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Adenovirus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention, and management of adenovirus infections after solid organ transplantation. Adenovirus is an important cause of infectious complications in both stem cell transplant and SOT patients, causing a range of clinical syndromes including pneumonitis, colitis, and disseminated disease. The current update of the guidelines highlights that adenovirus surveillance testing should not be performed in asymptomatic recipients. Serial quantitative PCR might play a role in the decision to initiate or assess response to therapy in a symptomatic patient. The initial and most important components of therapy remain supportive care and decrease in immunosuppression. The use of antiviral therapy is not supported by prospective randomized clinical trials. However, intravenous cidofovir is considered the standard practice for treatment of severe, progressive, or disseminated adenovirus disease in most transplant centers. Intravenous immunoglobulin may be beneficial, primarily in a select group of patients with hypogammaglobulinemia. Future approaches to treatment of adenovirus disease may include administration of adenovirus-specific T-cell therapy.

KEYWORDS
infectious, infection and infectious agents, adenovirus, solid organ transplant and transplantation

1 | INTRODUCTION

Adenoviruses, non-enveloped, lytic double-stranded DNA viruses are causing mostly self-limited respiratory, gastrointestinal, or conjunctival disease in immunocompetent patients throughout the year.[1] Adenoviruses are classified into seven subgroups (A-G) based on hemagglutination properties, DNA homology, and oncogenic potential in rodents; the subgroups can be further divided into 67 immunologically distinct serotypes based on neutralization by specific animal antisera, by genomic sequencing and bioinformatics analysis; even more, different genotypes have been described within the same serotype.[2,3] Few serotypes, particularly from subgroup C, are capable of inducing a latent infection in tonsils, adenoids, intestine, lymphocyte, and urinary tract.[2,4]

Although there is no consensus on the definitions of adenovirus infection and disease, we propose to maintain the same definitions published in the previous guidelines.[5] Asymptomatic adenovirus infection is defined as detection of adenovirus in patients from stool, blood, urine, or upper airway specimens (by viral culture, antigen tests, or PCR) in the absence of signs and symptoms associated with adenovirus

disease.[6] Adenovirus disease is defined as the presence of attributable organ signs and symptoms combined with adenovirus detection in the biopsy specimens (immunohistochemical stain) or from bronchoalveolar lavage or cerebrospinal fluid (culture, antigen detection, or PCR), in the absence of another diagnosis.[2,7] A positive adenovirus PCR from tissue or fluid and a negative immunohistochemical stain is not consistent with invasive disease. A positive adenovirus PCR test result from tissue or fluid is difficult to interpret in the absence of immunohistochemical confirmation. Adenovirus disease is considered disseminated if two or more organs are involved, not including viremia.[2,8] The ability of adenovirus to establish latency may lead to challenges in the interpretation of the presence of DNA in clinical specimens.

2 | EPIDEMIOLOGY

Adenovirus infections occur throughout the year without seasonal variability.[9] Adenovirus infections can be acquired de novo, through reactivation of a latent infection of the recipient or from the transplanted organ.[6] Early adenovirus disease post-transplantation suggests either adenovirus reactivation or donor-derived infection.[6,10] Transmission of adenovirus occurs by the respiratory route via infected aerosols, person-to-person contact, fomites, or by the fecal-oral route.[1] Most infections are sporadic, but nosocomial transmission has been described among hospitalized solid organ transplant recipients.[6,8,11]

Adenovirus infections are endemic in pediatric populations and people living in close quarters (ie, college students and military recruits).[1] The true incidence of adenovirus infection is not well defined. Adenovirus appears to be more commonly isolated in pediatric than adult solid organ transplant recipients, reflecting the epidemiology of adenovirus infections in children (Table 1).[12-14] Transient self-limited adenovirus viremia during the first year post-transplant is not uncommon, with an incidence of 7.2% in a surveillance study of adult SOT patients.[4,8] The incidence of adenovirus infections among pediatric solid organ transplant recipients depend on the allograft type (Table 1), with the majority of the infections being diagnosed within the first few months post-transplantation.[6,10-12,15-22] There is even less data in adult SOT regarding the incidence of adenovirus infections in different allografts (Table 1), but similar to pediatric recipients, most of the infections are described early after transplantation.[23,24] Very few cases of adenovirus infections have been reported in adult intestinal transplantation.[25] Late infections, most likely primary infections by a new adenovirus strain, have also been described in pediatric and adult SOT recipients.[26,27]

TABLE 1 Incidence of adenovirus infection by organ transplanted

Allograft type	Reported adenovirus incidence (%)
Pediatric transplantation	
Liver	3.5-38
Heart, heart-lung, lung	7-50
Kidney	11
Intestinal, multivisceral	4.3-57.1
Adult transplantation	
Liver	5.8
Heart, heart-lung, lung	6-22.5
Kidney	4.1-6.5
Intestinal, multivisceral	N/A

3 | CLINICAL MANIFESTATIONS

Adenovirus infections in SOT recipients can range from asymptomatic to severe, prolonged, disseminated disease, and have a significant impact on morbidity, mortality, and graft survival.[2,14] Clinical manifestations depend on the site of infection and the type of transplanted organ, with the allograft being frequently involved. In liver transplant recipients, adenovirus can affect the gastrointestinal, respiratory and urinary tracts, with hepatitis being the most common manifestation.[11,12] This can present as fever, stomatitis, enteritis, pneumonia and elevated transaminase levels.[12] Lung transplant recipients infected with adenovirus can present with acute flu-like illness, diffuse alveolar damage, necrotizing pneumonia or chronic changes (bronchiolitis obliterans, interstitial fibrosis or bronchiectasis).[10,17,24] Severe and fatal adenoviral infections have been reported in adult lung transplant recipients.[10,17] In intestinal transplants, enteritis is common; patients present with fever, diarrhea, and increase ostomy output; up to 35% of these patients progress to disseminated adenovirus disease.[6,22,28] Adenovirus usually involves the distal ileum, presumably due to its increased density of lymphatic tissue, but may affect the jejunum and the colon.[6,29] Kidney transplant recipients can present with hematuria, dysuria, and fever; hemorrhagic cystitis and graft dysfunction are more often described in adult than pediatric renal transplant recipients.[9,23,30] Common extra-renal manifestation in these patients includes orchitis, gastroenteritis, and pneumonia.[23,31] Clinical significance of adenovirus infections in heart transplantation is not well defined, but increased risk of rejection, coronary vasculopathy, ventricular dysfunction, and graft loss have been described.[32,33]

Data regarding the risk factors for adenovirus infection in solid organ transplant recipients are emerging: (a) Age has been found to be an independent risk factor for adenovirus infection[22]; young children (<5 years old) are at increased risk of infection, likely because they are immunologically naïve and have higher exposure.[13,14,19] (b) Allograft type appears to correlate with the risk of adenovirus infections, with the highest rates being reported in intestinal transplantation. A large amount of lymphoid tissue in the allograft poses a high risk of rejection, requiring more intense immunosuppressive regimens; lymphoid tissue could also be the source of persistent latent adenovirus infections.[6,11,14,21,22,25,28] (c) The degree of immunosuppression seems to be an independent risk factor demonstrated by the highest rates of infections in the first months after transplantation or after rejection episodes[12,23,34] and by the resolution of infections with reduction in

immunotherapy alone.[14] (d) Use of adenovirus sero-mismatch has also been considered to be a risk factor for infection, although this is not routinely performed in current practice.[2,9]

Several factors might increase the risk of progression from asymptomatic infection to adenovirus disease: isolation of the virus early after transplantation, persistent isolation of the virus from one site, isolation of the virus from more than one site, initial high viral load in blood, and intensification of immunosuppression.[6,11,23] However, in adult solid organ transplant recipients, asymptomatic viremia is common (6.5%-22.5%) and the risk of progression to adenoviral disease seems to be low, but still to be defined[8,24]; routine screening for adenovirus DNA-emia is not recommended for solid organ transplant recipients.[9]

4 | DIAGNOSTIC STRATEGIES

The available diagnostic methods for adenovirus infections are as follows: viral culture, direct antigen detection, molecular methods, and histopathology. Serology and electron microscopy are available, but not routinely used in clinical practice.[2,9] The diagnostic methods used depend on the site of infection and the sample collected. Recovery of adenovirus from urine, respiratory, or stool specimens by culture or PCR does not confirm adenovirus disease since patients can asymptomatically shed for prolonged periods of time.[2,9,34,35] Accordingly, recovery of adenovirus should be correlated with clinical symptoms, detection of the virus from other sites and histopathologic findings.

All adenovirus serotypes, with the exception of serotypes 40 and 41, grow well in human epithelial cells and produce a characteristic cytopathic effect after 2-28 days, which can be followed by serotyping.[1,2] Expedited results can be obtained by centrifugation in shell vial assays with immunofluorescent monoclonal antibody staining, but serotyping cannot be performed. The rapid antigen detection kits commercially available yield rapid and specific results, but their sensitivity and specificity in the solid organ transplant population is not studied. Prior to the widespread availability of nucleic acid testing (NAT) or PCR-based testing approaches, immunofluorescence assays were often used for respiratory specimens. For stool samples, enzyme immunoassays continue to be used for rapid diagnosis of gastrointestinal disease.[2] Most of the assays detect the common adenovirus serotypes (such as serotypes 1, 2, 3, 5, 7, 40, and 41).

Amplification and detection of the viral genome using polymerase chain reaction (PCR) is a widely used tool for detection of adenovirus, largely supplanting viral culture and other older diagnostic methods.[3] PCR is highly sensitive (the lower limit of detection ranges from 100 to 1000 copies/mL) and rapid. Qualitative and quantitative assays PCR methods are available. Blood, respiratory secretions, tissue specimens, and stool can be tested by PCR. The sensitivity of the assay depends not only on the specimen, but also on methods of sample processing, DNA extraction, the primers used, and the amplification platform employed. For patients with clinical symptoms concerning for adenovirus infection, the relevant clinical specimen should be sent for PCR-based testing. A new method of molecular testing called immune-PCR may hold promise of increased sensitivity for stool testing as it eliminates the need for nucleic acid extraction.[36] Serotyping of virus may be performed by sequencing amplified virus, which is available through the Centers for Disease Control, and may be important in potential outbreak investigations.[37]

Assays specifically targeting adenovirus are considered more sensitive and specific than multiplex stool or respiratory assays that include adenovirus as one of multiple pathogens detected.[38] In addition, while multiplex assays typically only test for a selected number of serotypes, adenovirus-specific assays target conserved regions within the adenovirus genome, and therefore should be able to detect all adenovirus serotypes.[3,39] There are case reports of sequence polymorphisms causing underestimation of adenovirus viral loads.[40] If new serotypes with sequence diversity at the conserved regions targeted by PCR primers continue to emerge, PCR-based test performance may be impaired. Therefore, if new adenovirus serotypes are observed to cause clinical disease, existing diagnostic assays may need to be adapted if they are to continue to serve as "pan-adenovirus" screening tests.

Serial quantitative PCR could be useful regarding decision to initiate therapy and monitoring response to therapy. Persistently high or rising viral loads (0.5-1.0 log increase) may signal the need for intervention, whereas decreasing viral loads might correlate with clinical improvement.[23,41,42] Monitoring of the kinetics of PCR testing results may be valuable, especially since we do not have a set threshold value to start therapy. In HCT recipients, detection of adenovirus in the stool often precedes the detection of adenovirus in blood, likely because the gastrointestinal tract serves as a reservoir for reactivation.[29,36] However, there are no data regarding the possible value of testing stool sample to predict disseminated adenoviral disease in solid organ transplant recipients. Prolonged, asymptomatic detection of adenovirus by PCR in blood has been described in a kidney transplant recipient, with uncertain clinical significance.[44]

Results from molecular testing assays should be correlated with the histopathology, when available, and clinical presentation to differentiate between asymptomatic infection and disease. Histopathologic evaluation remains the gold standard for the diagnosis of invasive adenoviral disease.[1,9,35] Adenovirus-infected cells, so-called "smudge cells" have large nuclei with basophilic inclusions and a thin rim of cytoplasm. The presence of the virus within tissue can be confirmed through immune-peroxidase and in situ hybridization staining.[2] In the kidney, adenovirus interstitial nephritis is diagnosed by a tubulocentric mixed inflammatory infiltrate with focal necrosis surrounding virally infected tubules, with rare tubular epithelial cells with "smudge cell" morphology, but often demonstrating granulomatous features.[45] In adenovirus enteritis, a focal mixed inflammatory infiltrate with focal necrosis may be seen with rare "smudge cells" and an accompanying disorganization of the superficial epithelium.[45] It is important to accurately diagnose viral disease as some of the histological manifestations can be confused with T cell-mediated rejection, especially in kidney transplant recipients.[45]

The role of T cell-mediated immunity in control of adenovirus is demonstrated by (a) poor outcomes in HSCT patients with absolute

lymphocyte counts <300 cells/μL and (b) clearance of viremia in correlation with increase lymphocyte counts and detection of adenovirus-specific $CD4^+$ and $CD8^+$ T cells.[46] The most immunogenic part of the adenovirus capsid is the hexon protein, which has been used to monitor for the appearance of adenovirus-specific T cells.[14,47] The ability to monitor solid organ transplant recipients for the presence of an effective immune response might be useful for identifying patients in need of initiation or continuation of potentially toxic antiviral therapy, especially for pediatric patients at increased risk for adverse clinical complications.[46]

Summary recommendations:

- Surveillance testing for adenovirus should not be performed in asymptomatic SOT recipients (strong, low).
- Detection of adenovirus by culture or PCR testing should be correlated with clinical symptoms, detection of the virus from other sites, and histopathologic findings to establish whether disease is present (strong, low).
- Testing of serial quantitative PCR may assist in the decision to initiate therapy and in monitoring response to therapy as there is not an established threshold value at which to start therapy (weak, low).
- Histopathologic analysis of biopsy samples demonstrating evidence of adenovirus disease remains the gold standard for diagnosis (strong, high). Immunohistochemical staining for adenovirus may be useful to distinguish infection from rejection.
- PCR-based testing on blood, stool, or respiratory secretions, as appropriate, should be used to detect adenovirus when histopathologic diagnosis is not possible (strong, moderate).
- Assessment of a patient's adenovirus-specific immune response may help gauge the need for adenovirus therapy in the future.

5 | TREATMENT

The initial step and the most important component of therapy remains supportive care and decrease in immunosuppression.[48]. Currently there is no consensus on which immunosuppressive agent to reduce or discontinue or when to restart immunosuppression.[48] The role of immune recovery during the course of the infection is highlighted by the resolution of viremia after reduction of immunosuppression.[6,23,25,28,49] It is generally difficult to determine if the resolution of the disease could be attributed to addition of antiviral therapy, versus reduction of immunosuppression, or to the combination of these interventions.[6,34]

The use of antiviral agents is not supported by prospective randomized clinical trials, and there are no antiviral agents approved by FDA for the treatment of adenovirus infections. The use of cidofovir[16,50,51] and ribavirin[42,53] is based on case reports and case series.

Cidofovir, a nucleotide analog of cytosine that inhibits viral DNA polymerase, has in vitro activity against all serotypes[2,9,10,14,23,25,28,33] (but it has been associated with significant nephrotoxicity [up to 50%] and neutropenia [up to 20%]).[54,55] In most transplant centers, intravenous cidofovir is considered the standard practice for treatment of severe, progressive, or disseminated adenovirus disease. Regimens of cidofovir are generally based on center-specific protocols. Two commonly used regimens are used for the management of adenoviral disease, although the efficacy of the two regimens has not been directly compared: 1 mg/kg three times a week[56] or 5 mg/kg/wk[54] for 2 weeks followed by 5 mg/kg every other week until complete resolution of the symptoms and documentation of three negative adenovirus samples, one week apart, from the sites that were originally positive.[2,9,18,34,41] Although the first regimen might be less nephrotoxic,[56] it might be associated with breakthrough cytomegalovirus and herpes simplex infections, and the emergence of antiviral resistance.[57,58] The dosage should be adjusted based on renal function: for adults with creatinine clearance <50 mL/min and pediatric patients with creatinine clearance <0.3 mL/min/kg, the dose should be decreased to 0.5 mg/kg three times a week[59]; for patients on hemodialysis, consideration should be given in stopping the hemodialysis 1 hour before and 4 hours after cidofovir administration to allow intracellular distribution of the drug.[59] Probenecid (0.5-1.25 g/m^2) should be administered 3 hours before, 2-3 hours and 8 hours after the administration of cidofovir to prevent nephrotoxicity.[18,41,56,59] Pre- and post-treatment hydration (normal saline solution at 5 mL/kg/h) should be administered along with probenecid.[2,9,34,56] Patients receiving cidofovir should be monitored for changes in renal function by measuring serum creatinine, urine protein, and neutrophil count prior to each dose administration. Plasma adenovirus viral load monitoring showed that virologic response to cidofovir correlated with clinical improvement and survival.[41,43] In contrast, failure to have ≥1.0 log decline in viral load in the first two weeks of therapy could be associated with progressive clinical symptoms, persistent rises in viral load, and death secondary to symptomatic disease.[41] Limited data suggest that high adenovirus viral load before initiation of treatment and long interval between the onset of symptoms and administration of treatment might be risk factors for poor response to cidofovir.[41]

A lipid conjugate of cidofovir (CMX001, Brincidofovir, Chimerix Inc) is in development. Brincidofovir seems to have several advantages: good oral bioavailability, no nephrotoxicity, achieves higher intracellular levels of active drug compared to cidofovir,[60] 5-fold to >2500-fold more potent against adenoviruses based on IC_{50} as compared to the unmodified parent compounds.[61] In a retrospective study using Brincidofovir as salvage therapy in 13 patients with adenovirus disease, two-thirds demonstrated a sustained decrease in viral load and had a survival advantage, which could not be explained by immune recovery alone[62]; in another retrospective study in HSCT patients, Brincidofovir demonstrated to be highly effective controlling adenovirus viremia during the lymphopenic phase.[63] In addition, therapy was well tolerated in this mainly pediatric population of immunocompromised patients.[62] Brincidofovir rapidly and effectively cleared adenovirus viremia in a cohort of SOT and other immunocompromised patients (n = 43); lower adenovirus burden correlated with improved survival.[64] However, the dose-limiting

toxicities in the previously published studies were gastrointestinal (nausea, vomiting, diarrhea, anorexia), which appear to be more common in HSCT recipients.[64,65]

Ribavirin, a nucleoside analog, seems to have antiviral activity only against subtype C adenoviruses (serotypes 1, 2, 5, and 6)[66] and did not reduce significantly the viral titers in treated patients when used as intravenous therapy at doses ranging from 10 to 60 mg/kg qday.[42,51,66] The main side effect is anemia.[2,9,51]

There is no rationale for using ganciclovir for the treatment of adenovirus infections, since ganciclovir requires phosphorylation to achieve its active state and adenovirus lacks thymidine kinase.[67] Nitazoxanide might play a role in the treatment of adenovirus enteritis. However, the data are limited to a small study that evaluated efficacy of nitazoxanide in immunocompetent patients with mild-to-moderate severity of the disease.[68]

Antibody preparations have been used in several cases of adenovirus disease.[69,70] Although antibody preparations have biologic plausibility, their benefit remains unclear, as no impact on virologic response was noted.[26] Transplant recipients with severe hypogammaglobulinemia (IgG levels <350 mg/dL) seem to be at higher risk of opportunistic infections compared to patients with IgG >350 mg/dL, and they might benefit from immunoglobulin administration[71] Adoptive T-cell therapy may have promise as a future treatment option, but there remain minimal data of its utility in solid organ transplant recipients. See under "Research Issues" below for further discussion.

Summary recommendations:

- Reduction of immunosuppressive regimen, if possible, should be the initial approach in the treatment of adenovirus infections (strong, moderate).
- Cidofovir should be considered as the preferred antiviral agent for the treatment of adenovirus disease (strong, low). Hyperhydration (strong, very-low) and probenecid (strong, moderate) should be administered to minimize the risk of nephrotoxicity. The ideal dose and frequency of cidofovir administration is not known. Dose adjustment should be performed for renal insufficiency (strong, moderate).
- If indicated, antiviral treatment should be continued until complete resolution of the symptoms and documentation of three negative adenovirus samples from the sites that were originally positive (strong, moderate).
- Administration of cidofovir for asymptomatic adenovirus infection is not usually necessary, and the risk of nephrotoxicity should be weighed against the risk of disease progression (strong, low).
- Ribavirin and ganciclovir are not recommended for the treatment of adenovirus infections (strong, very-low).
- Nitazoxanide might be a therapeutic option for adenovirus enteritis in solid organ transplant recipients (weak, low).
- Intravenous immunoglobulins might be beneficial, mainly in selected group of patients with hypogammaglobulinemia (weak, low).
- Adoptive T-cell therapy is a promising emerging option, but there are no data yet to support its use in SOT recipients.

6 | PREVENTION

Outbreaks of adenovirus infections have been reported in hospital or institutional settings.[72] CDC/HICPAC guidelines recommend contact and droplet precautions during hospitalization for the duration of illness to prevent nosocomial transmission.[72] The duration of contact and droplet precautions in immunocompromised hosts might need to be extended due to prolonged shedding of adenovirus A live oral adenovirus vaccine (type 4 and 7) is approved for military population (age 17-50 years),[73] but as a live virus, is contraindicated for use in the transplant population. Administration of this vaccine in the pre-transplant period has not been studied; it offers immunity limited to two serotypes that are not necessarily the most common in transplantation. The vaccine would be contraindicated after transplantation.

Summary recommendations:

- Contact and droplet precautions are recommended during hospitalization (strong, high).
- The duration of contact and droplet precautions in immunocompromised hosts might need to be extended due to prolonged shedding of the adenovirus (weak, low).

7 | RESEARCH ISSUES

To understand the need for antiviral treatment we need to learn the natural history of adenovirus infection in SOT and the utility of blood adenovirus viral load monitoring for identification of patients at risk of developing disease. Randomized, multicentered, placebo-controlled trials evaluating new treatment options (such as brincidofovir) and some of the current therapies (intravenous immunoglobulins) for efficacy and safety in the treatment of adenovirus disease in transplant recipients are also warranted.

Limited data show that low absolute lymphocyte count at the time of adenovirus viremia and recovery of lymphocytes count might be predictors of adenovirus disease and outcome.[6,14,23,25,28] Although, enhancement of adenovirus-specific immunity through antigen-specific cytotoxic T lymphocyte (CTL) infusion might improve outcomes in adenovirus disease in HSCT,[74,75] there are no available data in solid organ transplant recipients. These so-called virus-specific T cells (VSTs) have a growing track record of safety and efficacy in stem cell transplantation against intractable viral infections, including adenovirus. For most of these protocols, lymphocytes are incubated with overlapping peptide pools representing the hexon antigen to expand the pool of VSTs, followed by assessment of adenovirus-specific T-cell activity by measuring interferon-gamma expression after adenovirus antigen stimulation.

There are three main sources of T cells in use with potential for application to solid organ transplantation: 1. The first approach is to identify and expand adenovirus-specific VSTs from the donor's stem cells.[77,78] This is a convenient potential source in the setting of

HSCT and has the advantage of being less likely to cause an alloreactive immune response. Donor cells can be isolated and banked at the time of stem cell donation for later use, if needed. This method allowed for relatively quick generation of VSTs, with resolution of adenovirus viremia in eight out of eight patients in whom it was tried and no evidence of GVHD.[79] However, for solid organ transplantation its use might be limited to patients receiving organs from living donors. 2. The second approach is to use a third party but related donor with haploidentical matching to the transplant recipient.[80] This method was tried successfully in recipients of unrelated umbilical cord blood transplants with adenovirus infection, either refractory to antiviral therapy or lack of availability of antiviral therapy. Reconstitution of ADV-specific immune response as measured by ELISpot correlated with virus clearance. This strategy could be applied to solid organ transplant recipients with a haploidentical donor and might be an important approach for pediatric patients, especially intestinal transplant patients who are at highest risk for adenovirus disease and who might have parents or older siblings who could donate PBMC. 3. The third and perhaps most attractive approach from a solid organ transplant perspective is the generation of so-called "off-the-shelf" VSTs from unrelated PBMC (peripheral blood mononuclear cells) donors, which are then expanded against a host of viral antigens (adenovirus, EBV, CMV, HHV-6, and BKV) to generate pentavalent T-cell lines.[81,82] HLA typing and virus-specific immune analysis is performed on the donors so that the HLA profile and efficacy against the five virus species is known at the time of banking. In a clinical trial, HSCT recipients with viral infections refractory to antiviral treatment or reduction in immune suppression received VSTs matched at one to seven of eight HLA alleles. Seven patients received treatment for persistent adenovirus, with a cumulative response rate of 71.4%. No correlation was observed between viral load reduction in patients who received low (1-3 alleles matched) versus high (4-8 matching alleles) HLA-matched VST lines. VSTs persisted for up to 12 weeks post infusion. This third party approach does not require a related donor as source of PBMC, and furthermore would allow a quicker response given VSTs are made ahead of time. This strategy could be applied to SOT patients of any age with intractable ADV infection (as well as CMV, EBV, BKV) and might prevent mortality associated with severe viral infections. Limitations include difficulty in finding appropriate VSTs for transplant recipients with uncommon HLA types. Although a hypothetical risk for triggering rejection exists, a signal for increased rates of GVHD was not seen in the HSCT population, and the VSTs are temporary. This hypothetical risk might be preferable to the rejection risk posed by long periods of time with reduced immunosuppression.

Several studies are ongoing to evaluate the safety, persistence and efficacy of viral antigen-specific CTL infusions in HSCT for therapy and prophylaxis of adenovirus, EBV, and CMV infections. CTLs are derived from original donors including cord blood and most closely, HLA-matched donors (clinicaltrials.gov). Although this intervention for adenovirus has not been studied in the solid organ transplant population, an initial study in adult solid organ transplant recipients with autologous EBV-specific CTL has been published and serves as proof of concept.[74,76,83] Theoretically, this therapy might be associated with increased risk of rejection or GVHD, but preliminary data have not reported this; non-specific alloreactive T cells could be selected out during CTL preparation to reduce this risk.[76] VST therapy may become a future component of adenovirus treatment.

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CONFLICT OF INTEREST

DF Florescu has received a research grant from Chimerix Inc and served as consultant for Chimerix Inc JM Schaenman has no conflict of interest to declare.

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