UC Irvine

UC Irvine Previously Published Works

Title

Community-acquired respiratory viruses in solid organ transplant.

Permalink

https://escholarship.org/uc/item/8m00w4xg

Journal

Current Opinion in Organ Transplantation, 24(4)

Authors

Nam, Hannah
Ison, Michael

Publication Date

2019-08-01

DOI

10.1097/MOT.0000000000000663

Peer reviewed

Community Acquired Respiratory Viruses in Solid Organ Transplant

Hannah H Nam[1], **Michael G Ison**[1]

[1]Northwestern University Feinberg School of Medicine

Abstract

Purpose of review: Respiratory viruses are common in solid organ transplant (SOT) recipients and recognized as a significant cause of mortality and morbidity. This review examines the literature on influenza and non-influenza viruses in the SOT recipient.

Recent findings: Advances in immunosuppression and antimicrobial prophylaxis have led to improved patient and graft survival, yet respiratory viruses continue to be a common cause of disease in this population. Influenza viruses have received top priority regarding prevention and treatment, while advances in molecular diagnostic tests detecting an array of other respiratory viruses have expanded our knowledge about the epidemiology and impact of these viruses in the both the general population and SOT patients. Effective treatment and prevention for non-influenza respiratory viruses are only emerging.

Summary: Respiratory viruses can contribute to a wide array of symptoms in SOT, particularly in lung transplant recipients. The clinical manifestations, diagnosis, and treatment options for influenza and non-influenza viruses in SOT patients are reviewed. PCR and related molecular techniques represent the most sensitive diagnostic modalities for detection of respiratory viruses. Early therapy is associated with improved outcomes. Newer classes of antivirals and antibodies are under continuous development for many of these community acquired respiratory viruses.

Corresponding author: Michael G. Ison, MD, MS, Northwestern University Feinberg School of Medicine, 645 N Michigan Avenue Suite 900, Chicago, IL 60611, USA, Office: 312-695-4186, Fax: 312-695-5088, mgison@northwestern.edu.
Co-author: Hannah H. Nam, MD, Northwestern University Feinberg School of Medicine, 645 N Michigan Avenue Suite 900, Chicago, IL 60611, USA

Introduction

Advances in surgical technique, immunosuppression, and antimicrobial prophylaxis have led to improved patient and graft survival among solid organ transplant (SOT) recipients. Nonetheless, infections remain a common complication in transplantation. Community acquired respiratory viral (CARV) infections, in particular, are a common cause of morbidity and mortality.

Since multiplex nucleic acid testing (NAT) has been widely available in general health care in resource-rich countries, a wide range of CARVs have been attributed to disease among SOT recipients. This includes a wide array of RNA viruses such as influenza A and B, respiratory syncytial virus (RSV; recently renamed human orthopneumovirus), parainfluenza virus (PIV), rhinovirus, human metapneumovirus (hMPV), and coronavirus (1). In addition, DNA viruses, such as adenovirus, polyomavirus, and bocavirus, may also be responsible for cases of respiratory tract infection. CARVs have been attributed to a range of diseases from mild congestion and rhinorrhea to more severe tracheobronchitis and pneumonia (1, 2). SOT recipients often present with mild or atypical symptoms and fever may be absent, leading to delayed diagnosis.

The rate of progression to LRTI is greater with certain viruses such as influenza, RSV, and PIV, with the pediatric age group, early after transplantation, in lung transplant recipients, and with a greater net state of immunosuppression, especially when there is significant lymphocyte depletion (3). The outcomes of respiratory infections are strongly associated with the site of involvement, net state of immunosuppression, lower respiratory tract involvement and early initiation of antiviral therapy. Patients who are heavily immunosuppressed, have LRTI, and those 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 SOT recipients, as well as available preventative and therapeutic strategies.

Epidemiology and Diversity of CARVs

The incidence and seasonality of respiratory viral infections are reflective of what one would expect from healthy community contacts of the transplant recipient. Influenza, human metapneumovirus, and respiratory syncytial virus (or human orthopneumovirus) typically occur most commonly from November through April in the Northern hemisphere, whereas rhinovirus is more common in the fall and spring while parainfluenza virus (PIV) and adenovirus occur throughout the entire year. Severity is typically worse early post-transplant or with recent use of lymphocyte depleting antibodies. Rhinovirus is consistently the most commonly identified respiratory viral infection and is typically associated with mild self-limited respiratory symptoms, although more serious complications can occur. After rhinovirus, coronavirus, PIV, RSV, and influenza are the most prevalent. Prolonged asymptomatic shedding, especially with coronavirus and rhinovirus, is common in SOT recipients.

Diagnosis

Clinically it is challenging distinguish influenza from infections caused by other viruses based on clinical symptoms alone (4). Since SOT patients are on medications that modulate the inflammatory response, symptoms associated with CARVs are typically less severe and less common than in normal healthy hosts (5), especially in patients with severe lymphopenia (6). No single symptom or symptom complex correlates sufficiently to influenza to be able to make a diagnosis clinically (4); with frequent co-circulation of other respiratory viruses that are known to cause influenza-like illness. Further, even in patients infected with influenza, cardinal symptoms may be absent or exceptionally short lived. In the largest study to date, fever was present in approximately 60%, sore throat was present in about 35% and myalgias in less than 40% of infected SOT recipients at presentation.(7)

Current microbiologic testing required to definitively diagnose influenza include serology, rapid antigen detection, direct fluorescent antibodies (DFA), culture, and molecular diagnostics (8). Molecular diagnostics such as PCR are considered the gold standard for diagnosis of multiple respiratory viruses, due to their enhanced sensitivity and specificity as well as speed of diagnosis. Those that detect a wide range of pathogens are preferred and have been found consistently superior to other diagnostic methods in transplant populations (8, 9). While PCR has excellent sensitivity, poorly collected specimens can result in false negative results. Likewise, patients with lower tract infection may have negative nasal swab testing in up to 20% of cases; as such, sampling of the lower tract may be required to establish a diagnosis. Serology lacks sensitivity in transplant patients. Rapid antigen testing is fast, but only are available for influenza and lack sensitivity (40–69%) in novel pandemic viruses (10, 11). While DFA is rapid and effective, many viruses do not have commercially available antibodies, limiting the sensitivity of these methods (9).

Influenza Viruses

There are four species of influenza virus that circulate in humans: A, B, C and D. Influenza A and B are responsible for seasonal epidemics of the disease. Rates of infection among SOT recipients vary depending on the specific population, type of immunosuppression used, and circulating influenza strain. Likewise, seasonal variability in vaccine efficacy contributes to the variability of rates in the SOT population.

Seasonal influenza is typically associated with a self-limited infection, usually of the upper airway, in otherwise healthy patients and most non-lung SOT recipients (12). In general, there are been few studies of influenza in SOT recipients with most of the studies focused on lung transplant recipients (3, 13–17). Influenza may affect up to 48% of transplant patients during the winter months (16), with mortality ranging from 2–4% (7, 18). Even higher mortalities of up to 21% were observed in lung transplant recipients with preexisting grade 3 bronchiolitis obliterans syndrome (BOS) during the 2009 H1N1 epidemic(18, 19). Donor-derived influenza is a rare event that is of particular concern in lung transplant recipients (14).

The epidemiology and significance of influenza in nonlung SOT recipients is less well understood; in general, while severe disease can occur, most non-lung SOT recipients will have milder disease, particularly when treated early. Influenza in the SOT population has been associated with the development of acute rejection, and in the case of lung transplant with chronic rejection, or chronic lung allograft dysfunction (CLAD) (17, 20–22). Typically, progressive and severe complications such as viral pneumonia, secondary bacterial and fungal pneumonia, and extrapulmonary complications are seen more commonly amongst lung transplant recipients (23).

Prevention and Treatment of Influenza

Prevention of infection is best achieved through respiratory hygiene, vaccination of recipients and their close contacts, and appropriate contact and droplet precautions in the hospital setting. Data on immunogenicity of vaccines is thought to be reduced in SOT patients, especially early post-transplant (24–26). Existing data suggests that responses are only minimally reduced compared to healthy controls and are associated with reduction in infection and morbidity and mortality when infection develops despite vaccination (7, 27). Efforts to improve on influenza vaccine have led to studies of adjuvanted vaccines, intradermal vaccines, prime-boost approaches and the use of high dose influenza vaccine. While results from most studies showed modest benefits with alternative vaccine strategies, a single center study found that high dose vaccine was significantly more immunogenic than standard dose vaccines (28). Post-exposure prophylaxis with a lower prophylactic dose is not recommended, but rather empiric treatment with therapeutic dosing of oseltamivir should be considered in high risk patient such as those with lung transplant or on rejection treatment as long as started within 48 hours of a confirmed significant exposure. Additionally, in patients predicted to have poor responses or when vaccine is not available, seasonal prophylaxis can be considered and has been demonstrated to be associated with significantly lower rates of culture or PCR-confirmed influenza infections (23).

To date, there are no prospective studies of antiviral therapy specifically in SOT recipients (29). Therefore, the optimal regimen and duration of antiviral therapy has been incompletely defined; likewise the role of combination therapy has yet to be studied. Available data for neuraminidase inhibitors (NAIs), though, do strongly suggest early therapy may be associated with improved outcomes (3, 7, 30). As such, any SOT patient presenting with symptoms suggestive of influenza should be started on appropriate antiviral therapy prior to diagnostic test results, even if the symptoms have been going on for more than 48 hours. Longer durations of therapy are recommended by many experts and our approach is to treat for at least 10 days, with longer durations with patients with continued symptoms and ongoing evidence of viral replication.

Novel antiviral therapies for the treatment of influenza include polymerase inhibitors such as favipiravir, pimodivir, and baloxavir. Baloxavir was recently globally approved for treatment of uncomplicated influenza (31–34). Studies in the SOT population are currently lacking. Given the high rate of resistance emerging with baloxavir therapy in healthy patients, it would be predicted that resistance emergence would be a significant concern among immunosuppressed patients; as such, baloxavir monotherapy is not recommended for

transplant patients. Combination therapy has not been studied in transplant patients but could be considered in patients presenting with severe illness; such approaches likely will require repeat dosing every 3 days as is being studied in hospitalized patients (ClinicalTrials.gov Identifier:). Unfortunately, there are no current data on drug interactions with baloxavir and common immunosuppressions which is concerning given the role of CyP450 in the metabolisms of baloxavir. Studies of baloxavir combination therapy are, therefore, needed before such approach is considered for routine use in transplant patients.

Human Respiratory Syncytial Virus (RSV)

There are two antigenic types of RSV (recently renamed human orthopneumovirus) called RSV-A and -B which co-circulate in the community, with local variance to their abundance. In SOT, RSV has the highest impact in the first year-post transplant except in lung transplant recipients where the detection rates remain similar over time post-transplant (35, 36). Progression to LRTI is the most common in lung transplant recipients, with increased risk of progression early post-transplant due to lymphocyte-depleting antibody therapy or in patients with significant lymphocytopenia (37, 38).

Ribavirin, IVIG, and steroids have been studied for the treatment of RSV with mixed results. In SOT, ribavirin has become standard of care despite the lack of randomized controlled trials demonstrating efficacy. Aerosolized ribavirin is expensive, teratogenic, and requires a special room for administration, and therefore many centers have begun using oral ribavirin instead (39). There is no significant difference in 6-month outcomes between oral and inhaled ribavirin therapy for RSV infection after lung transplant (40, 41). Palivizumab is an anti-RSV monoclonal antibody that is indicated for RSV prevention in children but has not been studied in SOT recipients.

Multiple drugs are undergoing investigation for the treatment of RSV (42–47). Only 2 investigational drugs have been studied, to date, in the lung transplant populations: ALN-RSV01 and Presatovir. ALN-RSV01 is a small interfering RNA that targets RSV. Two studies in lung transplant patients have been completed and use was associated with a significant decrease in new or BOS/CLAD at day 180 (13.6% vs 30.3%, p=0.058). The effect was enhanced when started early at less than five day from symptom onset. However, no significant impact on viral parameters or symptom scores was observed and the drug is no longer being studied.(43, 48) Presatovir (oral GS-5806) is an oral small molecule fusion inhibitor that has completed phase 2 studies. In the phase IIb studies in lung transplant recipients (ClinicalTrials.gov Identifier), presatovir did not result in improved viral or clinical outcomes.(49) Several trials for RSV vaccines are also underway, but no current vaccine is available.

Human Parainfluenza Viruses (PIV)

The incidence of PIV is about 5–7% in lung transplant recipients. Traditional diagnostics covered only PIV-1, −2, and −3, with consistent PIV-4 data being entered only following the use of multiplex NAT. Outbreaks with PIV-3 occur annually with distribution over the spring and summer months, and is also the most frequent serotype found in lung transplant patients

(50–53). PIV infection in lung transplant patients involves the lower respiratory tract between 10–66% of cases (50). In addition to the immediate effects of the virus, PIV LRTI has been associated with long-term pulmonary dysfunction in lung transplant patients with high rate of development of CLAD or chronic rejection (21, 50).

There are no vaccines or approved drugs with clear clinical benefit against PIV. Many clinicians will administer IVIG, and occasionally oral or aerosolized ribavirin for high risk patients, despite lack of evidence for efficacy. Studies using DAS181, a novel inhaled host-active antiviral, for the treatment of PIV in immunocompromised hosts have been completed but data have not yet been published (ClinicalTrials.gov Identifier:).

Human Metapneumovirus (hMPV)

The impact of hMPV in SOT is not well defined, as most of the studies are limited to lung transplant recipients. One study shows HMPV in ~7% of patients with symptoms in half, and two-thirds with LRTI with tracheobronchitis (35). A link between HMPV infection and acute rejection within 3 months, followed by CLAD has been suggested as well (54). Further large prospective multicenter studies are needed to define further risk factors and clinical impact of hMPV. No studies of antiviral agents have been conducted for hMPV, although ribavirin can be considered based on data suggesting efficacy *in vitro*.

Other CARV in SOT

A number of other viruses have been detected in respiratory samples including rhinovirus (RhV), coronavirus (CoV), adenovirus (AdV), and bocavirus. Unfortunately, information on clinical presentation and impact is limited to case series in SOT. There is significant uncertainty regarding these agents due to known prolonged asymptomatic shedding (55) and variety of sero-/geno-types of RhVs, CoVs, and AdVs that are not well differentiated in multiplex NAT diagnostics. Further dedicated clinical and diagnostics studies are needed to understand the role of the CARVs in SOT recipients.

Rhinovirus (RhV)

RhV has been shown in up to 11% of lung transplant patients (56), with both upper respiratory tract infection (URTI) as well as LRTI. There is some evidence that suggests LRTI with RhV is independently associated with acute rejection and CLAD, although most studies have not found a significant association with RhV and acute or chronic rejection (35).

Coronavirus (CoV)

Animal CoV are known for respiratory zoonosis as seen in the past SARS-outbreak and the ongoing MERS-CoV outbreaks. CoV has been linked to severe pneumonia SOT, with significant disease in lung transplant. A study from Switzerland identifies CoV in BAL samples of 5.4% of SOT recipients, with 62% showing signs of LRTI represented by abnormal radiographic findings and 31% requiring ICU admission (57). Whether the lower tract changes were due to coronavirus are less clear and most patients have no significant

clinical sequellae from most coronavirus infections. MERS- and SARS-coronavirus is an exception and severe, often fatal disease can occur.

Adenovirus (AdV)

AdV are known to persist for prolonged times in lymphoid rich tissues with corresponding asymptomatic shedding from urine and stool even in healthy hosts for months to years (58, 59). While AdV can cause approximately 1–10% of febrile respiratory tract disease in adults and children, immunocompromised children with SOT can develop organ-invasive disease (60). AdV may have a predilection for involvement of the transplanted allograft. In renal transplant recipients, AdV involvement is most frequently not respiratory disease, but renal allograft nephritis and hemorrhagic cystitis. These cases are generally not associated with mortality in the modern era and typically do not require antiviral therapy; reduction of immunosuppression is usually sufficient to clear infection over a period of weeks (61, 62). AdV in pediatric lung transplant recipients is associated with CLAD (63), while no association with CLAD was found in adults (35). AdV can also disseminate to other organs and cause parapneumonic effusions, hepatitis, gastrointestinal disease, and rarely central nervous system disease (64–66). The mainstay of treatment is to reduce immunosuppression. While evidence for efficacy is lacking, cidofovir dosed 1mg/kg three times weekly or 5mg/kg weekly for 2 weeks then every other week have been most widely utilized for treatment of clinically significant infections; this is typically combined with hydration and co-administration with probenecid to reduce the risk of nephrotoxicity. To improve outcomes, allow oral administration and reduce the risk of renal and bone marrow toxicity, brincidofovir, a lipid ester of cidofovir is currently being developed (67). Patients with confirmed clinically significant adenovirus infections are eligible for an expanded access protocol for compassionate use of brincidofovir (ClinicalTrials.gov Identifier:).

Conclusions

CARVs are common in SOT recipients and can lead to a broad array of infections causing morbidity and mortality. Understanding their clinical impact is important to optimize further strategies on prevention and treatment. Treatment options for many of the CARVs are limited to supportive care and reduction of immunosuppression, while currently approved therapeutic antiviral options are only available for influenza and RSV. Early therapy is associated with the best outcomes. Newer classes of antivirals and antibodies are under continuous development for many of these viruses. Hopefully, these newer options will lead to a reduction of impact caused by respiratory viruses on the transplant population.

Acknowledgements

References:

1. Ison MG. Respiratory viral infections in transplant recipients. Antivir Ther. 2007;12(4 Pt B):627–38. [PubMed: 17944270]

2. Ison MG, Hirsch HH. Influenza: a recurrent challenge to transplantation. Transpl Infect Dis. 2010;12(2):95–7. [PubMed: 20487416]

3. Ison MG. Influenza, including the novel H1N1, in organ transplant patients. Curr Opin Infect Dis. 2010;23(4):365–73. [PubMed: 20581671]

4. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Archives of internal medicine. 2000;160(21):3243–7. [PubMed: 11088084]

5. Vilchez RA, McCurry K, Dauber J, Lacono A, Griffith B, Fung J, et al. Influenza virus infection in adult solid organ transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2002;2(3):287–91.

6. Peck AJ, Englund JA, Kuypers J, Guthrie KA, Corey L, Morrow R, et al. Respiratory virus infection among hematopoietic cell transplant recipients: evidence for asymptomatic parainfluenza virus infection. Blood. 2007;110(5):1681–8. [PubMed: 17502457]

7**. Kumar D, Ferreira VH, Blumberg E, Silveira F, Cordero E, Perez-Romero P, et al. A Five-year Prospective Multi-center Evaluation of Influenza Infection in Transplant Recipients. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2018.Prospective 5-year study to evaluate the epidemiology of symptomatic influenza infection in solid organ transplant and hematopoietic stem cell transplant recipients. Influenza vaccination was associated with significant decrease in disease severity with odds ratio 0.49 [0.21–0.55, p<0.001], while early antiviral treatment was associated with improved outcomes.

8. Ison MG, Rosenberg ES. RNA respiratory viruses. In: Hayden RT, Carrol KC, Tang YW, Wolk DM, editors. Diagnostic microbiology of the immunocompromised host ASM Press; 2008 p. 141–60.

9. Kuypers J, Campbell AP, Cent A, Corey L, Boeckh M. Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. Transpl Infect Dis. 2009;11(4):298–303. [PubMed: 19453994]

10. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States, 2009. MMWR Morbidity and mortality weekly report. 2009;58(30):826–9. [PubMed: 19661856]

11. Drexler JF, Helmer A, Kirberg H, Reber U, Panning M, Muller M, et al. Poor clinical sensitivity of rapid antigen test for influenza A pandemic (H1N1) 2009 virus. Emerging infectious diseases. 2009;15(10):1662–4. [PubMed: 19861069]

12. Hayden FG, Palese P. Influenza Virus In: Richman DD, Whitley RJ, Hayden FG, editors. Clinical virology. 3rd ed: ASM Press; 2009 p. 943–76.

13*. Bridevaux PO, Aubert JD, Soccal PM, Mazza-Stalder J, Berutto C, Rochat T, et al. Incidence and outcomes of respiratory viral infections in lung transplant recipients: a prospective study. Thorax. 2014;69(1):32–8. [PubMed: 24025442] Prospective study on viral infections in lung transplant recipients collected by wide panel molecular assays showing incidence of infection at 0.83 per patient year (95% CI 0.45 to 1.52) with picornaviruses found most frequently. Hospitalization rates were highest for influenza and parainfluenza at 50%. Asymptomatic viral carriage was uncommon.

14. Meylan PR, Aubert JD, Kaiser L. Influenza transmission to recipient through lung transplantation. Transpl Infect Dis. 2007;9(1):55–7. [PubMed: 17313474]

15. Ison MG, Sharma A, Shepard JA, Wain JC, Ginns LC. Outcome of influenza infection managed with oseltamivir in lung transplant recipients. J Heart Lung Transplant. 2008;27(3):282–8. [PubMed: 18342750]

16. Gottlieb J, Schulz TF, Welte T, Fuehner T, Dierich M, Simon AR, et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation. 2009;87(10):1530–7. [PubMed: 19461490]

17. Garantziotis S, Howell DN, McAdams HP, Davis RD, Henshaw NG, Palmer SM. Influenza pneumonia in lung transplant recipients: clinical features and association with bronchiolitis obliterans syndrome. Chest. 2001;119(4):1277–80. [PubMed: 11296201]

18. Kumar D, Michaels MG, Morris MI, Green M, Avery RK, Liu C, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. The Lancet infectious diseases. 2010;10(8):521–6. [PubMed: 20620116]

19. Ng BJ, Glanville AR, Snell G, Musk M, Holmes M, Chambers DC, et al. The impact of pandemic influenza A H1N1 2009 on Australian lung transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2011;11(3):568–74.

20. Khalifah AP, Hachem RR, Chakinala MM, Schechtman KB, Patterson GA, Schuster DP, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med. 2004;170(2):181–7. [PubMed: 15130908]

21. Billings JL, Hertz MI, Savik K, Wendt CH. Respiratory viruses and chronic rejection in lung transplant recipients. J Heart Lung Transplant. 2002;21(5):559–66. [PubMed: 11983546]

22. Gabriel R, Selwyn S, Brown D, Crossland JM, Loughridge LW, Morgan MN, et al. Virus infections and acute renal transplant rejection. Nephron. 1976;16(4):282–6. [PubMed: 175308]

23. Ison MG. Antiviral therapies for respiratory viral infections in lung transplant patients. Antivir Ther. 2012;17(1 Pt B):193–200. [PubMed: 22311542]

24. Baluch A, Humar A, Eurich D, Egli A, Liacini A, Hoschler K, et al. Randomized controlled trial of high-dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013;13(4):1026–33.

25. Birdwell KA, Ikizler MR, Sannella EC, Wang L, Byrne DW, Ikizler TA, et al. Decreased antibody response to influenza vaccination in kidney transplant recipients: a prospective cohort study. Am J Kidney Dis. 2009;54(1):112–21. [PubMed: 19185404]

26*. Cordero E, Roca-Oporto C, Bulnes-Ramos A, Aydillo T, Gavalda J, Moreno A, et al. Two Doses of Inactivated Influenza Vaccine Improve Immune Response in Solid Organ Transplant Recipients: Results of TRANSGRIPE 1–2, a Randomized Controlled Clinical Trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2017;64(7):829–38. [PubMed: 28362949] Phase 3, randomized, controlled, multi-center trial on influenza vaccine effectiveness in solid organ transplant recipients. Booster strategy 5 weeks following the standard influenza vaccine dose is safe and effective, while inducing an increased antibody response when compared to single dose of standard influenza vaccination.

27. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. The Lancet Infectious diseases. 2009;9(8):493–504. [PubMed: 19628174]

28**. Natori Y, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, et al. A Double-Blind, Randomized Trial of High-Dose vs Standard-Dose Influenza Vaccine in Adult Solid-Organ Transplant Recipients. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2018;66(11):1698–704. [PubMed: 29253089] Randomized, double-blind trial comparing standard-dose to high-dose influenza vaccination in adults solid-organ transplant recipients. High-dose vaccination demonstrated significantly better immunogenicity than standard-dose vaccination.

29**. Manuel O, Estabrook M. RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical transplantation. 2019:e13511. [PubMed: 30817023] Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation to review the diagnosis, prevention, and management of RNA viruses in the pre- and post-transplant period. Viruses reviewed include influenza, RSV, parainfluenza, rhinovirus, human metapnuemovirus and coronavirus.

30. Kumar D, Morris MI, Kotton CN, Fischer SA, Michaels MG, Allen U, et al. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2010;10(1):18–25.

31*. Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med. 2018;379(10):913–23. [PubMed: 30184455] Report of phase 2 and 3 prospective, randomized trials of baloxavir versus oseltamivir versus placebo in acute uncomplicated influenza. Baloxavir was demonstrated to be safe and associated with more rapid virologic clearance of virus compared to oseltamivir and placebo and more rapid clinical improvement compared to placebo. Resistance was noted in 9.7% of subjects.

32. Heo YA. Baloxavir: First Global Approval. Drugs. 2018;78(6):693–7. [PubMed: 29623652]

33. Ison MG, Portsmouth S, Yoshida Y, Shishido T, Hayden F, Uehara T. LB16. Phase 3 Trial of Baloxavir Marboxil in High-Risk Influenza Patients (CAPSTONE-2 Study). Open Forum Infectious Diseases. 2018;5(suppl_1):S764–S5.

34. Takashita E, Morita H, Ogawa R, Nakamura K, Fujisaki S, Shirakura M, et al. Susceptibility of Influenza Viruses to the Novel Cap-Dependent Endonuclease Inhibitor Baloxavir Marboxil. Front Microbiol. 2018;9:3026. [PubMed: 30574137]

35**. Peghin M, Hirsch HH, Len O, Codina G, Berastegui C, Saez B, et al. Epidemiology and Immediate Indirect Effects of Respiratory Viruses in Lung Transplant Recipients: A 5-Year Prospective Study. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2017;17(5):1304–12.A 5-year prospective cohort study of respiratory viral infections in lung transplant recipients showing approximately half of upper respiratory tract infections are caused by picornaviruses, while pneumonias are mainly caused by paramyxoviruses and influenza. Psuedomonas aeruginosa was associated with lower respiratory disease, while CMV was associated with upper respiratory tract infection.

36. Hynicka LM, Ensor CR. Prophylaxis and treatment of respiratory syncytial virus in adult immunocompromised patients. Ann Pharmacother. 2012;46(4):558–66. [PubMed: 22395247]

37. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2013;56(2):258–66. [PubMed: 23024295]

38. Kmeid J, Vanichanan J, Shah DP, El Chaer F, Azzi J, Ariza-Heredia EJ, et al. Outcomes of Influenza Infections in Hematopoietic Cell Transplant Recipients: Application of an Immunodeficiency Scoring Index. Biol Blood Marrow Transplant. 2016;22(3):542–8. [PubMed: 26638804]

39**. Beaird OE, Freifeld A, Ison MG, Lawrence SJ, Theodoropoulos N, Clark NM, et al. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative. Transplant infectious disease: an official journal of the Transplantation Society. 2016;18(2):210–5. [PubMed: 26923867] Management strategies for RSV and other non-influenza respiratory viruses were assessed over 13 Midwestern transplant centers. Treatment of RSV in immunocompromised patients varied greatly as while most centers would treat lower respiratory tract infection, treatment of upper respiratory tract infection was variable. No consensus was found regarding the use of oral versus inhaled ribavirin, or the use of IVIG.

40. Li L, Avery R, Budev M, Mossad S, Danziger-Isakov L. Oral versus inhaled ribavirin therapy for respiratory syncytial virus infection after lung transplantation. The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation. 2012;31(8):839–44.

41. Fuehner T, Dierich M, Duesberg C, DeWall C, Welte T, Haverich A, et al. Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. Antivir Ther. 2011;16(5):733–40. [PubMed: 21817195]

42. DeVincenzo J, Cehelsky JE, Alvarez R, Elbashir S, Harborth J, Toudjarska I, et al. Evaluation of the safety, tolerability and pharmacokinetics of ALN-RSV01, a novel RNAi antiviral therapeutic directed against respiratory syncytial virus (RSV). Antiviral Res. 2008;77(3):225–31. [PubMed: 18242722]

43*. Gottlieb J, Zamora MR, Hodges T, Musk AW, Sommerwerk U, Dilling D, et al. ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients. The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation. 2016;35(2):213–21.

44. DeVincenzo JP, Whitley RJ, Mackman RL, Scaglioni-Weinlich C, Harrison L, Farrell E, et al. Oral GS-5806 activity in a respiratory syncytial virus challenge study. N Engl J Med. 2014;371(8):711–22. [PubMed: 25140957]

45. Brookes DW, Coates M, Allen H, Daly L, Constant S, Huang S, et al. Late therapeutic intervention with a respiratory syncytial virus L-protein polymerase inhibitor, PC786, on respiratory syncytial virus infection in human airway epithelium. Br J Pharmacol. 2018;175(12):2520–34. [PubMed: 29579332]

46. Chemaly RF, Dadwal SS, Bergeron A, Ljungman PT, Kim Y-J, Cheng GS, et al. A phase 2b, randomized, double-blind, placebo-controlled trial of presatovir (GS-5806), an oral fusion inhibitor for the treatment of RSV upper tract respiratory tract infection in hematopoietic-cell transplant recipients BMT Tandem; Salt Lake City, UT 2018 p. LBA7.

47. Marty FM, Chemaly RF, Bergeron A, ljungman PT, Kim Y-J, Boeckh MJ, et al. A phase 2b, randomized, double-blind, placebo-controlled trial of presatovir (GS-5806), an oral fusion inhibitor for the treatment of RSV lower tract respiratory tract infection in hematopoietic-cell transplant recipients BMT Tandem; Salt Lake City, 2018 p. LBA6.

48. Simon A, Karsten V, Cehelsky J, Shah S, Gollob J, Meyers R, et al. Results of a phase 2b multi-center trial of ALN-RSV01 in respiratory syncytial virus (RSV)-infected lung transplant patients. European Respiratory Journal. 2012;40(Suppl 56):P1476.

49. Gottlieb J, Torres F, Haddad T, Dhillon G, Dilling DF, Knoop C, et al. A Phase 2b Randomized Controlled Trial of Presatovir, an Oral RSV Fusion Inhibitor, for the Treatment of Respiratory Syncytial Virus (RSV) in Lung Transplant (LT) Recipients. The Journal of Heart and Lung Transplantation. 2018;37(4):S155.

50. Vilchez RA, Dauber J, McCurry K, Iacono A, Kusne S. Parainfluenza Virus Infection in Adult Lung Transplant Recipients: An Emergent Clinical Syndrome with Implications on Allograft Function. American Journal of Transplantation. 2003;3(2):116–20. [PubMed: 12603206]

51. Vilchez RA, McCurry K, Dauber J, Iacono A, Keenan R, Zeevi A, et al. The epidemiology of parainfluenza virus infection in lung transplant recipients. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2001;33(12):2004–8. [PubMed: 11702289]

52. Vilchez R, McCurry K, Dauber J, Iacono A, Keenan R, Griffith B, et al. Influenza and parainfluenza respiratory viral infection requiring admission in adult lung transplant recipients. Transplantation. 2002;73(7):1075–8. [PubMed: 11965034]

53. Wendt CH, Fox JM, Hertz MI. Paramyxovirus infection in lung transplant recipients. J Heart Lung Transplant. 1995;14(3):479–85. [PubMed: 7654733]

54. Dosanjh A. Respiratory metapneumoviral infection without co-infection in association with acute and chronic lung allograft dysfunction. Journal of inflammation research. 2015;8:79–82. [PubMed: 25848314]

55. Byington CL, Ampofo K, Stockmann C, Adler FR, Herbener A, Miller T, et al. Community Surveillance of Respiratory Viruses Among Families in the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) Study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015;61(8):1217–24. [PubMed: 26245665]

56*. Ambrosioni J, Bridevaux PO, Aubert JD, Soccal P, Wagner G, Kaiser L. Role of rhinovirus load in the upper respiratory tract and severity of symptoms in lung transplant recipients. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2015;64:1–5. [PubMed: 25728070] A prospective cohort of 116 lung transplant recipients were assessed for the role of Rhinovirus and its effects. Rhinovirus infections were found to be very frequent, with relatively high viral load found in asymptomatic patients as well. Higher symptom scores were associated with higher rhinovirus load as well.

57. Garbino J, Crespo S, Aubert JD, Rochat T, Ninet B, Deffernez C, et al. A prospective hospital-based study of the clinical impact of non-severe acute respiratory syndrome (Non-SARS)-related

human coronavirus infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2006;43(8):1009–15. [PubMed: 16983613]

58. Kapusinszky B, Minor P, Delwart E. Nearly Constant Shedding of Diverse Enteric Viruses by Two Healthy Infants. Journal of Clinical Microbiology. 2012;50(11):3427. [PubMed: 22875894]

59. Kalu SU, Loeffelholz M, Beck E, Patel JA, Revai K, Fan J, et al. Persistence of adenovirus nucleic acids in nasopharyngeal secretions: a diagnostic conundrum. The Pediatric infectious disease journal. 2010;29(8):746–50. [PubMed: 20308936]

60. Michaels MG, Green M, Wald ER, Starzl TE. Adenovirus infection in pediatric liver transplant recipients. J Infect Dis. 1992;165(1):170–4. [PubMed: 1727887]

61*. Engen RM, Huang ML, Park GE, Smith JM, Limaye AP. Prospective Assessment of Adenovirus Infection in Pediatric Kidney Transplant Recipients. Transplantation. 2018;102(7):1165–71. [PubMed: 29762251] Adenovirus infections were assessed in a prospective single-center cohort study of pediatric kidney transplant recipients. While adenovirus infection were common in this population with frequent symptomatic disease, syptoms from adnovirus were often mild and not associated with significant decline in graft function. Based on this data, routine monitoring for adnovirus viremia was not thought to be warranted.

62. Lachiewicz AM, Cianciolo R, Miller MB, Derebail VK. Adenovirus causing fever, upper respiratory infection, and allograft nephritis complicated by persistent asymptomatic viremia. Transpl Infect Dis. 2014;16(4):648–52. [PubMed: 24966111]

63. Liu M, Worley S, Arrigain S, Aurora P, Ballmann M, Boyer D, et al. Respiratory viral infections within one year after pediatric lung transplant. Transpl Infect Dis. 2009;11(4):304–12. [PubMed: 19422670]

64. Centers for Disease C, Prevention. Acute respiratory disease associated with adenovirus serotype 14--four states, 2006–2007. MMWR Morbidity and mortality weekly report. 2007;56(45):1181–4. [PubMed: 18004235]

65. Kandel R, Srinivasan A, D'Agata EM, Lu X, Erdman D, Jhung M. Outbreak of adenovirus type 4 infection in a long-term care facility for the elderly. Infection control and hospital epidemiology: the official journal of the Society of Hospital Epidemiologists of America. 2010;31(7):755–7.

66. Shen CF, Wang SM, Ho TS, Liu CC. Clinical features of community acquired adenovirus pneumonia during the 2011 community outbreak in Southern Taiwan: role of host immune response. BMC infectious diseases. 2017;17(1):196. [PubMed: 28270104]

67. Miles CD, Florescu MC, Florescu DF. What do we know about adenovirus in renal transplantation? Nephrology Dialysis Transplantation. 2013;28(8):2003–10.

68. Abbas S, Raybould JE, Sastry S, de la Cruz O. Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2017;62:86–93. [PubMed: 28739424]

69. Milstone AP, Brumble LM, Barnes J, Estes W, Loyd JE, Pierson RN 3rd, et al. A single-season prospective study of respiratory viral infections in lung transplant recipients. The European respiratory journal. 2006;28(1):131–7. [PubMed: 16510454]

Key Points:

- Respiratory viruses can cause a wide array of symptoms in the solid organ transplant (SOT) recipient with increased morbidity and mortality, particularly in lung transplant recipients, when compared to healthy subjects.

- The gold standard for diagnosis of respiratory viral infections is multiplex PCR.

- There is proven morbidity benefit in SOT patients who receive early antiviral therapy and annual influenza vaccination even despite reduced immunogenicity of vaccines this population.

- Multiple therapeutic and preventative options are currently under development for a wide array of respiratory viruses.

Table 1.

Key Features of Respiratory Viral Infections: Epidemiology & Treatment Options (13, 16, 35, 63, 68, 69)

Type of Virus	Incubation Period (Days)	Infection Prevention Principles	Distribution of RVIs in SOT (%)	Treatment Options
ADV	5–9	Standard precautions; contact precautions; droplet precautions	1–25	Cidofovir; brincidofovir
Coronavirus *	2–14	Standard precautions; contact precautions; droplet precautions; airborne precautions	13–29	ND
hMPV	4–6	Standard precautions; contact precautions	4–7	ND
Influenza	1–4	Standard precautions; droplet precautions; aerborne with invasive ventilation; seasonal vaccination; post-exposure prophylaxis with oseltamivir	2–16	Oseltamivir; zanamivir; peramivir; balaxovir
PIV	2–6	Standard precautions; airborne precautions; droplet precautions	3–18	Ribavirin (aerosolized, IV, or po) ± IVIG? DAS-181?
RSV	3–7	Standard precautions; contact precautions; droplet precautions	6–20	Ribavirin (aerosolized, IV, or po) ± IVIG; palivizumab?
Rhinovirus/ Enterovirus	1–9	Standard precautions; droplet precautions	21–62	ND

*
Including Middle East Respiratory Syndrome

ADV: Adenovirus; hMPV: Human Metapneumovirus; PIV: Parainfluenza Virus; RSV: Respiratory Syncytial Virus