Adenoviruses are nonenveloped double-stranded DNA viruses that were first isolated from adenoidal cells in 1953 as part of a project searching for the virus causing the common cold. There are currently 57 recognized serotypes of human adenovirus, which can be divided into the subgroups (or species) A to G. There is tropism among these subgroups, with subgroups A and F typically causing infection of the gastrointestinal tract, and subgroups B, C and E showing tropism for the respiratory tract.1 Epidemic keratoconjunctivitis is predominantly caused by serotypes of subgroup D.

ADENOVIRUS INFECTIONS IN THE IMMUNOCOMPETENT HOST

Adenovirus is typically transmitted from person-to-person by respiratory droplets, and less commonly by the conjunctival route. The incubation period is relatively short, ranging between 2 and 14 days. Epidemiological data suggest that the majority of adenovirus infections occur in the first 5 years of life, with a peak incidence during the first 2 years.2,3 Adenovirus infections are common, accounting for approximately 5–15% of upper respiratory tract and approximately 5% of lower respiratory tract infections during childhood.4,5 In temperate climates, the peak incidence of adenoviral respiratory infections occurs during the winter months. In immunocompetent individuals, adenovirus infections are generally mild and self-limiting. Typical manifestations in immunocompetent children include pharyngitis, otitis media, bronchiolitis, gastroenteritis and keratoconjunctivitis. Primary adenovirus infection results in production of neutralizing antibodies, which are thought to confer lifelong immunity against the particular serotype. However, some individuals shed adenovirus in the stool for weeks to months; others develop longstanding asymptomatic infection with persistence of adenovirus in lymphoepithelial tissue. The latter phenomenon complicates the interpretation of results in the transplant setting, as discussed in the subsequent section.

ADENOVIRUS INFECTIONS IN THE IMMUNOCOMPROMISED HOST

During the last 2 decades, adenovirus has emerged as an important pathogen in immunocompromised individuals, particularly in the transplant setting. Adenovirus infection occurs in up to 40% of pediatric human stem cell transplant (HSCT) recipients, and in approximately 5–10% of solid organ transplant recipients.5–8 Further at-risk groups include children with primary or secondary immunodeficiency, including those with severe combined immunodeficiency or HIV infection, and children undergoing chemotherapy for malignancy. It is important to note that these patients frequently develop more severe manifestations, such as hemorrhagic cystitis and hemorrhagic enteritis, and, less commonly, encephalitis, pneumonia, hepatitis, nephritis and multiorgan failure. In the solid organ transplant setting, adenovirus disease typically affects the transplanted organ, the underlying mechanism for which is incompletely understood. Well-documented risk factors for adenovirus disease in the transplant setting include T cell depletion (eg, the use of T cell–depleted grafts, alemtuzumab or antithymocyte globulin), allogenic HSCT and young age.1,6,9

DIAGNOSTIC METHODS

A wide range of diagnostic methods is available for the detection of adenovirus infection. Conventional culture can take up to 5–10 days for a positive result; shell vial assays need shorter incubation times and have high sensitivity. Direct immunofluorescence staining provides more rapid results, and can be done on nasopharyngeal aspirates, bronchoalveolar lavage fluid and conjunctival scrapings. Serology has limited usefulness, as a positive result may simply reflect previous infection. Nevertheless, a significant rise in antibody titer in paired serum samples can sometimes be informative. Polymerase chain reaction, typically using primers that bind to conserved regions in the hexon gene, has high specificity and sensitivity, and is ideally suited for clinical samples from normally sterile sites, including blood and cerebrospinal fluid.

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Positive polymerase chain reaction results from upper respiratory tract specimens (ie, throat swabs and nasopharyngeal aspirates) and stool samples are difficult to interpret, as they may reflect viral shedding, rather than being indicative of adenoviral disease. Currently, most transplant centers routinely use real-time polymerase chain reaction, which allows the quantification of viral load in blood. Analysis of the viral load, particularly when done serially, can provide valuable information to guide treatment decisions. There is good evidence that a viral load >10^6 copies/mL in blood and/or a 10-fold rise are poor prognostic indicators. Measuring viral load can also help in the monitoring of response to treatment.1,9,10

**TREATMENT OF ADENOVIRUS DISEASE IN THE IMMUNOCOMPROMISED HOST**

The decision-making process for starting antiviral treatment for adenovirus in immunocompromised children is complex, and a detailed discussion is beyond the scope of this review, but can be found elsewhere.1 Factors that have to be taken into account include the age of the patient (prognosis is generally worse in children compared with adults), the type of transplant (prognosis is worse in HSCT than in solid organ transplant), the degree and duration of immunosuppression and the likely time frame for immune recovery. To date, there are no published randomized controlled trials on the treatment of adenoviral disease.

Most experts agree that in an asymptomatic patient, detection of adenovirus from nasopharyngeal aspirates, urine or stool samples does not necessarily warrant treatment. Conversely, most agree that treatment is indicated in a symptomatic patient in whom adenovirus is detected from the corresponding site of the disease in the absence of an alternative explanation. Currently, there is no consensus on the treatment of immunocompromised patients with adenovirus viremia alone. However, several centers have moved to using preemptive treatment for all patients in whom adenovirus is detected in blood (ie, irrespective of viral load), which appears to have led to a reduction in fatal outcome compared with historical figures.8,11

Currently, there are no antiviral agents that are approved for the treatment of adenovirus. Furthermore, in the absence of published randomized controlled trials the optimal antiviral agent for treating adenovirus disease remains uncertain. Antiviral agents that have been shown to have activity against adenovirus in vitro or in animal models include ganciclovir, zalcitabine, vidarabine and ribavirin. Successful treatment with ribavirin has been reported in a number of immunocompromised patients.12-14 However, more recent data have revealed that ribavirin only has activity against species C adenoviruses (serotypes 1, 2, 5, 6).15 The currently available data, despite their limitations, suggest that cidofovir is the most effective drug for the treatment of adenovirus disease. Recent, comparatively large studies using cidofovir in HSCT patients have reported a considerable reduction in adenovirus-related mortality compared with historical data.11,16 The optimal dosing regimen for intravenous cidofovir remains controversial. Notably, data to support the notion that a 1 mg/kg 3 times a week regimen is less nephrotoxic than the conventional 5 mg/kg once a week regimen remain limited.17 Recent reports on CMX001, an orally bioavailable lipid formulation of cidofovir that is potentially less nephrotoxic, have been encouraging, but more data are needed.18,19 A multicenter phase II/III study investigating CMX001 is currently underway.

There is good evidence that reducing immunosuppression has a substantial impact on the control of adenovirus disease in transplant patients, and should therefore be considered whenever possible.20-22 Directed immunotherapy, including adoptive transfer of adenovirus-specific T cells, in patients who show poor response to antiviral treatment is likely to play an increasing role in the future.21,22

**REFERENCES**