Prevention and Treatment of Respiratory Virus Infection

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Abbreviations

AdV	Adenovirus
CoV	Coronavirus
FLU	Influenza
hMPV	Human metapneumovirus
HSV1–2	Herpes simplex 1–2
IVIG	Intravenous immunoglobulin
LRTI	Lower respiratory tract infection
MERS-CoV	Middle East respiratory syndrome coronavirus
PIV	Parainfluenza
PPE	Postexposure prophylaxis
PrEP	Pre-exposure prophylaxis
RBV	Ribavirin
RhVs	Rhinovirus
RSV	Respiratory syncytial virus
RVs	Respiratory virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SOT	Solid organ transplant
URTI	Upper respiratory tract infection

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9.1 Introduction

Respiratory viruses (RVs) are increasingly recognized as a major cause of morbidity and mortality in solid organ transplant recipients, especially within the lung transplant population. Respiratory viral infections are typically caused by rhinovirus (RhVs), coronavirus (CoV), respiratory syncytial virus (RSV), influenza (FLU), parainfluenza (PIV), human metapneumovirus (hMPV), and adenovirus (AdV) (Table 9.1). Respiratory infections can also be caused by viruses less commonly associated with the respiratory tract such as cytomegalovirus (CMV), human herpesviruses (HSV1, HSV2), and varicella zoster virus (VZV) that will be discussed in another chapter (Chap. 6). A detailed discussion of other newer respiratory viruses (Table 9.1) is beyond the scope of this chapter, since they have not been widely studied in immunocompromised patients and their clinical impact is not fully understood. However, these viruses should be considered in the differential diagnosis of patients presenting with severe lower tract disease, especially if clinical history indicates potential exposure. The newer RVs are more challenging to diagnose since they are not included in the routinely available diagnostic tests and optimal management has not been defined.

Table 9.1 Classification and distribution of major and minor respiratory viral infections in SOT

Major RVs	Distribution (%) in SOT
• Rhinovirus (RhVs)	21–62
• Coronavirus (CoV)	13–29
• Influenza virus (FLU)	2–16
• Respiratory syncytial virus (RSV)	6–20
• Parainfluenza virus (PIV)	3–18
• Metapneumovirus (hMPV)	4–7
• Adenovirus (AdV)	1–25
Minor RVs	
• Cytomegalovirus (CMV)	
• Herpes simplex virus 1–2 (HSV1–2)	
• Varicella zoster virus (VZV)	
• Measles	
• *Enterovirus* + *Enterovirus* D68	
• *Parechovirus*	
• Parvovirus B19	
• Bocavirus	
• CoV HKU1 and NL63	
• Middle East respiratory syndrome CoV (MERS-CoV)	
• Severe acute respiratory syndrome CoV (SARS-CoV)	
• Polyomaviruses KI and WU	

RVs respiratory viruses, *SOT* solid organ transplant

9.2 Clinical Manifestations

The definition of RV disease includes (1) a new onset of symptoms and (2) at least one respiratory symptom and (3) the clinician's judgment that the illness is due to an infection [1]. An upper respiratory tract infection (URTI) is defined with the onset of sore throat, rhinorrhea, or hoarseness. A lower respiratory tract infection (LRTI) is defined as new onset of shortness of breath, cough, sputum, rales, hypoxemia, and/or wheezing. When symptoms of LRTI are associated with a new pulmonary infiltrate (on chest radiograph or chest computed tomography), pneumonia is distinguished from tracheobronchitis.

Many common respiratory viral infections in SOT patients are mild, self-limiting upper respiratory tract infection (URTI) and do not require hospitalization. However, compared to immunocompetent hosts and due to alterations in cellular and humoral immunity, infections can cause protracted symptoms with greater risk of progression to LRTI, prolonged periods of viral shedding, and increased mortality. In SOT, LRTIs have been associated with increased risk of adverse complications and subsequent development of fungal, viral, and bacterial superinfections [2]. Although these complications may appear in the context of any type of transplantation, pediatric, lung, and heart-lung transplantation recipients appear to have the greatest risk of respiratory viral infections with more severe courses and complications [2–4].

In addition to their direct, cytopathic, and tissue-invasive effects, RVs can create an inflammatory environment that leads to local and systemic microbially determined immune modulation (MDIM) [5]. MDIM may increase the alloimmune and autoimmune responses that increase susceptibility to other opportunistic infections and are associated with the development of acute and chronic rejection. The greatest risk appears from data in lung transplant recipients, although data on this topic in the literature are conflicting [2, 5, 6].

In transplantation overall, RhV and CoV are the most common etiological agents, causing mostly mild URTI, with LRTI less frequently described. In contrast, FLU and other paramyxovirus (RSV, PIV, and hMPV) have a greater association with LRTI and particularly acute and chronic rejection in adult lung transplant recipients [2, 5] (Tables 9.1 and 9.2). Outcomes of infection are associated strongly with site of involvement, net state of immune suppression, and availability and use of antiviral agents.

9.3 Diagnosis

The clinical diagnosis of RVs can be difficult, since SOT recipients often present with mild or atypical symptoms and signs, which are often overlapping and not always specific for any one viral agent. Fever can be absent in SOT with pneumonia or can be the sole presenting sign. In addition bacterial and fungal coinfections may occur.

The distribution of RV infections throughout the year suggests that seasonal patterns of RV circulation in SOT are similar to those circulating in the general

Table 9.2 Seasonality, diagnostic tools, clinical presentation, treatment regimens, prevention, and isolation precaution for major RVs

Virus	Family and type	Seasonality	Diagnostic test	Clinical presentation	Treatment regimens	Prevention	Isolation recommendation
RhVs	Picornavirus RNA	All year-round with higher peaks in fall and spring	RT-PCR Cell culture Serology	Mostly URTI, LRTI	Primary: none Alternative: none	Prophylaxis: none Vaccine: none	Standard, contact and droplet
CoV	*Coronaviridae* RNA	Winter and spring	RT-PCR Serology	Mostly URTI, LRTI	Primary: none Alternative: none	Prophylaxis: none Vaccine: none	Standard precautions but SARS and MERS require contact, droplet, and airborne precautions
FLU	*Orthomyxoviridae* RNA	Winter between December and February	RT-PCR IF IA Cell culture Serology Susceptibility test	URTI, LRTI (pneumonia, ARDS, obliterative bronchiolitis) ± encephalitis, myocarditis, and myositis	Primary: oseltamivir or zanamivir Alternative: peramivir or DAS181 For oseltamivir resistant strains: zanamivir (active), peramivir (reduced susceptibility), or DAS181 (research/ compassionate use currently) M2 Inhibitors (amantadine and rimantadine): no longer recommended (not useful for influenza B, H1N1, H3N2) for high resistance rates (>95%)	Prophylaxis: oseltamivir 75 mg or zanamivir 2 puffs OD PrEP: OD for influenza season (12 weeks) PPE: OD prophylaxis or therapeutic regimen for 7–10 days very early after exposure Vaccine: yearly trivalent or quadrivalent inactivated influenza vaccination	Standard, contact, and droplet
RSV	*Paramyxoviridae* RNA	Fall and winter	RT-PCR IF IA Cell culture Serology	URTI, LRTI	Primary: oral, intravenous, or inhaled ribavirin ± IVIG[b] ± palivizumab[c] ± steroids[d] Alternative: intravenous ribavirin	Prophylaxis: palivizumab or IVIG PrEP: once a month during RSV season in pediatric transplant	Standard and contact

PIV	*Paramyxoviridae* RNA	PIV 1: fall and winter PIV 2: fall and winter PIV 3: spring and summer PIV 4: not well established	RT-PCR IF Cell culture Serology	PIV 1: croup, URTI PIV 2: croup, URTI PIV 3: URTI, LRTI PIV 4: rarely cause disease	Primary: none Alternative: oral, intravenous, or inhaled ribavirin ± IVIG[b]	Prophylaxis: none Vaccine: none	Standard and contact
hMPV	*Paramyxoviridae* RNA	Winter and spring	RT-PCR IF Serology	URTI, LRTI	Primary: none Alternative: oral, intravenous or inhaled ribavirin ± IVIG[b]	Prophylaxis: none Vaccine: none	Standard and contact
AdV	*Adenoviridae* DNA	All year-round	RT-PCR[a] IF Cell culture Serology	URTI, LRTI, gastroenteritis, nephritis, hepatitis, hemorrhagic cystitis, encephalitis disseminated infection	Primary: cidofovir ± IVIG[b] Alternative: brincidofovir (research/compassionate use currently), ribavirin, ganciclovir	Prophylaxis: none Vaccine: none	Standard, contact and droplet

[a]Adenovirus is unique in that, although PCR is the preferred diagnostic test, negative testing from the upper or lower airway may not exclude infections. RT-PCR should be applied on respiratory specimen, blood (quantitative viral load testing) and other compartments depending on clinical presentation (urine, cerebrospinal fluid)

[b]Intravenous immunoglobulin therapy at a dose of 500 mg/Kg the first day, followed by a repeated dose after 48 h

[c]Palivizumab 15 mg/kg once a month; maximum of 5 doses per season

[d]Methylprednisolone is increased at a dose of 1 mg/kg/day, followed by gradually tapering over 2 weeks to reach a maintenance dose of approximately 0.1–0.2 mg/kg/day

AdV adenovirus, *CoV* coronavirus, *FLU* influenza, *hMPV* human metapneumovirus, *HSV1–2* herpes simplex virus 1–2, *IA* immunoassay, *IF* Immunofluorescence, *IVIG* intravenous immunoglobulin, *LRTI* lower respiratory tract infection, *MERS-CoV* Middle East respiratory syndrome coronavirus, *OD* once daily, *PIV* parainfluenza, *PrEP* pre-exposure prophylaxis, *PPE* postexposure prophylaxis, *RhVs* rhinovirus, *RSV* respiratory syncytial virus, *RT-PCR* real time PCR, *SARS-CoV* severe acute respiratory syndrome coronavirus, *URTI* upper respiratory tract infection

population [2, 3]. Consequently, vigilance regarding circulating community RV infections is required while caring for SOT recipients.

Rapid and reliable laboratory diagnosis is required in SOT with respiratory syndrome to significantly impact on patient care and management. The ideal method of sampling has also come into question, as the yield of viral specimen may differ depending on the specimen source. All SOTs with suspected RV infection should have a nasopharyngeal sample tested by PCR, including nasopharyngeal swab (NPS), wash, or aspirate. Between common respiratory specimens collected from the upper respiratory tract, NPS are preferred, since they are practical for widespread use and comparable in sensitivity to nasopharyngeal aspirates or bronchoalveolar lavage (BAL) for the detection of all major RVs [1, 7, 8]. NPS should be collected diligently by trained staff, using the standardized procedures of the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/urdo/downloads/speccollectionguidelines.pdf; https://www.youtube.com/watch?v=DVJNWefmHjE) [9]. If upper tract samples fail to document the RV cause of the respiratory illness and clinical or radiologic evidence of lower tract involvement exists, BAL should be performed for RV testing [7].

The array of diagnostic tools for RVs in immunocompromised patients has greatly increased over the last few years, and diagnosis can be performed using real-time PCR (RT-PCR) techniques, antigen detection, and serology (Table 9.3) [9].

The sensitivities of contemporary molecular diagnostic techniques have been substantially improved, allowing for the rapid simultaneous detection of a wide variety of conventional and emerging RVs in respiratory samples. At present, real-time multiplex nucleic acid amplification testing (multiplex NAT) based on the RT-PCR technology is the preferred diagnostic tool for studying RVs in immunocompromised patients and is incorporated into many of the current guidelines [1, 7]. Both laboratory-developed and commercial RT-PCR assays are currently available, differing in specificity and sensitivity (ranges from 72% to 100%, with best sensitivity seen for FLU and lower sensitivities for ADV and PIV). With the aim of overcoming technical complexity of PCR-based testing, fully automated RT-PCR instrument for rapid detection of RV has been tested in immunocompromised patients with promising results with a turnaround time of approximately 1–2 h [10]. Therefore, clinicians should be aware of the performance characteristics of the assay performed (https://www.cdc.gov/urdo/downloads/speccollectionguidelines.pdf). Of note that regarding ADV, negative testing from the upper or lower airway may not exclude infections particularly for SOT with disseminated disease if there is limited to no involvement of the respiratory tract. RT-PCR should be applied on respiratory specimen, blood (quantitative viral load testing), and other compartments depending on clinical presentation (urine, cerebrospinal fluid).

It is important to remember, however, that despite the excellent sensitivity, poorly collected samples may yield false-negative results, and results may greatly vary depending on the quality of the swab. The high sensitivity of these methods also has drawbacks, such as frequent detection of viruses in asymptomatic individuals and prolonged detection of viruses in patients who have already clinically recovered [2, 3].

Table 9.3 Laboratory methods for diagnosis of the major human respiratory viruses. From Hodinka (https://www.youtube.com/watch?v=DVJNWefmHjE) modified

Clinical methods	Specimen	RVs tested	Sensitivity	Specificity	Test time	Comments
Multiplex nucleic acid amplification tests—real-time PCR (RT-PCR)	NPS, BAL	RSV, FLU, PIV, AdV, hMPV, RhVs, CoVs	High	High	15 min–8 h	(+): new reference standard; superior performance characteristic (−): frequent detection of viruses in asymptomatic individuals; negative testing for AdV from the upper or lower airway may not exclude infection
Direct antigen detection tests						
– Immunofluorescence (IF)	NPS, BAL	RSV, PIV 1, PIV 2, PIV 3, AdV, hMPV Not RhVs or CoVs	Moderate	Moderate-high	1–2 h	(+): rapid, multianalyte detection (−): not available for RhVs or CoVs ; moderately complex and subjective reading
– Immunoassay (IA)	NPS, BAL	RSV, FLU (mostly) adenovirus	Low-moderate	Moderate-high	≤15 min	(+): fast and simple to use (−): amenable to point-of-care testing; suboptimal in SOT; some commercial kits do not distinguish between FLU A and B

(continued)

Table 9.3 (continued)

Clinical methods	Specimen	RVs tested	Sensitivity	Specificity	Test time	Comments
Virus culture systems						
– Shell vial or microwell plate	NPS, BAL NPS, BAL	RSV, FLU, PIV 1, PIV 2, PIV 3, AdV, hMPV	Low-moderate	High	1–3 days	(+): rapid centrifugation-assisted cultures for select viruses (−): less sensitive than tube cultures; not available for the growth of all viruses
– Conventional tube		RSV, FLU, PIV, AdV, RhVs (A and B)	Low-moderate	High	3–14 days	(+): capable of growing any virus; allows confirmation of virus viability and test of antiviral susceptibility (−): involves considerable time, labor, and resources; Group C RhVs, MPV, and CoVs do not routinely grow in standard cell culture
Serology	Blood	RSV, FLU, PIV, AdV, hMPV, RhVs, CoVs	NA	NA	NA	(+): used for research, epidemiologic studies and analyze the immune response to vaccination (−): not useful for diagnosis; need collection of blood samples at acute illness and 4–6 weeks after

(+) positive, (−) negative, *AdV* adenovirus, *BAL* bronchoalveolar lavage, *CoV* coronavirus, *FLU* influenza, *hMPV* human metapneumovirus, *NA* not applicable, *NPS* nasopharyngeal swab, *PIV* parainfluenza virus, *RhVs* rhinovirus, *RSV* respiratory syncytial virus, *RVs* respiratory virus, *SOT* solid organ transplant, *URTID* upper respiratory tract infectious disease

The major challenge is to determine association between the presence of microbial nucleic acids and a clinical syndrome in individual patients. Quantification of the virus may be a helpful result interpretation, since high viral loads are associated with the presence of symptoms and may be related to the severity of the clinical symptoms [9].

Antigen detection techniques, which include immunofluorescence (IF) and immunoassay (IA), are fast and have high specificity but are only available for specific viruses and their sensitivity less than molecular methods. This technique is not available for viral respiratory infections caused by RhV or CoV and is moderately complex, and interpretation of results is subjective [9]. A number of commercial IA are available for RSV and FLU (A and B) and require little technical expertise. However, false-negative and false-positive results can be generated. A low prevalence of circulating virus within the community decreases the positive predictive value of the test. For FLU, rapid IA has shown high specificity but low sensitivity (20–70%) as compared to other assays, making them suboptimal for SOT recipient, particularly in clinical decision-making for antiviral therapy [11].

Antiviral susceptibility testing for RVs is primarily focused on influenza, and both phenotypic and genotypic assays can be tested, although such testing is not widely available in local or commercial labs.

Antiviral resistance is of considerable concern among immunocompromised patients infected with influenza virus, and testing should be strongly considered in SOT undergoing treatment who fails to have an appropriate clinical response within 3–5 days of initiating antiviral therapy or who has a relapsing course despite ongoing therapy.

9.4 Treatment Options, General Considerations

In the absence of available treatment options and of strong evidence of effectiveness for any particular therapy, treatment strategies differ widely among centers [12]. Limited understanding of (1) risk factors for progression to severe LRTI and poor outcomes and (2) indirect inflammatory effects of viral infection impact opinions on appropriate interventions for respiratory viral infections. RV infections, particularly cause by influenza virus, are a risk factor for subsequent bacterial and fungal superinfections. In cases of LRTI, secondary infections must be ruled out and appropriately treated, and initiation of oral or nebulized antifungal prophylaxis to prevent invasive fungal infections should be evaluated in high-risk patients [1, 2, 12].

Management in transplant patients is generally focused on reduction of immunosuppression feasible to speed resolution of viral infection. Treatment options for RVs are limited (Tables 9.2 and 9.4). Resistance patterns may change and affect recommended antiviral strategies. Consequently, clinicians should consult national health authority regularly for updated recommendations, especially for influenza.

Table 9.4 Antiviral agents

Drug	Mechanism of action	Spectrum	Standard dose and duration of treatment	Hepatic and renal adjustment	Pediatric dose	Drug interactions[a] and toxicity
Ribavirin	Broad-spectrum nucleoside analog activity against DNA and RNA viruses	RSV hMPV PIV 1–4 CoV FLU AdV	Inhaled (SPAG, negative pressure room): 6 gm daily aerosolized continuously over 12–18 h or 2 gm every 8 h over 1–4 h each for 7–10 days Intravenous: 15–25 mg/kg/day in three divided doses for 7–10 days. Some authors use loading dose 35 mg/kg in three divided doses the first day Oral: 15–25 mg/kg/day in three divided dose for 7–10 days	No hepatic adjustment No renal adjustment but use with caution if CrCl <50 mL/min	Inhaled: 20 mg/mL as the starting solution in the drug reservoir Oral: Children ≥2 years and adolescents: 15 mg/kg/day in two divided doses	No drug interactions Inhaled RBV: teratogenic potential, bronchospasm, cough, nausea, rash, decreased pulmonary function, conjunctival irritation; can potentially be deposited in the ventilator delivery system Oral/intravenous: hemolysis, insomnia, lactic acidosis, rash hyperbilirubinemia and leukopenia

Oseltamivir	Neuraminidase inhibitor (NAI)	FLU A and B	Oral: 75 mg every 12 h for 5–10 days Some authors suggest double dose (150 mg every 12 h) in severe cases or in case of insufficient response to therapy or/and extended duration of treatment to 10 days in case of in critically ill patients and persistent viral shedding Intravenous: compassionate use	No hepatic adjustment Renal adjustment: CrCl ≥30 mL/min: 75 mg every 12 h (for treatment), 75 mg every 24 h (for prophylaxis) CrCl <30 mL/min: 75 mg every 24 h (for treatment), 75 mg every 48 h (for prophylaxis) HD/CAPD: 30–75 mg after dialysis CRRT: 75 mg every 12 h	For child of any weight >2 weeks <1 year old: 3 mg/kg/dose every 12 h For child ≥1 year old: ≤15 kg: 30 mg every 12 h 16–23 kg: 45 mg every 12 h 24–40 kg: 60 mg every 12 h >40 kg: 75 mg every 12 h Indicated for prevention in child ≥1 year old; for the treatment in child > 2 weeks	No drug interactions Gastrointestinal upset, hypersensitivity reactions, hepatotoxicity, neurotoxicity, rashes In children oseltamivir has been associated with neuropsychiatric adverse events
Zanamivir	Neuraminidase inhibitor (NAI)	FLU A and B	Nasal: 10 mg 2 puffs every 12 h for 5–10 days. Rare reports of inhaled zanamivir failure Intravenous: compassionate use	Approximately 4–17% of inhaled dose absorbed into plasma No hepatic adjustment No renal adjustment	Indicated for prophylaxis in children ≥5 years old and for treatment in children ≥7 years old: same dose than adults	No drug interactions Bronchospasm: cannot be used in patients on ventilators because obstruction of filters

(continued)

Table 9.4 (continued)

Drug	Mechanism of action	Spectrum	Standard dose and duration of treatment	Hepatic and renal adjustment	Pediatric dose	Drug interactions[a] and toxicity
Peramivir	Neuraminidase inhibitor (NAI)	FLU A and B	Intravenous: 600 mg every 24 h for 5–10 days Approved in China, Japan, South Korea, and the United States	No hepatic adjustment Renal adjustment: CrCl ≥50 mL/min: 600 mg IV every 24 hCrCl 30–49 mL/min: 200 mg IV every 24 hCrCl 10–29 mL/min: 100 mg IV every 24 h CrCl <10 mL/min: 100 mg single dose, than 15 mg every 24 h HD: administer post dialysis based on renal function: 100 mg on day 1 then 100 mg 2 h after HD CAPD/CRRT: no recommendations	Children 181 days to 5 years: 12 mg/kg OD Children 6–17 years: 10 mg/kg every 24 h for 5 days (maximum of 600 mg every 24 h) CrCl ≥50 mL/min: 600 mg IV every 24 hCrCl 30–49 mL/min: age 6–17 years: 2.5 mg/kg every 24 h; age 180 days to 5 years: 3 mg/kg every 24 hCrCl 10–29 mL/min: age 6–17 years: 1.6 mg/kg every 24 h; age 180 days to 5 years: 1.9 mg/kg every 24 h CrCl <10 mL/min: age 6–17 years: 1.6 mg/kg on day 1 then 0.25 mg/kg every 24 h age 180 days to 5 years: 1.9 mg/kg on day 1 then 0.3 mg/kg Hemodialysis: age 6–17 years: 1.6 mg/kg on day 1 then 1.6 mg/kg 2 h after HD Age 181 days to 6 years: 1.9 mg/kg on day 1 then 1.9 mg/kg 2 h after HD	No drug interactions Gastrointestinal intolerance, neutropenia, neuropsychiatric disturbances, rash, hyperglycemia

Laninamivir	Neuraminidase inhibitor (NAI)	FLU A and B	Inhaled: 40 mg every 24 h 20 mg daily for 2 days is recommended for prophylaxis Approved in Japan	No hepatic adjustment No renal adjustment Approximately 15% of inhaled dose absorbed into plasma	Age <10 years: 20 mg every 24 h	No drug interactions
Cidofovir	Nucleotide analog activity against DNA viruses	AdV Herpesvirus JC virus	Intravenous: induction of 5 mg/kg IV once weekly × 2 weeks Maintenance: 5 mg/kg IV once every 2 weeks (minimum two doses) or 1 mg/kg IV three times per week for 2 weeks + probenecid + hydration[b] Intravescical: 5 mg/Kg in 100 mL of NS (for hemorrhagic cystitis)	No data on hepatic adjustment No renal adjustment but if CrCl <55 mL/min or urine protein ≥100 mg/dL: avoid use Changes in renal function during therapy: If serum creatinine increases by 0.3–0.4 mg/dL: reduce dose to 3 mg/kg; If serum creatinine increases ≥0.5 mg/dL or development of ≥3 + proteinuria: discontinue therapy No data on dialysis	Infants ≥6 months <3 years IV: 1 mg/kg/dose every other day or three times weekly for 4 consecutive weeks	Cidofovir: dose dependent nephrotoxicity, proteinuria, glycosuria, metabolic acidosis Fanconi syndrome, bone marrow toxicity Probenecid: fever, gastrointestinal symptoms, rash, asthenia, ocular diseases Caution: the use of tacrolimus or cyclosporine with cidofovir may enhance the risk of nephrotoxicity

[a]Drug interactions are focused on interactions with immunosuppressive therapy: steroids, cyclosporine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil
[b]Probenecid: 2 g 3 h prior to cidofovir dose, then 1 g at 2 h and 8 h after completion of the infusion. Hydration: patients should also receive 1 L of normal saline intravenously infused over 1–2 h immediately prior to each cidofovir infusion. If tolerated, a second liter may be administered over 1–3 h at the start of cidofovir infusion or immediately following infusion

AdV adenovirus, *CAPD* continuous ambulatory *peritoneal dialysis*, *CoV* coronavirus, *CrCl creatinine clearance*, *CRRT* continuous renal replacement therapy, *FLU* influenza, *HD* hemodialysis, *hMPV* human metapneumovirus, *NS* normal saline, *PIV* parainfluenza, *RSV* respiratory syncytial virus, *SPAG* small particle aerosol generator

In our opinion treatment efforts should be always performed in any SOT with LRTI or in lung transplant and heart-lung transplantation recipients both with URTI and with LRTI, due to increased morbidity and mortality [12].

Reconstitution of the immune system appears to be important in overcoming RV infections. Clearly, the currently available treatment option is a clinical dilemma [6, 7, 13]. There are numerous reports in the literature citing the use of intravenous immunoglobulin (IVIG) as part of therapy for viral infections in immunocompromised patients. Hypogammaglobulinemia has been associated with an increased risk of opportunistic infections in SOT, but not to community-acquired RVI. However, some experts recommend considering the addition of IVIG for severe RV infection in SOT [13].

The use of monoclonal antibodies is limited to the treatment of RSV. Immunotherapy including transfer of RV-specific T lymphocytes from healthy donors is under investigation and has been reported to be safe and effective when performed early in the course of the infection for hMPV, adenovirus, RSV, and PIV. At the same time, virus-associated immune modulation may sometimes be deleterious in RVs due to local inflammatory responses. Adjunctive therapy with corticosteroids has been purposed for SOT with influenza and RSV and for lung transplant recipients with any RVs with LRTI because of the risk of both acute and chronic rejection [13].

9.5 Prevention, General Considerations

Treatment options for RVs are limited, and maximizing prevention measures against viral infections in SOT is mandatory.

RVs are potential community and nosocomial pathogens that can be spread by staff or visitors with mild upper respiratory illness. Overall awareness among SOT, healthcare personnel, family members, and caregivers about the potential deleterious outcomes of RV infections in SOT and the importance of early detection of infection may have a significant impact on the incidence of RV infections and risk of transmission [1].

Strict adherence to hand hygiene, contact precautions, and respiratory droplet isolation are required to reduce RV nosocomial spread and outbreaks during hospitalization (Table 9.2) (https://www.cdc.gov/infectioncontrol/guidelines/isolation/). The appropriate length of isolation for patients with laboratory proven RVs is debated, as prolonged shedding is a common finding in SOT patients, but viral load thresholds for infectivity are unknown. Infection control measures should be maintained until the patient is discharged home or until PCR is negative. Stringent hygiene precautions should be also applied in community settings, where SOT recipients should avoid close contact with individuals with respiratory tract infections [1]. The influenza virus is currently the only CARV that can be prevented with vaccination [14].

9.6 Prevention and Treatment of Specific RVs

9.6.1 Influenza

Three main viral strains have been recently associated with human infection, namely, influenza A/H1N1, influenza A/H3N2, and influenza B. Influenza infection in SOT causes significant morbidity and mortality compared to general population [15]. In studies performed in 2009 H1N1 pandemic, the proportion of patients who required hospitalization varied between 73% and 96%, and one of every five patients suffered severe complications with 7–8% mortality [15].

Treatment The mainstay of treatment for influenza A and B are the neuraminidase inhibitors (NAI), mainly oseltamivir (Tables 9.2 and 9.4) [16]. Doubling the treatment dose of oseltamivir in hospitalized patients with influenza does not seem to increase virologic efficacy, except perhaps for influenza B infections or in case of oral absorption concerns, with no evidence of emergence of oseltamivir resistance [17, 18]. Zanamivir is used less frequently than oral oseltamivir, likely due to the inhaled delivery route, although it has shown better activity against influenza B and few cross-resistance with oseltamivir.

Regarding intravenous formulations, if available, intravenous zanamivir or peramivir can be considered in SOT recipients who are severely ill despite oral oseltamivir, in case of concerns with oral absorption, although experience with these drugs in SOT recipients is lacking [1]. Parenteral zanamivir is currently available in Europe, and a single dose intravenous peramivir has been approved in the United States for treatment of uncomplicated influenza infections. However, peramivir use in SOT likely would require repeated dosing or switching to oral oseltamivir to complete therapy.

NAI resistance is currently uncommon (0.09–1.9% of isolates), especially for influenza A/H3N2 and influenza B viruses, but remains an area of growing concern. In case of high-level oseltamivir resistance (such as H1N1 viruses strains with H275Y substitution), peramivir usually preserves reduced susceptibility, but zanamivir is usually active. Another common resistance mutation (H274Y in H3N2) confers resistance to both oseltamivir and peramivir, but not zanamivir. Therefore, peramivir should not be used in patients with oseltamivir resistance unless the isolate is proven to be susceptible [16] (Tables 9.2 and 9.4). DAS181, an inhaled sialidase potentially inhibiting influenza and parainfluenza infection, has shown promising in vitro results of activity against oseltamivir-resistant influenza strains but failed to show superiority compared to placebo in previous studies in healthy subjects with influenza infection [17].

Treatment should be initiated as soon as possible since antiviral therapy is most likely to provide benefit when initiated within the first 48 h of illness in SOT, with a reduced rate of influenza-associated complications (admission to ICU, use of invasive ventilation, and death) [15]. However, benefit has been demonstrated even with

delayed treatment, and most experts endorse influenza-specific antiviral treatment at any point in the illness. Further, treatment should not be delayed while awaiting diagnostic testing results or if a rapid antigen IA test is negative when clinical symptoms are suggestive of infection due to the poor sensitivity of rapid antigen tests (Table 9.3) [19].

In general, duration of antiviral therapy should be at least 5 days for SOT patients although some data suggest that longer duration (≥10 days) may be required, particularly in critically ill patients, those with pneumonia and persistent viral shedding.

Aside from advances in supportive care, no specific adjunctive therapies are routinely recommended. Corticosteroids have been shown to decrease the need for mechanical ventilation and progression to LRTI but at the cost of prolonged viral shedding and risk for invasive fungal coinfection. Corticosteroids are not routinely recommended but should be used if indicated for another reason such as concurrent acute rejection [17].

Prevention The main preventive strategy against influenza in SOT recipients remains the administration of yearly inactivated influenza vaccine. All transplant recipients and candidates, as well as family members, close contacts, and healthcare workers, should receive the influenza vaccine to provide herd immunity [14, 20] (Table 9.2). Influenza vaccines are available in inactivated (intramuscular or intradermal administration) and live-attenuated (intranasal) formulations. The live-attenuated vaccine is not recommended for immunocompromised recipients and close contacts, due to a potential risk of dissemination of the vaccine [14, 21].

Current guidelines recommend the standard injected inactivated influenza for SOT starting 2–6 month posttransplantation with option for administration as early as 1 month posttransplantation in an outbreak setting. If influenza vaccine was administered earlier than 2 months posttransplantation, when it is likely to be less effective, consideration may be given to administering a second dose of vaccine later in the influenza season [14, 20]. An association between vaccination and the development of the de novo antibodies and graft rejection is unproven.

A higher-dose vaccine in pediatric SOT and a booster strategy 5 weeks after standard influenza vaccination in adult SOT have shown to induce an increased antibody response compared with standard single dose. Whether or not protection is increased by use of higher-dose vaccine, adjuvants, booster doses, or quadrivalent versus trivalent vaccines constitutes an area of active research [21].

Clinical failure of influenza vaccination in SOT recipients has not been extensively studied, but most of the studies clearly suggest a reduced immune response in SOT, with a seroconversion rate that varies between 15% and 90%, although this is also dependent on the match between the vaccine and the circulating strains [20]. Vaccination has shown to attenuate adverse outcomes among SOT recipients with a lower incidence of pneumonia and shorter length of hospital stay [19, 22].

Beyond influenza vaccination, pre-exposure or postexposure chemoprophylaxis with either oseltamivir or zanamivir is approved (Tables 9.2 and 9.4) and may be

considered [7]. Caution should be used with prescribing oseltamivir for prophylaxis in patients exposed to an index case because prophylaxis has been associated with emergence of resistant mutants; therefore, monitoring and empiric therapy are generally recommended in these cases [17].

9.6.2 Respiratory Syncytial Virus

Respiratory syncytial virus has long been recognized as a concerning pathogen in immunocompromised hosts. In SOT, RSV infection typically manifests as an URTI with progression to LRTI in 27–67%. Risk factors for more severe disease after organ transplantation include infection in children under a year of age or lung transplantation [2, 4].

Treatment The use of ribavirin (RBV) for the treatment of RSV infection is controversial. In immunocompromised patients (mainly hematopoietic stem cell transplant recipients), RBV has been shown to decrease progression to LRTI when given to patients with URTI. Among SOT, the greatest experience with RBV is with lung transplant recipients. Based on published reports as well as self-reported treatment strategies in surveys from SOT centers, lung and heart-lung recipients often receive RBV for both RSV-related URTI and LRTI [12]. Due to lack of clear evidence of efficacy, wide variation in the management of RSV exists including variability often dependent on availability of the inhaled, intravenous, and oral RBV formulations [23]. Intravenous and inhaled RBV are not available in most European countries. Oral ribavirin appears to be an effective, well-tolerated alternative to intravenous or inhaled ribavirin, providing potential cost savings and reducing length of hospital stay [24] (Tables 9.2 and 9.4). ALN-RSV01, a small interfering RNA that targets the RSV nucleocapsid messenger RNA, has shown some early promise in potentially preventing chronic rejection in lung transplant recipients with RSV; this agent is no longer being developed clinically. In addition, there are a number of other small molecule therapies in various stages of development including early clinical trials [13].

Immunomodulators have also been investigated. Experts recommend considering the addition of an antibody preparation (palivizumab) and IVIG with or without corticosteroids for severe RSV infection in SOT, although data are limited to support this recommendation [12, 23]. A systematic review reported that any form of RBV, alone or in combination with an immunomodulatory agent, was effective in preventing progression from URTI to LRTI, with a trend toward better outcomes with inhaled RBV plus an immunomodulatory with monoclonal (palivizumab) or polyclonal antibody preparations (IVIG) (Table 9.2).

Prevention In addition to the general preventive measures, the only FDA-approved agent for the prevention of severe RSV infection in high-risk patients under the age of 2 years is palivizumab [23, 25]. Survey data suggest that antibody-based prophy-

laxis is used among pediatric transplant centers in young candidates and recipients. However, guidelines regarding the use of this agent in older children and adults do not exist, and the high combined with a lack of clear evidence of efficacy in SOT recipients precludes its wide-scale use (Table 9.2).

9.6.3 Parainfluenza Virus

In SOT patients PIV, most commonly PIV 3, is able to cause more serious and even fatal infections, which mostly occur in patients after lung transplantation [26]. An outbreak of PIV 3 infections in a kidney transplant unit demonstrated that all infections were mild and symptoms resolved spontaneously without associated mortality [27].

Treatment There are no currently approved antiviral treatments for parainfluenza disease. Treatment is supportive and includes reduction in immunosuppression. Oral, aerosolized, and intravenous RBV and/or IVIG and corticosteroids have been used off-label in PIV with variable results and no impact on mortality [28]. DAS181 has been used to treat PIV infections in immunocompromised patients and has shown encouraging results including reduction in PIV quantitative viral load and overall outcomes [28]. Clinical trial results are pending.

Prevention Outbreaks caused by PIV have been reported previously [27], and patients with known or suspected PIV should be isolated with standard contact precautions. There are no approved vaccines or prophylactic antiviral agents.

9.6.4 Human Metapneumovirus

Human metapneumovirus has a clinical pattern similar to RSV and is a significant cause of disease in transplant recipients [3]. hMPV Has been associated with LRTI (pneumonia) and high hospitalization rates [2].

Treatment There is no approved drug for the treatment for hMPV respiratory infection. Supportive therapy is the main treatment although RBV alone or with IVIG could be considered for the management of LRTI and severe cases of hMPV in SOT [29].

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.6.5 Rhinovirus

Rhinovirus has more than 100 serotypes in 3 different species: A, B, and the more recently characterized C. Rhinoviruses are the leading cause of community-acquired

RV infections, and that finding is in agreement with the knowledge that this RV is the primary cause of acute viral respiratory illnesses [2, 3]. Infections with rhinovirus are usually mild and self-limiting URTI, although significant LRTI has been described in lung transplant recipients [2, 3]. Prolonged shedding for over 6 months with minimal symptoms has been reported in lung transplant recipients.

Treatment No specific treatment is approved for rhinovirus infection.

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.6.6 Coronavirus

Coronavirus generally results in self-limited disease but may progress to LRTI. The most common types of HCoV are OC43, 229E, HKU1, and 25 NL63. Severe acute respiratory syndrome coronavirus (SARS-CoV) and

Middle East respiratory syndrome coronavirus (MERS-CoV) are novel coronavirus that have been responsible for recent acute respiratory syndrome epidemics.

Treatment There are no antivirals licensed for the treatment of HCoV infections, and therapy consists of supportive care. RBV has been used for the treatment of LRTI caused by coronavirus during the outbreak of SARS, and the use of RBV in combination with interferon-α-2a on MERS-CoV has been reported. However, this combination has not been reported in SOT, and there are no specific data to recommend RBV for the treatment of CoV infection in SOT recipients [13].

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.6.7 Adenovirus

Adenovirus is a double-stranded DNA virus of the family *Adenoviridae*, with 7 subgroups (A–G) and 52 serotypes.

In contrast to many of the other community-acquired RVs, adenoviral infection can occur from primary acquisition or through reactivation. The transplanted organ is typically the site of infection, and pneumonia is most frequent in lung transplant recipients [30]. Of note, commercial RT-PCR assays differ in sensitivity and specificity for adenovirus (AdV), and quantitative AdV PCR from blood may also be obtained to aid in diagnosis (Tables 9.2 and 9.3).

Treatment Treatment is supportive and includes reduction in immunosuppression. The optimal timing for therapeutic intervention during the course of illness is unclear. Existing data suggests that cidofovir and brincidofovir, an orally bioavailable lipid conjugate of cidofovir, may provide the highest likelihood of antiviral efficacy. Brincidofovir appears to have increased in vitro and in vivo efficacy

against AdV for treatment of serious infections with less renal and bone marrow toxicity than cidofovir (Table 9.4). RBV does not appear to have significant anti-AdV activity in humans and is generally not recommended to treat serious AdV infections. The use of IVIG remains controversial because it does not appear to have a clear benefit at this time. Adoptive T-cell transfer has generally been limited to a few centers (predominantly in hematopoietic stem cell transplantation) and has been reported to be safe and effective when performed early in the course of the infection [30].

Prevention There are no approved vaccines or prophylactic antiviral agents.

9.7 Conclusions

Longitudinal prospective surveillance using molecular diagnostics is needed to understand the true epidemiology and clinical spectrum of respiratory viral diseases in SOT, particularly in non-lung population. Optimal timing, duration, and treatment indication for RVs are a dilemma that needs to be clarified in clinical practice. The efficacy of adjuvant immunogenic therapies remains controversial. Maximizing prevention and infection control measures against RVs in SOT is essential (Table 9.5).

Table 9.5 Key points for RV infections in SOT

Epidemiology and clinical presentation
• There is increasing recognition of infections caused by RVs as a major cause of morbidity and mortality in SOT • In addition to their direct, cytopathic, and tissue-invasive effects, RVs can create a microbially determined immune modulation The impact of RVs in acute and chronic rejection remains controversial, with the greatest risk in lung transplant recipients • Pediatric solid organ, lung transplant, and heart-lung transplantation recipients appear to have the greatest risk of both RVs infections and more severe complications • Rhinovirus and coronaviruses are the most common etiological agents • Influenza and other paramyxovirus (RSV, PIV, and hMPV) have a greater propensity to produce LRTID
Diagnosis
• Diligent collection of respiratory specimens and knowledge of the limitations of the assay used by your laboratory are essential for interpreting the results • Nasopharyngeal swabs (NPS) are preferred for the detection of all major RVs • Bronchoalveolar lavage is the preferred specimen for diagnostic testing in LRTID with negative NPS • Laboratory diagnostic methods include virus culture, rapid antigen detection tests, the reverse-transcriptase polymerase chain reaction (RT-PCR) and other nucleic acid amplification assays, and serology • Nucleic acid amplification tests, mainly RT-PCR, are the best diagnostic tools for studying RVs in SOT

Table 9.5 (continued)

Treatment
• Treatment options remain limited and consist of supportive care, reduction of immunosuppression and, if available, antiviral therapy • The use of immunomodulatory agents (intravenous immunoglobulin, monoclonal antibodies, RV-specific T lymphocytes or augmented corticosteroid therapy) is a clinical dilemma • SOT should receive antiviral therapy with a neuraminidase inhibitor (NAI, either oseltamivir or zanamivir) when influenza is suspected, before laboratory confirmation • Treatment of influenza with M2 inhibitors (amantadine and rimantadine) is not recommended for high resistance rates • Treatment for influenza with NAI should be initiated as soon as possible (<48 h) for optimal benefit, however and all symptomatic patients should receive antiviral therapy, irrespective of symptom onset • Duration of therapy should be minimum of 5 days, but longer duration of therapy (≥10 days) may be required in critically ill patients • Double dosing of oseltamivir is not recommended but may be considered in severe cases or in case of insufficient response to therapy • The use of intravenous zanamivir or peramivir can be considered in patients not responding to oseltamivir therapy or for whom oral absorption is a concern • In case of high-level oseltamivir resistance, zanamivir is usually active • The efficacy of ribavirin (aerosolized, intravenous, or oral) for the treatment of RSV infection in SOT recipients has not been determined • In severe cases of LRTIs with RSV, PIV, and hMPV infections in SOT recipients, therapy with ribavirin (aerosolized, intravenous, or oral) may be used, alone or in combination with an immunomodulatory agents
Prevention
• Maximizing prevention infection control measures against RVs in SOT is mandatory • SOT recipients should avoid close contact with individuals with respiratory tract infections • The main preventive strategy against influenza remains the administration of yearly trivalent inactivated influenza vaccine in all SOT recipients and their relatives • Influenza vaccination is safe in SOT recipients, even in the early posttransplant period • Oseltamivir may be used as pre-exposure and postexposure prophylaxis in selected patients • The use of palivizumab for prevention of RSV infection is not recommended in adult SOT recipients

FLU influenza, *hMPV* human metapneumovirus, *LRTID* lower respiratory tract infectious disease, *NPS* nasopharyngeal swab, *PIV* parainfluenza, *RBV* ribavirin, *RSV* respiratory syncytial virus, *RVs* respiratory viruses, *SOT* solid organ transplant

References

1. Manuel O, Lopez-Medrano F, Keiser L, Welte T, Carratala J, Cordero E, et al. Influenza and other respiratory virus infections in solid organ transplant recipients. Clin Microbiol Infect. 2014;20(Suppl 7):102–8.
2. 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. Am J Transplant. 2017;17(5):1304–12.
3. 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.

4. Arslan D, Danziger-Isakov L. Respiratory viral infections in pediatric solid organ and hematopoietic stem cell transplantation. Curr Infect Dis Rep. 2012;14(6):658–67.
5. Vu DL, Bridevaux PO, Aubert JD, Soccal PM, Kaiser L. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. Am J Transplant. 2011;11(5):1071–8.
6. Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect. 2014;20(Suppl 7):4–9.
7. Manuel O, Estabrook M, Practice ASTIDCo. RNA respiratory viruses in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):212–9.
8. Lachant DJ, Croft DP, McGrane Minton H, Prasad P, Kottmann RM. Nasopharyngeal viral PCR in immunosuppressed patients and its association with virus detection in bronchoalveolar lavage by PCR. Respirology. 2017;22(6):1205–11.
9. Hodinka RL. Respiratory RNA viruses. Microbiol Spectr. 2016;4(4). https://doi.org/10.1128/microbiolspec.DMIH2-0028-2016
10. Hammond SP, Gagne LS, Stock SR, Marty FM, Gelman RS, Marasco WA, et al. Respiratory virus detection in immunocompromised patients with FilmArray respiratory panel compared to conventional methods. J Clin Microbiol. 2012;50(10):3216–21.
11. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza – recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(1):1–24.
12. 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. Transpl Infect Dis. 2016;18(2):210–5.
13. Grim SA, Reid GE, Clark NM. Update in the treatment of non-influenza respiratory virus infection in solid organ transplant recipients. Expert Opin pharmacother. 2017;18(8):767–79.
14. Danziger-Isakov L, Kumar D, ASTIDCo P. Vaccination in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):311–7.
15. 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. Lancet Infect Dis. 2010;10(8):521–6.
16. Gubareva LV, Besselaar TG, Daniels RS, Fry A, Gregory V, Huang W, et al. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2015–2016. Antiviral Res. 2017;146:12–20.
17. Ison MG. Antiviral treatments. Clin Chest Med. 2017;38(1):139–53.
18. Lee N, Hui DS, Zuo Z, Ngai KL, Lui GC, Wo SK, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza a and B infections. Clin Infect Dis. 2013;57(11):1511–9.
19. 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. Clin Infect Dis. 2018;67(9):1322–9.
20. Cordero E, Manuel O. Influenza vaccination in solid-organ transplant recipients. Curr Opin Organ Transplant. 2012;17(6):601–8.
21. Chong PP, Avery RK. A comprehensive review of immunization practices in solid organ transplant and hematopoietic stem cell transplant recipients. Clin Ther. 2017;39(8):1581–98.
22. Perez-Romero P, Aydillo TA, Perez-Ordonez A, Munoz P, Moreno A, Lopez-Medrano F, et al. Reduced incidence of pneumonia in influenza-vaccinated solid organ transplant recipients with influenza disease. Clin Microbiol Infect. 2012;18(12):E533–40.
23. Danziger-Isakov LA, Arslan D, Sweet S, Benden C, Goldfarb S, Wong J. RSV prevention and treatment in pediatric lung transplant patients: a survey of current practices among the International Pediatric Lung Transplant Collaborative. Pediatr Transplant. 2012;16(6):638–44.
24. Burrows FS, Carlos LM, Benzimra M, Marriott DJ, Havryk AP, Plit ML, et al. Oral ribavirin for respiratory syncytial virus infection after lung transplantation: efficacy and cost-efficiency. J Heart Lung Transplant. 2015;34(7):958–62.

25. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):415–20.
26. 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. Am J Transplant. 2003;3(2):116–20.
27. Helantera I, Anttila VJ, Loginov R, Lempinen M. Parainfluenza 3 infections early after kidney or simultaneous pancreas-kidney transplantation. Am J Transplant. 2017;17(3):809–12.
28. Russell E, Ison MG. Parainfluenza virus in the hospitalized adult. Clin Infect Dis. 2017;65(9):1570–6.
29. Raza K, Ismailjee SB, Crespo M, Studer SM, Sanghavi S, Paterson DL, et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. J Heart Lung Transplant. 2007;26(8):862–4.
30. Ison MG, Hayden RT. Adenovirus. Microbiol Spectr. 2016;4(4). https://doi.org/10.1128/microbiolspec.DMIH2-0020-2015