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# Respiratory Viruses: Influenza, RSV, and Adenovirus in Kidney Transplantation



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**Summary:** Although advances in immunosuppression and antimicrobial prophylaxis have led to improved patient and graft survival, respiratory viruses continue to be a common cause of morbidity and mortality in immunocompromised populations. We describe the clinical manifestations, diagnosis and treatment options for influenza, respiratory syncytial virus and adenovirus infection in the kidney transplant population.

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Advances in surgical technique, immunosuppression, and antimicrobial prophylaxis have led to improved patient and graft survival among renal transplant recipients. Nonetheless, infections remain a common complication of transplantation. Respiratory viral infections, in particular, are a common cause of morbidity and mortality. The incidence and seasonality of respiratory viral infections in transplant patients is reflective of what one would expect from healthy community contacts of the transplant patient. Influenza, human metapneumovirus and respiratory syncytial virus (RSV) typically occur most commonly from November through April in the Northern Hemisphere, whereas rhinovirus is more common in the fall and spring and parainfluenza virus (PIV) and adenovirus occur throughout the entire year. The rate of infection reflects that of age-matched immunocompetent

patients. Nonetheless, children become infected more commonly than adult transplant patients and severity typically is worse early post-transplant or with recent use of lymphocyte-depleting antibodies. Rhinovirus is consistently the most commonly identified respiratory viral infection and typically is associated with mild self-limited upper respiratory symptoms, although more serious complications can occur. After rhinovirus, coronavirus, PIV, RSV, and influenza are the most prevalent.<sup>1-6</sup>

Clinical presentation of respiratory viral infections reflects the typical symptoms experienced by non-immunocompromised patients, although atypical and asymptomatic presentations, particularly for rhinovirus, are seen more commonly in transplant recipients than in otherwise healthy individuals.<sup>2,7,8</sup> Respiratory viruses are detected five times more frequently when the recipient is having respiratory symptoms.<sup>2</sup> The rate of progression to lower tract disease is greater with certain viruses (ie, influenza, RSV, and PIV), with pediatric age group, early onset after transplantation, and greater net state of immune suppression (with highest rates with lymphodepletion).<sup>7</sup> Outcomes of infection are associated strongly with site of involvement, net state of immune suppression, and availability and use of antiviral agents. Patients who are more heavily immune suppressed, who have lower tract involvement, and who fail to receive timely antiviral therapy are more likely to experience a complicated course or die. In this review, we outline the optimal diagnostic strategies to detect respiratory viruses, the epidemiology of key respiratory viral infections in renal transplant patients, as well as available preventative and therapeutic strategies.

## DIAGNOSIS OF RESPIRATORY VIRAL INFECTIONS

There are few specific signs or symptoms that are unique to any one virus. In general, respiratory viral infections trigger the release of local and systemic cytokines that generally are responsible for the signs and symptoms of respiratory viral infections that

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patients may experience. Given that similar cytokines are released in response to the various respiratory viruses, the clinical picture often is clinically challenging to discriminate. As a result, a specific diagnosis of the infecting virus requires laboratory techniques. In general, a diagnosis can be made through detection of serologic responses to viral infection, detection of virally encoded proteins (antigen detection), detection of viral RNA/DNA, or through cell culture. Serology typically is limited to studies because it requires collection of acute (at time of illness) and convalescent (4-6 weeks after recovery) antibody titers. As such, it is of limited benefit for an acute diagnosis and transplant patients may fail to mount a normal antibody response. Historically, viral cultures were considered the gold standard, but the advent of molecular diagnostics has shown that viral cultures have variable sensitivity of certain viruses and may miss 5% to 70% of infections. The cultures are laborious and can take 2 to 7 days to become positive. Rapid shell vial culture techniques provide more rapid results and enhanced sensitivity by concentrating the virus and using antigen detection. Viral antigens can be detected by fluorescent antibodies applied to primary clinical specimens or culture, or by colorimetric detection of specific viral proteins. They generally have the advantage of providing relatively rapid results but may have limited sensitivity, particularly in the case of rapid antigen detection methods in adult transplant recipients. Molecular diagnostics (ie, polymerase chain reaction [PCR]) have become more widely available and have the advantage of allowing multiplexing and thereby detecting multiple viruses in one test. In addition, these assays generally have the highest sensitivity of available diagnostic testing. It is important to remember, however, that despite the excellent sensitivity, poorly collected samples may yield false-negative results and that patients with lower respiratory tract infection may have negative testing of upper respiratory tract specimens. Finally, the diagnostic sensitivity for individual viruses varies by the specific assay being used as well. As a result, diligent collection of specimens and knowledge of the limitations of the assay used by your laboratory are essential for interpreting the results.

For both influenza and RSV, a large number of rapid antigen assays are available for the rapid detection of the specific virus. Although a positive result generally represents true infection, these assays have poor sensitivity, particularly in the immunocompromised adult patient.<sup>9,10</sup> Multiplex reverse-transcriptase PCR (RT-PCR) tests are now the preferred way to diagnose influenza and parainfluenza in the transplant setting even though they do require more time, expertise, and specialized equipment.<sup>11</sup> Although very sensitive and specific, variations in the genome of the virus infecting an individual patient can yield false-negative results on

the RT-PCR tests.<sup>12</sup> For the other respiratory viruses, PCR is the preferred diagnostic strategy because of low yields with culture and limited fluorescent antibody availability. Adenovirus is unique in that, although PCR is the preferred diagnostic test, negative testing from the upper or lower airway may not exclude infections.<sup>13,14</sup> Some assays detect some but not all of the serotypes.<sup>14</sup> Furthermore, adenovirus replication can occur in the absence of clinical symptoms and positive testing must be contextualized with the patients presenting signs and symptoms. Adenovirus can cause a range of clinical diseases and respiratory involvement may occur late. As a result, detection of other compartments, including blood, urine, and cerebrospinal fluid, should be considered depending on the clinical presentation of the patient. Finally, unlike PCR assays for the other viruses, there are clear methodologies for quantitative viral load testing for adenovirus. Such quantitative viral load testing allows careful monitoring of trends to determine the need for antivirals, the case of persistent or increasing viral loads, and response to antiviral therapy. Finally, adenovirus diagnostics typically requires biopsies of involved tissues to assess for histopathologic changes compatible with adenovirus infection. Such pathology is helpful in distinguishing local infection (ie, adenovirus interstitial nephritis) from organ rejection or other pathology.<sup>14</sup>

## INFLUENZA

### Virology

Influenza is an orthomyxovirus that is typed as A, B, or C. Influenza A viruses are negative-sense, single-stranded, segmented RNA viruses further classified into subtypes on the basis of their surface hemagglutinins (HA; H1-16) and neuraminidases (NA; N1-9).<sup>15</sup> Antigenic drift occurs when there are small changes in individual amino acids of the HA or NA that develop over time that allow the virus to evade existing humoral immunity; such antigenic drift accounts for the need to update component viruses in influenza vaccines over time.<sup>15</sup> Alternatively, antigenic shift occurs when an entirely novel HA or NA circulates in the population; this often results in a pandemic, as the world recently experienced with the emergence of the novel A/H1N1 virus in 2009.<sup>16,17</sup>

### Epidemiology

In general, there have been few studies of influenza in solid-organ transplant recipients and most have focused on lung transplant recipients.<sup>18-35</sup> As a result, the epidemiology and significance of influenza in nonlung solid-organ transplant recipients is less well

understood. Nonetheless, the induction and maintenance immune suppression used is similar and directly impacts the number and function of lymphocytes.<sup>36</sup> Because lymphocytes are critical for the control and clearance of influenza,<sup>37</sup> all organ transplant recipients are at increased risk of influenza infection and its complications.<sup>38</sup>

Seasonal influenza typically is associated with a self-limited infection, typically of the upper airway.<sup>37</sup> Immunocompromised patients with influenza had more severe disease/complications, longer viral shedding, and more antiviral resistance, although showing fewer clinical symptoms and signs on clinical assessment.<sup>39</sup> Influenza may affect up to 48% of transplant patients during the winter months<sup>19,29</sup>; typically, however, somewhere between 1% and 4% of patients are infected annually.<sup>20,26</sup> More severe infections, including pneumonia, and an increased risk of bacterial and fungal superinfections have been described in recipients of solid-organ transplant recipients.<sup>19,20,29,38</sup>

### Clinical Manifestations of Influenza

The best data on influenza in transplant patients comes from a large study that collected data retrospectively on 115 cases of novel influenza A/H1N1 among US and Canadian transplant recipients (38 kidney, 23 liver, 22 heart, 18 lung, and 14 other transplant recipients).<sup>40</sup> The median time since transplant was 3.8 years. Cough (91% for adult and 92% for pediatric) and fever (80% for adult and 95% for pediatric) were the most common symptoms, although they were less common than in immunocompetent patients. Likewise, symptoms commonly associated with influenza such as myalgia (52% in adult and 49% in pediatric) and sore throat (35% for adult and 59% for pediatric) occurred infrequently in the transplant population. Sixty-one percent were lymphopenic at the time of presentation and 65% required hospitalization.<sup>40</sup> Twenty-five percent developed pneumonia, typically viral pneumonia, and 13% were admitted to the intensive care unit.<sup>40</sup>

### Prevention

Influenza can be prevented through the use of vaccination or antiviral medications. The influenza vaccination currently is recommended for all transplant patients and their close contacts by the Advisory Committee on Immunization Practices, the American Society for Transplantation Infectious Diseases Community of Practice, and the International Society for Heart and Lung Transplantation.<sup>41–43</sup> Because of the risk of replication and disease, use of the live attenuated inhaled vaccine is contraindicated in transplant recipients and is discouraged for close contacts.<sup>41,43</sup> If

there is a limited supply of vaccine and only live attenuated vaccine is available, use in close contacts can be considered with strict attention to good hand hygiene practices and minimization of contact with secretions (eg, sharing of foods and drinks, direct saliva contact).<sup>41</sup>

Unfortunately, the rate of influenza vaccination among transplant recipients and their close contacts remains low in part because of outdated concerns by some clinicians about the safety and efficacy of the inactivated injectable vaccine. To date, there have been more than 40 studies of seasonal and pandemic vaccines in transplant patients; these recently were reviewed in detail.<sup>41,44</sup> Although the relative vaccine efficacy has been variable, the safety of the intervention is without a doubt. There is no associated increased risk of allograft rejection after influenza vaccination—as such, patients should be encouraged to receive the vaccine annually and do not need any special monitoring post-transplant.<sup>41,43,44</sup>

The influenza vaccine typically has slightly reduced efficacy compared with healthy controls, whether measured by antibody or T-cell responses to mitogen.<sup>41,43–45</sup> Although the evidence is even more limited among transplant recipients, injectable vaccine is effective in preventing laboratory-confirmed influenza, even in patients with limited serologic response to vaccine.<sup>46</sup> The efficacy of vaccine likely depends on lymphopenia and the net state of immune suppression in the individual patient; patients on enhanced immune suppression, vaccinated early post-transplant, and who recently have received lymphocyte-depleting agents and/or rituximab may have reduced responses to vaccine and alternative preventative strategies can be considered.<sup>41,43,44</sup> Because of this slightly decreased response to vaccine, all close contacts of transplant patients, including associated health care workers, should be vaccinated. This may reduce the risk of disease exposure by protecting those around the patient.<sup>41,43</sup>

In patients with contraindications to vaccination or in those individuals who would be predicted to have poor response to vaccine (enhanced immune suppression, recent lymphodepletion, or use of rituximab), the use of antiviral prophylaxis could help protect the individuals from influenza. Because of widespread resistance to the M2 inhibitors, currently only neuraminidase inhibitors are recommended for prophylaxis. Oseltamivir is effective for prophylaxis and generally is well tolerated in immunocompetent and immunocompromised patient groups.<sup>28,47–56</sup> A recent prospective study of seasonal oseltamivir 75 mg once a day versus placebo documented a marked reduction of RT-PCR–proven influenza infections (5 versus 20 infections) in individuals receiving prophylaxis during the 12-week period of peak influenza circulation in the

community.<sup>57</sup> Several immunocompetent patients have developed oseltamivir resistance after being placed on oseltamivir 75 mg once a day prophylaxis after exposure to an index case; typically, antivirals were started more than 24 hours after exposure and ongoing asymptomatic replication was possible.<sup>58</sup> As such, if postexposure prophylaxis is considered in an immunocompromised patient, many would recommend use of full treatment doses (twice daily) for 5 to 10 days after exposure to prevent both clinically significant infection and emergence of antiviral resistance.<sup>18,58</sup>

Strict attention to infection control practices should be used in all settings where transplant patients receive care. This is important because nosocomial transmission of influenza, and other respiratory viruses, has been well documented in transplant settings. This transmission can occur from infected patients, visitors, or clinical staff. Current Centers for Disease Control guidelines are updated constantly and should be reviewed annually and with the outbreak of any new virus.

Finally, influenza has been documented to be transmitted from organ donors to recipients, typically through lung transplantation.<sup>21,59</sup> It is important to recognize that individuals who are severely ill with influenza may become transiently viremic, particularly if infected with a new or animal-derived strain of influenza.<sup>18,60</sup> As such, donors with documented influenza replication should not be used because lung donors and patients at risk for viremia should not be used as donors.<sup>18</sup> Donor-derived influenza transmission is likely to result in an atypical clinical presentation and testing of nontypical specimens (stool, urine, and blood) should be considered.<sup>18</sup> If donor-derived disease is considered, it should be reported to the local organ procurement organization immediately to alert the clinicians caring for other recipients. If organs are used from a donor who is confirmed to be infected with influenza, use of systemic active antivirals at full treatment dose for 5 to 10 days post-transplant should be considered.<sup>18</sup>

## Treatment

Two classes of antivirals currently are available to treat influenza: M2 inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir, laninamivir [in Japan only], and peramivir [in China, Japan, South Korea, and the United States only]). Widespread resistance among all circulating strains of influenza currently precludes the use of M2 inhibitor resistance at this time.<sup>61,62</sup>

Neuraminidase inhibitors are active against most influenza A and B viruses. Rarely, resistance may emerge, limiting the efficacy of individual neuraminidase inhibitors, typically during the course of treatment

of influenza in the setting of prolonged shedding.<sup>39,63,64</sup> Resistance to neuraminidase inhibitors can occur secondary to mutations in the neuraminidase or hemagglutinin gene, or both.<sup>65</sup> The specific mutation determines which antivirals the specific virus is resistant to and the degree of cross-resistance.<sup>65</sup> Most recent strains have been resistant secondary to a H274Y mutation in the NA gene associated with significant increases in the 50% inhibitory concentrations of oseltamivir and, to a lesser extent, of peramivir.<sup>65</sup> Different mutations may occur, especially if antivirals other than oseltamivir are used in the patient. Resistance should be considered in any patient who develops influenza after recent exposure to antiviral agents, used as either treatment or prophylaxis, or if there is failure to improve clinically despite 5 to 7 days of antiviral therapy.<sup>65</sup> In addition, patients with prolonged shedding should be tested serially to detect emergence of resistance.<sup>65</sup> When testing for resistance, either phenotypic assays or assays that genotypically can detect a wide range of mutations (ie, not just the H274Y mutation) should be used.<sup>65</sup> As soon as resistance is considered, switching to an agent with predicted activity, typically zanamivir, should be considered.

There have been no prospective studies of the optimal timing, dose, or duration of antivirals in lung transplant recipients.<sup>7,66</sup> A number of studies have reviewed the outcomes of antiviral therapy retrospectively, with most involving lung transplant recipients; in general, none of these studies included serial quantitative assessments of viral replication and few studies had robust serial qualitative assessments of viral replication.<sup>3,4,26,67,68</sup> In general, antiviral therapy appears to decrease mortality and reduces the risk of the development of viral pneumonia if started early; delayed initiation of therapy is associated with a higher frequency of progression to pneumonia and death in most studies.<sup>3,4,67,68</sup> There appears to be benefit in these patients even if symptoms have been ongoing for longer than 48 hours. As a result, all transplant patients with suspected influenza should be initiated on antiviral therapy irrespective of the duration of symptoms; therapy should not await diagnostic studies. Furthermore, because patients with lower tract involvement may have negative nasal swab testing, even by PCR, therapy should continue until influenza has been ruled out in both the upper and lower airway.

In general, oseltamivir has been well tolerated. Shedding may be prolonged and, as a result, longer courses than the usual 5-day course likely are required in transplant recipients.<sup>4,69</sup> Most experts recommend treating until eradication of replication is confirmed.<sup>18,66,70</sup> Few studies have investigated the safety and efficacy of inhaled zanamivir or intravenous peramivir in transplant patients. Nonetheless, these



should be considered as alternative therapies to oseltamivir. If intravenous therapy is believed to be needed, intravenous peramivir should be given 600 mg/d, or the renally adjusted dose, for 5 to 10 days; single-dose intravenous peramivir is not appropriate for transplant patients.

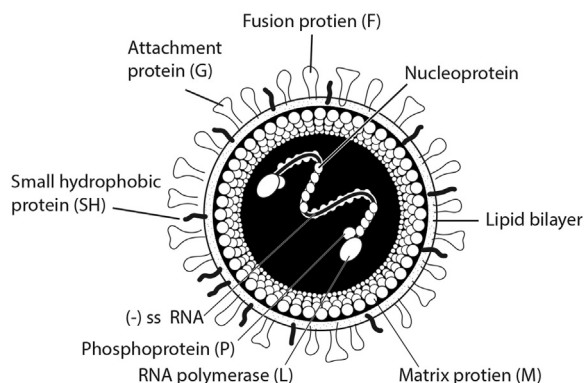
## RESPIRATORY SYNCYTIAL VIRUS

### Virology

RSV is an enveloped, single-stranded, negative-sense RNA virus. It initially was isolated in chimpanzees in 1956, and then later in human infants.<sup>71,72</sup> It is a member of the Paramyxoviridae family. Human beings and chimpanzees are the only host for RSV and there are two antigenic types: A and B. There may be co-circulation of viruses with one subtype predominating.<sup>71</sup> The strains have 81% nucleotide identity.<sup>73</sup> RSV lacks hemagglutinin and neuraminidase activity, and its surface has transmembrane surface glycoprotein spikes<sup>73</sup> (Fig. 1). The genome contains 10 genes encoding proteins, with one gene encoding two overlapping reading frames and a second gene having a second start codon for the protein Gs. The proteins encoded include a transcription processivity factor (M2-1), a transcription regulatory protein (M2-2), and the matrix protein. There are proteins that along with M2-1 are associated with the RNA-containing nucleocapsid complex. These proteins are nucleoprotein, phosphoprotein, and polymerase proteins. There are also three transmembrane surface proteins that are fusion, attachment glycoprotein, and the proposed small hydrophobic viroporin protein. Gs is a truncated form of G that is secreted.<sup>71,73,74</sup>

### Epidemiology

RSV is a ubiquitous virus. It can infect the upper and lower respiratory tracts. RSV infects all ages, with infants and young children being the most affected. It



**Figure 1.** Respiratory syncytial virus.

is suspected that by 2 years of age most children will have experienced at least one RSV infection.<sup>75</sup> In the United States the major RSV season typically runs from November to late March or early April. Although children are infected most often compared with adults, RSV infection can cause severe illness with high rates of morbidity and mortality in the elderly and immunocompromised, in particular, patients with lymphopenia.<sup>10,76,77</sup> In the immunocompromised population, including stem cell transplant and solid-organ transplant (SOT) patients, RSV infection may progress to severe and life-threatening lower respiratory tract infection.<sup>76</sup> At one center, SOT infection accounted for approximately half of their immunocompromised population infections.<sup>78</sup> Depending on the transplanted organ, there is a wide range of mortality rates (0.4%-40%) in patients with solid-organ transplantation.<sup>76,77,79</sup> The majority of the published literature regarding RSV infection and SOT has been in lung transplant patients. However, there are increasing data in renal transplant patients. Even without specific therapy, mortality from RSV infection in adult renal transplant patients has been low.<sup>80,81</sup>

### Clinical Manifestations of RSV

Symptoms of infection with RSV are similar to other respiratory viruses. Symptoms often may include fever, cough, nasal and sinus congestion and pain, labored breathing, headache, and even wheezing if a lower respiratory tract infection is present. Fever is present in 35% to 58%, cough is present in approximately 90%, and rhinorrhea is present in 53% to 89% of patients.<sup>73,78,82</sup> Imaging with radiographs or with computed tomography (CT) can yield a variety of findings. A case series of solid-organ transplant RSV infection, including kidney, described roentgenograms with normal findings, unilateral and focal consolidation, or diffuse interstitial opacities. Ground-glass opacities, lung nodule diffuse disease, and consolidation may be present on CT. Pleural effusions and small cavitations also may be observed.<sup>78</sup> However, CT abnormalities may be observed in only 28% to 90% of patients.<sup>77,78,83</sup> The duration of viral shedding in healthy adults is approximately 4 days, however, in SOT and stem cell transplant populations it averages approximately 20 days and can be more than 60 days.<sup>78,84</sup>

### Treatment of RSV Infection

The optimal treatment of RSV infection in the renal transplant population is not well defined. Supportive therapy remains the mainstay of therapy.<sup>76</sup> In the stem cell transplant population the use of therapy with ribavirin remains controversial.<sup>76</sup> However, there are

data to suggest that treatment with aerosolized ribavirin with or without an immunomodulator such as intravenous immunoglobulin (IVIG) can provide benefit, especially when treating upper respiratory tract disease to prevent progression to lower respiratory tract disease.<sup>85–87</sup> There also are data supporting oral ribavirin use in the stem cell transplant population.<sup>88</sup> In the solid-organ transplant population, treatment with antiviral agents and immunomodulators remains undefined.<sup>89</sup> Much of the data regarding SOT and RSV therapy is in lung transplant patients. There is a paucity of data in renal transplant patients. In a subgroup of six renal transplant patients (one liver/kidney, one pancreas/kidney), three of six patients were treated using either inhaled (two of three) or oral (one of three) ribavirin. The liver/kidney patient did not receive any antiviral therapy. Only one patient received inhaled ribavirin and IVIG. The kidney/pancreas patient received inhaled ribavirin and palivizumab, a humanized monoclonal antibody against RSV. One kidney transplant patient received inhaled ribavirin, IVIG, and palivizumab. None of the six patients died. Five of the patients were on prednisone, tacrolimus, and mycophenolate mofetil. One patient was on mycophenolate mofetil and sirolimus.<sup>78</sup> The duration of ribavirin (inhaled and/or oral) is generally 5 to 14 days.<sup>78,86,88</sup> The data remain inconclusive on the outcome and mortality benefit of palivizumab as treatment for RSV in the stem cell and SOT population.<sup>84,86,90–93</sup> Duration of IVIG therapy (500 mg/kg every 48 hours) generally ranges from 1 to 6 days.<sup>84,87</sup> Table 1 shows common treatment considerations in patients with moderate to severe infection caused by RSV.

## ADENOVIRUS

Adenovirus (AdV) originally was isolated in 1953 from human adenoid samples, and soon after was recovered from patients with respiratory disease. More than 60 different types have been identified as causing several types of clinical syndromes including upper and lower respiratory tract infection, fulminant hepatitis, and epidemic keratoconjunctivitis, as well as disseminated disease and transplanted kidney infection in kidney transplant recipients.<sup>73,94</sup> In contrast to other

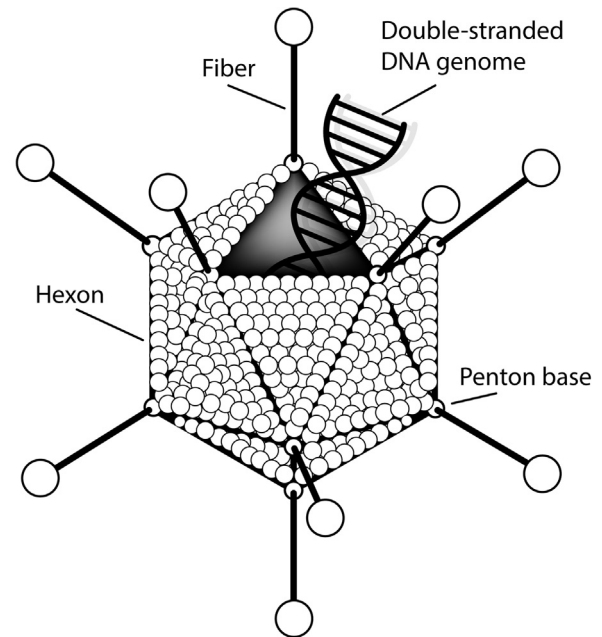


Figure 2. Adenovirus.

viral infections such as RSV and influenza, there is no seasonal predilection for adenoviral infection.<sup>13,14</sup>

## Virology

Adenovirus is a nonenveloped, double-stranded DNA virus of the family *Adenoviridae*. It is characterized by an icosahedral capsid composed of three major proteins called hexon, penton, and fiber. A total of 252 capsomere subunits form 20 surfaces and 12 vertices where penton and fiber proteins are located. The fiber protein is important for interaction with cellular receptors<sup>73</sup> (Fig. 2). There are seven subgroups, termed A through G, and 52 serotypes, in which there are different genotypes identified within the serotypes.<sup>14</sup> Adenovirus is ubiquitous, with subtypes A, B, C, D, and E. Adenovirus is known to circulate globally and be implicated in outbreaks.<sup>95</sup> Tissue tropism accounts for certain subgroups and serotypes correlating with different disease manifestations (Table 2). For example, disseminated disease has been associated with subgroups A, B2, C, and F.<sup>13,14</sup> Although subtype D is associated for the most part with epidemic keratoconjunctivitis, it has been shown to cause disseminated disease in a renal transplant patient.<sup>96</sup> Hemorrhagic cystitis is associated with subgroups B1 and B2 and serotypes 7, 11, 34, and 25; respiratory tract disease is associated with subgroups B1, B2, C, and E, and serotypes 3, 4, 7, 11, 16, 21, 34, 35, and 50; and gastrointestinal disease is associated with subgroup F, serotypes 40, 41, and 52.<sup>13,14</sup>

**Table 1.** Common Treatment Considerations for Moderately to Severely Ill Patients With RSV Infection

Inhaled ribavirin <sup>114</sup> 2 g inhaled over 2-3 hours every 8 hours or 6 g over 18 hours daily for 7-10 days or
Oral ribavirin <sup>88</sup> 600-800 mg orally twice daily for 5-10 days
In addition to one of the earlier-described options, also may use IVIG 500 mg/kg intravenously every other day for 1-6 days

**Table 2.** Adenovirus Serotypes and Associated Disease

Subgroup	Serotypes	Common Presentation
A	12, 18, and 31	Disseminated disease (31)
B1	3, 7, 16, 21, 50, and 55	Respiratory tract disease Hepatitis (3,7) Myocarditis (7,21) Hemorrhagic cystitis (7) Conjunctivitis (7) Meningoencephalitis (7)
B2	11, 14, 34, and 35	Respiratory tract disease Hemorrhagic cystitis (11,34,35) Disseminated disease (11,34,35)
C	1, 2, 5, and 6	Respiratory tract disease Conjunctivitis (1,2,5) Hepatitis (1,2,5) Meningoencephalitis (2,5) Disseminated disease (1,2,5)
D	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, and 56	Keratoconjunctivitis (8,19,37)
E	4	Respiratory tract disease
E	4	Conjunctivitis
F	40, 41	Gastroenteritis Disseminated disease (40)
G	52	Gastroenteritis

Adapted with permission from Ison et al<sup>13</sup> and Echavarría et al.<sup>115</sup>

Numbers in parentheses represent most predominant serotypes associated with.

## Epidemiology

By the age of 5 years, 70% to 80% of individuals have serologic evidence of past exposure, and by 10 years of age most individuals have evidence of exposure.<sup>73,97</sup> Exposure may occur through different means because AdV may cause several disease manifestations. Transmission can occur through fomites, aerosolized droplets, fecal-oral spread, or infected tissue or blood. In addition, latent infection can occur. AdV has been shown to reside in lymphoid tissue and renal parenchyma, and may be reactivated in immunocompromised patients.<sup>95,98</sup>

AdV infection or detection can occur at any time in the post-transplant period, even as little as 1 week post-transplant in SOT recipients.<sup>99</sup> Asymptomatic carriage and shedding of AdV has been noted to occur for weeks to months in gastrointestinal disease, prolonged periods with AdV viruria, and even over a year of asymptomatic detection of AdV DNAemia in renal transplant patients.<sup>73,96,100</sup> In kidney transplant recipients, risk factors for AdV infection include pediatric age, use of antilymphocyte antibodies, and donor-positive/recipient-negative AdV serostatus. Asymptomatic viremia is common in SOT recipients, with one study showing a rate of 6.5% in renal transplant patients, but viremia alone is not associated with risk of progressive disease, and routine screening for AdV DNAemia is not recommended.<sup>13,95,99</sup>

## Clinical Manifestations Associated With Adenovirus

Adenovirus may be detected as asymptomatic shedding, such as in stool or urine, or in the presence of clinical disease, therefore it is important to distinguish true disease from asymptomatic shedding. In the immunocompromised populations, particularly in SOT patients, AdV typically involves the transplanted organ. Although infection tends to be less common and serious in renal transplant patients, mortality rates of up to 18% have been reported in renal transplant patients, and these patients have been shown to develop several AdV clinical diseases.<sup>73,101</sup> Common presentations of disease in renal allograft patients include hemorrhagic cystitis and interstitial nephritis.<sup>102</sup> Symptoms of hemorrhagic cystitis typically include fever and hematuria, with or without dysuria or suprapubic pain. In interstitial nephritis, allograft biopsy findings are variable and can include interstitial infiltrates of lymphocytes, monocytes, plasma cells, and neutrophils. Viral inclusions may be observed, and granulomas may be present as well. The granulomatous changes and viral cytopathic effects can serve as an important clue in differentiating AdV infection from acute rejection. There is tubular cell necrosis with viral cytopathic effects, although the glomeruli appear to be free of inflammation. The blood vessels, for the most part, are free of inflammation, but rare findings of fibrin accumulations in the arterial walls has been



described.<sup>14,96,103</sup> Many of these infections are self-limiting, however, necrotizing tubulointerstitial nephritis, allograft dysfunction leading to dialysis, and obstructive uropathy can occur.<sup>95</sup> Adenovirus upper respiratory tract disease, pneumonitis, gastrointestinal disease, and disseminated disease, in which two or more organs are effected, all have been described in renal transplant recipients as well.<sup>96,100,102</sup>

## Treatment

Asymptomatic viremia may occur frequently and most AdV infections in renal transplant patients are minor and self-limiting. The mainstay of treatment remains reduction of immunosuppression, although the optimal changes to the immunosuppressive regimen are not known.<sup>14</sup> There remains no standard or consensus on the optimal antiviral medication regimen. The guanoside analog ribavirin has not been shown to be efficacious in AdV infection and is not recommended.<sup>13,104</sup> In vitro activity of ganciclovir against AdV has been reported, as have case reports in treating AdV infections.<sup>105–107</sup> Although there are no prospective randomized clinical trials, there are data to support the use of the nucleoside analog of cytidine monophosphate, cidofovir, for AdV infection. It has become the standard of care in some medical centers.<sup>14</sup> Cidofovir acts by promoting viral DNA chain termination because it is taken up as a substrate by the viral DNA polymerase.<sup>101</sup> In immunocompromised populations cidofovir has been noted to decrease viral load. The decrease in viral load in turn also has correlated with clinical improvement.<sup>14,95,100,108</sup> There can be a significant risk of nephrotoxicity (up to 50%) with the use of cidofovir. The other significant side effects that should be monitored with the use of cidofovir include neutropenia (up to 25%), decreased intraocular pressure (24%), anterior uveitis (11%), and metabolic acidosis.<sup>14,109</sup> Currently, two main dosing regimens are supported by the literature. The first is a three times weekly regimen dosed at 1 mg/kg intravenously and the second is 5 mg/kg intravenously weekly. Initial dosing should continue for a minimum of 2 weeks followed by cidofovir 5 mg/kg intravenously every other week with monitoring for resolution of symptoms and three negative AdV PCRs from the originally affected sites.<sup>13,14,104,110</sup> Dosing adjustments must be made for renal function. Hemodialysis should be avoided for 1 hour before and 4 hours after dosing to allow for intracellular distribution of cidofovir.<sup>14</sup> A lipid-linked derivative of cidofovir, brincidofovir (formerly CMX001; Chimerix, Durham, NC), has shown promise in its in vitro and in vivo activity against AdV. Brincidofovir's lipid moiety allows it to be administered orally rather than intravenously, allows it to enter cells readily, and, once the lipid moiety is cleaved,

does not allow it to leave the cells easily.<sup>101,111</sup> Importantly and surprisingly given the parent compound, brincidofovir is non-nephrotoxic.<sup>112,113</sup> Use of IVIG or lymphocyte infusion remains controversial because it does not appear to have a clear benefit at this time.<sup>13,95,96,100,102,104</sup>

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