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 antiadenovirus 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 tolerated. 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-adenovirus therapies, such as intravenous ribavirin, is clearly required to demonstrate the most effective and least toxic therapy. Pediatrics 2002;110(1).

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; IVG, intravenous gammaglobulin.

Adenovirus infections are exceedingly common in childhood.1 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.2–4 Most of these infections are asymptomatic, mild, or self-limited; resolve within 2 weeks; and induce type-specific immunity.1,4 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.5,6 The incidence of severe adenovirus disease in pediatrics is increasing in association with the growth in numbers of immunocompromised children.7–10 Case fatality rates as high as 50% to 80% have been described.5,6,11,12 There are no approved antiviral agents with proven efficacy for the
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. 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 (PCR) assay in blood from case 2. Adenovirus serotyping was performed on isolates from 3 children (cases 1–3) by neutralization assay. Adenovirus was identified by characteristic histologic changes and by immunohistochemistry using an immunoperoxidase technique with a murine anti-adenovirus monoclonal antibody.

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 corticosteroids 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.

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

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

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

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

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).
raphic 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 36 post-OHT), 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/mm³ [66%]; CD3+DR+ T-cell count, 20/mm³ [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 cytology 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, hypertension, progressive pneumonia, and adenovirus pneumonia, 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 lymphangiomia.

**DISCUSSION**

Immunocompetent children rarely develop severe adenovirus disease.1,3 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.5,11,12,14 It has been estimated that 11% of all transplant recipients develop adenovirus disease at some time after transplantation.6 Although adenovirus pneumonia is common in solid-organ transplant recipients, the transplanted organ is often also
ment of choice for infection with hemorrhagic fever viruses. An IV loading dose (as recommended by the manufacturer and used in this series) ensures that therapeutic levels are achieved quickly. Renal excretion, which accounts for approximately one third of the drug’s elimination, ensures high levels of ribavirin in renal and bladder tissues, which may explain reports of therapeutic success in patients with adenovirus cystitis.

The most common adverse effect of IV ribavirin is
<table>
<thead>
<tr>
<th>Report/Reference</th>
<th>Age</th>
<th>Predisposing Condition</th>
<th>Site of Adenovirus Disease</th>
<th>Adenovirus Serotype</th>
<th>Interval From Onset of Symptoms to Treatment</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard et al⁸</td>
<td>Child</td>
<td>SCT</td>
<td>Enteritis</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>SCT</td>
<td>Cystitis</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>SCT, GVHD</td>
<td>Pneumonia, disseminated</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>SCT</td>
<td>Cystitis</td>
<td>NR</td>
<td>RV, DLI</td>
<td>Failed to respond</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>SCT</td>
<td>Cystitis, nephritis</td>
<td>NR</td>
<td>RV, cidofovir, IVGG</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hale et al⁹</td>
<td>7 y</td>
<td>ALL, BMT, GVHD</td>
<td>Cystitis, pneumonia</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 y</td>
<td>AML, BMT, GVHD</td>
<td>Cystitis, pneumonia</td>
<td>NR</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murphy et al¹⁶</td>
<td>8 y</td>
<td>AML, BMT, GVHD</td>
<td>Cystitis</td>
<td>NR</td>
<td>RV, DLI</td>
<td>Failed to respond</td>
<td></td>
</tr>
<tr>
<td>Cassano¹⁷</td>
<td>9 y</td>
<td>AML, BMT, GVHD</td>
<td>Cystitis</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Kapelushnick et al¹⁸</td>
<td>3 y</td>
<td>WAS, BMT, GVHD</td>
<td>Colitis</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Arav-Boger et al¹⁹</td>
<td>13 mo</td>
<td>OLT</td>
<td>Hepatitis, disseminated</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCarthy et al²⁰</td>
<td>14 mo</td>
<td>ALL</td>
<td>Disseminated</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Wulfraat et al²¹</td>
<td>8 mo</td>
<td>SCID, BMT</td>
<td>Pneumonia</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Hromas et al²²</td>
<td>7 y</td>
<td>ALL, BMT</td>
<td>Nephritis, enteritis</td>
<td>11 d</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
</tr>
<tr>
<td>20 y</td>
<td>MDS, BMT</td>
<td>Colitis</td>
<td>12 d</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 y</td>
<td>ALL, BMT</td>
<td>Pneumonia</td>
<td>11 d</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 y</td>
<td>NHL, BMT</td>
<td>Nephritis</td>
<td>11 d</td>
<td>RV</td>
<td>Died of AV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribaud et al²³</td>
<td>17 y</td>
<td>ALL, SCT</td>
<td>Colitis, disseminated</td>
<td>7 d</td>
<td>RV, cidofovir</td>
<td>Recovered after cidofovir</td>
<td></td>
</tr>
<tr>
<td>La Rosa et al²⁴</td>
<td>Mean 36 y</td>
<td>AML, BMT, GVHD</td>
<td>Cystitis, pneumonia</td>
<td>Mean 5 d</td>
<td>RV</td>
<td>Clinically improved</td>
<td></td>
</tr>
<tr>
<td>Bordigoni et al²⁵</td>
<td>Median, 9.5 y</td>
<td>SCT</td>
<td>Asymptomatic infection</td>
<td>NR</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Liles et al²⁶</td>
<td>25 y</td>
<td>ALL, BMT</td>
<td>Cystitis, nephritis</td>
<td>11 d</td>
<td>RV</td>
<td>Recovered</td>
<td></td>
</tr>
</tbody>
</table>

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.\textsuperscript{41,42} This anemia is rarely symptomatic, it reverses after cessation of treatment and is not associated with aplasia.\textsuperscript{36,38,42} 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,\textsuperscript{38,39}; 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.\textsuperscript{38} 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.\textsuperscript{8,15,24} However, the use of newer rapid diagnostic tests, such as PCR, may permit earlier diagnosis and treatment.\textsuperscript{43–45}

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.\textsuperscript{34} 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 Echavarria et al,\textsuperscript{45} 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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