Hematological and bone marrow effects of ribavirin in rhesus monkeys. *Toxicol Appl Pharmacol.* 1984;74:163–172
  43. Tsutsumi H, Ouchi K, Ohsaki M, et al. Immunochromatography test for rapid diagnosis of adenovirus respiratory tract infections: comparison with virus isolation in tissue culture. *J Clin Microbiol.* 1999;37:2007–2009
  44. Raty R, Kleemola M, Melen K, Stenvik M, Julkunen I. Efficacy of PCR and other diagnostic methods for detection of respiratory adenoviral infections. *J Med Virol.* 1999;59:66–72
  45. Echavarría M, Forman M, van Tol MJD, et al. Prediction of severe disseminated adenovirus infection by serum PCR. *Lancet.* 2001;358: 384–385

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