

Respiratory Viral Infections in Transplant Recipients

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Respiratory Viral Infections in Transplant Recipients



Respiratory Viral Infections in Transplant Recipients

- Influenza
- Rhinovirus
- CMV
- RSV
- HPIV
- HSV
- Adenovirus
- HMPV

HSV Pneumonia



HSV Pneumonia



- HSV pneumonia is caused predominately by HSV type 1 and rarely by HSV type 2 .
- HSV type 1 pneumonia is uncommon.

HSV Pneumonia

- **Predisposing host factors include :**
- **Severe burns**
- **Acquired immunodeficiency syndrome (AIDS)**
- **Malignancy**
- **Organ transplantation**
- **Trauma from intubation**
- **Smoke inhalation**
- **Chronic cigarette smoking**

HSV Pneumonia

- **There are two possible routes for lower respiratory tract involvement:**
- **Aspiration or extension of oropharyngeal infection into the lower respiratory system .**
- **Hematogenous spread in patients with sepsis.**

HSV Pneumonia

- **Patients with respiratory infection may show:**
- **Fever**
- **Productive cough**
- **Shortness of breath**
- **Signs of upper airway obstruction caused by pseudomembranes related to tracheal ulcers.**

Proven HSV Pneumonia



- **Proven HSV pneumonia if HSV was the only pathogen identified by PCR in the BAL specimen in concurrence of cytopathologic effect and/or HSV positive IHC in cells obtained from the same BAL specimen.**

Probable HSV Pneumonia



- Probable HSV pneumonia was defined by the presence of HSV and other pathogens in combination with cytopathologic effect and/or HSV positive IHC in cells obtained from the same BAL specimen.

Possible HSV Pneumonia



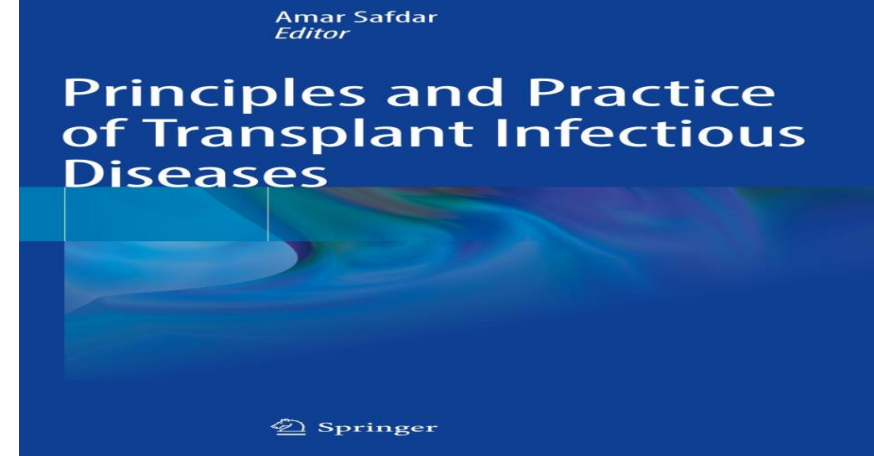
- Possible HSV pneumonia if HSV was identified by PCR (with viral load $> 10^5$ copies/mL) in the BAL specimen with or without other pathogens despite no cytological or IHC evidence of

HSV Pneumonia

- **HSV infection can show three forms of pulmonary involvement at pathologic evaluation:**
- **Necrotizing tracheobronchitis**
- **Necrotizing pneumonia**
- **Interstitial pneumonitis**

- HSV pneumonia commonly shows patchy bilateral consolidation and GGO with lobular, segmental, or subsegmental distribution. Reticular opacity also can be present. Pleural effusion is common. The presence of small or larger centrilobular nodules is controversial; however, they can be due to viral pneumonia itself, multiple hemorrhagic nodules, or coexisting fungal pneumonia.



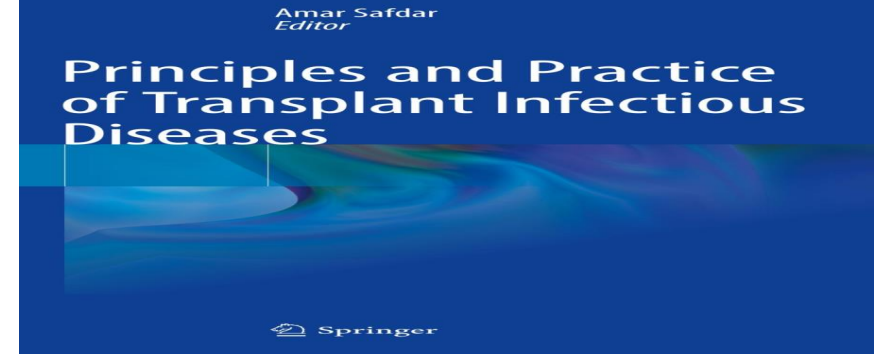


- **Intravenous Acyclovir at a higher dose (5–10 mg/kg every 8 h)** should be considered for disseminated, cerebral, visceral, or extensive mucocutaneous HSV disease.
- A minimum of 14 days of treatment is recommended for severe disease, and others have **extended the duration to as long as 21 days in cases of pneumonia**.

CMV Pneumonia

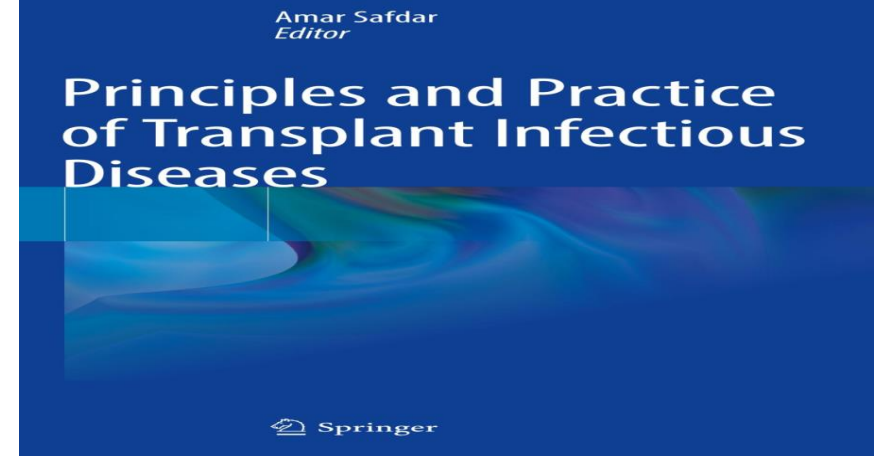


CMV Pneumonia



- Can cause life-threatening pulmonary infection in immunocompromised patients owing to reactivation of the latent virus or infusion of CMV-seropositive marrow .
- Transplantation and long-term corticosteroid therapy are important risk factors.
- CMV infection is a frequent complication of both hematopoietic stem cell transplantation and solid-organ transplantation.

CMV Pneumonia



- Patients undergoing mismatched or unrelated donor graft transplants
- Indication for HSCT (cancer vs. other disorders)
- T cell depletion
- Acute GVHD
- High-dose (1 mg/kg per day) corticosteroid use promote risk for CMV infection in this population

Prevention and Treatment of Cytomegalovirus Infections in Solid Organ Transplant Recipients



Christine E. Koval, MD

KEYWORDS

- CMV • Cytomegalovirus • Herpesvirus infection • Solid organ transplantation
- CMV prophylaxis • CMV treatment

KEY POINTS

- Cytomegalovirus (CMV) prophylaxis and preemptive monitoring have reduced the incidence of early CMV disease in solid organ transplantation, but late disease has emerged as a significant problem.
- CMV-specific cell-mediated immunity (CMI) is required to control CMV in the absence of antiviral therapy, and achieving strong CMI without coincident allograft rejection is the ultimate goal of CMV management strategies.
- Measurement of CMV-specific CMI may help refine CMV prophylaxis and preemptive monitoring strategies.
- Valganciclovir remains the mainstay of CMV treatment but comes at the cost of frequent myelosuppression.
- Letermovir is a newly approved antiviral with strong activity against CMV and minimal side effects and may change the landscape of CMV management.

Risk factors for cytomegalovirus disease in SOT

	High Risk	Intermediate Risk	Lower Risk	Comments
CMV serostatus	CMV IgG D+/R–	CMV IgG D+/R+, CMV IgG D–/R+	CMV IgG D–/R–	Falsely positive (blood products, IVIG) Falsely negative (loss of antibody, CVID) Equivocal results in donor: interpret as positive Equivocal results in recipient: interpret as negative Not all serologic testing products equivalent
Immunosuppression	Antilymphocyte antibodies (thymoglobulin, alemtuzumab, OKT3)	MMF, azathioprine, tacrolimus, cyclosporine, high-dose steroids	Maintenance steroids mTOR inhibitors	Increased risk for all agents, with higher doses
Organ transplanted	Lung Pancreas Intestine	Heart composite tissue	Liver Kidney	Burden of latently infected cells Higher levels of immunosuppression
CMV-specific cell-mediated immunity	Low	Intermediate	High	Data limited May be useful at guiding prophylaxis and preemptive prevention strategies

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY

 **Clinical TRANSPLANTATION**
The Journal of Clinical and Translational Research

Cytomegalovirus in solid organ transplant recipients— Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Raymund R. Razonable¹ | Atul Humar^{2,3}

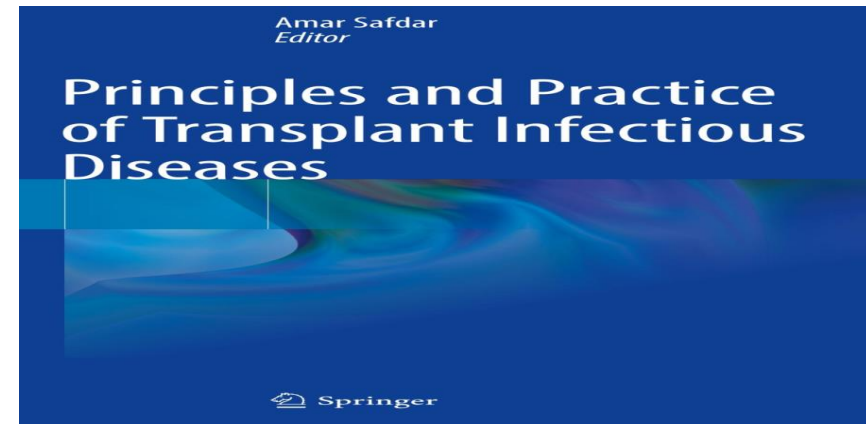
Proven or definite

- **Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with :**
- **CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques.**

Probable

- **Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with:**
- **Detection of CMV by viral isolation and rapid culture of BALF, or quantitation of CMV DNA in BALF.**

- **Presence of CMV by (+) PCR is not adequate.**
- **It has been proposed that in HSCT recipients, isolation of other opportunistic pathogens like filamentous fungi in the setting radiologic features consistent with IFD probably indicates fungal pneumonia rather than CMV pneumonia, when such a diagnosis is based on (+) CMV PCR alone.**



Pulmonary cytomegalovirus (CMV) DNA shedding in allogeneic hematopoietic stem cell transplant recipients: Implications for the diagnosis of CMV pneumonia.

Piñana JL, et al. J Infect. 2019.

[Show full citation](#)

Abstract

OBJECTIVES: To date no definitive cut-off value for cytomegalovirus (CMV) DNA load in bronchoalveolar lavage (BAL) fluid specimens has been established to discriminate between CMV pneumonia and pulmonary CMV DNA shedding in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients.

METHODS: The current retrospective study is aimed at assessing the range of CMV DNA loads quantified in BAL fluid specimens from allo-HSCT patients with pneumonia in which different microorganisms were causally involved.





- **CMV DNA load cut-off of 500 IU/ml in BAL fluid was found to have a positive predictive value of ~50% for the presence of probable CMV pneumonia in BMT.**
- **Presence of CMV DNA in BAL fluid specimens at levels >500 IU/ml, in addition to:**
 - **Receipt of corticosteroids**
 - **low lymphocyte counts at the time of BAL sampling****was associated with increased pneumonia-attributable mortality**

Cytomegalovirus Viral Load in Bronchoalveolar Lavage to Diagnose Lung Transplant Associated CMV Pneumonia.

Lodding IP, et al. Transplantation. 2018.

[Show full citation](#)

Abstract

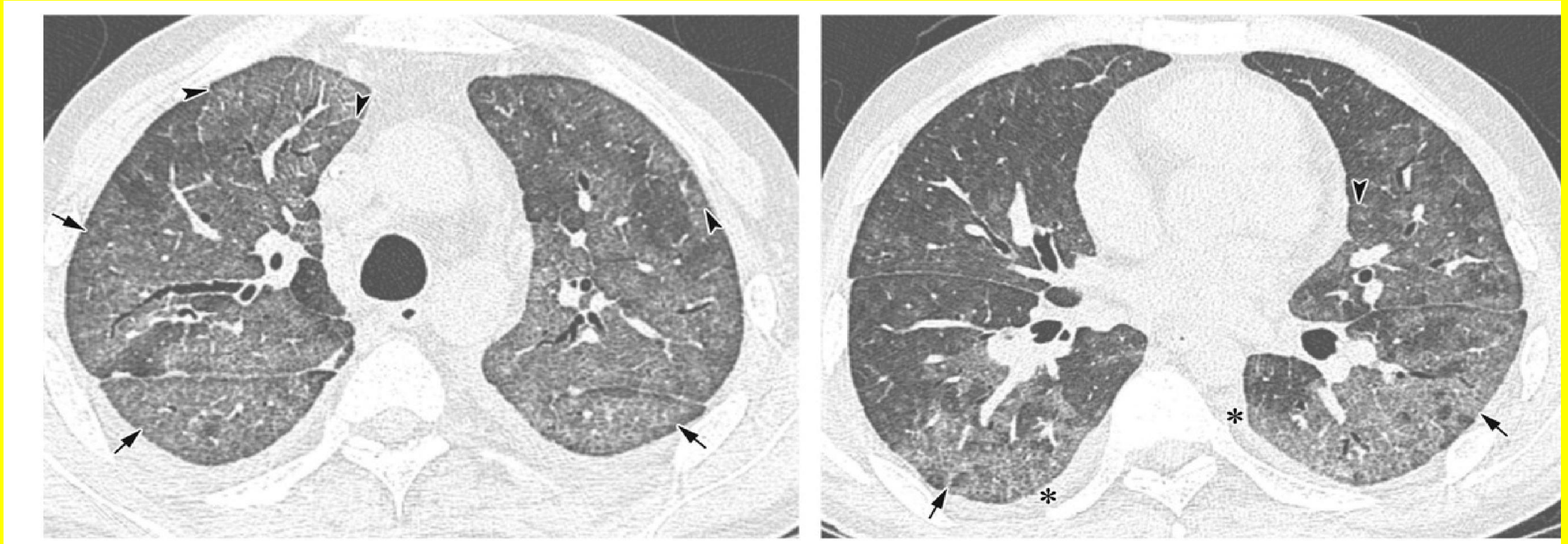
BACKGROUND: The diagnostic yield for cytomegalovirus (CMV) polymerase chain reaction (PCR) viral load in bronchoalveolar lavage (BAL) or in plasma to diagnose CMV pneumonia in lung transplant recipients remains uncertain and was investigated in a large cohort of consecutive lung transplant recipients.





- **CMV in BAL was at the optimum cutoff (4545 IU/mL) with a corresponding sensitivity of 91% and specificity of 77% in lung transplant.**

- The predominant radiologic findings are bilateral asymmetric GGO, poorly defined small centrilobular nodules, and airspace consolidation. Thickened interlobular septa also are observed. However, masses and masslike infiltrates can be more common in patients with AIDS than in non-AIDS patients

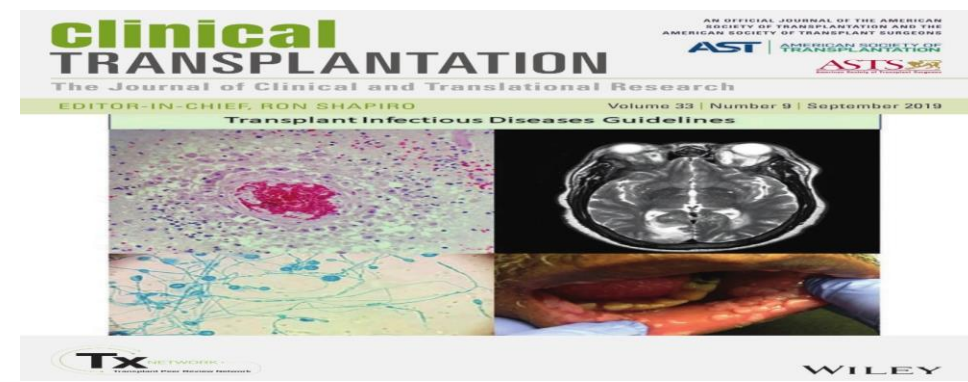




- **Intravenous Ganciclovir is the recommended initial treatment for severe or life-threatening CMV disease, those with very high viral load and those with questionable gastrointestinal absorption.**
- **Because of the risk of nephrotoxicity, Foscarnet and Cidofovir are considered second-line alternative drugs for SOT recipients unable to tolerate Valganciclovir or intravenous Ganciclovir**



- Until clinical trials demonstrate its efficacy and safety in the SOT population, **Letermovir** is not recommended for treatment of CMV disease after SOT.



- Antiviral treatment of CMV disease should be continued until the following criteria are met :
 - Resolution of clinical symptoms
 - Virologic clearance below a threshold negative value based on laboratory monitoring with CMV QNAT once a week
 - Minimum 2 weeks of antiviral treatment



- The addition of IVIg or CMV-Ig to antiviral treatment of CMV disease may be considered for patients with:
- Life-threatening disease
- CMV pneumonitis
- Possibly other severe forms of disease
- Drug-resistant virus
- Those with hypogammaglobulinemia



Review

Cytomegalovirus Infections after Hematopoietic Stem Cell Transplantation: Current Status and Future Immunotherapy

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Drugs	Mechanisms	Indication or Primary Endpoint in Clinical Trials, Dosing Regimens if Possible	Main Adverse Events and Considerations
Letermovir	CMV terminase inhibitor that targets the UL56 viral subunit	Prophylaxis of CMV infection and disease in CMV-seropositive recipients of an allogeneic HSCT 480 mg PO or IV once daily through 100 days post transplantation (coadministration with cyclosporine: If cyclosporine is initiated after starting letermovir, decrease the next letermovir dose to 240 mg once daily; if cyclosporine is discontinued after starting letermovir, increase the next letermovir dose to 480 mg once daily; if cyclosporine is interrupted due to high cyclosporine levels, no dose adjustment of letermovir is needed)	Nausea, vomiting Has not been studied as an agent for treatment; has multiple drug interactions; lacks activity against other herpesviruses including HSV and VZV
Maribavir	UL97 viral protein kinase inhibitor	Not approved yet Clinical trials for treatment in transplant recipients with CMV infections that are refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir; preemptive treatment in adult transplanted patients presenting with asymptomatic viremia	Taste disturbance Lower risk of hematotoxicity and absence of clear nephrotoxicity
Brincidofovir	Inhibits DNA polymerase, orally bioavailable formulation prodrug of cidofovir	Not approved yet Clinical trials for prophylactic or preemptive treatment of CMV infections; can be administered twice a week due to a long half-life	Diarrhea No excessive risk of nephro- and hematotoxicity

Prevention and Treatment of Cytomegalovirus Infections in Solid Organ Transplant Recipients



Christine E. Koval, MD

KEYWORDS

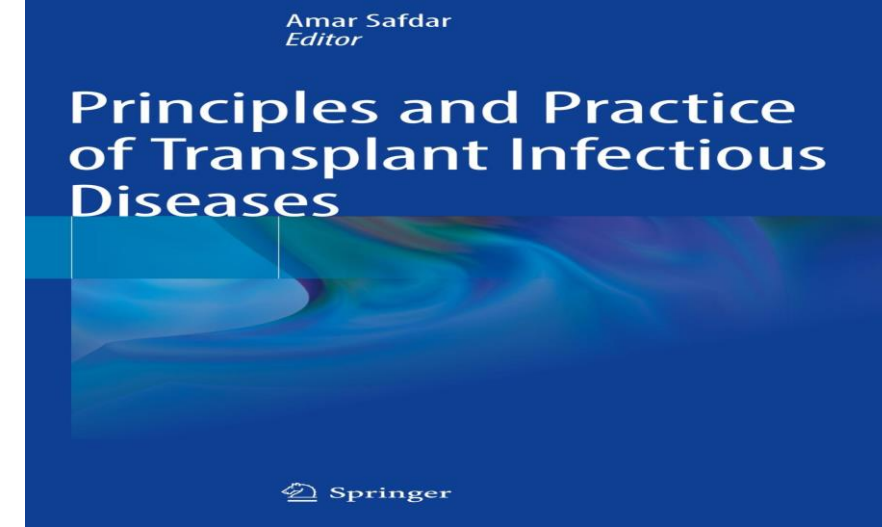
- CMV • Cytomegalovirus • Herpesvirus infection • Solid organ transplantation
- CMV prophylaxis • CMV treatment

KEY POINTS

- Cytomegalovirus (CMV) prophylaxis and preemptive monitoring have reduced the incidence of early CMV disease in solid organ transplantation, but late disease has emerged as a significant problem.
- CMV-specific cell-mediated immunity (CMI) is required to control CMV in the absence of antiviral therapy, and achieving strong CMI without coincident allograft rejection is the ultimate goal of CMV management strategies.
- Measurement of CMV-specific CMI may help refine CMV prophylaxis and preemptive monitoring strategies.
- Valganciclovir remains the mainstay of CMV treatment but comes at the cost of frequent myelosuppression.
- Letermovir is a newly approved antiviral with strong activity against CMV and minimal side effects and may change the landscape of CMV management.

Antivirals available for treatment of cytomegalovirus disease

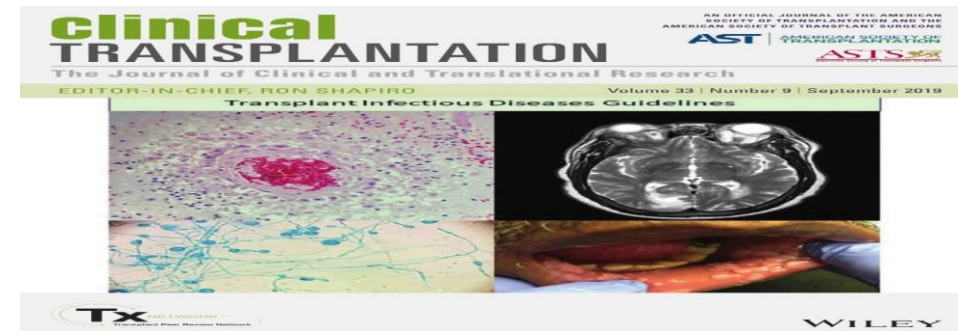
	Indication	Dosage	Side Effects	Comments
Valganciclovir Oral High dose	CMV infection • CMV DNA $<1 \times 10^5$ IU/mL ^a CMV disease GCV resistance ($<5 \times$ GCV EC50)	900 mg twice daily 1350–1800 mg twice daily	Leukopenia Anemia Thrombocytopenia	Dose adjust for renal impairment Consider adequacy of GI absorption Oral option after initial therapy with IV ganciclovir
Ganciclovir Intravenous High dose	CMV infection • CMV DNA $>1 \times 10^5$ IU/mL ^a CMV disease requiring hospital admit ^a GCV resistance ($<5 \times$ GCV EC50)	5 mg/kg every 12 h 7.5–10.0 mg/kg every 12 h	Leukopenia Anemia Thrombocytopenia	Dose adjust for renal impairment Can change to oral valganciclovir to complete course
Foscarnet Intravenous	CMV infection or disease with GCV resistance ($\geq 5 \times$ GCV EC50)	90 mg/kg every 12 h	Nephrotoxicity Electrolyte wasting Cytopenias	Dose adjust for renal impairment Hospital admission usually required for hydration, initial monitoring of renal function, K, Mg, Ca, P
Cidofovir Intravenous	CMV infection or disease refractory and resistant to GCV and FOS	5 mg/kg weekly $\times 2$ then every 2 wk	Highly nephrotoxic	Alternative lower doses used
Letermovir Oral Intravenous	Primary CMV infection? Secondary CMV infection? CMV disease? CMV with GCV and/or FOS resistance	480 mg daily (240 mg daily with CSA)	Peripheral edema Headache Nausea Diarrhea	CYP3A4 inhibitor Increases concentration of CSA Increased concentration by CSA May increase concentration of tacrolimus Not active against HSV or VZV



- In patients with pulmonary edema and circulatory volume overload that may be exacerbated by IVIG, a reduced volume CMV-enriched immunoglobulins may exert less intravascular oncotic pressure and can be substituted in select clinical situations.



- After completion of full-dose antiviral treatment, secondary prophylaxis intended to prevent CMV relapse is **not recommended** as a routine practice for all patient, **but may be considered in subsets of high-risk patients** .



- If feasible, cautious reduction in immunosuppression should be considered in SOT patients presenting with CMV disease, especially if moderate to severe .
- ▪ Reduction in immunosuppression may not be feasible in patients with recent rejection or at heightened risk of rejection episodes.
- ▪ Reduction in immunosuppression should be strongly considered in SOT patients with severe lymphopenia and those with deficient nonspecific or CMV-specific T-cell function .

Adenovirus



Adenovirus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Diana F. Florescu¹  | Joanna M. Schaenman²  | on behalf of the AST Infectious Diseases Community of Practice

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Correspondence

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Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention, and management of adenovirus infections after solid organ transplantation. Adenovirus is an important cause of infectious complications in both stem cell transplant and SOT patients, causing a range of clinical syndromes including pneumonitis, colitis, and disseminated disease. The current update of the guidelines highlights that adenovirus surveillance testing should not be performed in asymptomatic recipients. Serial quantitative PCR might play a role in the decision to initiate or assess response to therapy in a symptomatic patient. The initial and most important components of therapy remain supportive care and decrease in immunosuppression. The use of antiviral therapy is not supported by prospective randomized clinical trials. However, intravenous cidofovir is considered the standard practice for treatment of severe, progressive, or disseminated adenovirus disease in most transplant centers. Intravenous immunoglobulin may be beneficial, primarily in a select group of patients with hypogammaglobulinemia. Future approaches to treatment of adenovirus disease may include administration of adenovirus-specific T-cell therapy.

KEYWORDS

infectious, infection and infectious agents, adenovirus, solid organ transplant and transplantation

Adenovirus

- **Severe cases caused by adenovirus have been associated with older age, chronic underlying conditions, and low absolute lymphocyte counts .**
- **Adenovirus infection exhibits more severe and fatal conditions with acute respiratory distress syndrome in immunocompromised patients.**

Adenovirus

- **Adenovirus infections occur throughout the year without seasonal variability.**
- **Adenovirus infections can be acquired de novo, through reactivation of a latent infection of the recipient or from the transplanted organ.**
- **Early Adenovirus disease post-transplantation suggests adenovirus reactivation or donor-derived infection.**

Incidence of Adenovirus infection by organ transplanted

Allograft type	Reported adenovirus incidence (%)
Pediatric transplantation	
Liver	3.5-38
Heart, heart-lung, lung	7-50
Kidney	11
Intestinal, multivisceral	4.3-57.1
Adult transplantation	
Liver	5.8
Heart, heart-lung, lung	6-22.5
Kidney	4.1-6.5
Intestinal, multivisceral	N/A

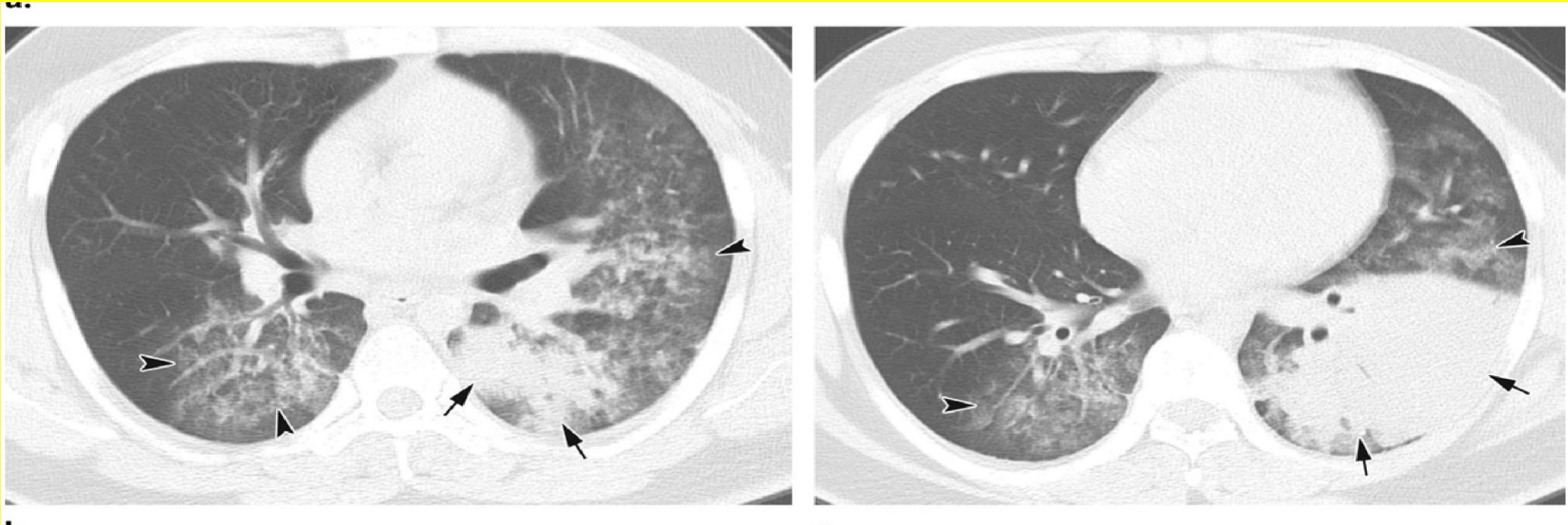
Adenovirus

- The available diagnostic methods for adenovirus infections are as follows:
- Viral culture
- Direct antigen detection
- Molecular methods
- Histopathology.
- Serology and electron microscopy are available, but not routinely used in clinical practice.
- Amplification and detection of the viral genome using polymerase chain reaction (**PCR**) is a widely used tool for detection of adenovirus.

Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

- **Adenovirus infection post BMT may be asymptomatic or present as an URTI, enteritis or cystitis.**
- **Adenovirus is now recognised as a significant pathogen in children following BMT with reported mortality rates as high as 60% in disseminated infection.**
- **Adenovirus can be detected in blood, stool, urine, throat swab or NPA/NPW**

- **Adenovirus pneumonia shows bilateral multifocal GGO with patchy consolidations on images and may show lobar or segmental distribution indicative of bronchopneumonia that resembles bacterial pneumonia**





Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- Adenovirus pneumonia is usually observed in AdV disseminated disease.
- Preemptive treatment is recommended as soon as viremia is higher or equal to 1000 copies/ml coupled with lymphocyte counts below 300/mm³ and CD4 T lymphocyte counts below 25/mm³.
- This is particularly important in high risk patients and those who received cord blood graft or are under steroid treatment.



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- For AdV, there is no proven role for Ganciclovir, Foscarnet or Immunoglobulin therapy in immunocompromised patients.
- There is anecdotal evidence of successful treatment of AdV with Ribavirin (Schleuning et al., 2004) but most studies have not been supportive.



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- **Successful Cidofovir treatment of AdV infections in immunocompromised hosts after HCT.**
- **Another novel compound is CMX001 (Hexadecyloxypropylcidofovir, Brincidofovir, Chimerix).**

Department of Clinical Haematology
Oxford BMT Programme

Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

- **Ribavirin may be considered in selected high-risk patients with LRTI, based on anecdotal reports.**



- Ribavirin seems to have antiviral activity only against subtype C adenoviruses (serotypes 1, 2, 5, and 6).
- Did not reduce significantly the viral titers in treated patients when used as intravenous therapy at doses ranging from 10 to 60 mg/ kg qday.

Correspondence

Oral ribavirin for severe adenovirus infection after allogeneic marrow transplantation

Bone Marrow Transplantation (2003) **32**, 1107–1108.
doi:10.1038/sj.bmt.1704276

- Oral Ribavirin 20 mg/kg was started again orally every 6 h for 5 days, followed by 10 mg/kg every 6 h for 4 days.

HPIV Infection



HPIV

- **HPIV is a single-stranded RNA virus and a member of the family Paramyxoviridae.**
- **HPIVs consist of four serotypes that cause respiratory illness by binding to the ciliated epithelium of the respiratory tract.**
- **The manifestations of HPIV infection are diverse, including otitis media, conjunctivitis, pharyngitis, croup, bronchitis, and pneumonia.**
- **HPIV infection is a common cause of disease and death in recipients of hematopoietic stem cell transplants and patients with hematologic malignancy.**

Parainfluenza Virus in Hospitalized Adults: A 7-Year Retrospective Study

Elliott Russell, Amy Yang, Sydney Tardrew, and Michael G. Ison

Divisions of Infectious Diseases and Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Background. Parainfluenza virus (PIV) is a cause of respiratory tract infection in children and the immunocompromised population, but its clinical manifestations, impact, and outcomes in hospitalized adults are not well studied.

Methods. This retrospective study included adults (≥ 18 years old) admitted to Northwestern Memorial Hospital or Prentice Women's Hospital (both in Chicago, Illinois) between 1 August 2009 and 31 July 2016 with a positive molecular test result for PIV. Epidemiologic, clinical, and outcomes data were collected from the enterprise data warehouse and patient electronic health records after institutional review board approval. Descriptive statistics were used to summarize the data.

Results. A total of 550 adults with a positive molecular test for PIV were identified. Differences in seasonality, clinical presentation, and prevalence between the different PIV serotypes (PIV-1, PIV-2, and PIV-3) were identified. The most common signs/symptoms were cough (88%), productive sputum (55%), fever (63%), and dyspnea (49%). Of the patients administered antibiotics, 349 (79.6%) had no confirmed bacterial infection throughout their hospitalization. The average length of hospitalization was 7.7 days. Presence of bacterial coinfection ($P = .01$), fungal coinfection ($P < .01$), decreased body mass index ($P = .03$), and increased respiratory rate ($P < .01$) were associated with significant differences in mortality rates.

Conclusions. PIV infection is associated with substantial morbidity in hospitalized adults. Such data will be useful in understanding the impact on epidemiology and outcomes if a PIV-specific vaccine becomes available. Furthermore, this highlights the need for novel preventive and therapeutic approaches to PIV infection.

Keywords. parainfluenza; virus; hospitalized; adults.

Parainfluenza Virus in Hospitalized Adults: A 7-Year Retrospective Study

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Divisions of Infectious Diseases and Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, Illinois

- This infection occurs predominantly (46.7%) from June to September.
- PIV-3 was the most prevalent serotype, accounting for 60% of infections. PIV-1 and PIV-2 accounted for 22% and 18% of the remaining cases, respectively.
- Most significantly, PIV-3 had a peak in prevalence over late spring and early summer, while PIV-1 peaked late fall and PIV-2 over the winter.
- Over the years of data collection, PIV-2 and PIV-3 had a steadily increasing prevalence, and PIV-1 showed a biannual pattern of infection rates.



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- PIV risk factors for progression to LRI are:
- Lymphopenia
- Steroid use
- Co-infections with other respiratory agents.

Outcomes in Invasive Pulmonary Aspergillosis Infections Complicated by Respiratory Viral Infections in Patients With Hematologic Malignancies: A Case-Control Study

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¹Department of Infectious Disease, Infection Control and Employee Health, and ²Department of Microbiology, The University of Texas MD Anderson Cancer Center, Houston

Background. Data regarding invasive pulmonary aspergillosis (IPA) following respiratory viral infections (RVIs) in patients with leukemia and/or hematopoietic stem cell transplantation (LHSCT) are limited.

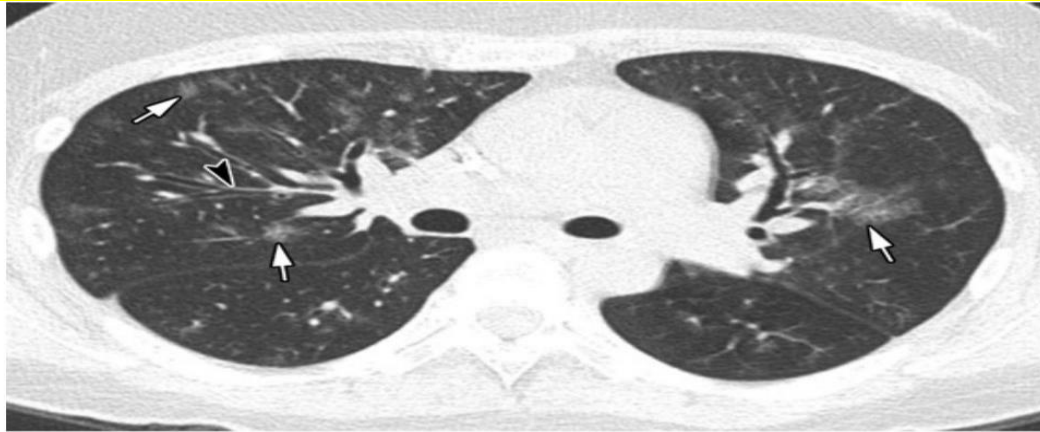
Methods. We conducted a retrospective case-control study of post-RVI IPA (2006–2016). Cases were patients who underwent LHSCT and had RVI due to respiratory syncytial virus (RSV), influenza virus (INF), or parainfluenza virus (PIV) followed by culture-documented IPA within 6 weeks. Controls had IPA only.

Results. We identified 54 cases and 142 controls. Among cases, 29 (54%) had PIV infection, 14 (26%) had INF infection, and 11 (20%) had RSV infection. The median time to IPA after RVI was 7 days. A greater percentage of cases (37 [69%]) than controls (52 [37%]) underwent allogeneic HSCT ($P < .0001$). Cases were more likely to be nonneutropenic (33 [61%] vs 56 [39%]; $P = .009$) and in hematologic remission (27 [50%] vs 39 [27%]; $P = .003$) before IPA. Cases were more likely to have monocytopenia (45 [83%] vs 99 [70%]; $P = .05$) and less likely to have severe neutropenia (21 [39%] vs 86 [61%]; $P = .007$) at IPA diagnosis. Prior use of an *Aspergillus*-active triazole was more common in cases (27 of 28 [96%] vs 50 of 74 [68%]; $P = .0017$). Median time to empirical antifungal therapy initiation was 2 days in both groups. Crude 42-day mortality rates did not differ between cases (22%) and controls (27%), but the 42-day mortality rate was higher among cases with IPA after RSV infection (45%) than among those with IPA following INF or PIV infection (13%; $P = .05$).

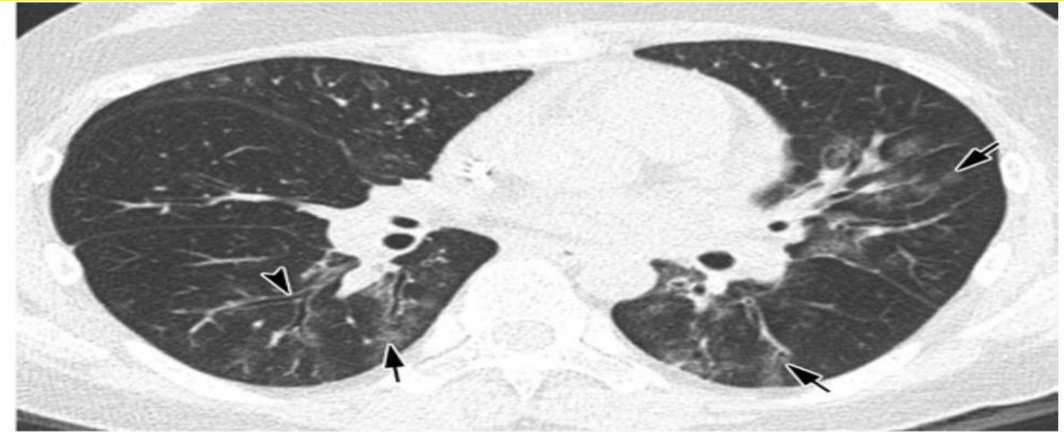
HPIV

- **Pulmonary co-pathogens, e.g., *Aspergillus fumigatus*, are often present in patients with pneumonia and highly contribute to mortality.**
- **Post-RVI IPA was defined as sputum, BAL (or bronchial wash), or tissue biopsy specimen cultures positive for *Aspergillus* species identified within 6 weeks after RVI.**

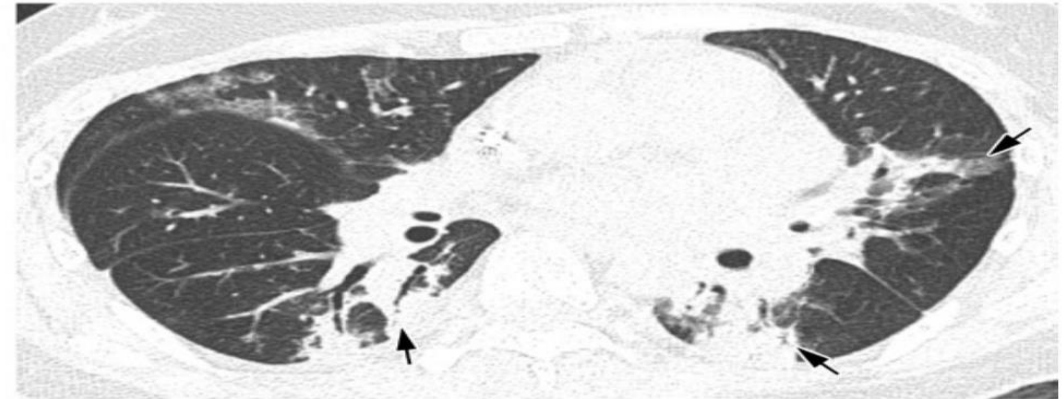
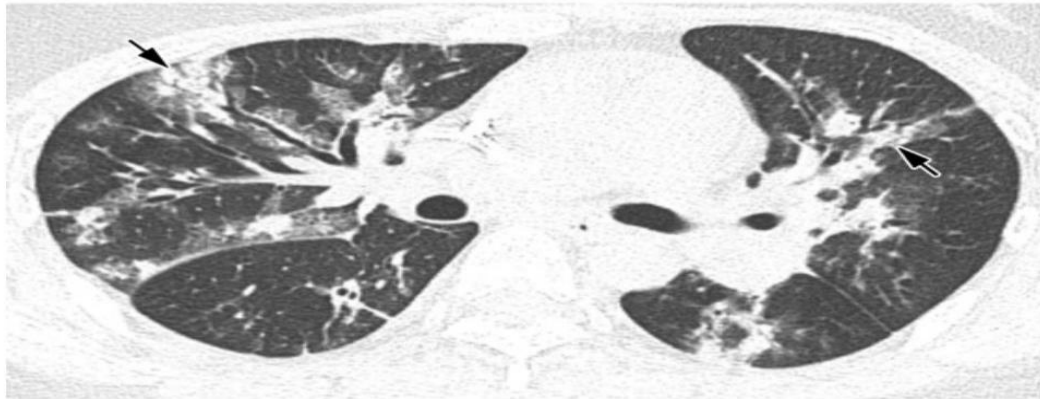
- **HPIV pneumonia shows multifocal patchy consolidation with GGO that hinders differentiation of viral from bacterial pneumonia, and approximately one-fourth of patients show centrilobular nodules with bronchial wall thickening**



a.



b.





Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- **No specific treatment for PIV infection is currently strongly recommended.**
- **However, current ECIL-4 guidelines suggest treatment with aerosolized Ribavirin or off-label use with systemic Ribavirin.**

Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

- Treatment of HPIV is generally supportive together with respiratory isolation.
- Reduction of steroid dosage where feasible and appropriate may be a valid approach.
- No proven anti-viral agent exists although some agents are in early phase clinical trials, including multivirus specific T-cell therapies.
- Ribavirin may be considered in selected high-risk patients with LRTI, based on anecdotal reports.
- Consider IVIG therapy in this patient group.



721.CLINICAL ALLOGENEIC
TRANSPLANTATION: CONDITIONING
REGIMENS, ENGRAFTMENT, AND ACUTE
TRANSPLANT TOXICITIES | NOVEMBER 13,
2019

**Oral Ribavirin with or without
the Addition of Immune
Globulin for the Treatment of
Lower Respiratory Tract
Infections Due to Respiratory
Syncytial Virus or
Parainfluenza in Patients after
Allogeneic Stem Cell
Transplantation**

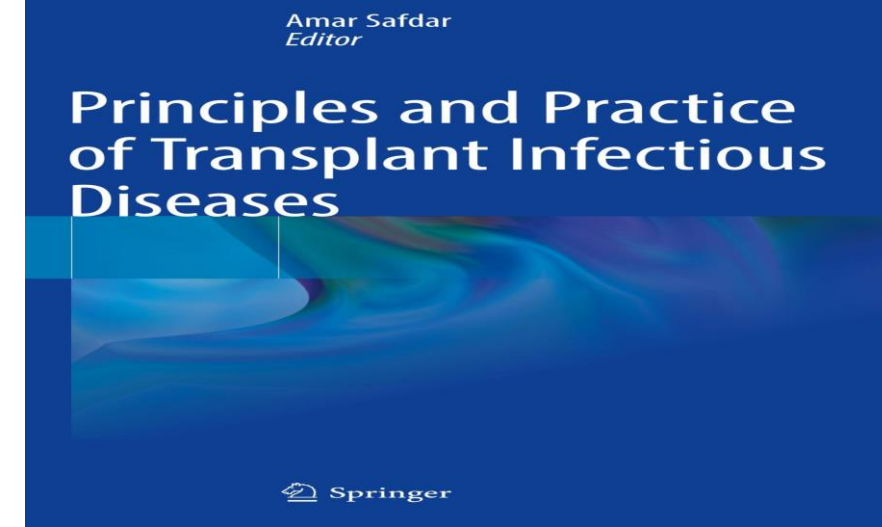
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Panagiotis Tsirigotis

Ribavirin was administered at a dose of 20-30mg/kg divided into 4 daily doses.

Treatment with ribavirin was continued until significant symptomatic and radiological improvement.

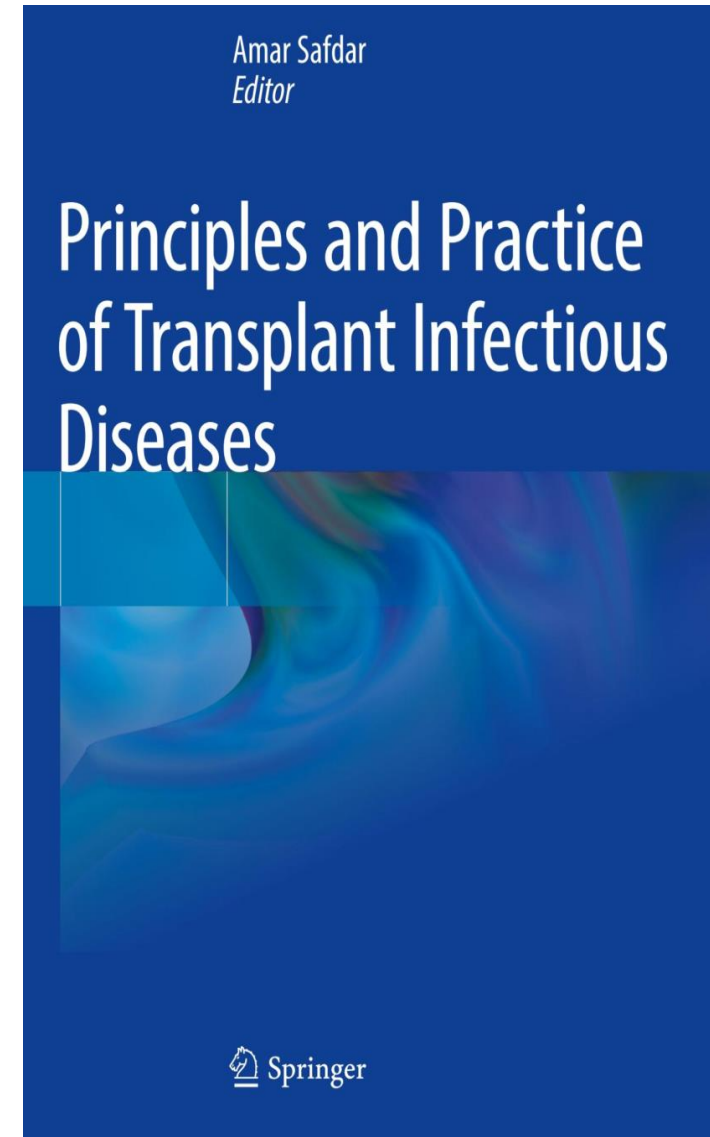
IVIgG was administered at a daily dose of 400mg/kg for a total dose of 2 g/kg.

Oral Ribavirin has an excellent efficacy and safety profile.
Complete and fast resolution of



- **For HSCT, both aerosolized and oral Ribavirin have been employed, although some patients received intravenous Ribavirin when they did not respond to aerosolized or oral treatment.**
- **Successful treatment of PIV LRTI has been reported in heart transplant recipients with aerosolized Ribavirin or with intravenous Ribavirin plus methylprednisolone as well as in a kidney transplant recipients with aerosolized Ribavirin and IVIG .**

- **DAS181 is a novel sialidase fusion protein with activities against multiple strains of influenza and PIVs.**
- **It has been used for PIV treatment in a small number of HSCT and lung transplant recipients.**

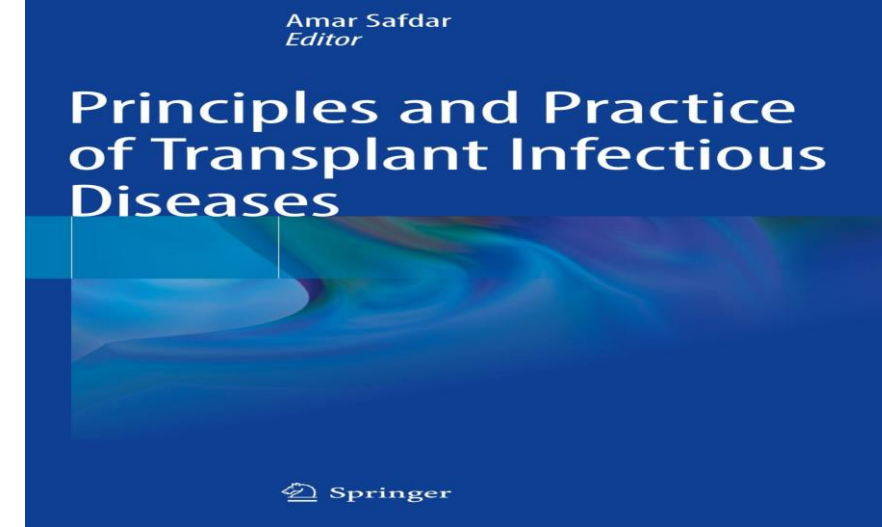


RSV Infection



RSV Infection

- **Human RSV infection leads to bronchiolitis, pneumonia, and asthma in all age groups; infants, young children, and immunocompromised hosts are likely to present with severe respiratory infection.**



- **For SOT recipients, RSV-associated mortality rate is significantly lower than that experienced in HSCT .**
- **Mortality rates among lung transplant patients of up to 20% have been reported.**

RSV Infection

- **RSV infection was noted to be common in adults who require admission to an intensive care unit from November to February**



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- Risk factors for progression to LRI include :
- Advanced age
- Lymphopenia
- Myeloablative regimen
- Steroid use
- GVHD
- Pre-engraftment infection



Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies

Fareed Khawaja and Roy F. Chemaly

Department of Infectious Diseases, Infection Control and Employee Health, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

In the USA and other western nations, respiratory syncytial virus is one of the most commonly encountered respiratory viruses among patients who have been diagnosed with a hematologic malignancy or who have undergone a stem cell transplant. Multiple studies have been performed to evaluate the complications associated with respiratory syncytial virus infections. Other studies have evaluated therapeutic agents and strategies in which these agents can be used. There have also been numerous reports of outbreaks in bone marrow transplant units and oncology wards, where infection control measures have been invaluable in controlling the spread of disease. However, despite these novel approaches, respiratory syncytial virus continues to be potentially fatal in immunocompromised populations. In this review, we discuss the incidence of respiratory syncytial viral infections, risk factors associated with progression from upper respiratory tract infection to lower respiratory tract infection, other complications and outcomes (including mortality), management strategies, and prevention strategies in patients with a hematologic malignancy and in hematopoietic cell transplant recipients.

Immunodeficiency Scoring Index (ISI)

- Six factors were included in the scoring index:
- Neutropenia of less than 500 neutrophils/mL (3)
- Lymphopenia of less than 200 lymphocytes/mL (3)
- Age greater than 40 years (2)
- Graft-versus-host disease (1)
- Steroid use (1)
- Myeloablative chemotherapy (1)
- And time from HCT (1)
- On the basis of the total score, the ISI stratifies HCT recipients with RSV URTI into **Low-risk (score of 0-2)**, **Medium-risk (score of 3-6)**, and **High-risk (score of 7-12)** categories

Immunodeficiency Scoring Index (ISI)

- Allogenic HCT recipients with **high ISI** scores experienced progression to pneumonia after being diagnosed with **RSV, Influenza, Coronavirus, or Adenovirus**



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

Criteria	Weighing criteria	Assigned weights (score)
ANC < 500/ μ L	>2.5	3
ALC < 200/ μ L	>2.5	3
Age $\geq$ 40 years	2.0-2.5	2
Myeloablative conditioning regimen	<2.0	1
GVHD (acute or chronic)	<2.0	1
Corticosteroids within the last 30 days	<2.0	1
Recent or pre-engraftment allo-HCT	<2.0	1
Low risk: 0–2 score, moderate risk 3–6 score, high risk 7–12 score		



Refinement of Estimates of Mortality Risk Using the Radiologic Severity Index in Hematologic Malignancy Patients with Respiratory Syncytial Virus Infection

Pattern score	Predominant radiologic pattern in lung zone	Volumetric score	Extent of volumetric radiologic involvement
1	Normal lung	0	0% (normal)
2	Ground-glass opacities	1	1–24%
3	Consolidation	2	25–49%
		3	50–74%
		4	75–100%

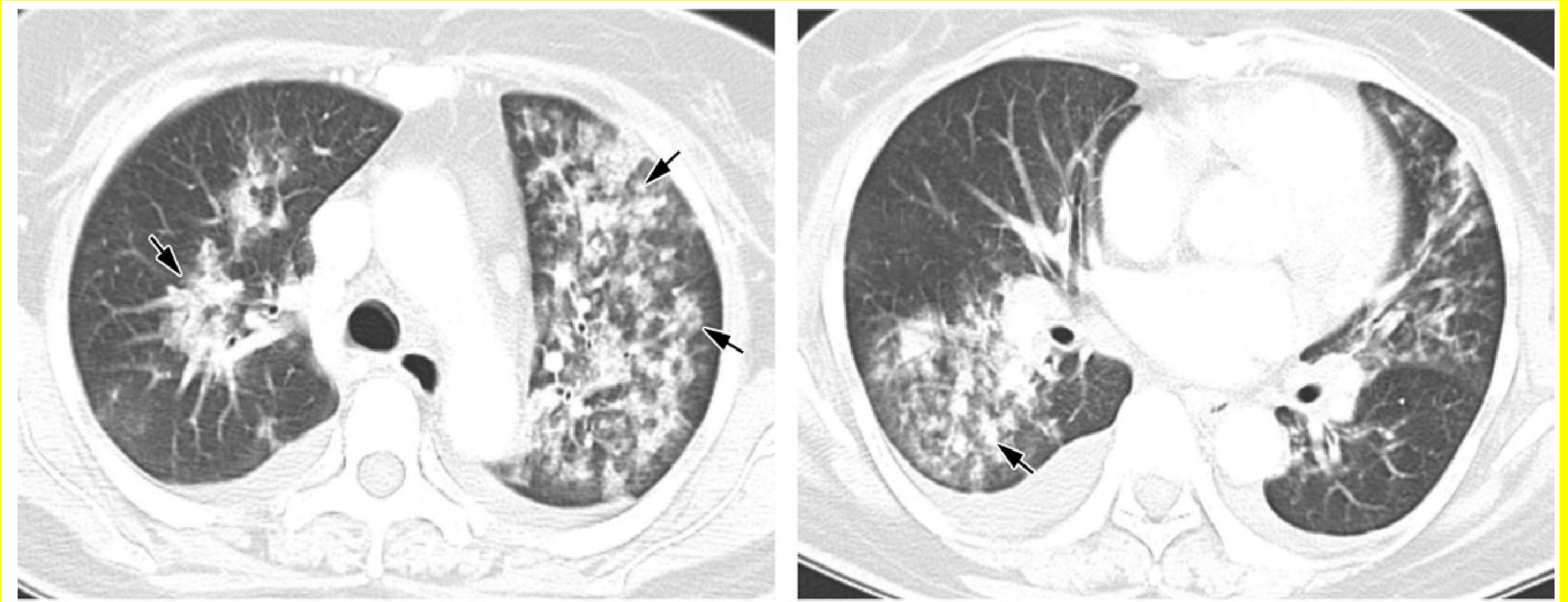
Guidance on the use of Oral Ribavirin in the Treatment of Respiratory Viruses

Purpose of Guideline:

To provide guidance on the use of ribavirin for treatment of respiratory syncytial virus (RSV) in oncology patients and lung transplant recipients.

- **Symptoms of upper respiratory tract infections:**
- **Influenza-like symptoms /No infiltrate on chest x-ray.**
- **Symptoms of Lower respiratory tract infection symptoms:**
- **Cough, Increased oxygen requirement, wheezing , New infiltrate on chest x-ray**

- **RSV shows an air waycentric distribution, with areas of tree-in-bud opacity and bronchial wall thickening, with or without consolidation along the bronchovascular bundles**



Purpose of Guideline:

To provide guidance on the use of ribavirin for treatment of respiratory syncytial virus (RSV) in oncology patients and lung transplant recipients.

- **Patients to be considered for therapy of RSV:**
- **Receipt of allogeneic or autologous hematopoietic stem cell transplant (HSCT) within the past 30 days .**
- **Receipt of allogeneic or autologous HSCT AND absolute lymphocyte count less than 300 cells/mm³ .**
- **Receipt of allogeneic HSCT with active graft versus host disease (GVHD) on immunosuppressants.**
- **Leukemia or HSCT patients with absolute neutrophil count less than 500 cells/mm³**
- **All lung transplant recipients**

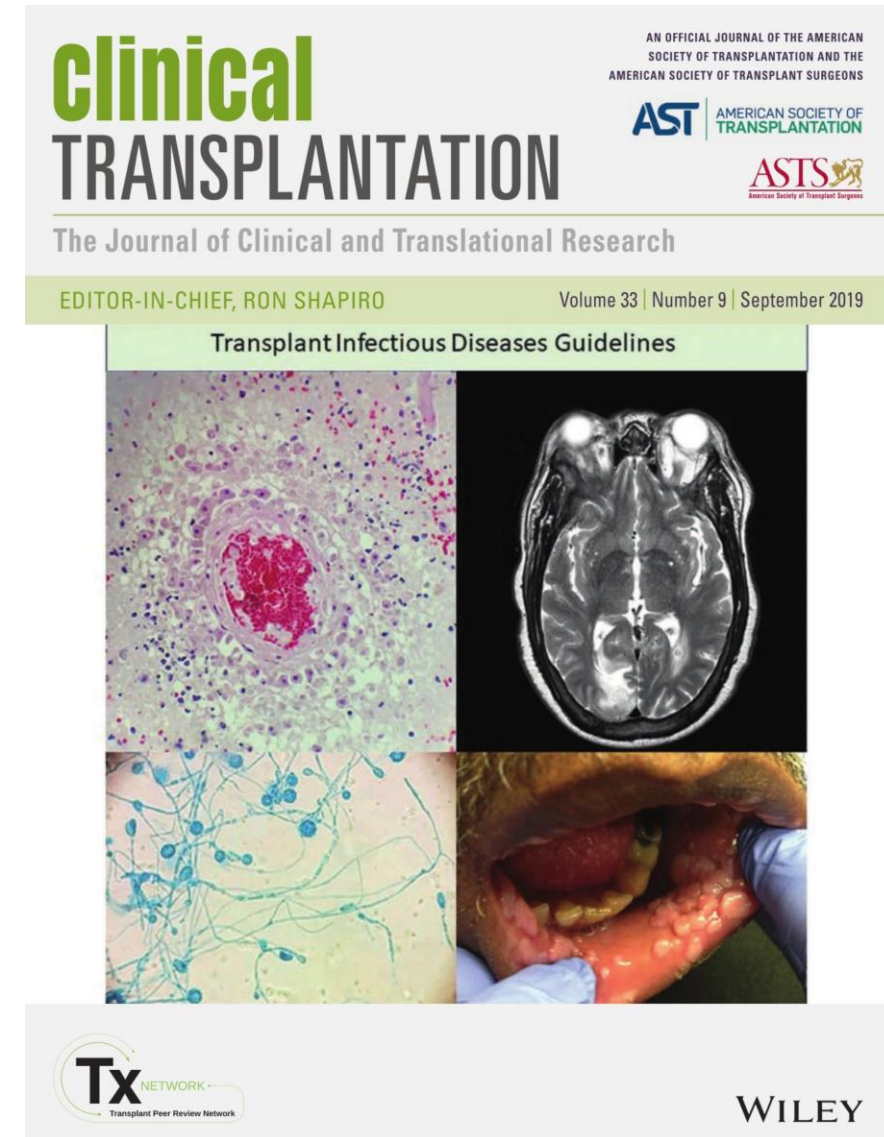
Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

- **Empiric use of Ribavirin is not recommended.**
- **Only patients who have a positive molecular test for RSV and Symptoms and signs of lower respiratory tract infection (clinical, imaging).**
- **Treatment may be considered occasionally in patients with upper respiratory tract infection.**

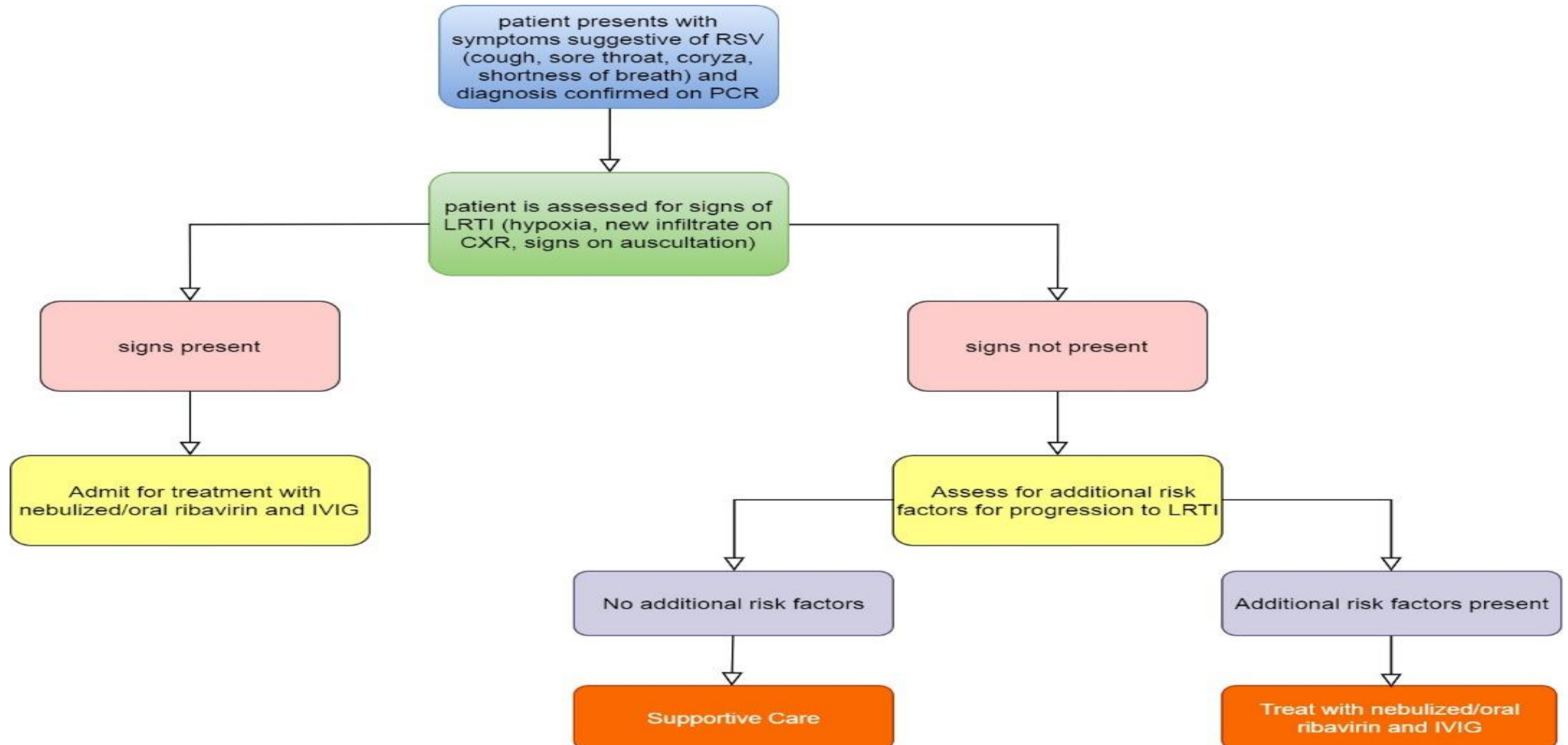
Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

- The following are associated with high risk for progression from URTI to LRTI:
- Pre-engraftment ,lymphopenia $<0.3 \times 10^9/l$, > 60 years, GVHD, mismatched, haploidentical related or umbilical cord blood donor transplant, neutropenia $<0.5 \times 10^9/l$.
- It is generally only patients on immunosuppression or within 12 months of transplant who will require therapy.

- Lung and heart-lung recipients are usually treated for both upper or lower respiratory tract infection.



Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

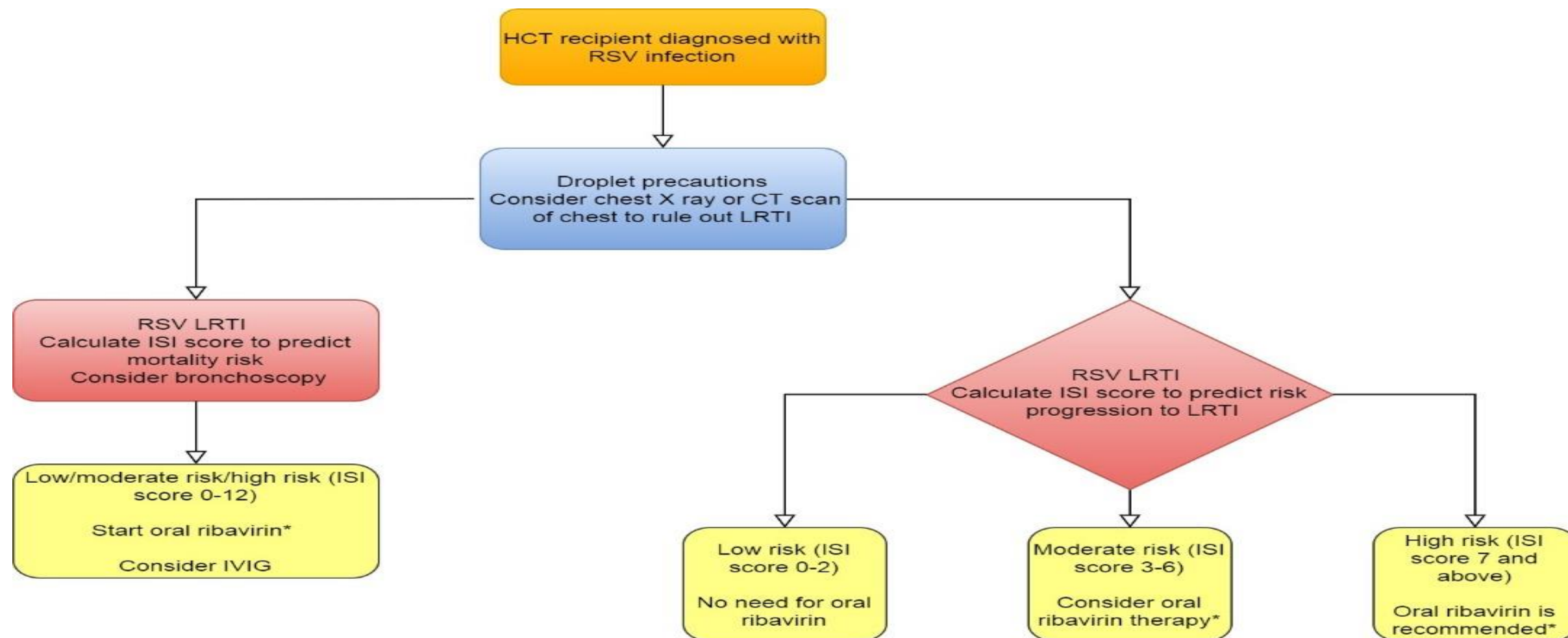




Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies

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Guidance on the use of Oral Ribavirin in the Treatment of Respiratory Viruses

Purpose of Guideline:

To provide guidance on the use of ribavirin for treatment of respiratory syncytial virus (RSV) in oncology patients and lung transplant recipients.

Table 5: Guideline Recommendations and Levels of Evidence

Recommendation	Evidence Level [◇]
Oral ribavirin should be a treatment consideration only in patients who meet the following criteria: symptoms of upper or lower respiratory tract infection, a positive molecular test for RSV, and are at high risk of disease progression.	BIII
The recommended dose of oral ribavirin is 15-20mg/kg/day divided and given TID for 7-10 days.	BIII
Palivizumab is not recommended for addition to ribavirin for the treatment of RSV in immunocompromised oncology patients.	CIII
The addition of IVIG (500mg/kg IV QOD x 3-5 doses) to ribavirin therapy should be reserved for allogeneic HSCT patients with LRTID or who are at high risk for progression to LRTID.	CIII

◇ Recommendations categorized per the Infectious Disease Society of America - United States Public Health Service grading system for ranking recommendations (see table 6 below).

Article Navigation

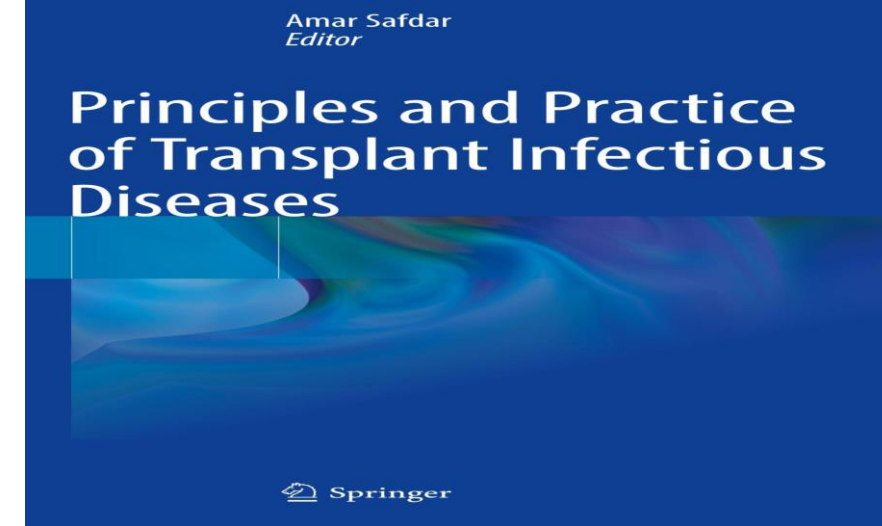
Oral Versus Aerosolized Ribavirin for the Treatment of Respiratory Syncytial Virus Infections in Hematopoietic Cell Transplant Recipients

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Terri Lynn Shigle, Amrita Prayag,
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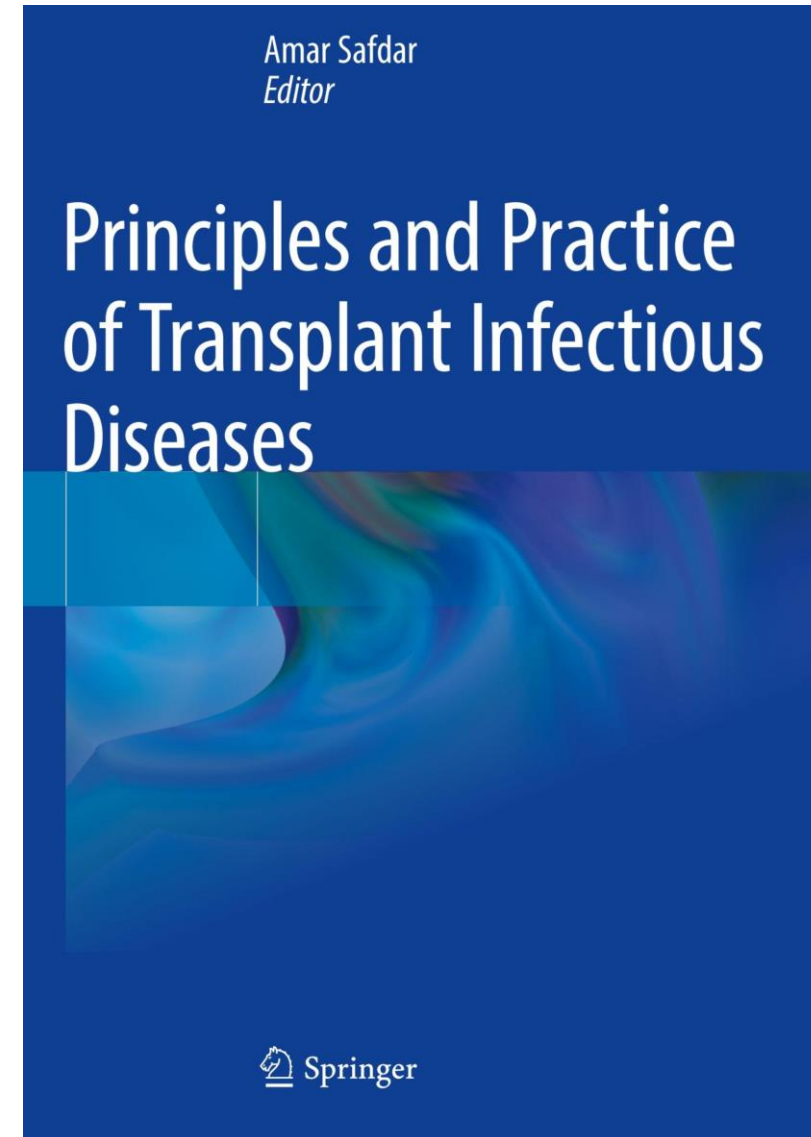
Published: 08 September 2018

- HCT recipients with RSV infections had similar outcomes when treated with aerosolized or oral RBV.
- Oral Ribavirin may be an effective alternative to aerosolized RBV, with potential significant cost savings.



- **Similar to the HSCT population, the mainstay of treatment for paramyxoviral infections in SOT populations has been aerosolized or oral Ribavirin .**
- **Combination of aerosolized Ribavirin, IVIG, and corticosteroids was found to be safe and effective in preserving lung function in lung transplant recipients after RSV or PIV infections**

- More recently, a new agent **Presatovir (GS-5806)**, an orally bioavailable antiviral agent that inhibits fusion of RSV with host cell membranes, is being developed for treatment of RSV infection.



HMPV Infection



HMPV Infection

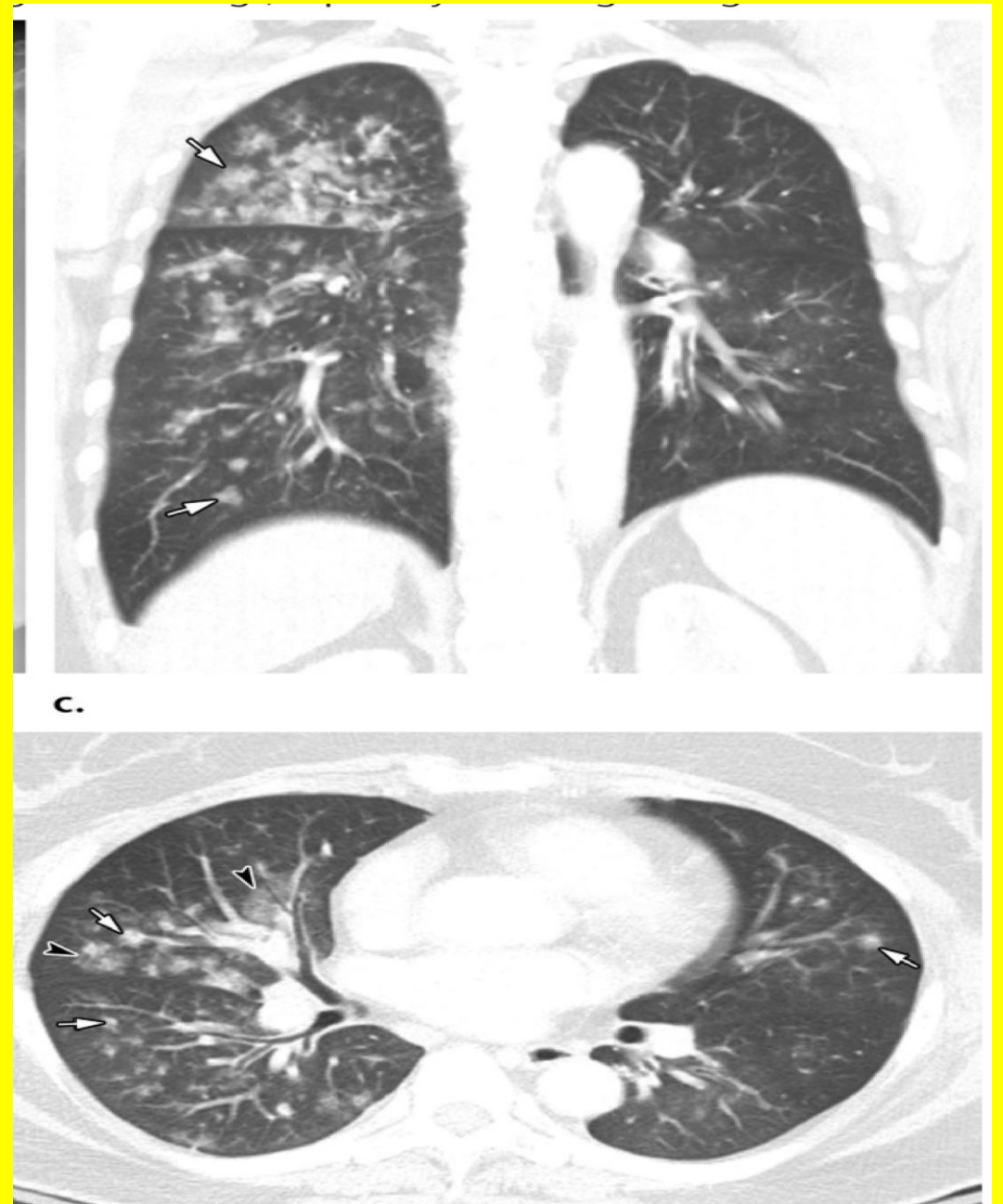
- **Structure of the virus is similar to that of RSV, and this virus can cause upper and lower respiratory tract infection.**
- **Prevalent during winter months.**
- **HMPV infection causes severe pneumonia with mortality of 10%–40% in Hematopoietic stem cell transplant recipients, with a 5% incidence of infection.**
- **Approximately 60% of hematopoietic stem cell transplantation recipients with HMPV infection progress to pneumonia; the risk factors of progression to pneumonia are systemic high-dose corticosteroid use and low lymphocyte counts.**



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- For HMPV, risk factors for mortality include
- Length between HCT and infection
- Neutropenia
- Lymphopenia
- Low monocyte count at diagnosis
- Steroid dose before diagnosis of ≥ 1 mg/kg

- Radiographs in patients with HMPV pneumonia show multilobar infiltrations .bilateral ill-defined centrilobular nodules, branching centrilobular nodules, and GGO are noted in patients with hematologic malignancy . Pleural effusion is not common.

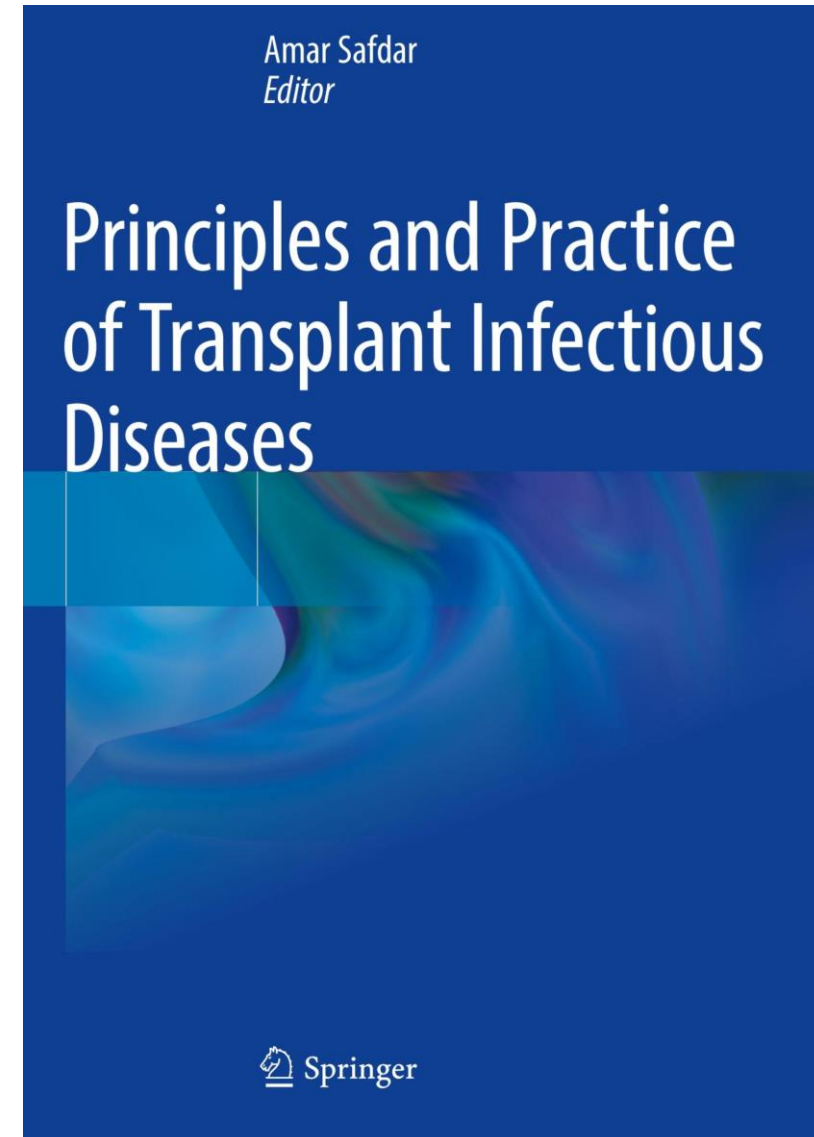




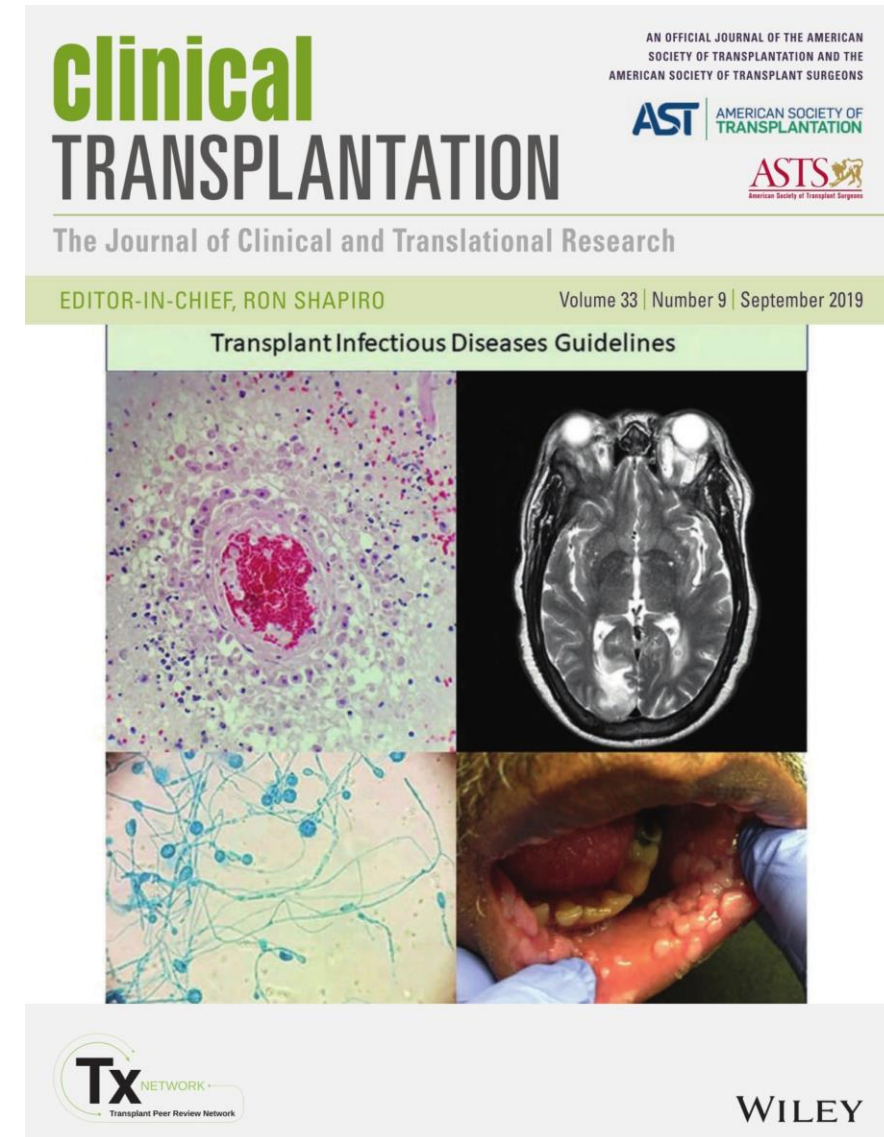
Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

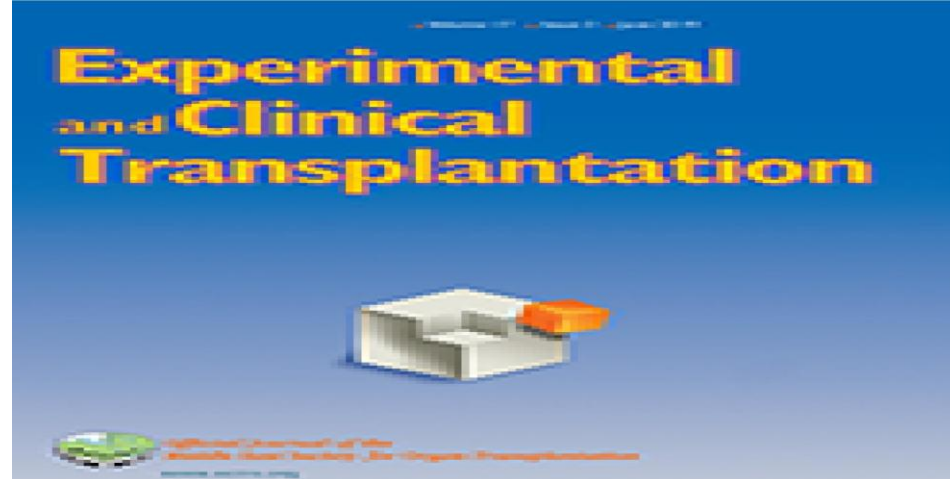
- Even if several small reports support the use of Ribavirin with or without IVIG for HMPV infection, a larger study showed no protective effect of Ribavirin to reduce HMPV progression and mortality.
- To date, antiviral therapy is not recommended to cure or to prevent infection progression even in patients at higher risk of HMPV progression.
- No licensed therapeutics or vaccines exist.

- **Suggested that Ribavirin with IVIG may be considered as a treatment option for patients with severe disease , but this approach is not routinely used.**



- Suggested that Ribavirin with or without Immunoglobulin can be considered for the management of severe cases of HMPV but supportive care remains the mainstay of treatment.





Clinical Outcomes of Paramyxovirus Infections in Lung Transplant Recipients Treated With Oral Ribavirin: A Two-Center Case Series

Bryan Garcia,¹ Nirmal Sharma,¹ Kevin Johnson,² Juan Salgado,³ Keith Wille¹

Objectives: Paramyxoviruses contribute to morbidity and mortality after lung transplant and are associated with bronchiolitis obliterans syndrome. Oral ribavirin has been used off-label for treatment of paramyxo-viruses in immunosuppressed patients; however, data supporting its use for this purpose are lacking.

Materials and Methods: We conducted a retrospective review to evaluate clinical outcomes of lung transplant recipients infected with paramyxoviruses and received treatment with oral ribavirin at 2 tertiary referral centers. Patients who were diagnosed with paramyxo-virus infection by polymerase chain reaction testing between January 2011 and December 2014 and who received oral ribavirin were included. Clinical outcomes included pulmonary function testing, infection severity, and adverse events related to treatment.

Results: Twenty-six patients were diagnosed with a paramyxovirus and received oral ribavirin. The changes in mean forced expiratory volume 1 second from preinfection to infection onset and from infection onset to postinfection were significant (1.79 ± 0.13 to 1.61 ± 0.12 L and 1.61 ± 0.12 L to 1.74 ± 0.12 L; $P = .0001$). Similar results were seen in subgroup analysis when respiratory syncytial virus and parainfluenza infections were evaluated independently.

Conclusions: Use of oral ribavirin for treatment of paramyxovirus infections in lung transplant recipients was safe and associated with recovery of lung function.



- **Intravenous Ribavirin is not commercially available in the United States, and the clinical utility of inhaled Ribavirin is limited for high cost, its need for a negative pressure room ,the potential for bronchospasm, and its ability to obstruct the ventilator circuit.**
- **Oral Ribavirin is well tolerated, is a lower cost medication and is increasingly being utilized for the treatment of RSV infections in lung transplant recipients.**



ARTICLE

**Clinical Outcomes of Paramyxovirus
Infections in Lung Transplant
Recipients Treated With Oral Ribavirin:
A Two-Center Case Series**

*Bryan Garcia,¹ Nirmal Sharma,¹ Kevin Johnson,² Juan
Salgado,³ Keith Wille¹*

- **Patients infected with a paramyxovirus were given oral Ribavirin at a dose of 400 to 600 mg either twice per day or 3 times per day using standard weight-based dosing for 7 to 10 days pending clinical recovery**

Community-Acquired Respiratory Paramyxovirus Infection After Allogeneic Hematopoietic Cell Transplantation: A Single-Center Experience

Yasmin Spahr,^{1,2} Sarah Tschudin-Sutter,² Veronika Baettig,² Francesca Compagno,⁵ Michael Tamm,³ Jörg Halter,⁴ Sabine Gerull,⁴ Jakob Passweg,⁴ Hans H. Hirsch,^{2,5,a} and Nina Khanna^{2,6,a}

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Background. Paramyxoviruses include respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (MPV), which may cause significant respiratory tract infectious disease (RTID) and mortality after allogeneic hematopoietic cell transplantation (HCT). However, clinical data regarding frequency and outcome are scarce.

Methods. We identified all paramyxovirus RTIDs in allogeneic HCT recipients diagnosed by multiplex polymerase chain reaction between 2010 and 2014. Baseline characteristics of patients, treatment, and outcome of each episode were analyzed; ie, moderate, severe, and very severe immunodeficiency (verySID) according to HCT ≤ 6 months, T- or B-cell depletion ≤ 3 months, graft-versus-host disease, neutropenia, lymphopenia, or hypo-gammaglobulinemia.

Results. One hundred three RTID episodes in 66 patients were identified (PIV 47% [48 of 103], RSV 32% [33 of 103], MPV 21% [22 of 103]). Episodes occurred in 85% (87 of 103) at >100 days post-HCT. Lower RTID accounted for 36% (37 of 103). Thirty-nine percent (40 of 103) of RTID episodes required hospitalization and more frequently affected patients with lower RTID. Six percent progressed from upper to lower RTID. Overall mortality was 6% and did not differ between paramyxoviruses. Sixty-one percent (63 of 103) of episodes occurred in patients with SID, and 20.2% (19 of 63) of episodes occurred in patients with verySID. Oral ribavirin plus intravenous immunoglobulin was administered in 38% (39 of 103) of RTIDs, preferably for RSV or MPV ($P \leq .001$) and for SID patients ($P = .001$). Patients with verySID frequently progressed to lower RTID ($P = .075$), required intensive care unit transfer, and showed higher mortality.

Conclusion. Paramyxovirus RTID remains a major concern in allogeneic HCT patients fulfilling SID and verySID, emphasizing that efficacious and safe antiviral treatments are urgently needed.

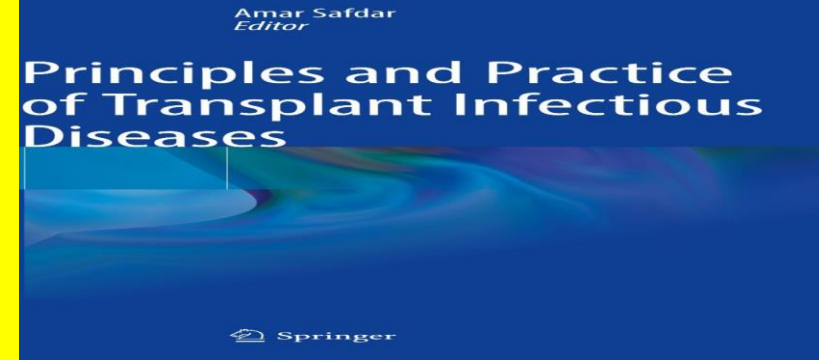
Keywords. human metapneumovirus (MPV); IVIG; parainfluenza virus (PIV); respiratory syncytial virus (RSV); ribavirin.

- guidelines recommended RBV was usually administered orally with a loading dose of 10 mg/kg bodyweight followed by 200 mg three-times daily (tid) and was thereafter increased to 400 mg tid on day 2 and to 600 mg tid on day 3.

Influenza

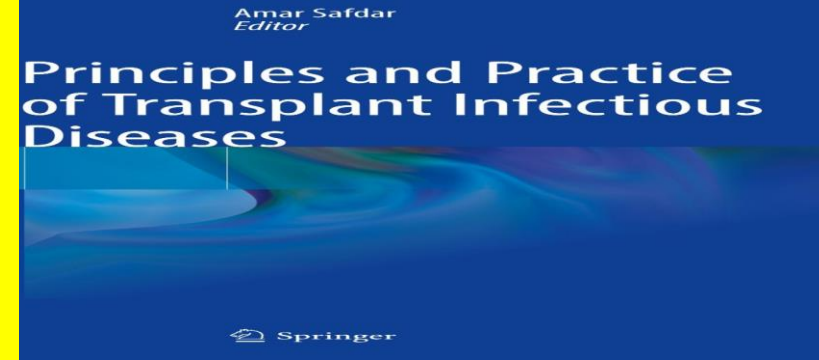


Influenza



- **The main risk factor for disease progression to LRTI**
- **Lymphopenia**
- **Allogeneic HSCT**
- **Infection during early post-transplant period**
- **Presence of graft-versus-host disease**
- **Myeloablative preparatory regimen**
- **Delayed initiation of antiviral therapy**

Influenza

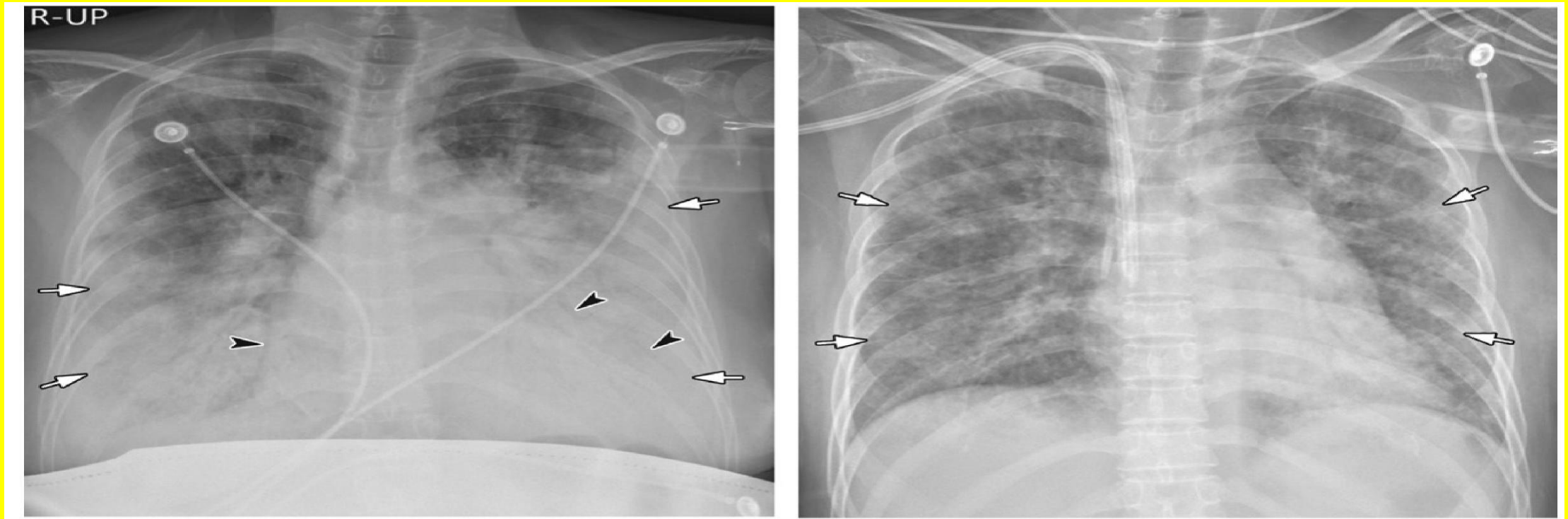


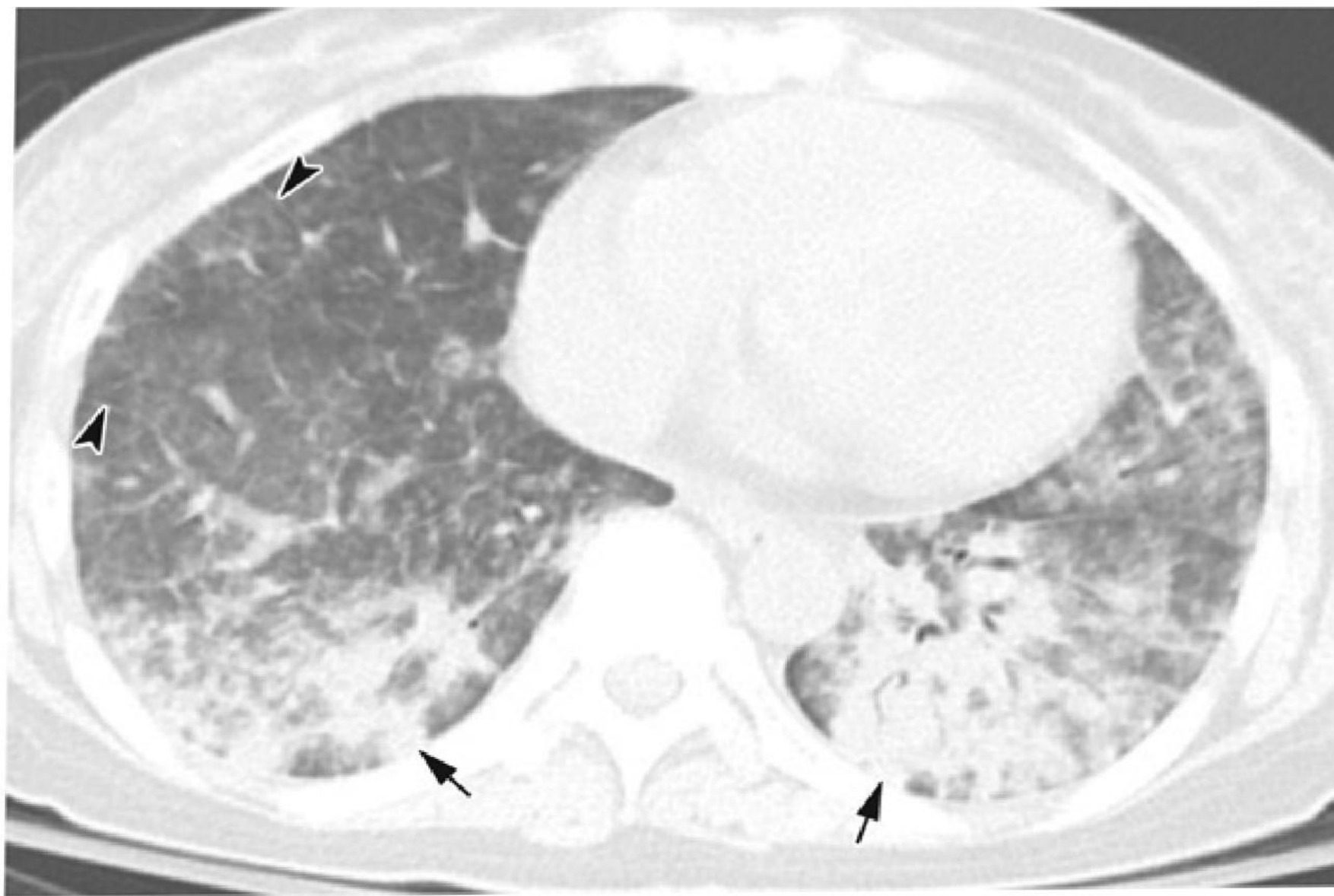
- **Concomitant corticosteroid use has not been associated with an increased risk for progression to LRTI.**
- **Need for mechanical ventilation, or patients given systemic higher doses (≥ 1 mg/kg) of corticosteroids may be predisposed to prolonged viral shedding.**

Influenza

- **The most common presenting symptoms were cough (91%), fever (85%), myalgias (51%), gastrointestinal symptoms (44%), rhinorrhea (43%), and sore throat (43%).**
- **Atypical presentations may occur in those with significant immunosuppression, which may include fever as the only presenting symptom or afebrile patient with rhinorrhea alone.**

- Radiographs in patients with influenza pneumonia show bilateral reticulonodular areas of opacity with or without focal areas of consolidation, usually in the lower lobes. Poorly defined patchy or nodular areas of consolidation that become rapidly confluent and represent either diffuse alveolar damage. Pleural effusion is rare.





Influenza

- **Lobular consolidation can be especially helpful in diagnosis of bacterial superimposed infection .**
- **Gram stain and culture of sputum or bronchoalveolar lavage also are helpful methods to confirm the superimposed bacterial infection when it is suspected.**

Influenza

- **Influenza can also cause a variety of extrapulmonary complications including myocarditis, myositis, encephalopathy, renal failure, severe diarrhea, and pneumomediastinum .**
- **Virus-associated hemophagocytic syndrome has been reported as a severe complication of pandemic H1N1 leading to multiorgan failure.**

RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Oriol Manuel¹ | Michele Estabrook² | on behalf of the American Society of Transplantation Infectious Diseases Community of Practice

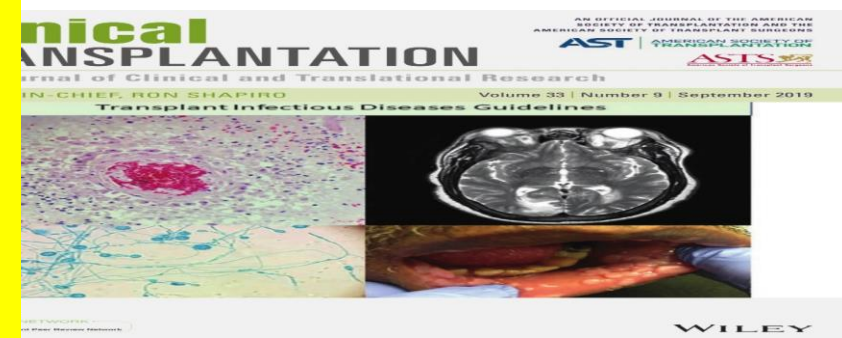
- **Risk of complications of influenza appears to be higher in SOT recipients as compared to the general population, particularly the incidence of pneumonia (up to 22%-49% in transplant recipients).**
- **Allograft dysfunction and acute rejection have been observed after severe cases of influenza.**

Risk factors for severe influenza in SOT recipients include:

- Use of antilymphocyte globulin
- Diabetes mellitus
- Pneumonia
- Bacterial and fungal co-infection
- Early infection (<3 months) after transplantation.
- Nosocomial acquisition of influenza has been described as a risk factor for admission to ICU.



Influenza

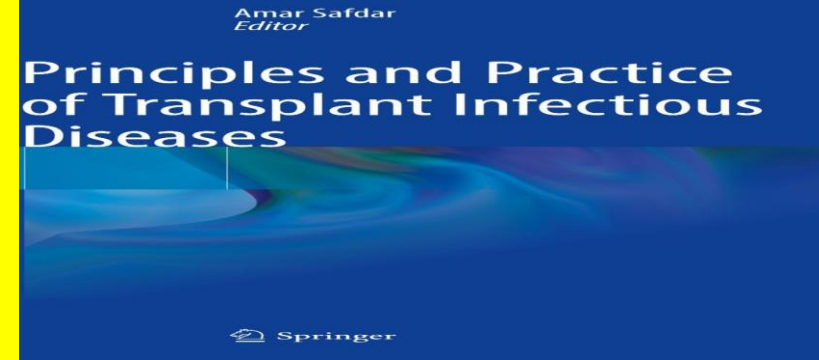


- The median duration of viral shedding among allogeneic HSCT recipients was between 11 and 12 days compared to 1 week among recipients of autologous transplants .
- Prolonged viral shedding beyond 2 weeks and, for months has been described in HSCT recipient.
- Risk factors for prolonged viral shedding include the use of corticosteroids at dosages ≥ 1 mg/kg per day and use of bone marrow and cord blood versus peripheral blood stem cell.

Influenza

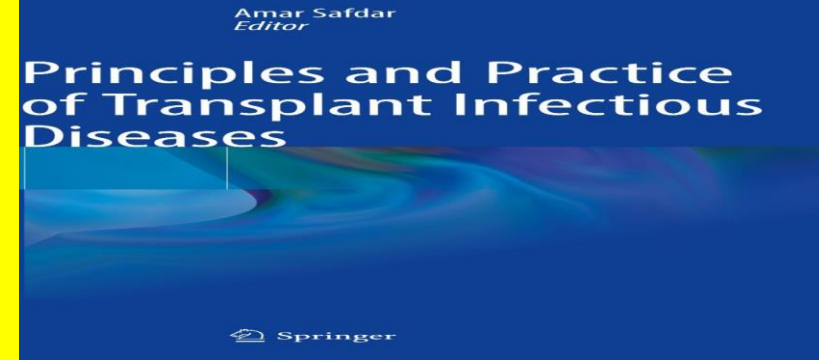
- **There are several methods available for detection of influenza including:**
 - **Rapid antigen**
 - **Direct immunofluorescence antibody (DFA)**
 - **Viral culture**
 - **PCR**
 - **PCR was found to have the greatest sensitivity and specificity.**

Influenza



- In those patients undergoing chemotherapy or with gastrointestinal graft-versus-host disease, some experts suggest using the higher dose in transplant patients particularly if absorption is uncertain, in those patients with severe LRTI or who are critically ill.

Influenza



- **Some experts recommend treating all SOT recipients until viral replication has ceased.**
- **Authors recommend checking PCR once a week and treat until negative .**
- **Suggested a 10-day course for HSCT recipients and extending treatment in those patients with pneumonia, ongoing symptoms, or viral shedding.**

Influenza

- Monitoring of viral replication in nasopharyngeal swabs by PCR can help to guide infection control practices.
- Should **generally not be used to guide duration of antiviral therapy**



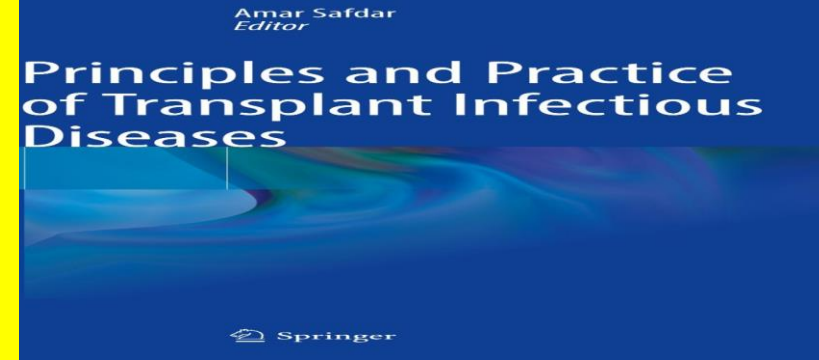
Influenza

- In severe cases, double dosing **150 mg of oseltamivir twice a day** for normal kidney function is recommended by some experts with some anecdotal cases of positive outcomes in SOT recipients.



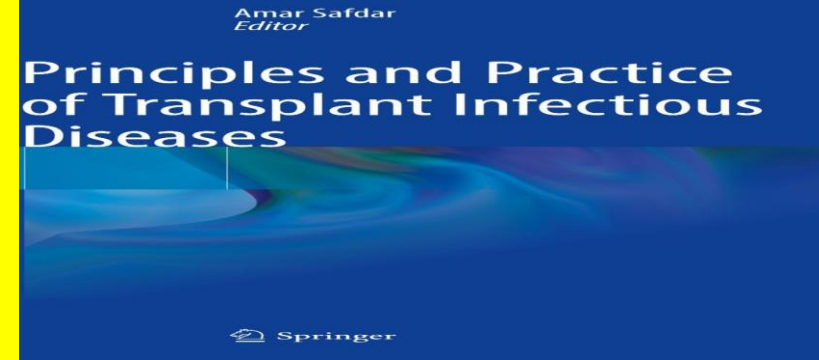
Antiviral agent	Dose	Parenteral formulation?	Side effects	Remarks
Oseltamivir	75 mg PO twice daily	Yes, investigational	Gastrointestinal: nausea, vomiting, diarrhea Neurologic: confusion, delirium, depressed consciousness (mostly reported among Japanese adolescents and adults)	Some experts recommend higher doses (150 mg PO BID) in transplant patients who are critically ill with LRTI
Zanamivir	2 puffs (10 mg) inhaled twice daily	Yes, investigational	Bronchospasm, cough, headache, dizziness, sinusitis, nausea, diarrhea	Little cross-resistance with oseltamivir
Peramivir	600 mg IV once daily	Yes (only available as parenteral formulation)	Gastrointestinal: nausea, vomiting, diarrhea Neutropenia	Cross-resistance with oseltamivir exists.
Amantadine	100 mg PO twice daily	No	Neurologic: insomnia, lethargy, inability to concentrate, dizziness Gastrointestinal: nausea	No longer routinely recommended due to high incidence of resistant influenza unless circulating strain known to be susceptible
Rimantadine	100 mg PO twice daily	No	Gastrointestinal Neurologic (less common than amantadine): lightheadedness, insomnia, inability to concentrate, nervousness	No longer routinely recommended due to high incidence of resistant influenza unless circulating strain known to be susceptible

Influenza



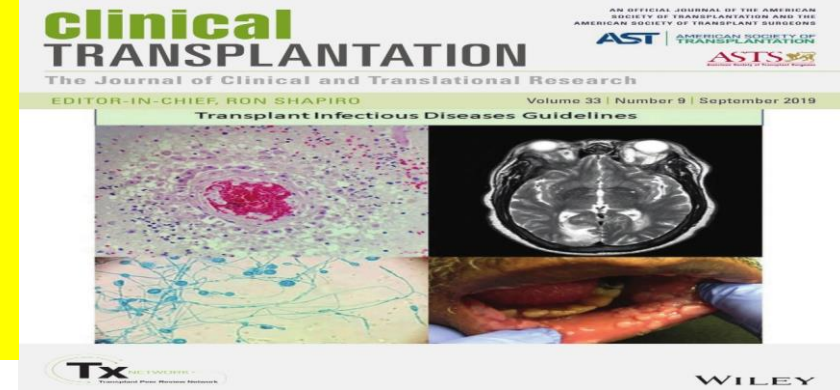
- **IV zanamivir** is currently available for use, and there is limited published experience among transplant recipients where it has been used with some benefit among patients with **Oseltamivir-resistant Influenza** or **severe disease**.

Influenza



- **Peramivir**, a parenteral neuraminidase inhibitor,
There are limited data regarding the use of Peramivir in transplant recipients.
- Of note, the H275Y mutation which confers Oseltamivir resistance also confers cross-resistance to Peramivir.

Influenza



- **Laninamivir** is a long-acting inhaled neuraminidase inhibitor that is approved in Japan for prophylaxis and treatment of influenza.
- **Intravenous Peramivir** is approved for use as a single dose, but repeated doses and/or step down with oral oseltamivir may be necessary for SOT recipients.
- **Intravenous Zanamivir** is available in Europe as investigational drug, but not currently approved

Influenza

- Use of Amantadine and Rimantadine for treatment of influenza is no longer recommended due to the high rate of resistance to these drugs (>95%)

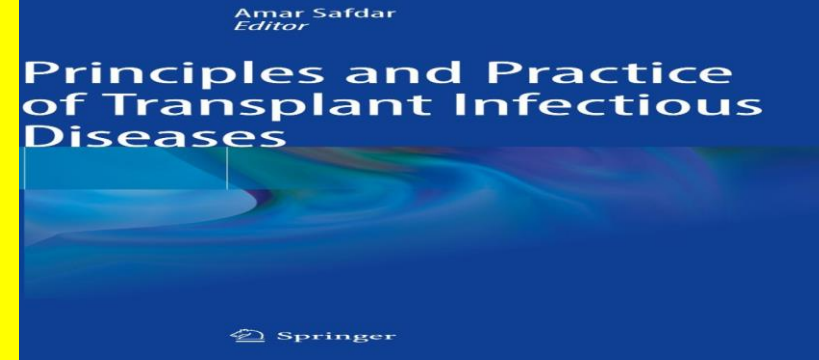


Influenza

- **Baloxavir** is a single-dose FDA-approved therapy for influenza with a novel mechanism of action, the inhibition of cap-dependent endonuclease.
- Baloxavir has shown efficacy in treating uncomplicated influenza in healthy subjects; however, data for its use in transplant recipients are lacking.



Influenza



- **There are currently no data that indicates a clear clinical benefit of combination antiviral therapy over single drug therapy.**

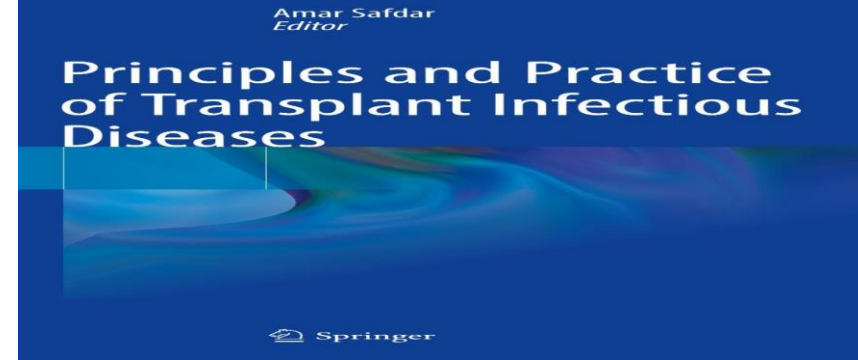
Rhinovirus



Rhinovirus

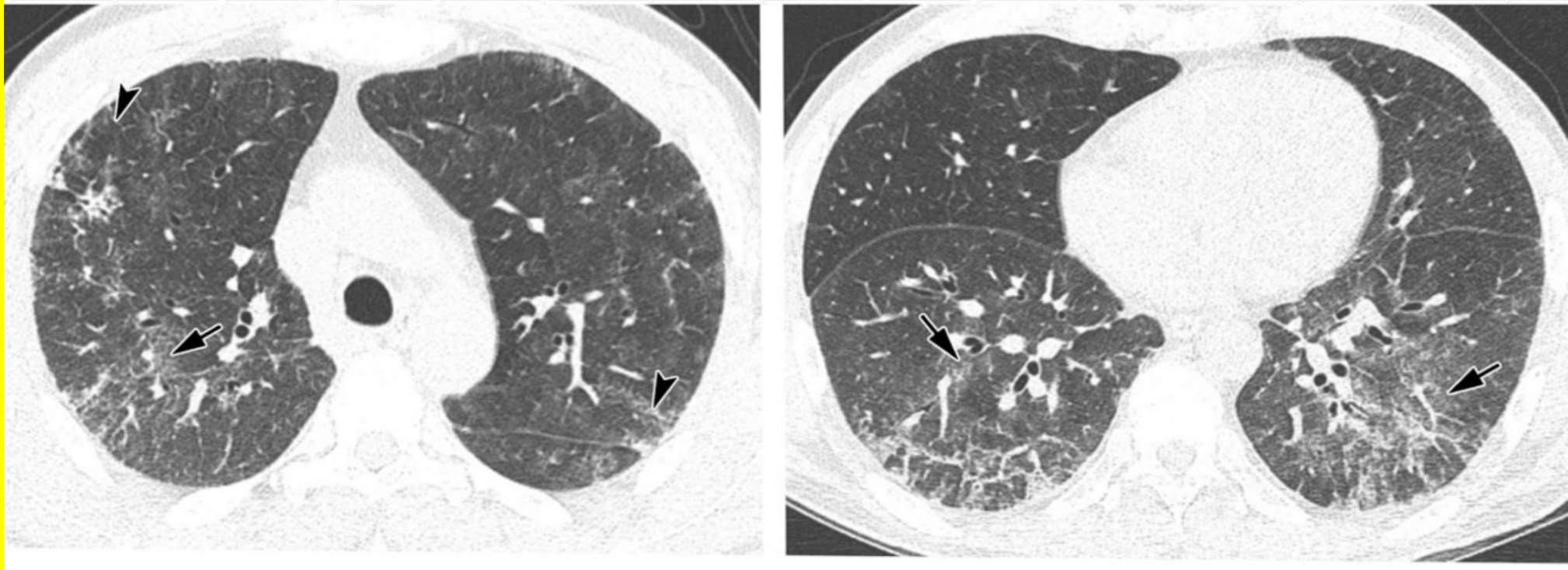
- **Rhinovirus is the predominant cause of the common cold during all four seasons but more frequently is detected in spring and autumn.**
- **Bacterial coinfection is not common (18.5%) and less than that with Influenza .**
- **Immunocompromised patients are more prone to infection.**

Rhinovirus



- **Fatal pneumonia associated with HRV have been reported among HSCT recipients .**
- **Suggested that HRV LRTI with viral detection in the BAL are associated with mortality rates similar to those seen with RSV, PIV, or Influenza viruses .**
- **For SOT, HRV are frequently isolated among lung transplant patients .**

- Patients with severe rhinovirus pneumonia, bilateral patchy consolidation with multifocal GGO and interlobular septal thickening are noted .



Rhinovirus

- **Currently, there are no specific agents licensed for the treatment of HRV.**

Amar Safdar
Editor

Principles and Practice of Transplant Infectious Diseases

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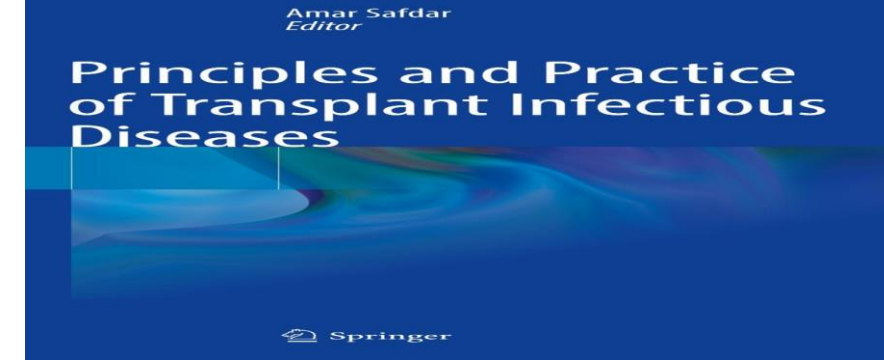


Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

- There is currently no recommendation of specific antiviral therapy due to the lack of effective agents against this viruse and the lack of clinical trials.
- **Vapendavir** is capsid binder under development for the treatment of RhV infections .

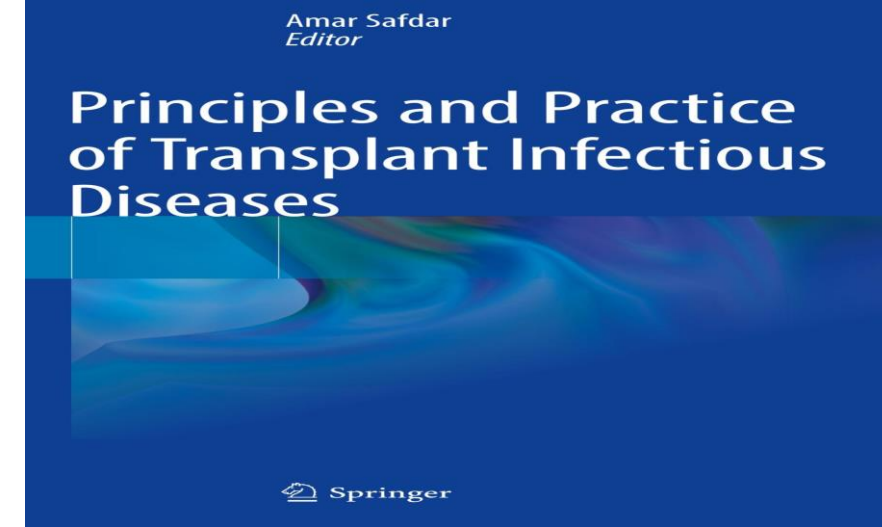


Diagnosis of RVI



- **Rapid antigen detection is available for Influenza and RSV and has the advantage of rapid result testing (within 15'), but suboptimal sensitivity (between 50% and 60%) and low predictive value.**
- **DFA testing is limited by lack of reagents for some of the viruses Rhinovirus.**
- **Serology is not useful for diagnosis of acute infection, but can be used for epidemiological studies in cases of Influenza, although some SOT recipients might not respond and antibody can wane quickly, even after infection.**
- **Finally, although viral cultures previously were considered the preferred diagnostic tests, they are not currently used in routine clinical practice.**

Diagnosis of RVI



- Reverse transcriptase **(RT)–PCR** is now routinely used for respiratory viral diagnosis for the detection of RNA viruses in respiratory secretions and has higher sensitivity than either viral culture or antigen detection assays, particularly in immunocompromised patients .
- Compared with culture, the sensitivity and specificity of RT-PCR techniques can reach 100% and 95–98%, respectively



Respiratory Virus Infections in Hematopoietic Cell Transplant Recipients

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Highly immunocompromised pediatric and adult hematopoietic cell transplant (HCT) recipients frequently experience respiratory infections caused by viruses that are less virulent in immunocompetent individuals. Most of these infections, with the exception of rhinovirus as well as adenovirus and parainfluenza virus in tropical areas, are seasonal variable and occur before and after HCT. Infectious disease management includes sampling of respiratory specimens from nasopharyngeal washes or swabs as well as sputum and tracheal or tracheobronchial lavages. These are subjected to improved diagnostic tools including multiplex PCR assays that are routinely used allowing for expedient detection of all respiratory viruses. Disease progression along with high mortality is frequently associated with respiratory syncytial virus, parainfluenza virus, influenza virus, and metapneumovirus infections. In this review, we discuss clinical findings and the appropriate use of diagnostic measures. Additionally, we also discuss treatment options and suggest new drug formulations that might prove useful in treating respiratory viral infections. Finally, we shed light on the role of the state of immune reconstitution and on the use of immunosuppressive drugs on the outcome of infection.

Keywords: hematopoietic cell transplantation, respiratory virus infection, co-infection, immunosuppression, antiviral therapy, investigational drugs, infection outcome

Treatment algorithm of respiratory viral infections after HCT.

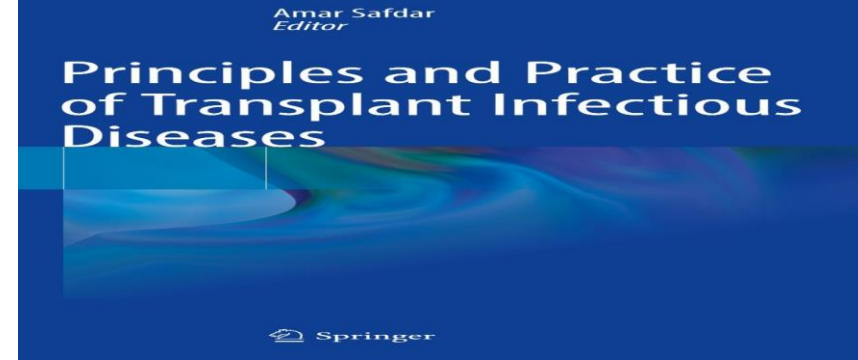
(1) Steroid dose withdrawal (if applicable) below 1 mg/kg/day (except for IFV)

(2) In case of LRI or high risk factors: start specific treatment

Virus	RSV	PIV	HMPV	RhV	AdV	IFV
First-line treatment recommendations	Oral Ribavirin 30mg/kg/day in 3 divided doses, 10 days				IV Cidofovir 5 mg/kg once a week (2w) and 5 mg/kg once every fortnight	Oral Oseltamivir 75 mg bid (30 mg bid 10–15 kg, 45 mg bid 16–23 kg,. 60mg bid 24-40 kg) for 10 days
Alternative treatment	IVIG IV Ribavirin Inhaled Ribavirin Palivizumab (young children)				Oral Brincidofovir (2mg/kg twice a week] Anti-ADV CTL	NAI: Inhaled Zanamivir IV Peramivir Zanamivir (if resistance)
Drugs/immunotherapy in development	GS-5806 MDT-637 ALX-0171 Favipiravir RSV-604 AL-8176 ALN-RSV01 RI-001	DAS 181 Anti PIV-3 CTL	MAb 338	Oral/nasal Pleconaril Vapendavir	HBX	Inhaled Laninamivir Nitazoxanide MEDI8852 VIS410

(3) Virus spread prophylaxis: hand hygiene, surgical mask, vaccination of family, prolonged isolation

AdV, adenovirus; HMPV, human metapneumovirus; RhV, rhinovirus; IFV, influenza virus ; IVIG, intravenous polyvalent immunoglobulins ; LRI, lower respiratory tract infection; NAI, neuraminidase inhibitor; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

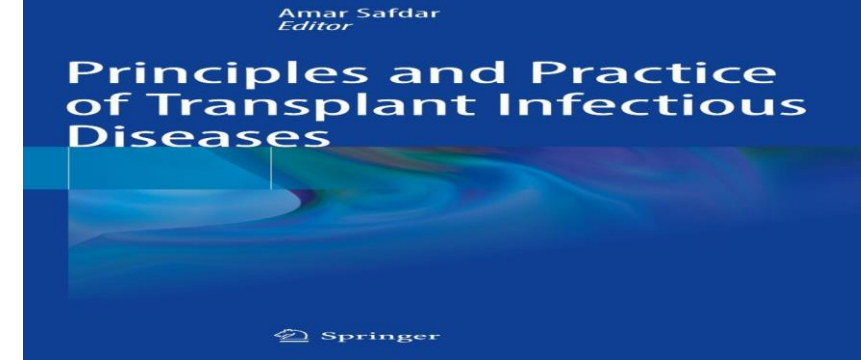


- **Oral Ribavirin** treatment in patients with **RSV**, **PIV**, or **HMPV** infection was associated with earlier recovery of graft function and prevention of BOS .

Reduction of Immunosuppression

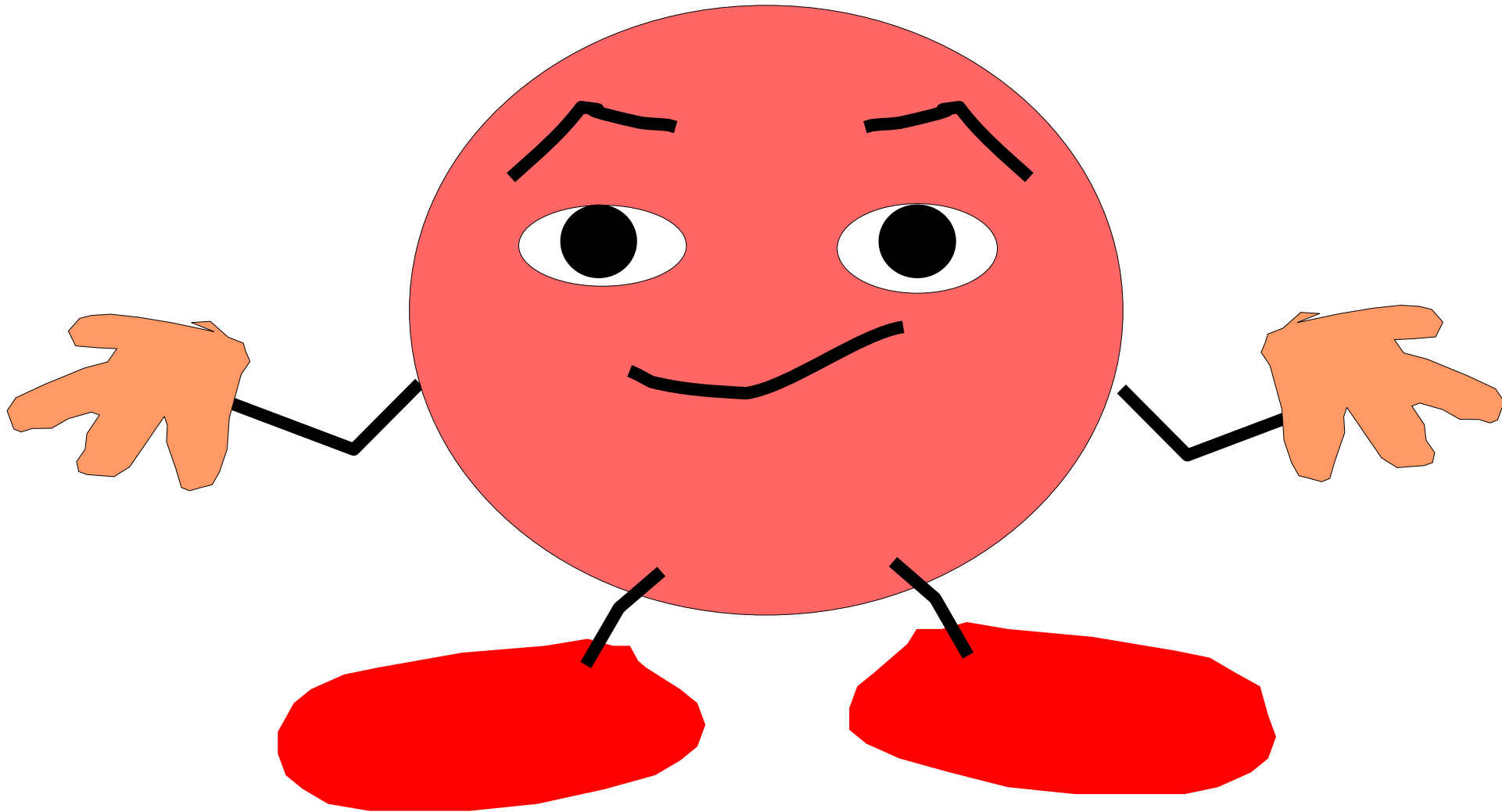
- Each time a respiratory tract infection is proven after HCT, a reduction of immunosuppressive treatment should be the response.
- Steroid dose greater than 1 or 2 mg/kg/day has been proven to be an independent risk factor for overall mortality in LRI with RhV , RSV , HMPV, and PIV.
- However, **no correlation between progression or mortality and steroid dose was found for IFV**

Recommendations for respiratory viral infections prior to hematopoietic stem cell transplantation



Virus	Recommendation for URTI	Recommendation for LRTI
RSV	Delay transplant if possible If not possible to delay, consider oral ribavirin	Delay transplant; consider ribavirin if delay is not feasible (anecdotal data)
Influenza virus	Delay transplant if possible and treat If not possible to delay, treat	Delay transplant and treat
Parainfluenza virus	Delay transplant if possible If not possible to delay, supportive care	Delay transplant; consider ribavirin if delay is not feasible (anecdotal data)
Metapneumovirus	Delay transplant if possible	Delay transplant; no data on ribavirin
Rhinovirus	No delay needed for URTI	Delay transplant for allogeneic transplant if feasible
Coronavirus	No data	No data
Bocavirus	No data	No data

CASE PRESENTATION



CASE PRESENTATION

- **A 36-year-old female underwent a liver transplant due to Autoimmune hepatitis . (cytomegalovirus [CMV] D+/R+) .**
- **One months after transplant, in February, he presented with two days history of dry cough, pleuritic chest pain, increasing shortness of breath, chills, fever, rhinorrhea, and myalgias.**
- **She had no known sick contacts.**

CASE PRESENTATION

- Her maintenance immunosuppressive medications included mycophenolate , prednisone and tacrolimus .
- Her antimicrobial prophylaxis consisted trimethoprim-sulfamethoxazole (TMP-SMX).
- She is an accountant but has not returned to work since transplant.
- She is married, has no children, and has not had any recent travel or unusual exposures.
- She has a dog but denies other animal exposures.

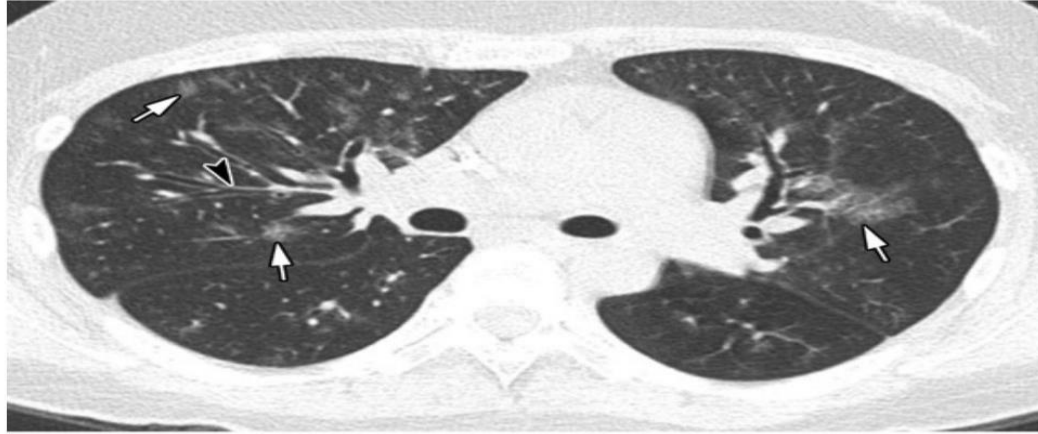
CASE PRESENTATION

- Exam findings on presentation were notable for ill appearance, with
- Fever of 38.3°C
- Tachypnea
- Tachycardic and hypoxia with a room air oxygen saturation of 89%.
- Blood pressure was 130/65 mm mercury.
- She had mild conjunctival injection bilaterally.
- Chest auscultation revealed diminished breath sounds at the right base and rales at the left base.

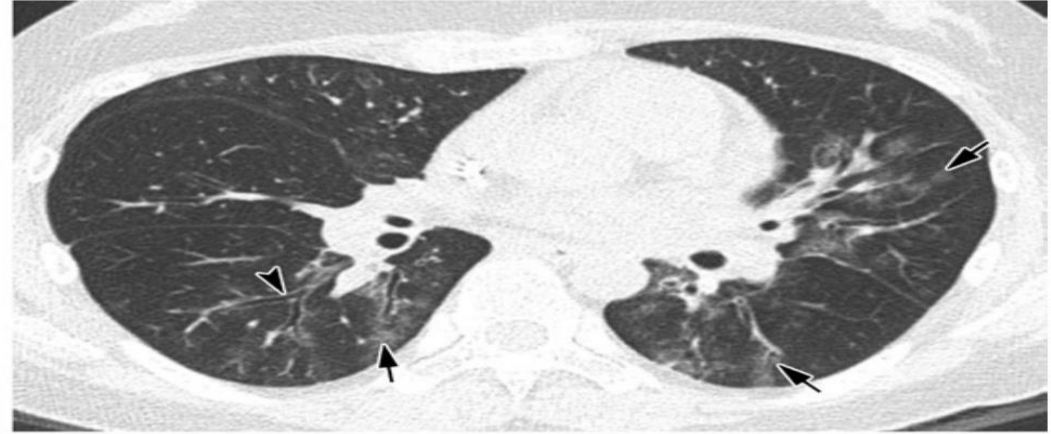
CASE PRESENTATION

- Her abdomen was soft and non tender, with an unremarkable appearing surgical wound, and with no tenderness overlying the allograft.
- No rash was present.
- Neurological examination was unremarkable.

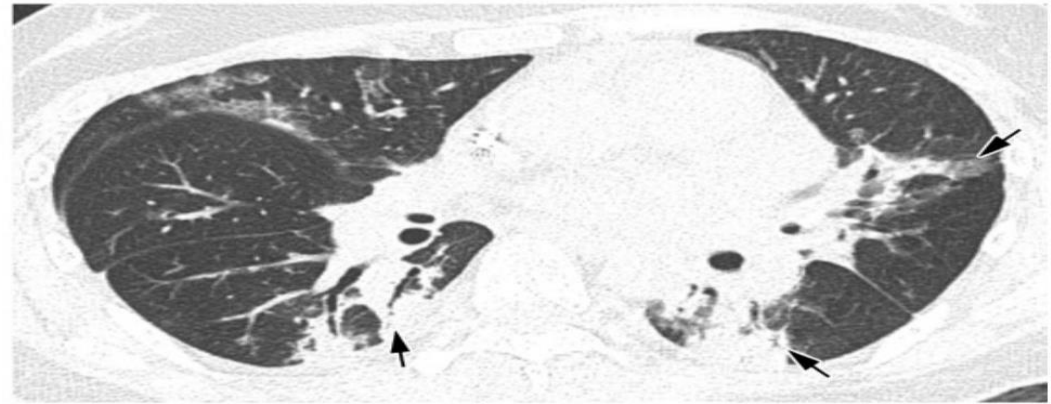
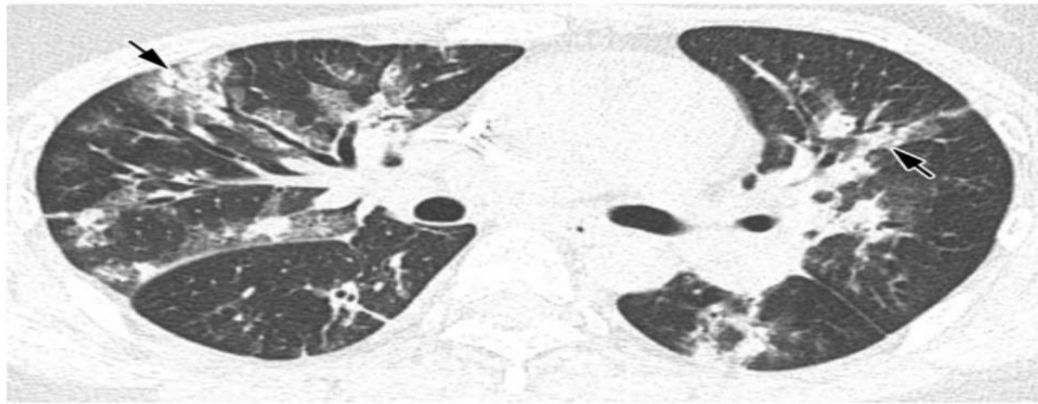
CASE PRESENTATION

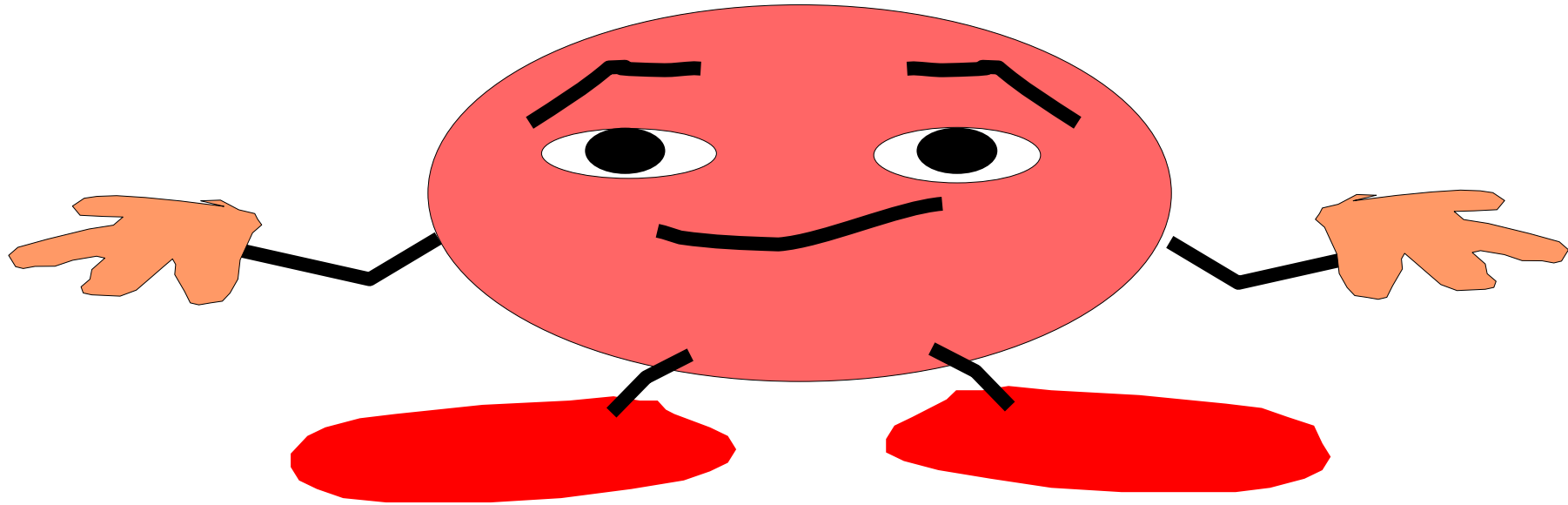


a.



b.





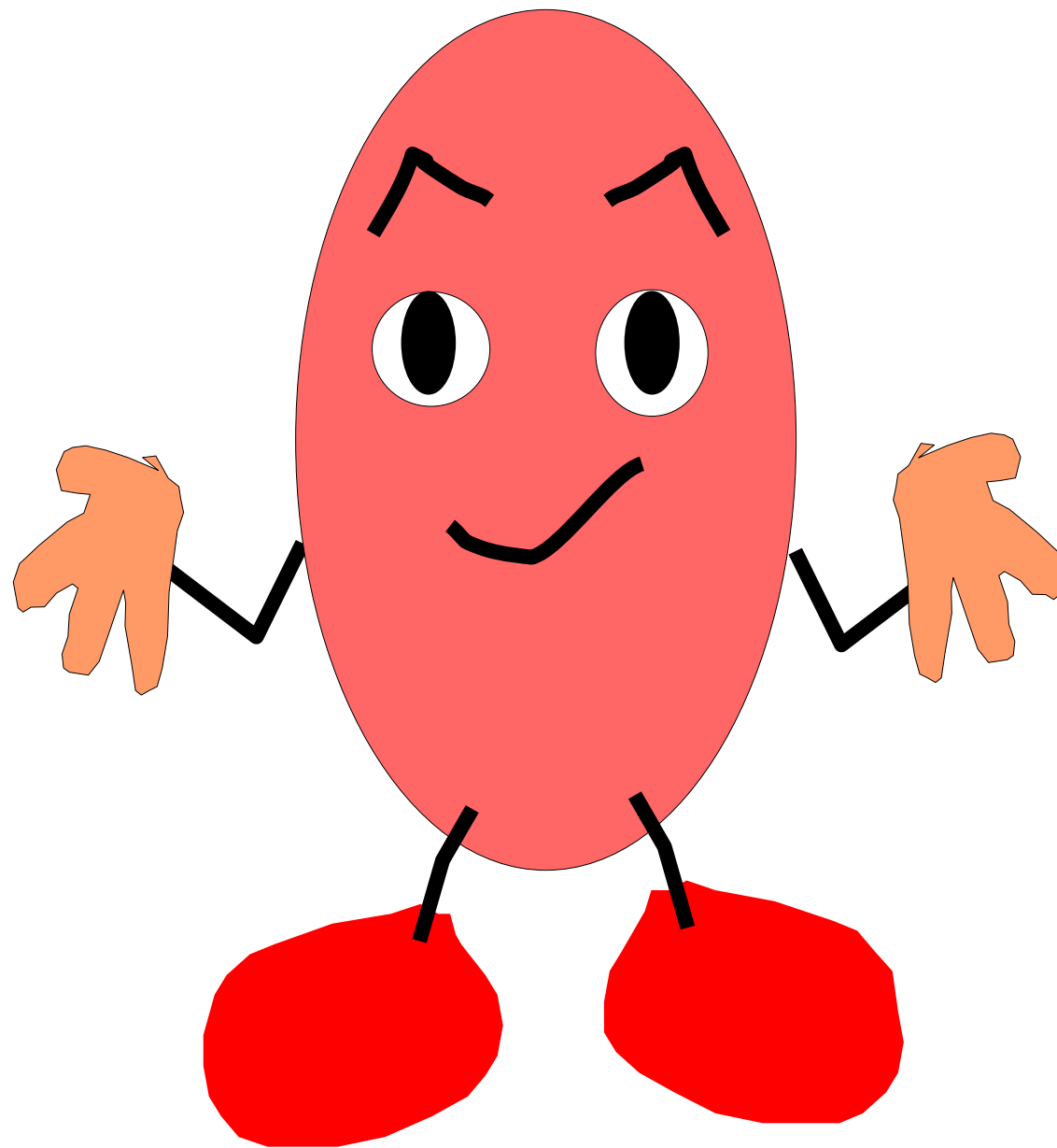
- **What disease entities should be considered to explain this patient's clinical syndrome of acute respiratory illness?**
- **How should a diagnosis be pursued?**

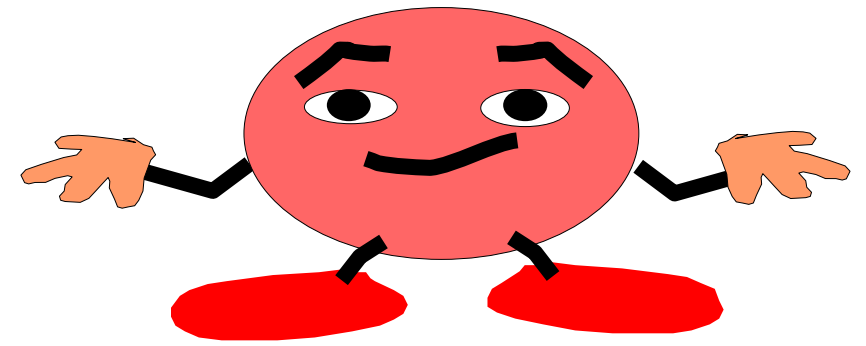
•CMV????

•PCP????

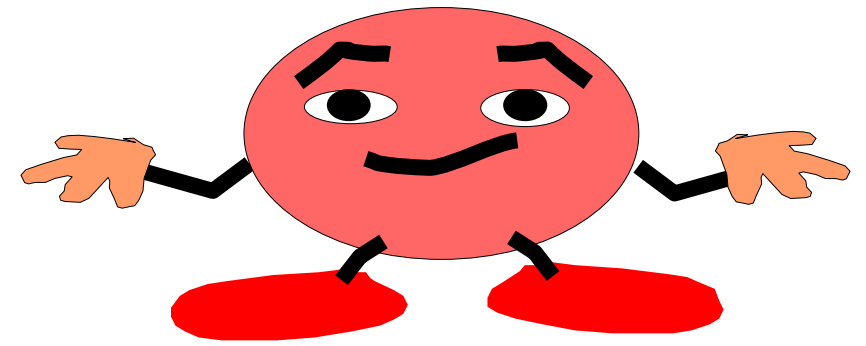
•RVI???

•Or?????



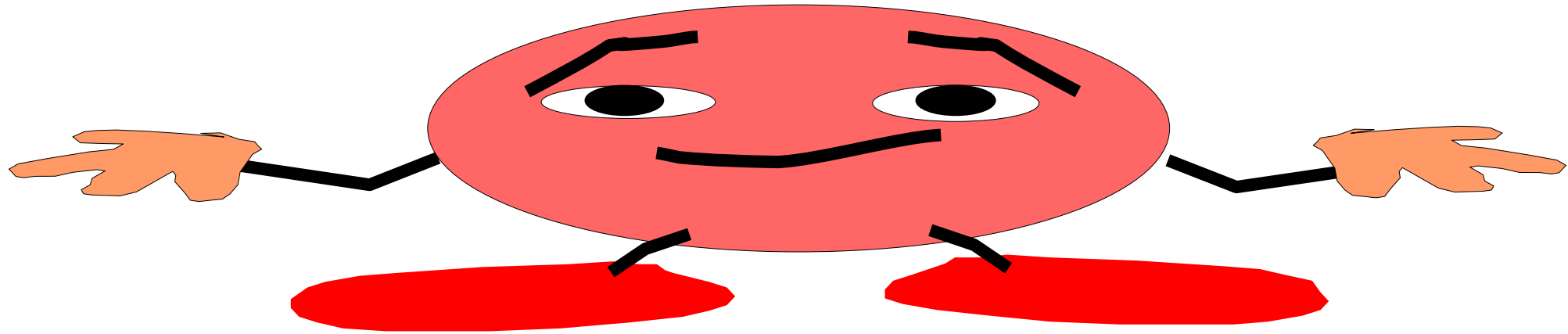


- **This patient is presenting with a constellation of signs and symptoms that point to a community-acquired respiratory virus infection (CARVI).**
- **The most commonly encountered pathogens are Rhinovirus, and Coronaviruses. Parainfluenza, Influenza, respiratory syncytial virus (RSV), Adenovirus, and HMPV**



Nasal swab was obtained and submitted for multiplex panel respiratory virus polymerase chain reaction testing.

- The following day it was reported as positive for PIV.**
- Bronchoscopy were done and BAL was positive for PIV & Aspergillosis pcr& GM.**
- The results of blood, urine, and sputum bacterial cultures were all negative.**



- **The patient was started on**
- **Oral Ribavirin**
- **IVIG (500mg/kg IV QOD x 5doses)**
- **Voriconazole**

Outcomes in Invasive Pulmonary Aspergillosis Infections Complicated by Respiratory Viral Infections in Patients With Hematologic Malignancies: A Case-Control Study

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Background. Data regarding invasive pulmonary aspergillosis (IPA) following respiratory viral infections (RVIs) in patients with leukemia and/or hematopoietic stem cell transplantation (LHSCT) are limited.

Methods. We conducted a retrospective case-control study of post-RVI IPA (2006–2016). Cases were patients who underwent LHSCT and had RVI due to respiratory syncytial virus (RSV), influenza virus (INF), or parainfluenza virus (PIV) followed by culture-documented IPA within 6 weeks. Controls had IPA only.

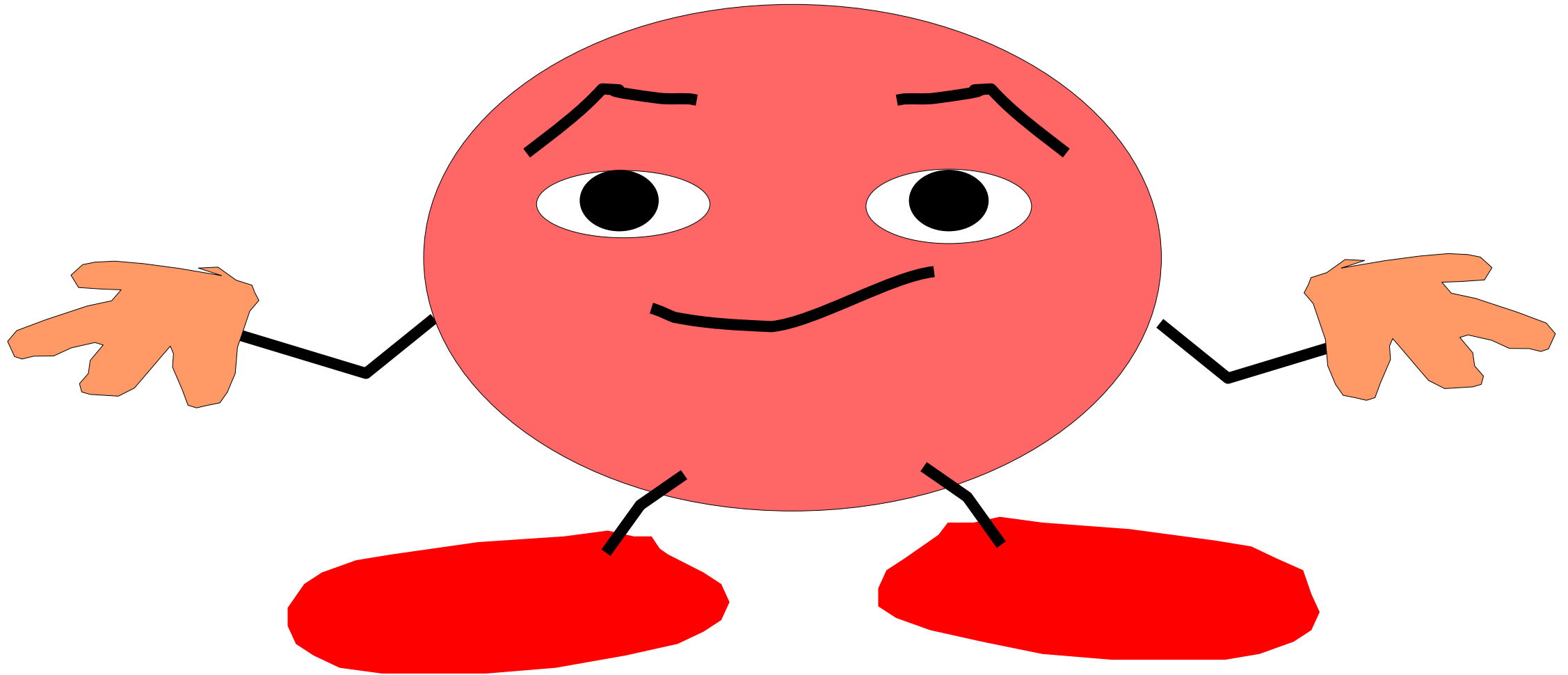
Results. We identified 54 cases and 142 controls. Among cases, 29 (54%) had PIV infection, 14 (26%) had INF infection, and 11 (20%) had RSV infection. The median time to IPA after RVI was 7 days. A greater percentage of cases (37 [69%]) than controls (52 [37%]) underwent allogeneic HSCT ($P < .0001$). Cases were more likely to be nonneutropenic (33 [61%] vs 56 [39%]; $P = .009$) and in hematologic remission (27 [50%] vs 39 [27%]; $P = .003$) before IPA. Cases were more likely to have monocytopenia (45 [83%] vs 99 [70%]; $P = .05$) and less likely to have severe neutropenia (21 [39%] vs 86 [61%]; $P = .007$) at IPA diagnosis. Prior use of an *Aspergillus*-active triazole was more common in cases (27 of 28 [96%] vs 50 of 74 [68%]; $P = .0017$). Median time to empirical antifungal therapy initiation was 2 days in both groups. Crude 42-day mortality rates did not differ between cases (22%) and controls (27%), but the 42-day mortality rate was higher among cases with IPA after RSV infection (45%) than among those with IPA following INF or PIV infection (13%; $P = .05$).

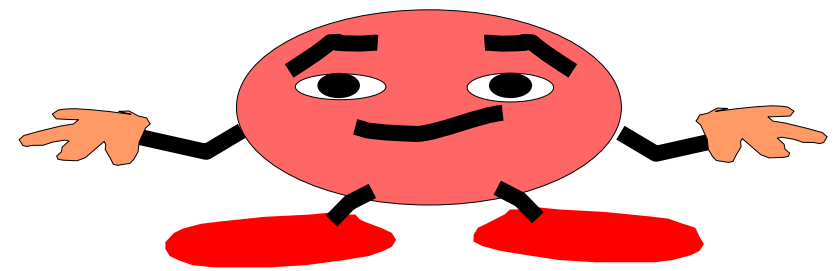
Conclusions. IPA had comparable outcomes when it followed RVI in patients who underwent LHSCT, and post-RVI IPA occurred more frequently in patients with prior allogeneic HSCT and was associated with leukemia relapse and neutropenia.

Keywords. *Aspergillus*; hematologic malignancy; influenza; parainfluenza; respiratory syncytial virus.

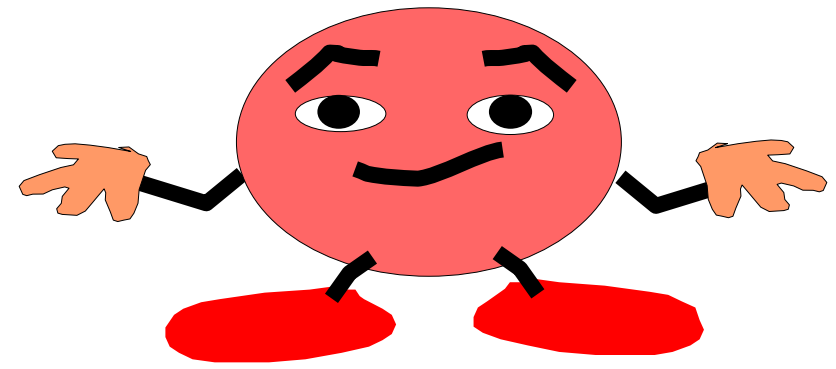
- Post-RVI IPA was defined as sputum, BAL (or bronchial wash), or tissue biopsy specimen cultures positive for *Aspergillus* species identified within 6 weeks after RVI.

CASE PRESENTATION

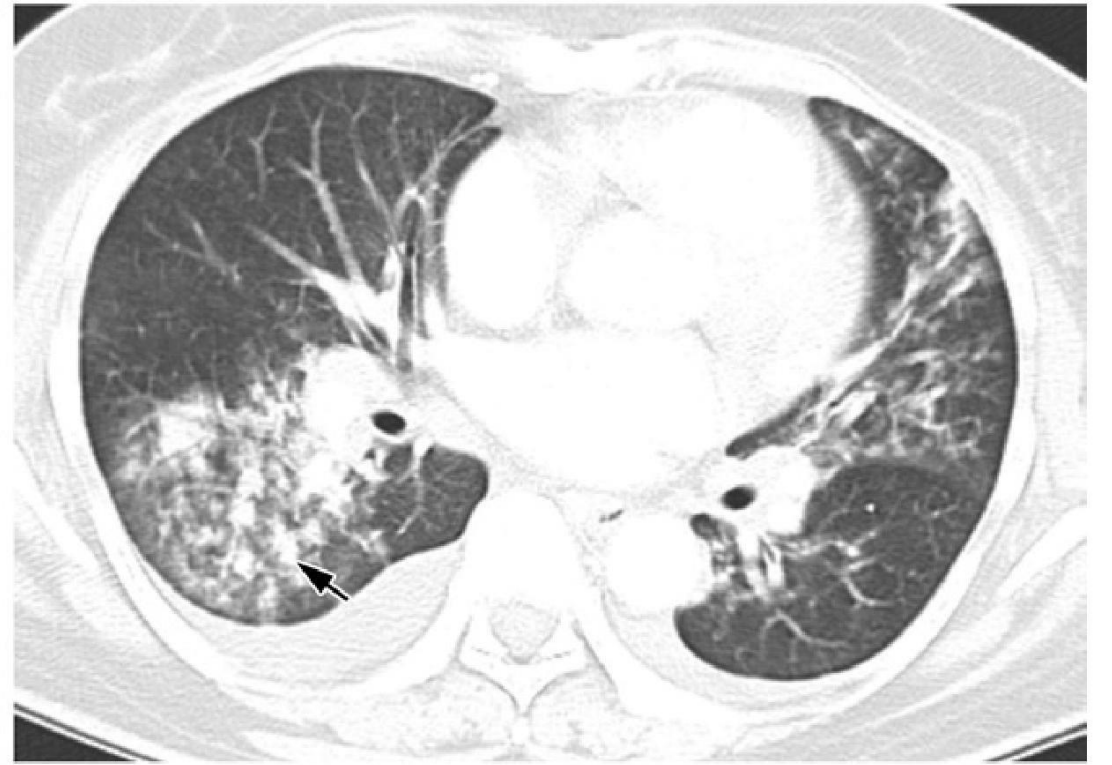
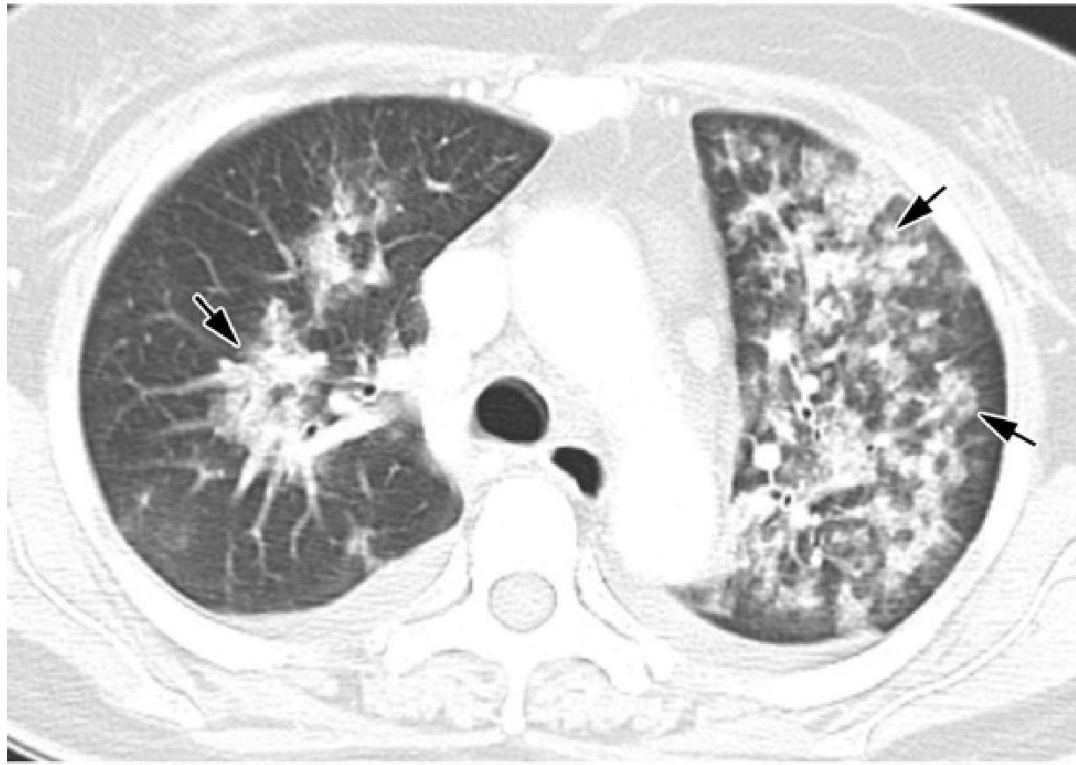
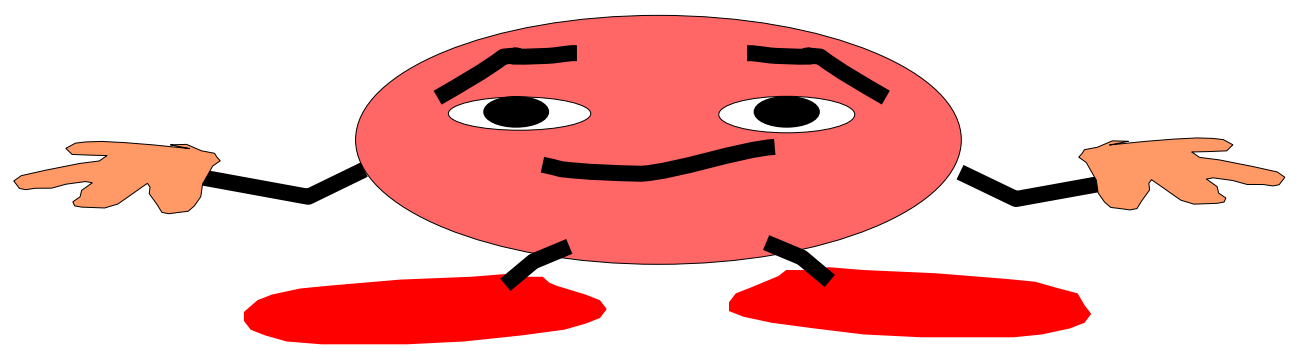


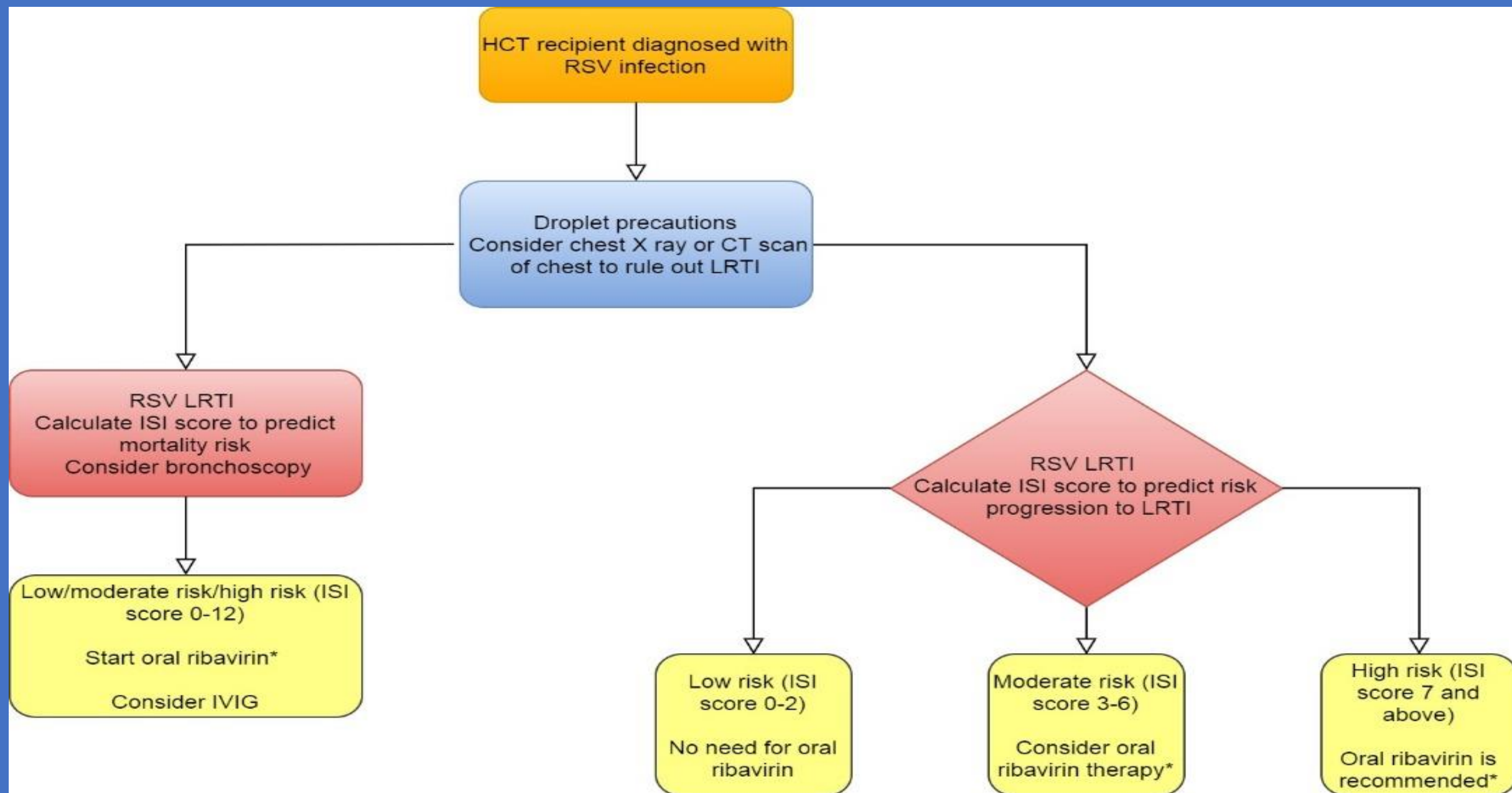


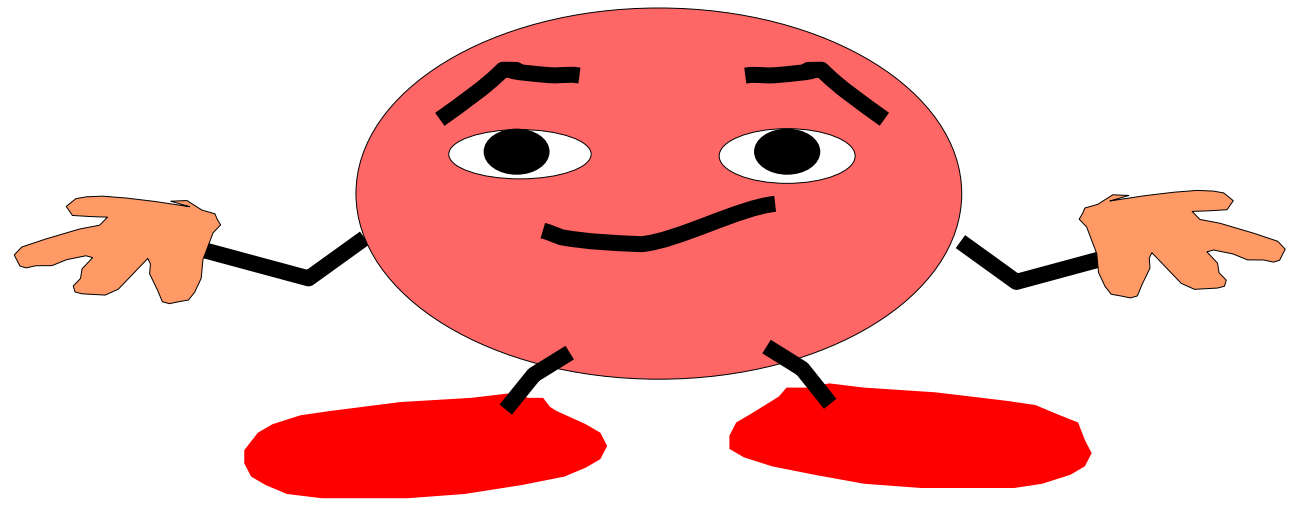
- **A 50-year-old female, 1 years after allogeneic HCT for acute myeloid leukemia, presented to the emergency room with 3 days of fever and upper respiratory symptoms, 1 day of shortness of breath, and a new oxygen requirement (5 L/min via nasal cannula).**
- **On physical examination, she had diminished and coarse breath sounds and was slightly tachypneic.**
- **The patient had GVHD treated with prednisone (,0.5 mg/kg per day) and sirolimus.**



- **Neutropenia less than 500 neutrophils/mL**
- **Lymphopenia less than 200 lymphocytes/mL**
- **The patient had a smoking history.**
- **Chest computed tomography showed scattered foci of ground glass infiltrates and centrilobular nodules and with areas of tree-in-bud opacity and bronchial wall thickening**







- A nasal swab was positive for RSV .
- Bronchoscopy were done and BAL was positive for RSV .
- high-risk (score of 7-12) ISI.
- The patient was started on oral ribavirin for 7 days.with
IVIG (500mg/kg IV QOD x 5doses)

Thank You!

