RESEARCH NOTE

Use of cidofovir in pediatric patients with adenovirus infection [version 1; referees: 2 approved, 1 approved with reservations]

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Abstract

Background: Adenoviruses contribute to morbidity and mortality among immunocompromised pediatric patients including stem cell and solid organ transplant recipients. Cidofovir (CDV), an antiviral compound approved by the FDA in 1996, is used for treatment of adenoviral (ADV) infections in immunocompromised patients despite concern of potential nephrotoxicity.

Methods: We conducted a retrospective 5-year review at Boston Children’s Hospital of 16 patients (mean age = 6.5 years) receiving 19 courses of CDV. During therapy all pertinent data elements were reviewed to characterize potential response to therapy and incidence of renal dysfunction.

Results: Of the 19 CDV courses prescribed, 16 courses (84%) were in patients who had a positive blood ADV Polymerase chain reaction (PCR) alone or in combination with positive ADV PCR/ Direct Immunofluorescence Assay (DFA) at another site. Respiratory symptoms with or without pneumonia were the most common presentation (10/19, 53%). In the majority of blood positive courses (10/16, 63%), viral clearance was also accompanied by clinical response. This was not the case in four courses where patients expired despite viral clearance, including one in which death was directly attributable to adenovirus. There was reversible renal dysfunction observed during the use of CDV.

Conclusions: CDV appeared safe and reasonably tolerated for treatment of ADV in this pediatric population and was associated with viral response and clinical improvement in the majority of patients but reversible renal dysfunction was a side effect. Further studies of the efficacy of CDV for immunocompromised children with ADV infection are warranted.
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Introduction
Adenovirus (ADV) is a common cause of respiratory infection in childhood. ADV infections are usually self-limited and asymptomatic in the immunocompetent host but have been recognized as a cause of significant morbidity and mortality in immunocompromised pediatric patients such as recipients of hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT). In these patients, ADV is an opportunistic pathogen that may lead to severe localized disease including pneumonia/pneumonitis, hepatitis, hemorrhagic cystitis or disseminated disease with multiorgan failure2–4. Case fatality rates in immunocompromised patients with ADV pneumonia have been reported to be as high as 60%7. Currently, there is no FDA-labeled product available for treatment of ADV infection though several agents have been administered for this indication including ribavirin, ganciclovir, vidarabine, immune globulin and cidofovir1,2,21.

Cidofovir (CDV), a nucleoside and phosphonate analogue is a broad-spectrum antiviral agent that inhibits viral DNA polymerase and has broad activity in vitro against multiple viruses including all serotypes of ADV12,22. CDV has an FDA indication for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Although this drug does not have an FDA indication for treating ADV, there is evidence of in vivo efficacy of CDV against ADV12,14. While CDV at a standard dose of 5mg/kg has been reported as primary therapy for treatment of ADV infection in pediatric and adult hematopoietic stem cell transplantation (HSCT) patients12,21, concern exists regarding potential nephrotoxicity. These associated adverse effects have limited the use of CDV for treatment of ADV infections in pediatric patients. To minimize potential toxicity of CDV, modified dosing regimens such as the use of 1 mg/kg three times have been utilized11.

Limited information regarding safety and efficacy of CDV in pediatric patients prompted us to review prior published studies in the literature and conduct a retrospective review of our inpatient use of CDV at Boston Children’s Hospital (BCH).

Methods
Following Institutional Review Board (IRB) approval (IRB-P00015576), a retrospective chart review was conducted for all hospitalized patients at Boston Children’s Hospital (BCH), who were prescribed CDV for adenovirus infection from January 2006 through December 2010. The following data were collected: (1) demographic information, (2) underlying disease state, (3) type of transplant, (4) duration of cidofovir therapy, (6) serum creatinine (SCr) (baseline, peak during therapy, and level up to 2 weeks post last dose), (7) concomitant nephrotoxins prescribed (acyclovir, amikacin, cyclosporine, foscarnet, gentamicin, liposomal amphotericin B, tacrolimus, tobramycin, vancomycin, and intravenous contrast media), (8) sites of ADV detection by viral direct fluorescent antibody (DFA), nucleic acid test, and/or culture, (9) viral quantitative PCR surveillance in blood and other sites of infection (all specimens were tested at least weekly before, during and to two weeks post last dose of CDV to evaluate for changes in viral load with a minimum three serial values being obtained before, during and at end of therapy); (10) symptoms of infection, and clinical course including response to therapy; (11) concomitant reduction of immunosuppression and (12) mortality and cause(s) of mortality. All blood sample testing for adenovirus quantitative PCR in blood was performed at the Boston Children’s Hospital Virology Laboratory using our laboratory developed test, the Argene adenovirus assay (bioMerieux, Cambridge, MA). The Argene adenovirus assay contains primers and probes selective for a 138 base pair (bp) sequence in the Hexon gene of the adenovirus. Using a 5’ nucleic acid assay, viral DNA is detected using the primers and fluorescent probes from the Argene assay kit by means of real time PCR in a Cepheid SmartCycler (Cepheid, Sunnyvale, CA).

Definitions
As there is no accepted definition for ADV infection or disease, we adopted definitions used in prior studies13. Specifically, definite adenovirus disease as follows: Non-gastrointestinal locations: Symptoms and signs from the appropriate organ combined with histopathological documentation of adenovirus and/or adenovirus detection by culture, antigen test, or nucleic acid test from biopsy specimens (liver or lung), BAL fluid, or cerebrospinal fluid and without another identifiable cause; Gastrointestinal location: Symptoms together with detection of adenovirus from biopsy material by culture, antigen test, or nucleic acid test.

Probable adenovirus disease as follows: Gastrointestinal tract: Detection of adenovirus in stool by culture, antigen test, or nucleic acid test together with symptoms; Urinary tract: Symptoms of dysuria or hematuria combined with detection of adenovirus by culture, antigen test, or nucleic acid test without another identifiable cause; and Respiratory tract: Symptoms and signs of pneumonia/pneumonitis combined with detection of adenovirus by culture, antigen test, or nucleic acid test without another identifiable cause.

Asymptomatic adenovirus infection as follows: any detection of adenovirus in an asymptomatic patient from stool, blood, urine, or upper airway specimens by viral culture, antigen tests, or PCR.

Adenoviremia was defined as the detection of >100 copies of ADV/mL of blood (this being the lower limit of detection of the assay). Viral clearance was defined as an ADV viral load of <100 copies in blood by quantitative PCR at the end of therapy. Viral response was defined as decrease in viremia by at least one log-fold. Clinical resolution was defined as resolution of symptoms and/or signs of infection. Renal dysfunction was defined as a ≥50% increase in SCr from baseline during the course of CDV therapy. The peak SCr during therapy was used to calculate the number of patients that experienced renal dysfunction.

Statistical analysis
Statistical analyses employed Prism 5 for Windows Version 5.04 (GraphPad Software Inc, CA). The Mann-Whitney test was used to assess risk of renal dysfunction. Trends in adenoviremia including pre-treatment viral load, changes in viral load during therapy, and post-treatment viral load were graphed.
Results

Dataset 1. Raw data for Figure 1
http://dx.doi.org/10.5256/f1000research.8374.d117321
Adenovirus blood viral load is represented in each column at each particular time in days (before or after onset of cidofovir treatment) for each patient.

Dataset 2. Raw data for Figure 2
http://dx.doi.org/10.5256/f1000research.8374.d117322
Nephrotoxicity - pre, peak and post serum creatinine levels in mg/dL are represented in each column for each patient.

From January 1, 2006 to December 31, 2010, a total of 16 pediatric patients received CDV for adenovirus infection at our hospital. These 16 patients received 19 courses (three patients received two separate CDV courses). The standard CDV dose of 5mg/kg weekly was used in all courses unless there was concern for renal dysfunction at the start of therapy in which case a dosing regimen of 1mg/kg three times a week was used. Patient demographics, primary diagnosis, clinical symptoms and course, and sites of adenovirus detection appear in Table 1. Patient age ranged from 0.75–20 years (mean 6.5 years). Seven (44%) patients were male. Underlying primary diagnosis included 8 (50%) HSCT (1 autologous), 4 (25%) SOT, 2 (12.5%) leukemia, and 2 (6.5%) defined as other. Duration of CDV therapy ranged from 5–82 days (median 33.5 days).

Table 1. Demographics, primary diagnosis, sites of ADV detection, clinical symptoms and course of patients included in the study. The age and gender distribution, primary diagnosis, sites of adenovirus detection, symptoms and clinical course of the patients included in the study are shown.

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Site(s) of ADV detection</th>
<th>Clinical symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>12</td>
<td>F</td>
<td>AML - Mismatched UD Cord SCT</td>
<td>Sp, S, R</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>1b</td>
<td>12</td>
<td>F</td>
<td>AML - Mismatched UD Cord SCT</td>
<td>Sp</td>
<td>Fever and Respiratory symptoms</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>M</td>
<td>Severe Idiosyncratic Immunodeficiency - MRD SCT</td>
<td>B, S</td>
<td>Prolonged fever</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>M</td>
<td>AML - Chemotherapy</td>
<td>B, S, U</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>F</td>
<td>Neuroblastoma - Autologous SCT</td>
<td>B, S, PF</td>
<td>Prolonged fever, pericardial effusion</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>F</td>
<td>Cystic Fibrosis - Lung Transplant</td>
<td>B, BAL</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>*6</td>
<td>1</td>
<td>F</td>
<td>Familial HLH - MUD SCT</td>
<td>B, Sp</td>
<td>Pneumonia, sepsis. Other co-infections including Enterococcus bacteremia, EBV viremia</td>
</tr>
<tr>
<td>*7</td>
<td>0.83</td>
<td>M</td>
<td>Persistent pulmonary hypertension, cardiomyopathy</td>
<td>B</td>
<td>Fever, sepsis, pneumonia. Other co-infections including stenotrophomonas bacteremia</td>
</tr>
<tr>
<td>8a</td>
<td>20</td>
<td>M</td>
<td>ALL - MRD SCT and MUD SCT</td>
<td>BAL, B, U</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>8b</td>
<td>20</td>
<td>M</td>
<td>ALL - MRD SCT and MUD SCT</td>
<td>S</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>F</td>
<td>Congenital Nephrotic Syndrome &amp; Hepatoblastoma - Combined Liver &amp; Kidney Transplant</td>
<td>B,Sp</td>
<td>Respiratory symptoms</td>
</tr>
<tr>
<td>*10</td>
<td>0.75</td>
<td>M</td>
<td>HLH - SCT</td>
<td>S, B, U</td>
<td>Fever, sepsis, diarrhea</td>
</tr>
<tr>
<td>*11</td>
<td>5</td>
<td>F</td>
<td>CID and Lymphoproliferative Disorder - Mismatched UD Cord SCT</td>
<td>B</td>
<td>Fever, respiratory symptoms, diarrhea, hemorrhagic cystitis</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>F</td>
<td>Congenital Cardiac Defect - Heart Transplant</td>
<td>B</td>
<td>Fever, sepsis</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>F</td>
<td>ALL - Chemotherapy</td>
<td>B, S</td>
<td>Fever, respiratory symptoms</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>F</td>
<td>Cerebral Palsy</td>
<td>B</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>15a</td>
<td>1.8</td>
<td>M</td>
<td>Hepatoblastoma - Multiviseral Transplant</td>
<td>B, S</td>
<td>Increased stoma output, rejection, biopsy proven ADV In stoma mucosa</td>
</tr>
<tr>
<td>15b</td>
<td>1.8</td>
<td>M</td>
<td>Hepatoblastoma - Multiviseral Transplant</td>
<td>B, S</td>
<td>Increased stoma output</td>
</tr>
<tr>
<td>*16</td>
<td>17</td>
<td>M</td>
<td>AML - MUD SCT</td>
<td>B, U</td>
<td>Hemorrhagic cystitis. Other co-infections including BK viruria and EBV viremia</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CID, congenital immunodeficiency; CML, chronic myelogenous leukemia; HLH, hemophagocytic lymphohistiocytosis; MRD, matched related donor; MUD, matched unrelated donor; Pt #, patient number; SCID, severe combined immunodeficiency disorder; SCT, stem cell transplant; UD, unrelated donor; Yrs, years; Site of adenovirus detection: S, stool, Sp, sputum, B, blood, BAL, bronchoalveolar lavage, R, respiratory DFA, CSF, cerebrospinal fluid, U, Urine, PF, Pericardial Fluid; *indicates patient expired

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Of the 19 courses prescribed (Table 1), two courses were prescribed in a patient with definite adenovirus disease of the gastrointestinal tract, 15 courses were prescribed in patients with probable disease and two courses were prescribed in patients with asymptomatic infection. Sixteen courses (84%) were in patients who had a positive blood ADV PCR either in whole blood only or in combination with positive ADV PCR of sputum, stool, urine, broncho-alveolar lavage (BAL) fluid, pericardial fluid or positive sputum adenoviral DFA sample. Respiratory symptoms were the most common presentation in 10 courses (53%) of which six courses were prescribed for patients with respiratory symptoms and radiological evidence of pneumonia. Two courses were prescribed in patients who presented with prolonged fevers; four courses were prescribed in patients who had worsening diarrhea and colitis, two of which were biopsy proven adenovirus infection; four courses were prescribed in patients with viral sepsis with or without pneumonia; and two courses were administered in patients with severe hemorrhagic cystitis. Two courses were prescribed in patients with asymptomatic respiratory tract infection and asymptomatic gastrointestinal infection respectively.

We further examined the 16 blood-positive courses to assess trends in ADV viral load pre-, during and post- CDV therapy (Figure 1). A quantitative reduction in viral load was seen in 15 blood positive courses (94%) with viral clearance achieved in 14 (88%). Of note, all solid organ transplant recipients treated with CDV also had concomitant decrease in their immunosuppression. A single patient (Patient 6) did not demonstrate viral response to therapy and expired. The majority of adenovirus blood-positive CDV courses (10/16, 63%) were associated with clinical improvement with viral clearance, however this was not the case in four courses. Patients 7, 10, 11 and 16 expired despite demonstrating viral clearance. Patients 6, 7 and 16 had multiple other co-infections. Patients 11 and 16 developed severe hemorrhagic cystitis. Patient 11 experienced significant complications of hemorrhagic cystitis including urinary tract obstruction, renal failure and bladder perforation. Patient 16 also had concomitant BK Polyoma virus detected in the urine.

Each patient’s medication profile was assessed to determine the number of additional nephrotoxic agents concomitantly prescribed during CDV therapy (from Day 1 to 7 days post last CDV dose). All 19 courses prescribed had at least one additional nephrotoxic agent prescribed during CDV therapy (Table 2). Four courses (21%) had only one additional nephrotoxic medication prescribed, five courses (26%) had two such medications prescribed, six courses (32%) had three prescribed, two courses (11%) had four prescribed, and two courses (11%) had five prescribed.

Administration of CDV was significantly associated with occurrence of renal dysfunction when comparing the peak Cr measured during CDV therapy to the baseline serum Cr (p=0.0016). Eleven courses (58%) were associated with development of renal dysfunction. Cr increased by a mean of ~50% from baseline during CDV therapy (Figure 2). Of the courses with elevation in serum creatinine, 64% demonstrated return to pre-treatment creatinine levels following cessation of CDV therapy. There was no statistically significant difference when assessing for increased risk of renal dysfunction if patients received ≤ 1 additional nephrotoxic agent or ≥ 2 additional nephrotoxic agents.

**Figure 1.** Kinetics of Adenovirus blood viral load under cidofovir treatment. Viral loads of 16 patients with quantitative blood adenovirus PCR treated with cidofovir, are shown. Day of therapy 0 denotes pre-treatment viral loads. Up to two post-treatment values are shown where available and informative. Each patient’s individual treatment duration is shown in the legend. + denotes patient expired.
Table 2. Additional nephrotoxic agents prescribed and changes in serum creatinine during cidofovir therapy. Absolute values for serum creatinine in mg/dL for each patient are represented pre-treatment, during treatment (peak serum creatinine), and post-treatment. Additional nephrotoxic agents that each patient received are also represented.

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Pre-treatment Serum Cr</th>
<th>Peak Serum Cr</th>
<th>Post-treatment Serum Cr</th>
<th>Additional nephrotoxic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.3</td>
<td>1.2</td>
<td>0.6</td>
<td>ambisome, cyclosporine, gentamicin</td>
</tr>
<tr>
<td>1b</td>
<td>0.6</td>
<td>1</td>
<td>0.6</td>
<td>cyclosporine</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
<td>cyclosporine, ganciclovir, pentamidine</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>0.6</td>
<td>0.2</td>
<td>vancomycin, ambisome, gentamicin</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>acyclovir</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>0.7</td>
<td>0.5</td>
<td>tacrolimus</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>ambisome, ganciclovir, pentamidine, tacrolimus, vancomycin</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td>0.5</td>
<td>0.7</td>
<td>gentamicin, tobramycin</td>
</tr>
<tr>
<td>8a</td>
<td>1</td>
<td>1.7</td>
<td>0.4</td>
<td>ambisome, vancomycin</td>
</tr>
<tr>
<td>8b</td>
<td>0.4</td>
<td>2.6</td>
<td>1.3</td>
<td>ganciclovir, tacrolimus, vancomycin</td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>2.7</td>
<td>0.6</td>
<td>chemotherapy</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>acyclovir, ambisome, cyclosporine, vancomycin</td>
</tr>
<tr>
<td>11</td>
<td>0.4</td>
<td>1.6</td>
<td>0.6</td>
<td>gentamicin, acyclovir, ambisome, cyclosporine, foscarnet, ganciclovir</td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
<td>1.6</td>
<td>0.6</td>
<td>gentamicin, ganciclovir, tacrolimus</td>
</tr>
<tr>
<td>13</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>ambisome, foscarnet, ganciclovir</td>
</tr>
<tr>
<td>14</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>vancomycin</td>
</tr>
<tr>
<td>15a</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>tacrolimus, vancomycin</td>
</tr>
<tr>
<td>15b</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>tacrolimus, vancomycin</td>
</tr>
<tr>
<td>16</td>
<td>0.3</td>
<td>0.5</td>
<td>0.3</td>
<td>cyclosporine, gentamicin, vancomycin, contrast</td>
</tr>
</tbody>
</table>

Pt #, patient number; Cr, creatinine; all creatinine values are in mg/dL.

Discussion

In this retrospective review of patients treated with CDV for adenovirus infection at our hospital during a 5-year period, we assessed the safety and potential efficacy of the medication in pediatric patients. Our review yielded a case series of 16 patients. While the number of patients is modest, this series adds to the existing literature describing the use of CDV in pediatric recipients of HSCT, SOT and chemotherapy for oncologic diagnoses (Table 3).

Similar to other studies the majority of our patients had received a HSCT or had an oncologic diagnosis and received chemotherapy. We identified eight publications describing the use of CDV for adenovirus infection in the setting of HSCT or oncologic diagnoses treated with chemotherapy (Table 3). Three of these studies reported viral clearance in 89–100% of their patients. We observed similar rates of viral clearance (88%) but this was not consistently associated with clinical improvement.
Table 3. Summary of studies describing use of cidofovir in pediatric HSCT and SOT recipient. Published studies in the literature describing use of cidofovir in pediatric HSCT and SOT recipients are summarized. Toxicities, and clinical outcomes reported in each study are highlighted.

<table>
<thead>
<tr>
<th>Study</th>
<th># Patients (N)</th>
<th>Clinical Setting</th>
<th>Median Age</th>
<th>Cidofovir dosage</th>
<th>Duration of cidofovir use</th>
<th>Potential Toxicity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman</td>
<td>14</td>
<td>HSCT</td>
<td>7 yrs</td>
<td>1 mg/kg/dose three times weekly × 9 doses or until clearance</td>
<td>3 weeks–8 months</td>
<td>Well tolerated; no toxicity reported</td>
<td>100% viral suppression 3 recurrences 4 expired (2 ADV-related)</td>
</tr>
<tr>
<td>Muller</td>
<td>10</td>
<td>HSCT</td>
<td>Not reported</td>
<td>5 mg/kg/dose weekly up to 6 weeks, then every other week for 3 more doses</td>
<td>3 weeks–6 months</td>
<td>30% nephrotoxicity (50% increase Cr)</td>
<td>9 virologic clearance 5 recurrences 1 expired (interstitial pneumonitis)</td>
</tr>
<tr>
<td>Anderson</td>
<td>7</td>
<td>HSCT</td>
<td>1.5 yrs</td>
<td>Preemptive therapy; 1 mg/kg/dose three times weekly × 3 weeks</td>
<td>3 weeks</td>
<td>Well tolerated without significant toxicity reported</td>
<td>No patient developed ADV viremia 2 expired (non-ADV related)</td>
</tr>
<tr>
<td>Bhadri</td>
<td>23</td>
<td>HSCT 87% HSCT 13% oncologic receiving chemotherapy</td>
<td>5.7 yrs</td>
<td>5 mg/kg/dose weekly, 3 mg/kg/dose weekly or 1 mg/kg/dose three times weekly</td>
<td>Median 6 weeks (1–26 weeks)</td>
<td>9% Grade 1 nephrotoxicity defined by increase of creatinine up to 1.5 times upper limit of normal</td>
<td>85% of 20 evaluable patients considered successful by Ljungman criteria 13 17 expired</td>
</tr>
<tr>
<td>Yusuf</td>
<td>57</td>
<td>HSCT 90% HSCT 10% oncologic receiving chemotherapy</td>
<td>8 yrs</td>
<td>5 mg/kg/dose weekly × 2 weeks, then every other week until 3 negative ADV samples</td>
<td>Median 60 days (1 week–9 months)</td>
<td>No toxicity reported</td>
<td>98% successful viral clearance 14% recurrence 29 expired (1 ADV-related death)</td>
</tr>
<tr>
<td>Legrand</td>
<td>7</td>
<td>HSCT</td>
<td>6.4 yrs</td>
<td>5 mg/kg/dose weekly × 3 wks then every other wk or 10 days</td>
<td>25–330 days</td>
<td>43% nephrotoxicity</td>
<td>71% deemed recovered 2 expired (1 ADV related death)</td>
</tr>
<tr>
<td>Sivaprakasam</td>
<td>8</td>
<td>HSCT</td>
<td>11 yrs</td>
<td>1 mg/kg/dose 3 times weekly (4 patients also received IV ribavirin 5 mg/kg 3 times daily)</td>
<td>Not reported</td>
<td>2 cases marrow failure, 1 case nephropathy</td>
<td>3 expired (attributed to ADV and GVHD)</td>
</tr>
<tr>
<td>Williams</td>
<td>9</td>
<td>HSCT</td>
<td>3 yrs</td>
<td>5 mg/kg/dose once weekly until 3 weeks of negative results or pt no longer high risk; if underlying renal dysfunction 1 mg/kg/ dose 3 times weekly</td>
<td>Median 8 doses (3–32 doses)</td>
<td>22% renal failure (compared to 80% untreated comparator group)</td>
<td>89% ADV clearance 3 expired (1 ADV related)</td>
</tr>
<tr>
<td>Engelmann</td>
<td>1</td>
<td>Liver transplant</td>
<td>7 months</td>
<td>6 mg/kg/dose × 1 with 1 repeat dose 6 days later</td>
<td>2 weeks</td>
<td>No toxicity reported</td>
<td>Liver rejection; reported to have slow recovery</td>
</tr>
<tr>
<td>Wallot</td>
<td>2</td>
<td>Liver transplant</td>
<td>8 months and 14 months</td>
<td>1 mg/kg/dose three times weekly</td>
<td>5–8 weeks</td>
<td>1 moderate neutropenia, 1 transient rise in creatinine</td>
<td>Blood PCR ADV clearance in both patients No deaths</td>
</tr>
<tr>
<td>Carter</td>
<td>1</td>
<td>Liver transplant</td>
<td>7 months</td>
<td>1 mg/kg/dose three times weekly</td>
<td>7 weeks</td>
<td>Transient acidosis and proteinuria</td>
<td>ADV viral culture and blood PCR became negative</td>
</tr>
<tr>
<td>Doan</td>
<td>4</td>
<td>Lung transplant</td>
<td>&lt;3 yrs</td>
<td>1 mg/kg/dose every other day to three times weekly plus IVIG (1 pt increased dose to 2 mg/kg/dose; 1 pt increased frequency to daily therapy × 2 weeks)</td>
<td>4 weeks</td>
<td>No toxicity reported</td>
<td>75% negative blood ADV PCR 1 death</td>
</tr>
</tbody>
</table>

Page 7 of 14
There are very few reports on the use of CDV for adenovirus infection in pediatric SOT recipients, which have largely been restricted to reports of children receiving liver or lung transplants\(^1\),\(^2\),\(^9\),\(^10\). We identified four publications reporting the use of CDV for adenovirus infection in pediatric SOT recipients limited to one to four per report and all of these children having received liver or lung transplants\(^1\),\(^2\),\(^9\),\(^10\). Doan et al.\(^9\) described children who had received lung transplants with reported viral clearance in three of their four patients. Our case series contributes patients who received several types of SOT including lung, heart, combined kidney and liver, and multi-visceral transplants. All patients with SOT in our series demonstrated viral clearance as well as resolution of symptoms, which may have reflected a combination of both the antiviral effect of CDV coupled with reduced immunosuppression.

Two-thirds of our patients experienced resolution of their symptoms and had an overall favorable clinical course with recovery. However, one-third died all of which were stem cell transplant recipients. With the exception of one patient it is unclear whether adenovirus was the direct cause of mortality in these patients. Our observations are consistent with what has been reported in the literature pertaining to outcomes in stem cell transplant recipients with adenovirus infections who have been treated with CDV\(^1\),\(^2\),\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\). Among SCT patients mortality remains high (10%–70%) even when clearance from blood is seen.

In our case series, renal dysfunction was common during CDV therapy with patients experiencing an average 50% increase of serum creatinine from their baseline. However, renal dysfunction was transient in the majority of patients with serum creatinine returning to baseline after cessation of CDV therapy. While some studies have reported no toxicities related to the use of CDV\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^9\),\(^10\), the transient nature of nephrotoxicity observed has been reported by other studies\(^2\),\(^3\),\(^4\). We were unable to detect any increased risk of nephrotoxicity associated with concomitant administration of additional nephrotoxic agents but this may reflect our small number of study participants.

Our study has several limitations. Most notably, the small number of patients precluded evaluation of other factors that may impact infection resolution such as immunosuppressive regimens, and additional factors that may impact degree of renal dysfunction. Nevertheless, our study adds to the limited reported literature of pediatric ADV patients treated with CDV.

### Data availability

F1000Research: Dataset 1. Raw data for Figure 1, 10.5256/f1000research.8374.d117321

F1000Research: Dataset 2. Raw data for Figure 2, 10.5256/f1000research.8374.d117322

### Author contributions

OL conceived the study. LG, AA and SJ collected data and prepared the first draft of the manuscript. LG, AP and DG performed data analysis. MH contributed to the preparation of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

### Competing interests

No competing interests were disclosed.

### Grant information

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### References

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10. Kitabayashi A, Hirokawa M, Kuroki J, et al.: Successful vidarabine therapy for...

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Ganapathi et al describe a case series of 16 patients who received a total of 19 courses of cidofovir for adenovirus infection. The authors provide virological data to demonstrate a response to cidofovir therapy, and provide additional data regarding renal function and co-administration of renal toxic medications. Ganapathi et al. provides unique data regarding the peak creatinine level during therapy with cidofovir, though this value is difficult to interpret given the confounding factors of other nephrotoxic agents.

This case series is an incremental addition to the number of published cases of pediatric patients infected by adenoviruses who were treated with cidofovir. The manuscript follows a similar format to the case series reported by Bhadri et al. (2009), with presentation of the effects on renal function, and a summarization of the literature.

The authors should summarize outcomes from all other case series to provide updated overall mortality and nephrotoxicity of CDV-treated adenovirus infections in hematopoietic stem cell transplants, solid organ transplants, or other patients. Such analyses may enhance the timeliness and utility of this manuscript.

In the discussion, the authors describe the potential benefit of cidofovir in solid organ transplant patients, in conjunction with reduced immunosuppression. However, without a comparative cohort of children who did not receive cidofovir or reduced immunosuppression, it would be difficult to draw this conclusion from the data presented. In addition, the authors do not discuss two interesting published papers. Humar et al. (2005) described a cohort of adult SOT patients with adenovirus viremia who did not receive cidofovir; all had spontaneous resolution of viremia with no deaths. In contrast, Seidemann et al. (2004) reported that 3 out of 5 pediatric SOT with adenoviremia (one also had a HSCT) died despite receiving cidofovir. The authors should absolutely cite these studies, especially Seidemann as it included pediatric SOT patients. In addition, the authors should highlight whether the positive outcomes in their SOT population are aligned with the adult study by Humar et al. (and the conclusion in that paper that treatment may not be necessary for adenoviremia in SOT patients); and contrast their results with those of Seidemann et al.

Specific comments
1. Methods: The authors should report their study site’s protocol for testing for adenoviruses, specifically, whether testing for adenoviruses was only performed on symptomatic patients, or if high-risk patients were routinely screened for adenovirus.

2. Methods: Probenecid is often co-administered with cidofovir. The authors should report if this drug was used in any of the courses of cidofovir, and what dosages. If probenecid was not used in all courses, the authors should analyze their data to investigate the role of probenecid in reducing nephrotoxicity.

3. Methods: It is not clear if adenovirus testing is completed on whole blood or serum. Later in the results, the authors state whole blood, but this should be explained in the methodology.

4. Methods: The authors should define pre-treatment/peak/post-treatment creatinine levels in their methodology. In addition, what defines pre-treatment creatinine? Is that the creatinine on the day of initiation of cidofovir? One week prior? Baseline from months prior? Defining this value is essential to the author’s statistical analysis.

5. Table 1: Patients should be ordered by diagnosis for better organization (as opposed to patient number); for example, the hematopoietic stem cell transplant patients should be grouped together, then the solid organ transplant patients should be grouped together. A column of outcomes should be added for greater clarity of which cases resulted in mortality, instead of the usage of an asterisk.

6. Results: Much of the information stated in the paragraph starting “Of the 19 courses prescribed” is redundant with the data presented in table 1, including the number of courses involving viremia, pneumonia, and GI symptoms. This paragraph can be consolidated, and the case characteristics presented as already implemented in Table 1.

7. Results: The authors should include a description of the patient’s response to cidofovir in Table 1. This would provide better organization and clarity in interpreting which characteristics were associated with response (or lack thereof) to therapy. It also would make the paragraph “We further examined the 16 blood-positive…” redundant, and this could be consolidated.

8. Figure 1: This figure might be easier to interpret if it were separated, for example, into two graphs of HSCT and SOT/other patients. It is difficult to follow 16 distinct virological lines in the current graph. In addition, the color choices for patients 4, 9, and 13 are too similar.

9. The statistical analysis of increased risk of renal dysfunction when receiving 1 vs >2 renal toxic medications should be omitted as currently presented. The authors do not describe whether the additional nephrotoxic agents were co-administered at the same time or for what duration. These are critical confounding variables that are necessary for interpretation of whether nephrotoxicity was associated with increased administration of additional nephrotoxic agents. Given that this review is retrospective, such information may or may not be available.

10. Figure 2 is a somewhat awkward way to describe SCr before and after CDV therapy. In addition, it is unclear how, if only 64% of patients with elevated SCr returned to baseline, the mean SCr after CDV was equal to baseline (in the right bar of Figure 2). The table describes the SCr data adequately, and Figure 2 could therefore be omitted.
11. The publication search criteria used to generate Table 3 should be explained in the methods. In their literature review, the authors should incorporate other pediatric adenovirus-cidofovir case reports and series that were not reviewed in this manuscript, including: Seidemann et al. (2004), Leruez-Ville et al. (2004), Nagafuji et al. (2004).

12. At least brief mention of the advent of brincidofovir for treatment of these patients with much reduced nephrotoxicity would be warranted.

References

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

doi:10.5256/f1000research.9007.r13587

Jeffrey Bergelson
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This paper reports the use of cidofovir for treatment of adenovirus infection in 16 pediatric patients, and provides detailed information about the patients’ clinical status, blood viral loads, and renal function throughout the treatment course.

I have only one major point for the authors to consider. Most patients survived, and a number had decreases in viral load within several weeks of the start of cidofovir therapy. However, the patient group was quite heterogeneous (one case had cerebral palsy, but no apparent immune dysfunction); in some cases the viral loads rose for a long time before they began to fall; and 4 of the 7 patients who had undergone allogeneic stem cell transplant died. I think the discussion should point out explicitly that it is difficult to conclude from these data whether or not cidofovir provided any clinical benefit.
Minor points:

1. Clarify the assay used for viral loads. Is it the Argene assay, or an in-house assay using some components of the Argene kit?

2. Clarify the definition of “viral response”. Is it a 10-fold decrease in titer?

3. Perhaps mention briefly why the asymptomatic patients were treated with cidofovir. It appears that one was a lung transplant patient (considered to be at high risk) and one a SCT patient with recurrent viremia.

4. Figure 2 adds little.

Typos, spelling, glitches:

Page 3. “These associated adverse effects”; THIS adverse EFFECT.
Page 3. “1 mg/kg three times” WEEKLY
Page 3. “Respiratory tract”; italicize
Page 3. “The peak SCr during therapy was used to calculate the number…” should be deleted.
Table 1. “multivisceral”
Page 5. “Respiratory symptoms were the most common presentation in 10 courses”; should be “…most common presentation (10 courses).”
Page 5. “Two courses were prescribed… respectively”; should be One course was prescribed in asymptomatic x, and one in y.
Page 5. “improvement with viral clearance, however”; comma should be a semicolon.
Page 6. “..one third died all of which”; ? …died, all of WHOM.”

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Competing Interests:** No competing interests were disclosed.
Miguel O’Ryan
Institute of Biomedical Sciences, Faculty of Medicine, Universidad de Chile, Santiago, Chile

This is a well written descriptive, retrospective study of a case series of immunocompromised children receiving cidofovir for treatment of mostly probable, few definite or asymptomatic adenovirus infections. Children had different underlying diseases including a few with solid organ transplantation. The series review is transparent, showing viral and clinical evolution as well as renal compromise in association with treatment. Most children cleared adenovirus with treatment but as the authors point out, also in association with improved immunity. Most but not all children clearing the virus improved clinically, a few died despite clearing the virus. Transient nephrotoxicity occurred in near 50% of children, but this occurred in association with other nephrotoxic treatments and was not a major problem. This review adds to the rather limited number of currently available series and although not providing any definite conclusion (clinicians will still have to balance several variables before deciding to use cidofovir or not) it adds helpful information for treating physicians that have to make these hard decisions.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.