Adenovirus Infections in Transplant Recipients

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Adenoviruses are increasingly recognized as contributors to morbidity and mortality among stem cell and solid-organ transplant recipients. Clinical presentations range from asymptomatic viremia to respiratory and gastrointestinal disease, hemorrhagic cystitis, and severe disseminated illness. The limited clinical data available support the use of cidofovir for many of these illnesses. Prospective studies are needed to better understand the pathogenesis of and therapeutic options for adenoviral infections in this patient population.

VIROLOGY AND EPIDEMIOLOGY

Adenoviruses (AdV) are nonenveloped, double-stranded DNA viruses associated with a wide range of clinical syndromes in humans [1]. There are 51 immunologically distinct types of adenoviruses, which are further classified into 1 of 6 (A–F) subgroups on the basis of hemagglutinin properties, DNA homology, oncogenic potential in rodents, and clinical disease (table 1) [2, 3].

Adenoviruses typically cause self-limited respiratory, gastrointestinal, or conjunctival disease throughout the year, without significant seasonal variation. Adenovirus infections are most common among children, people living in close quarters (such as college students and military recruits), and immunocompromised patients. Transmission can occur via inhalation of aerosolized droplets, direct conjunctival inoculation, fecal-oral spread, or exposure to infected tissue or blood [1]. The incubation period depends on the virus serotype and mechanism of transmission and can range from 2 days to 2 weeks [1]. Adenoviruses can establish lifelong asymptomatic infections in lympho-epithelial tissues [4–6]. Among transplant recipients, adenoviral infection has been associated with both de novo infection, particularly in pediatric recipients, and reactivation of latent infection [7, 8]; compelling circumstantial data suggest that most adenovirus infections in adults and subgroup C infections in children arise from reactivation. In both stem cell transplant recipients [9] and solid-organ transplant recipients [10], active disease and asymptomatic viremia have been demonstrated in the early period after transplantation when patients remain in controlled environments that are without evidence of associated nosocomial outbreaks [11, 12]. From these data, it is unclear whether latent viruses are of donor or recipient origin.

The incidence of adenovirus illness in transplant recipients remains unclear, because available studies have incorporated different definitions of disease, have used different diagnostic techniques, and have evaluated diverse patient populations; large prospective studies have not been performed.

In the stem cell transplantation population, the incidence of disease ranges from 3%–47% [12–22]. Available data suggest that adenoviral infections are more frequent in allogeneic stem cell transplant recipients, compared to those receiving autologous grafts (8.5%–30% vs. 2%–12%) [13, 14, 16, 19]; children, compared to adults (31%–47% vs. 13.6%) [12, 16, 19, 23]; patients who receive T cell–depleted grafts (45% vs. 11%) [15]; and patients with acute graft-versus-host disease (GVHD) [9, 16, 20, 22]. Severe lymphopenia (<300 cells/mm³) is associated with a progression to disseminated, and often fatal disease [3, 15].

Incidence data for adenoviral disease in solid-organ transplant recipients are even more limited than for stem cell transplant recipients. Adenoviral infections appear most commonly in liver transplant recipients, pediatric transplant recipients, patients who receive antilymphocyte antibodies, and patients with donor-positive/recipient-negative adenovirus status [11, 12].

CLINICAL PRESENTATION

Disease due to adenoviruses among immunocompetent patients is almost always self-limited and is typically associated with mild upper respiratory, gastrointestinal, or conjunctival
Adenoviruses cause a wider spectrum of clinical disease, with more end-organ involvement, disseminated disease, and higher mortality, among patients with compromised immune systems [2, 3]. The definition of infection with adenovirus is controversial, because detection of the virus does not always correlate with clinical symptoms, and other copathogens may contribute to the clinical syndrome. Infection with adenovirus is defined as the presence of the virus on culture, of the antigen by immunoassay findings, or of viral DNA by PCR in samples obtained from body fluid or tissue, irrespective of symptoms [3]. In contrast, adenoviral disease is typically defined as a symptomatic, tissue-invasive infection; definite adenovirus disease is defined as documented adenovirus nuclear inclusions on routine histopathologic samples and positive results of culture or PCR from tissue samples, excluding those obtained from the gastrointestinal tract [16]. Probable adenovirus disease is defined as a clinical syndrome with documented culture or PCR findings in samples obtained from ≥2 body sites without other identifiable causes [16]. Lastly, disseminated adenoviral disease is defined as documented disease in ≥2 end organs [3]. Viremia is present in most, but not all, patients with disseminated disease [21].

In hematopoietic stem cell transplant (HSCT) recipients, adenovirus is commonly associated with upper and/or lower respiratory tract infection, gastrointestinal disease, hepatitis, or cystitis. Progression to disseminated disease occurs in approximately 10%–20% of patients [9, 13, 19, 25, 26]. Respiratory tract disease ranges from mild upper-tract involvement, typically presenting nonspecific coldlike symptoms, to severe pneumonia [2, 3], and it is associated with subgroup C (Adv 1, 2, and 5), subgroup B (Adv 34 and 35), and subgroup A (Adv 31) viruses [3, 16, 22]. Gastrointestinal disease ranges from mild diarrhea to hemorrhagic colitis and is associated with subgroup B and C viruses [3, 16, 22]. Hepatitis is also frequently associated with subgroup C viruses (Adv 1, 2, and 5) [27, 28]. Hemorrhagic cystitis is most commonly associated with adenovirus type 11 and, less commonly, with subgroup B viruses (Adv 34 and 35) [2, 3]. The presence of adenovirus in the urine is almost universally associated with hemorrhagic cystitis [29], which rarely progresses to disseminated infection [29–40].

Most retrospective studies have documented the onset of adenovirus disease during the first 100 days following HSCT (median 36–90 days) [9, 11, 12, 15, 17, 19, 20, 41–43]; onset of adenovirus disease after 100 days has also been clearly documented, especially in adults [15, 16]. When screening for adenovirus was implemented, initial detection of the virus from any site occurred very early after transplantation (median time after transplantation, 17–21 days) and typically preceded development of end-organ disease [21, 44, 45]. The timing of infection depended on the age of the transplant recipient (earlier in children, later in adults) and the type of transplantation performed [3]. Adenovirus infections may be associated with graft failure or delayed engraftment. Additionally, coinfection with cytomegalovirus, Aspergillus species, or bacteria frequently occurs and may contribute to the poor outcomes associated with adenovirus disease [13, 17, 19]. Untreated, the mortality rate for HSCT recipients approaches 26% for all symptomatic patients, whereas pneumonia and disseminated disease portend more ominous outcomes (50% and 80%, respectively) [11, 12, 14].

Hemorrhagic cystitis, nephritis, pneumonia, hepatitis, enterocolitis, and disseminated disease have been described among solid-organ transplant recipients [46–56]. In liver transplant recipients, infection with adenovirus serotype 5 typically results in hepatitis, with a median time to onset of 55 days [25, 26], whereas serotypes 1 and 2 are more commonly associated with pneumonia. Enterocolitis occurs more commonly in small bowel transplant recipients and may mimic rejection [55, 56]. Adenoviral pneumonia is associated with graft loss, death, or progression to obliterative bronchiolitis for lung transplant recipients [48]. In one study of pediatric heart transplant recipients, detection of adenoviral genome copies in myocardial biopsy specimens was predictive of adverse clinical events, including coronary vasculopathy and graft loss (OR, 4.7 compared with adenovirus-negative patients; 95% CI, 1.3–17.1) [57].

**DIAGNOSIS AND MONITORING**

The diagnosis of adenoviral infections has classically depended on viral culture results [58]. Even under optimal conditions, characteristic cytopathic changes may take up to 21 days to occur [3]. Shell vial techniques have improved the speed and yield of traditional cultures [3]. Direct immunofluorescence and electron microscopy of respiratory secretion or tissue samples may be used to diagnose end-organ involvement [3]. Rapid testing of ocular, respiratory, and stool specimens may be performed with commercially available EIAs, although the sensitivity of these tests is limited [59].

Because the transactivating region of the E1A gene and the N-terminal region of the hexon gene are well conserved between serotypes [60, 61], traditional and quantitative real-time PCR techniques have been developed for diagnosis [10, 62–68]. Although false-negative results have been reported [69], these molecular methods have improved sensitivity over traditional methods [62, 70–74]. Any time that adenovirus disease is considered, blood specimens should be sent for quantitative viral load measurements; PCR detection of adenovirus can also be performed on stool, sputum, and biopsy specimens [27, 65, 68, 70, 71, 73–75]. Quantitative viral load measurements contribute to the diagnosis of infection and act as a surrogate that correlates with clinical response to therapy [67, 68]. Quantitative measurements of PCR findings are also useful for determining prognosis because increased viral load measurements...
having received cidofovir therapy [42]. In 4 of 6 patients; one-half of the patients studied died despite detection as part of routine screening, to symptomatic disease including 1 who received a combined liver and stem cell transplant recipients (n=1), in another limited study of pediatric HSCT recipients [10, 76]. Another limited study of pediatric HSCT recipients documented viremia by PCR findings in 42% of patients tested, although 64% of the patients cleared the virus without therapy [44]. Among pediatric HSCT recipients, adenoviremia, particularly when present over time, with high viral loads, or in the presence of lymphopenia and/or continued immunosuppression, may be a predictor of progression of disease [3]. Unfortunately, the outcomes of asymptomatic patients with adenoviremia are variable: one prospective study tested clinical specimens from pediatric HSCT recipients and found that specimens from 27% yielded positive PCR results [21]; a positive PCR result of urine, throat, and stool samples usually did not correlate with clinical disease. Eighty-two percent of patients with detectable adenoviremia died of infectious complications. The virus was first detected in blood samples a median of 3 weeks before clinical symptoms developed [21]. A retrospective study also demonstrated that adenoviremia was a strong predictor of fatal outcome; in this study, most of the patients were symptomatic at the time of initial viral identification [75]. Another retrospective study of pediatric HSCT recipients documented viremia by PCR findings in 42% of patients tested, although 64% of the patients cleared the virus without therapy [44]. Among pediatric HSCT recipients, adenoviremia, particularly when present over time, with high viral loads, or in the presence of lymphopenia and/or continued immunosuppressive therapy, may be a predictor of progression of disease [3].

Three studies have documented the natural history of asymptomatic adenoviremia in solid-organ transplant recipients. The incidence of adenovirus viremia was 6.5%, 6.7%, 8.3%, and 22.5% for adult kidney, heart, liver, and lung recipients, respectively [10, 76]. Few patients were symptomatic at the time that viremia was detected, viral loads in these patients were low, and none developed end-organ disease. There was no compromise of pulmonary function among the studied lung transplant recipients [10, 76]. Another limited study of pediatric liver (n=4) and stem cell transplant recipients (n=2, including 1 who received a combined liver and stem cell transplant) revealed progression from asymptomatic adenoviremia, detected as part of routine screening, to symptomatic disease in 4 of 6 patients; one-half of the patients studied died despite having received cidofovir therapy [42].

At this time, no consensus exists regarding the treatment of asymptomatic patients with detectable adenoviremia. Some experts have advocated a preemptive screening and treatment approach, particularly for pediatric HSCT recipients [3]. One such strategy involves weekly screening of stool, urine, throat, and blood samples for adenovirus by PCR [3]. In cases in which 2 samples are positive, in which there is evidence of end-organ disease, or in which there is severe lymphopenia or reduction of immunosuppression is not advisable, antiviral therapy should be considered [3]. Although some advocate screening all matched-unrelated donor or haplo-identical adult HSCT recipients for adenovirus, there is insufficient natural history data at this point to recommend for or against screening these individuals. Screening of asymptomatic adult solid-organ transplant recipients for adenovirus is not useful, because progression to disease is infrequent. Prospective, randomized, placebo-controlled trials are needed to evaluate the role of screening and preemptive treatment among HSCT recipients.

**MANAGEMENT OPTIONS**

Unfortunately, available in vitro susceptibility data from studies of currently available antiviral agents have been obtained using different techniques, cell lines, and viral isolates [11, 12, 77–85]. It is, therefore, difficult to compare the relative potencies of these agents. Table 2 lists the various agents that have in vitro efficacy against some adenovirus subgroups. The substantial rate of mortality among patients with adenovirus disease has prompted the use of many of these agents in transplant recipients; none of these agents, however, have been evaluated for efficacy in a prospective, randomized, placebo-controlled study.

**Cidofovir.** Cidofovir, a cytosine analogue that inhibits DNA polymerase. It is available only as an intravenous formulation, and its use can incur significant nephrotoxicity, as well as hematologic and possibly ocular toxicity [86–88]. Cidofovir is active against all serotypes of adenovirus [77, 80]. Animal models of ocular infection have clearly demonstrated virologic and clinical efficacy of cidofovir [77, 89–98]. In humans, however, data are still mostly retrospective in nature, but they suggest that cidofovir use is associated with significantly

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**Table 1. Infections associated with adenovirus subgroup and serotype.**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Serotype(s)</th>
<th>Major site(s) of infection</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>12, 18, 31</td>
<td>Respiratory tract, urinary tract, GI tract</td>
</tr>
<tr>
<td>B</td>
<td>3, 7, 16, 21, 11, 14, 34, 35</td>
<td>Respiratory tract, eye, urinary tract, GI tract</td>
</tr>
<tr>
<td>C</td>
<td>1, 2, 5, 6</td>
<td>Respiratory tract, urinary tract, GI tract</td>
</tr>
<tr>
<td>D</td>
<td>8–10, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49</td>
<td>Eye, GI tract</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>Eye, respiratory tract</td>
</tr>
<tr>
<td>F</td>
<td>40, 41</td>
<td>GI tract</td>
</tr>
</tbody>
</table>

**NOTE.** From [1–3]. GI, gastrointestinal.
lower rates of mortality, compared with data from historical controls or other antivirals [13, 18, 19, 38–41, 99–103]. Typically, 1 of 2 regimens is used for the management of adenoviral disease: 5 mg/kg every 1–2 weeks, or 1 mg/kg three times per week [18, 100]. Although the 1 mg/kg three times per week dosage is associated with less nephrotoxicity [18], the efficacy of the 2 regimens has not been directly compared. Additionally, the 1 mg/kg three times per week regimen is associated with breakthrough cytomegalovirus and herpes simplex virus infections [40, 104]. A recent study of 8 immunosuppressed patients (3 HSCT recipients, 2 liver–small bowel transplant recipients, 1 liver transplant recipient, 1 recipient with severe combined immune deficiency, and 1 with a T cell deficiency) with adenoviremia and invasive adenovirus disease were monitored by quantitative PCR analysis to determine their response to cidofovir (5 mg/kg every week for 2 weeks, then every other week) [68]. Five patients clearly responded virologically and clinically to cidofovir; the remaining 3 patients had stable viral replication and eventually died. Of note, there was a significant delay between onset of symptoms and institution of therapy in 3 fatal cases (median time to death, 18 days). A decrease in the viral load of ≥1 log in the 7–10 days after the first dose was administered was predictive of a successful outcome [68].

Recently, lipid esters of both cidofovir and a related compound, HPMPA ((S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine), have been developed to overcome the significant toxicity and limited bioavailability of cidofovir [105–107]. In vitro testing of these compounds suggest that they are 5- to 2500-fold more potent against adenovirus, in terms of IC50 values, than their unmodified parent compounds [78]. If preliminary studies in humans support these safety and oral bioavailability data [106, 107], these drugs could represent a new and potentially safer option in the prevention and management of adenoviral disease.

Ribavirin. Ribavirin only displays in vitro activity against those subgroup C viruses for which there is a wide variation in IC50 [80, 82]; few studies have revealed a mortality benefit with the use of this agent (mortality rate, 61%–77%) [13, 20, 27, 31, 35–37, 41, 67, 80, 108–122]. In one recent study, despite receiving ribavirin, all 4 immunocompromised children with disseminated adenovirus disease (3 with subgroup C viruses [1, 2, and 5]) died, and only 1 had a slight reduction in the level of viral DNA, as measured by quantitative PCR analysis [67]. Overall, there is not convincing evidence that ribavirin significantly reduces viral load, and its use is not associated with a meaningful reduction in mortality.

Ganciclovir. Ganciclovir is active against adenovirus at clinically achievable levels [81, 83, 84], but there are limited data for the efficacy of ganciclovir in the treatment of adenoviral infections [34, 123, 124]. Because ganciclovir is commonly used to prevent cytomegalovirus infection in transplant recipients, it would follow that the incidence of adenovirus infection should be lower in patients receiving ganciclovir prophylaxis. Indeed, 2 studies revealed that patients who did not receive ganciclovir for prophylaxis were at greater risk of developing adenoviral infection and disease (OR, 3.4; 95% CI, 2.1–5.6) [14, 125]. Alternatively, one prospective study of solid-organ transplant recipients revealed that 57% of patients who developed detectable adenovirus viremia did so while receiving cytomegalovirus prophylaxis therapy with either ganciclovir or valganciclovir [10]. Further studies are needed to clarify the role of ganciclovir in the management of adenovirus infections, particularly its role as an adjunct to more active therapy or for prevention of disease.

Zalcitabine. Zalcitabine displays in vitro activity against adenovirus in a clinically achievable range [79, 126, 127]. In a rat model of adenovirus pneumonia, zalcitabine was associated with a statistically significant reduction in the frequency of pneumonia development [128]. Studies in humans infected with adenovirus are lacking.

Vidarabine. Vidarabine is an adenosine analogue with marginal in vitro activity [85]. Activity is improved following

### Table 2. Available agents with activity against adenovirus.

<table>
<thead>
<tr>
<th>Compound [reference]</th>
<th>Availability</th>
<th>IC50 μmol/L</th>
<th>Clinically achievable concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin [80, 82]</td>
<td>Commerciala</td>
<td>12 to &gt;1000</td>
<td>10.75–18 μg/mL</td>
</tr>
<tr>
<td>Cidofovir [77, 80]</td>
<td>Commercialb</td>
<td>8.5–100</td>
<td>7.3–19.6 μg/mL</td>
</tr>
<tr>
<td>Lipid esters of cidofovir [78]</td>
<td>Investigational</td>
<td>0.5–2.0</td>
<td>...</td>
</tr>
<tr>
<td>HPMPA [78]</td>
<td>Investigational</td>
<td>0.5–2.2</td>
<td>...</td>
</tr>
<tr>
<td>Ganciclovir [81, 83, 84]</td>
<td>Commercialb</td>
<td>4.5–33</td>
<td>5.5–9 μg/mL</td>
</tr>
<tr>
<td>Zalcitabine [79]</td>
<td>Commercialb</td>
<td>0.05–0.83</td>
<td>7.6–25.2 ng/mL</td>
</tr>
<tr>
<td>Vidarabine [85]</td>
<td>Commercialb</td>
<td>175 to &gt;700</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** HPMPA, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine.

a IC50s were determined using different viral serotypes, cell types, and techniques and may not, therefore, be directly comparable.

b These compounds have been approved by the US Food and Drug Administration for other indications.
Vidarabine has been used successfully to treat hemorrhagic cystitis, but therapy has proven to be less successful for other forms of disease, and toxicity remains a significant limiting factor [30–33, 41, 85, 129–133].

**Immunotherapy.** Reduction of immunosuppression and the exogenous augmentation of the immune response may lead to reduction in viral loads and to improved survival. Unfortunately, acute GVHD among stem cell transplant recipients often makes reduction of immunosuppression impossible. Studies have clearly demonstrated an association between lymphocyte recovery and recovery from adenoviral infections in HSCT recipients [134]. As a result, exogenous lymphocyte therapy in the form of donor lymphocyte infusions has been successful in a few cases [23, 41, 135]. Unfortunately, donor lymphocyte infusion therapy is currently limited by the risk of exacerbation of GVHD, and by the ability to generate sufficient subgroup cross-reactive adenovirus-specific cytotoxic T lymphocytes ex vivo. Several groups are developing methods to produce adenovirus-specific cytotoxic T lymphocytes efficiently [136–139]. Donor lymphocyte infusion therapy holds promise for HSCT recipients, despite its limitations, but it requires further clinical study. The use of intravenous immunoglobulin has also been met with success for a small number of patients, but its use cannot be recommended without additional data [16, 111, 119, 140].

**CONCLUSIONS AND FUTURE DIRECTIONS**

Adenovirus infections in transplant recipients are increasingly recognized as significant causes of morbidity and mortality. Our understanding of adenovirus pathogenesis remains limited, and prospective studies describing the incidence and natural history of adenovirus infections in HSCT and solid-organ transplant patients are needed.

On the basis of available data, it is unclear which patients clearly warrant therapy. As with other serious infections, for patients with documented adenovirus infection, immunosuppression should be reduced as much as possible [141]. Cidofovir, despite its significant toxicity risk, is the agent with the clearest in vitro and in vivo data supporting its clinical application in patients with documented adenovirus disease. Patients with significant end-organ disease or disseminated disease would likely benefit from treatment with cidofovir, despite its potential for toxicity. Patients with hemorrhagic cystitis may be an exception, however, because disease may not disseminate if the immune system reconstitutes quickly and immunosuppression is decreased. The timing and utility of an intervention is less clear in asymptomatic patients. Although cidofovir appears to be associated with a lower incidence of adenovirus disease, no agent has been prospectively studied to prevent adenovirus disease, and data are too limited to recommend universal prophylaxis at this time.

In addition to identifying novel drugs, studies are needed to assess the impact of current drugs, alone and in combination, with the goal of improving efficacy or tolerability. In vitro and in vivo studies using experimental animal models [142] and prospective, randomized studies in patients with end-organ disease are needed to determine the safety and efficacy of current and novel antiviral agents, and to help identify the optimal timing of an intervention. Finally, prospective studies are needed to determine the efficacy of preemptive screening and treatment of adenovirus infection in asymptomatic HSCT recipients.

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