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

Dana J. Hawkinson, MD,[*] and Michael G. Ison, MD, MS, FIDSA, FAST[†,‡,§]

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.[1–6]

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.[2,7,8] Respiratory viruses are detected five times more frequently when the recipient is having respiratory symptoms.[2] 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).[7] 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

[*]*Division of Infectious Diseases, University of Kansas Medical Center, Kansas City, KS.*
[†]*Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL.*
[‡]*Division of Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, IL.*
[§]*Transplant and Immunocompromised Host Infectious Diseases Service, Northwestern University Comprehensive Transplant Center, Chicago, IL.*

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Address reprint requests to Dana J. Hawkinson, MD, Division of Infectious Diseases, University of Kansas Medical Center, 3901 Rainbow Blvd, Mailstop 1028, Kansas City, KS 66160. E-mail: dhawkinson@kumc.edu.

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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.[9,10] 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.[11] 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.[12] 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.[13,14] Some assays detect some but not all of the serotypes.[14] 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.[14]

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).[15] 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.[15] 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.[16,17]

Epidemiology

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