Significance of respiratory virus infections in HSCT: Not just a cold!

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- I have no conflict of interest to disclose related to this presentation

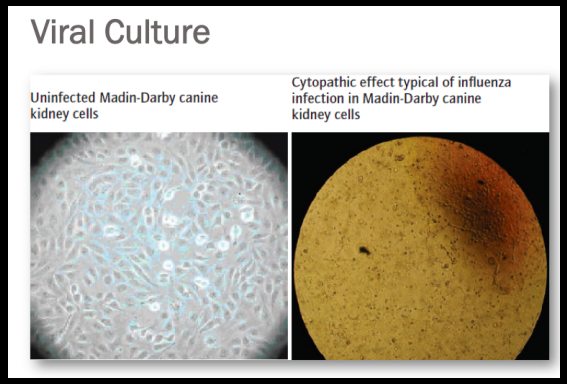
http://giphy.com/gifs/the-simpsons-brain-sneeze-aohvgsGTzqqYg

Learning objectives

- Appreciate the clinical significance of respiratory virus infections (RVI) in Hematopoietic Stem Cell Transplant (HSCT) recipients
- Review most relevant respiratory viruses affecting HSCT population
- Recognize which patients can be potentially treated
- Overview of available treatment and prevention options

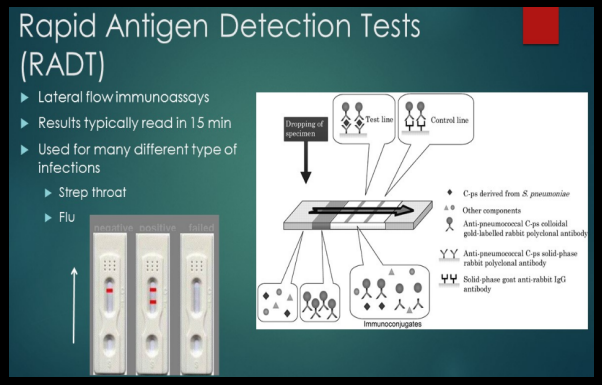
Advances in diagnostic technology are allowing identification of novel etiologic agents for “idiopathic” pneumonia

3-10 days. Sens/Spec +



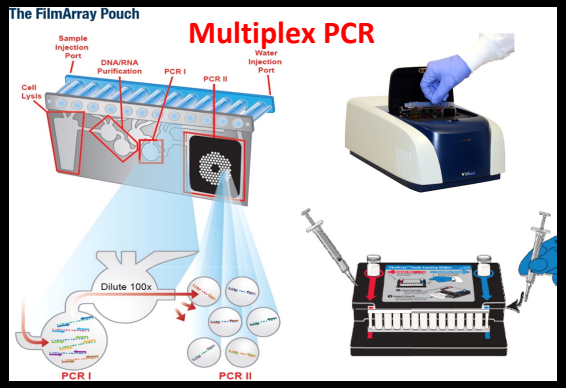
https://pt.slideshare.net/zionpattres/lab-diagnosis-of-viruses?ref=

15-30 mins. Sens/Spec ++



https://www.memorangapp.com/flashcards/32795/CMOD+2/

2-8 hours. Sens/Spec +++



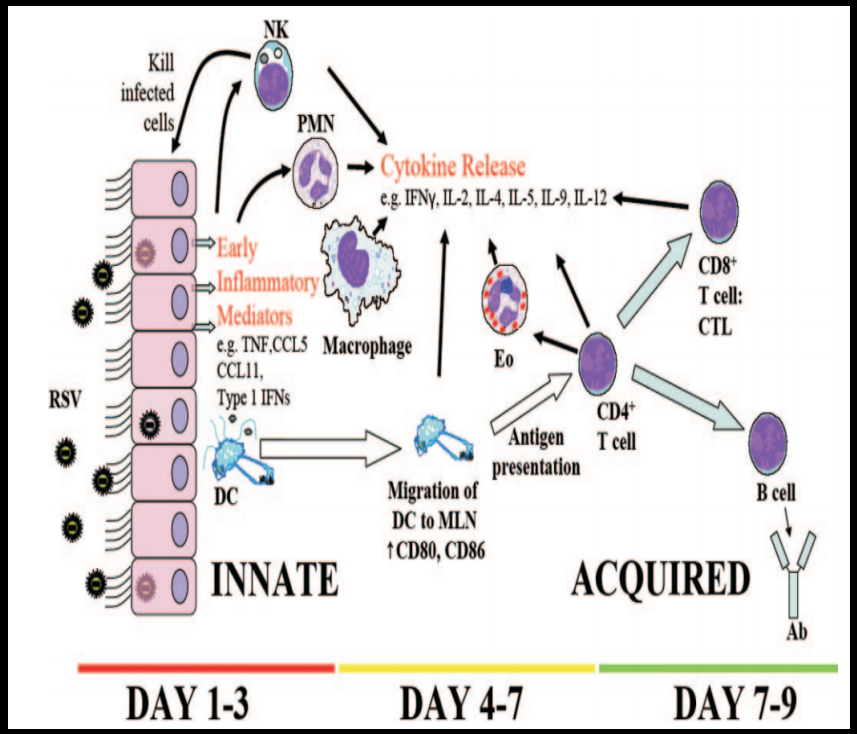
J. Clin. Microbiol. July 2011 vol. 49 no. 7 2449-2453

Rates of Disease Progression, and mortality due to RVI in HSCT

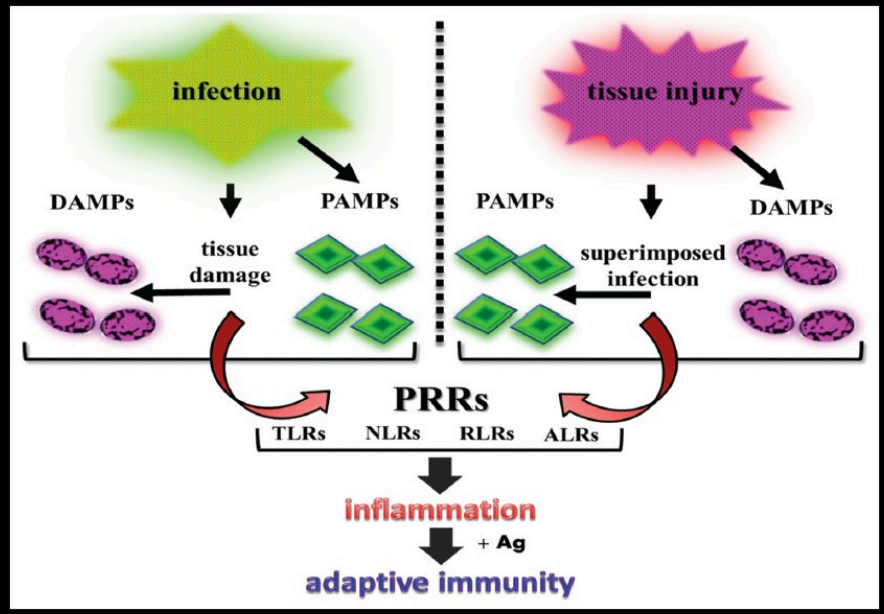
Virus	Infection Rates in First 100 Days (%)	Progression from URI to LRI (%)	Overall 30-day Mortality with LRI (%)	References
RSV	2–6	20–40	25–45	(13,25–27)
PIV	4–7	18–44	~35	
Influenza A/B	1–3	15–18	~25	
Metapneumovirus	3–6	25–41	~33	(28–30)
Rhinovirus	21	2–4	~20	(31–34)

Bowden et al. Community –Acquired Respiratory viruses. Chap 27. in Transplant Infections. 3rd edition. 2010

Immune response to RVI and chronic allograft dysfunction



Chronic inflammation



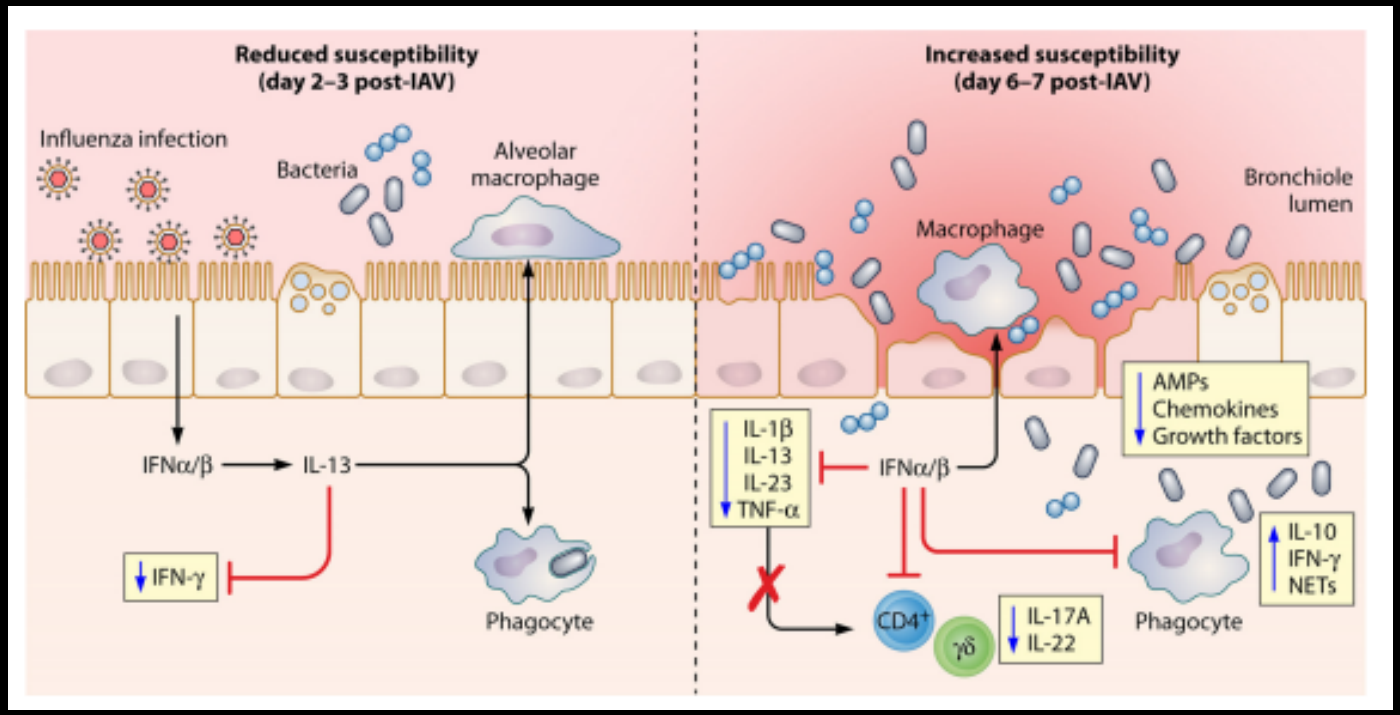
Prolonged viral shedding and innate immunity activation

Openshaw Et Al. Fig 2. CLINICAL MICROBIOLOGY REVIEWS, July 2005, P. 541–555

Gottlieb, Walter. Chronic allograft dysfunction: A model disorder of innate immunity. Biomed J 2013;36:209-228

(Image Courtesy of http://weknowmemes.com/2013/01/batman-on-flu-season/

Superinfection after influenza virus infection

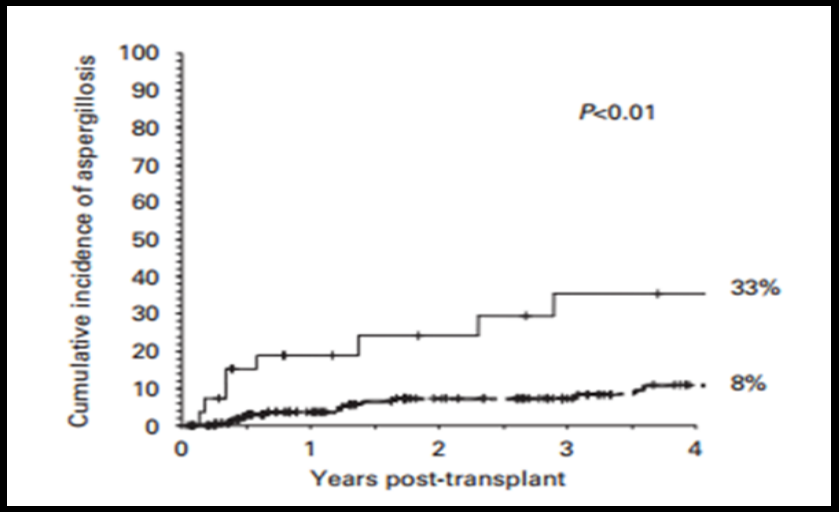


Murine Model

Epithelial damage
Neuraminidase activity enhance streptococcal adherence
Reduced phagocyte activity

Rynda-Apple et al. Infection and Immunity. October 2015 Volume 83 Number 10

Increased risk of Invasive Aspergillosis



Martino, R et al. Bone Marrow Transplantation Vol 44, pages749-756(2009):

219 Allo HSCT

27 developed IA (13%)

Risk Factors :

LRTI by respiratory virus (HR 4.3), GVHD (HR 2.9) and CMV infection (HR 2.8)

Marr, KA et Al. Blood, 15 December 2002 Volume 100, Number 13:

- 1682 HSCT recipients
- Patients with respiratory virus infections at day 40 post allo HSCT had a 2.1-fold increased risk of subsequent IA

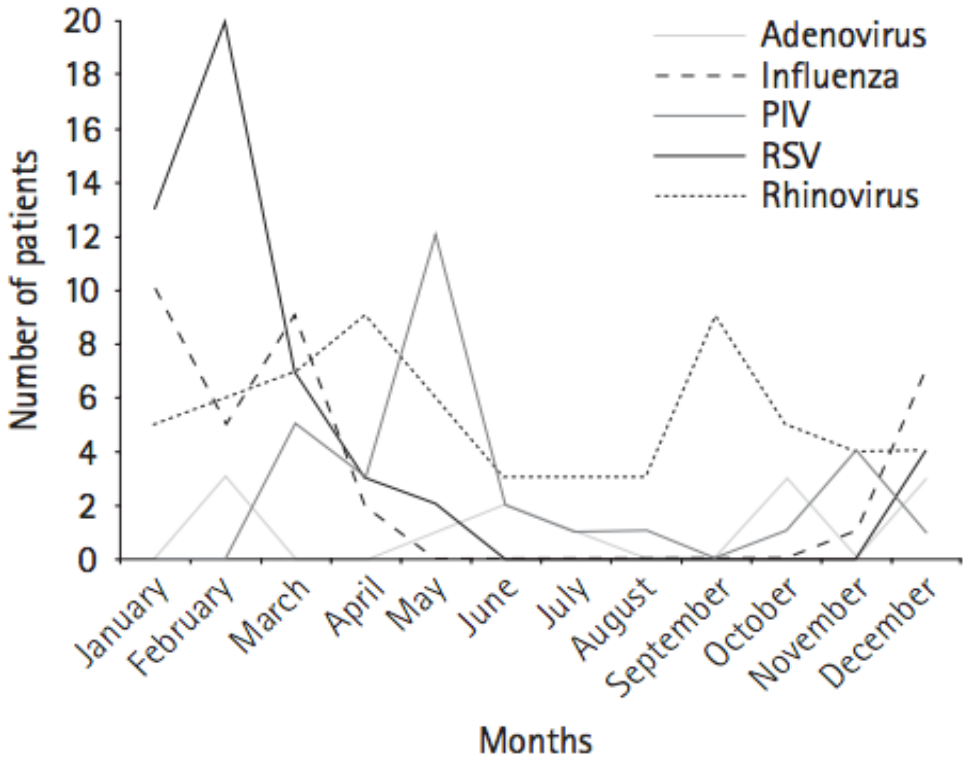
Complications of respiratory virus infections in transplant recipients

- LRTI (increased mortality)
- Acute and chronic allograft dysfunction
- GVHD
- Co infection (bacterial and fungal)
- Immune system exhaustion?

MOST RELEVANT RESPIRATORY VIRUSES IN HSCT RECIPIENTS

Seasonal distribution

Figure 1. Seasonal distribution of respiratory viral infections by pathogen



Adapted with permission from [14], copyright Elsevier and the Association of Professors of Medicine. The figure shows the total number of transplant recipients with individual viruses over a 3 year period. PIV, parainfluenza vrus; RSV, respiratory syncytial virus.

Ison, Michael G. Antiviral therapy. 2007

Respiratory viruses testing at MCV (Feb 2014- May 2016)

Inpatient and outpatient
2812 patients
4213 tests

Adenovirus	5.15%
Bordetella pertussis.	0.12%
Chlamydophila pneumoniae	0.09%
Coronavirus 229E	1.07%
Coronavirus HKU1	2.35%
Coronavirus NL63	2.56%
Coronavirus OC43	4.04%
Human Metapneumovirus	6.01%
Influenza A	0.31%
Influenza A 2009 H1	3.80%
Influenza A H1	0.07%
Influenza A H3	4.27%
Influenza B	2.71%
Mycoplasma pneumoniae	0.93%
Parainfluenza 1	1.40%
Parainfluenza 2	0.59%
Parainfluenza 3	4.18%
Parainfluenza 4	1.59%
Respiratory Syncytial Vir	**16.16%**
Rhinovirus/Enterovirus	**42.61%**

BMT inpatient units, BMT, Dalton and transplant clinics.

Adenovirus	3	0.44%
Coronavirus 229E	19	2.79%
Coronavirus HKU1	26	3.81%
Coronavirus NL63	13	1.91%
Coronavirus OC43	38	5.57%
Human Metapneumovirus	25	3.67%
Influenza A 2009 H1	15	2.20%
Influenza A H3	16	2.35%
Influenza B	8	1.17%
Parainfluenza 1	16	2.35%
Parainfluenza 2	1	0.15%
Parainfluenza 3	43	6.30%
Parainfluenza 4	17	2.49%
Respiratory Syncytial Vir	**139**	**20.38%**
Rhinovirus/Enterovirus	**302**	**44.28%**
Grand Total	682	100.00%

Courtesy of Christopher Doern, PhD. Associate Director of Clinical Microbiology at VCUMC

Influenza

http://www.who.int/mediacentre/factsheets/fs211/en/

Influenza A and B

- Incidence: 9.4 to 47% (among patients with respiratory infections). 1.3% overall
- Mortality: 4.5 up to 47.8%
- Clinical course: LRTI, secondary superinfection with fungal or bacterial pathogens. Emergence of M2 inh resistance
- Dx: Direct antigen Detection (DAD), PCR.
- Rx: Flu A or B - neuraminidase inhibitors (oseltamivir PO, Peramivir IV or zanamivir Inh), M2 inhibitor (amantadine and rimantadine - Flu A. RBV may be in combination

1918 pandemic flu infected 500 million, killed around 100 millions

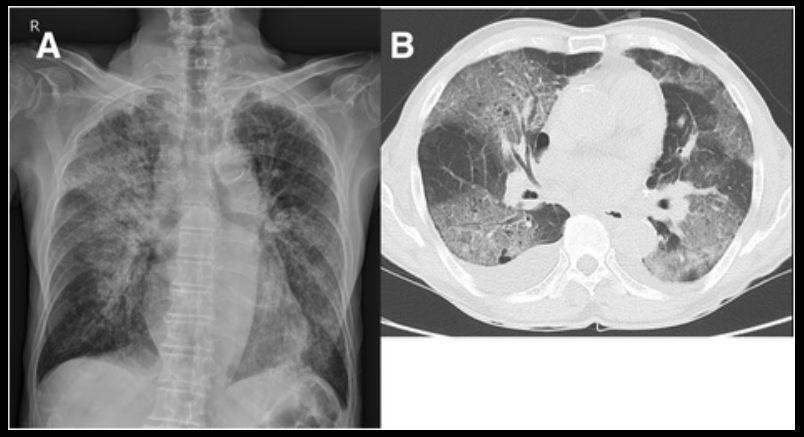
ARDS secondary to H1N1 infection

Edited from table 1. Kim et al. Semin Respir Crit Care Med. 2007 Apr;28(2)

Barton and Blumberg. Clin Chest Med 26 (2005)

RSV

- Incidence: 23.9-31 %(among patients with respiratory infection). Overall 8.7%
- Mortality: 6.5-26% (~80% if untreated from older reports)
- Clinical course URTI, LRTI, graft failure, airflow decline
- Year round transmission, peak in the cold seasons. Nosocomial outbreaks
- Dx: Viral culture, DAD, PCR.
- Rx: RBV, IVIG, Palivizumab



Journal of Medical Case Reports 2017. 11:353

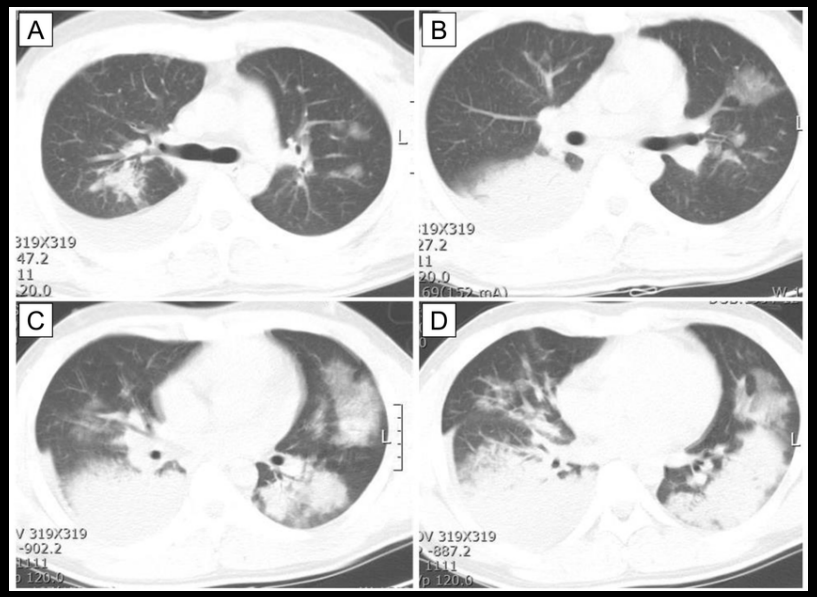
Edited from table 1. Kim et al. Semin Respir Crit Care Med. 2007 Apr;28(2)

Barton and Blumberg. Clin Chest Med 26 (2005)

Adenovirus

- Several serotypes
- Incidence 2.7-47%. Mortality 18-52.8%
- Clinical course : URTI,LRTI, extra - pulmonary manifestations (Enteritis, hemorrhagic cystitis, renal failure, hepatitis, CNS involvement), graft failure or delayed engraftment, dissemination
- Community acquired or reactivation. Peak at summer months
- DX: PCR
- Rx: Cidofovir. Gancyclovir and Acyclovir have poor activity. Reduction of immunosuppression

www.medscape.com



J Thorac Dis 2016;8(5):848-854

Edited from table 1. Kim et al. Semin Respir Crit Care Med. 2007 Apr;28(2)

Barton and Blumberg. Clin Chest Med 26 (2005)

Parainfluenza

- Incidence: PIV-3 > PIV1 > PIV2 > PIV4. 9.6-28% Among patients with respiratory infection. Overall 7.1-13.8%
- Mortality: 4 -75%
- Clinical course: URTI, LRTI, encephalitis. Common coinfection with *A. fumigatus* , CMV, RSV and other bacterial pathogens. Airflow decline
- High rate of asymptomatic shedding. Nosocomial transmission is common
- DX: Viral Culture, DAD , PCR
- Rx: +/- RBV, IVIG. DAS-181?

Edited from table 1. Kim et al. Semin Respir Crit Care Med. 2007 Apr;28(2)

Barton and Blumberg. Clin Chest Med 26 (2005)

HMPV

- Incidence: 3-4%
- Mortality: data obscured due to co-infection. ~12.5%
- Clinical course: URI, LRTI, respiratory failure, pulmonary hemorrhage
- Dx: Viral Culture, DAD, PCR
- Rx: ? Ribavirin, ?IVIG

Coronavirus

- Year round circulation, slight predominance in winter
- LRTI < 10% in HSCT
- Mortality estimated <10%
- Deadly coronaviruses: SARS and MERS
- Rx: Lack of antiviral agents and clinical trials

Edited from table 1. Kim et al. Semin Respir Crit Care Med. 2007 Apr;28(2)

Rhinovirus/Enterovirus

- Rhinoviruses:
  - Incidence: 7.8%
  - Mortality: Fatal cases reported
  - Clinical course: URI, LRTI (rare). Prolonged shedding
  - Supportive therapy

- Enteroviruses:
  - Incidence: 0.7% in BAL specimens. 6% in patients with respiratory infections
  - Mortality: Fatal cases reported
  - Clinical course: LRTI, ARDS, Meningitis -Encephalitis
  - Supportive therapy

Edited from table 1. Kim et al. Semin Respir Crit Care Med. 2007 Apr;28(2)

Highlights of clinical presentation in HSCT recipients

- Wide range of disease: URI -trachea-bronchitis – bronchiolitis – pneumonia
- Often present with mild or atypical symptoms and fever may be absent
- Viral shedding is usually prolonged
- Look for subsequent development of bacterial and fungal pneumonia

WHO NEEDS TO BE TREATED?

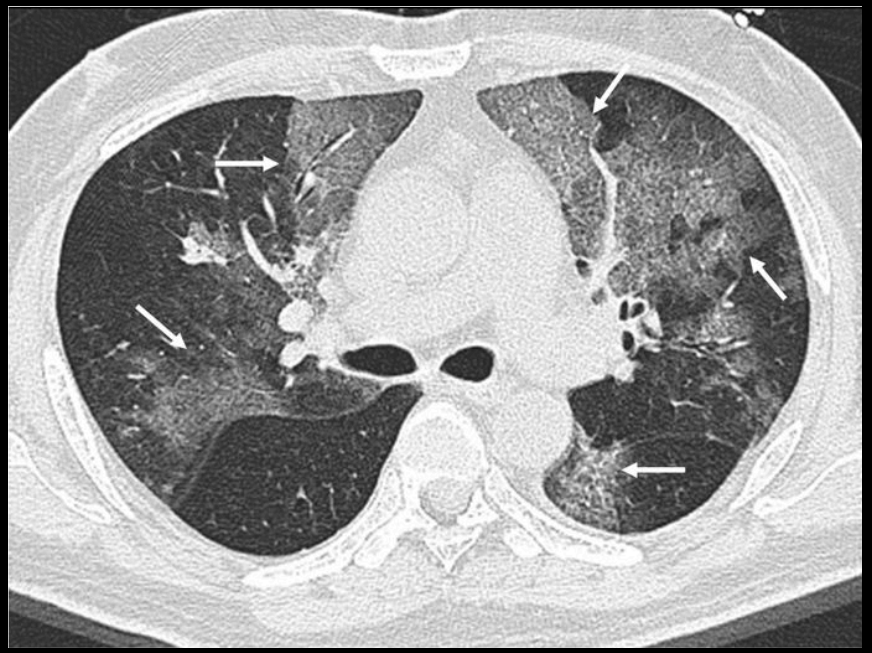


Table 2. Risk Factors of Respiratory Syncytial Virus–Associated Complications in Hematopoietic Stem Cell Transplantation Patients

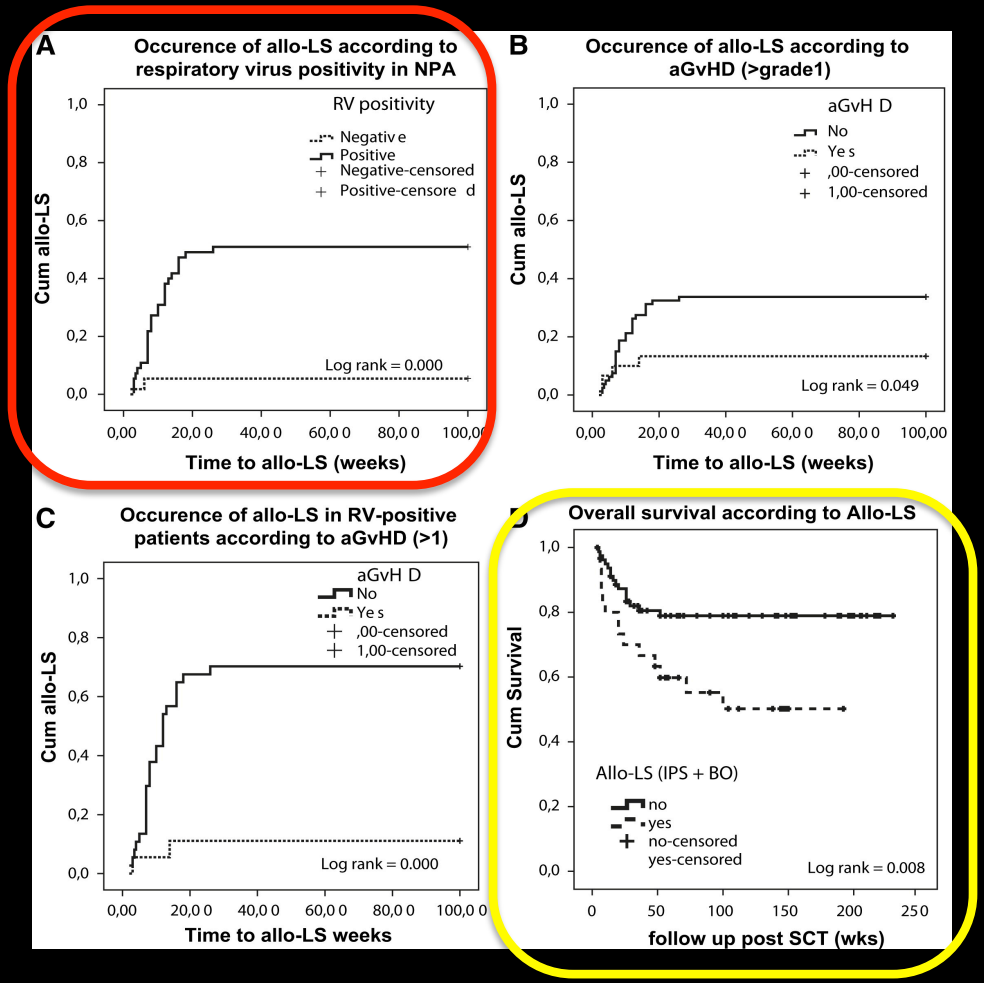
Progression to LRTID
• Lymphopenia $<0.2 \times 10^9$/L
• Older age
• Mismatched/unrelated donor
• Allogeneic HSCT <1 mo
• Neutropenia <500/μL
• No therapy with aerosolized ribavirin + IVIG
Mortality
• Preengraftment
• Lymphopenia $<0.2 \times 10^9$/L
• Allogeneic HSCT <1 mo
• Severe immunodeficiency
• Older age (>65 y)

Abbreviations: HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; LRTID, lower respiratory tract infectious disease.

Respiratory virus infections and Alloimmune lung syndrome (IPS,BOS, COP)

- 110 Ped allo HSCT
- 27% developed allo-LS strongly associated to RVI
  - 18 Idiopathic Pulmonary syndrome
  - 12 Bronchiolitis obliterans

- Overall survival is decreased associated Allo immune −Lung Syndromes



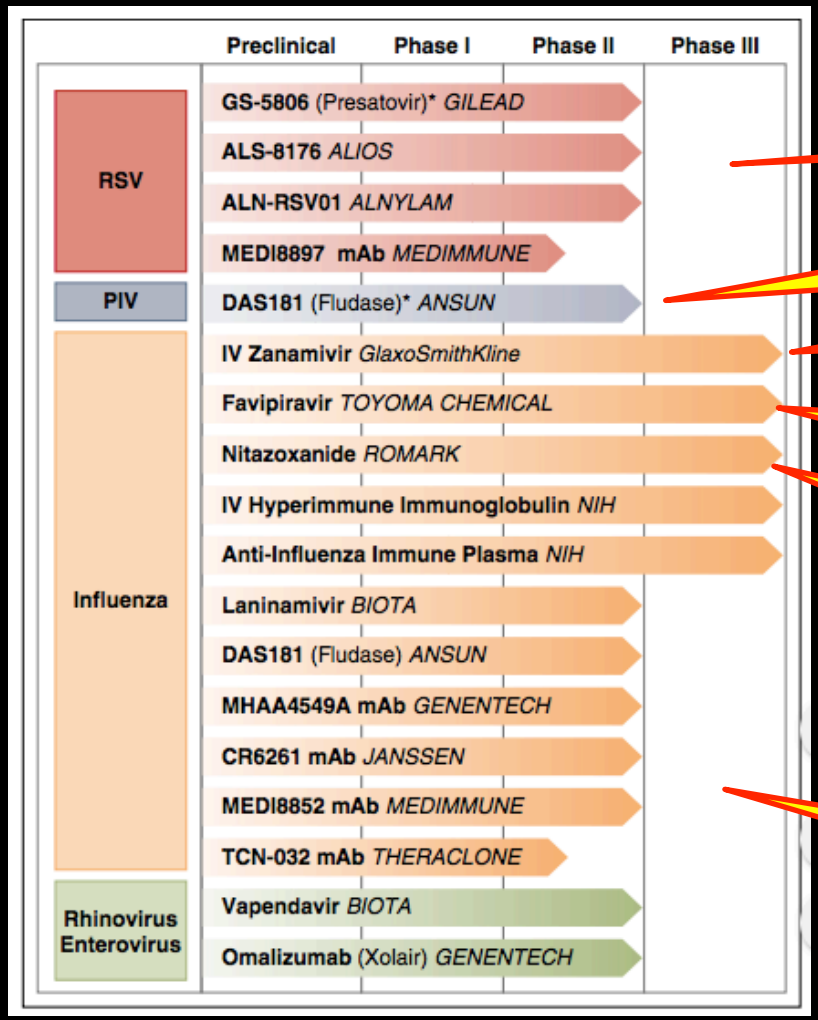
Biol Blood Marrow Transplant 16: 782-791 (2010)

Preventive Measures

Respiratory Virus.	Incubation Period (days)	Mode of transmission	Infection Prevention Principles
RSV	4.4	Direct or indirect contact; droplet	**S**tandard. **C**ontact and **D**roplet precautions.
ADV	5-9	Direct contact; aerosols; fecal-oral	**S**tandard. **C**ontact and **D**roplet precautions.
Influenza	1-4	Contact; droplet; aerosol	**S**tandard. **D**roplet precautions. **A**irborne with invasive ventilation; Seasonal vaccination; Post exposure prophylaxis with Oseltamivir
PIV	2.6	Direct contact; droplet; large particle aerosol	**S**tandard. **A**irborne and **D**roplet precautions.
hMPV	4-6	Direct contact; droplet; large particle aerosols	**S**tandard. **C**ontact precautions.
Rhinovirus/Enterovirus	1-9	Direct or indirect contact; large or small particle aerosol	**S**tandard. **D**roplet precautions.

De La Cruz et al. Int Journal of Inf Diseases. 2017

Therapies under development for HSCT and HM RVIs



ALS -8176: Nucleoside analog targeting RSV polymerase, demonstrated reduction on VL And disease severity.
ALN-RSV01. Small interfering RNA with robust VL decrease *in vitro* and mice.

Biol Blood Marrow Transplant. 2016 May;22(5):965-70. Epub 2016 Feb 22. (56% complete clinical response to DAS 181)

Available through FDA EIND. Useful for Oseltamevir resistance strains

PB1 inhibitor (of viral polymerase complex) approved for use against pandemic flu in Japan.

Rossignol, J. Antiviral Research 110 (2014) 94–103RossignolAntiparasitic drug, with broad spectrum antiviral activity (Flu, RSV, PIV, Coronavirus, Norovirus, . Blocks maturation of Hematugglutinin. No available data published yet from NCT01610245 (Oselt vs NTZ vs Oselt/NTZ vs placebo).

DiLillo et al. Nat Med. 2014 Feb;20(2):143-51. doi: 10.1038/nm.3443. Epub 2014 Jan 12. Broadly neutralizing hemagglutinin stalk-specific antibodies require FcγR interactions for protection against influenza virus in vivo.

Waghmare et al. BLOOD, JUNE 2016

Summary

- RVI are increasingly recognized as significant threat to Hematopoietic Stem Cell transplant recipients
  - High frequency of nosocomial acquisition, frequency of progression to pneumonia, secondary Alloimmune Lung syndromes and high mortality rate
- Influenza, RSV, PIV, HMPV and adenoviruses cause most serious disease in immunocompromised hosts
- Therapeutic options are currently limited, with few antiviral agents approved for clinical use
- Infection control measures and immunization against pathogens for which vaccines are available is important

Acknowledgements

- Infectious Diseases Division at Virginia Commonwealth University. Richmond, VA. USA.
- Bone Marrow Transplant Team at Massey Cancer Center. VCUHS.

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Questions?