

Viral Infections after Hematopoietic Cell Transplantation

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Important Viral Infections

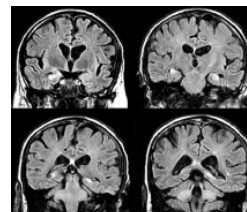
- CMV
- HHV-6
- Adenovirus
- EBV
- BK virus
- Respiratory viruses

Important Viral Infections

- CMV
- **HHV-6**
- Adenovirus
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- **Respiratory viruses**

HHV-6

Posttransplantation Acute Limbic Encephalitis (PALE)



Seeley et al. Neurology 2007

UCBT as Risk Factor for HHV-6 Pale

Table 3. Proportional Hazards Modeling of Risk of HHV-6-PALE after Allogeneic HSCT N = 1344

Characteristics	Univariable HR (95% CI)	P Value	Multivariable HR (95% CI)*	P Value
UCBT	1.45 (5.9-35.8)	<.0001	20.0 (7.3-55.0)	<.0001
Male	1.61 (0.6-4.2)	.34	NA	NA
Nonwhite	4.63 (1.4-15.5)	.01	NA	NA
Myeloablative conditioning	1.60 (0.6-4.0)	.31	NA	NA
Mismatched adult donor†	2.38 (0.7-8.2)	.17	4.3 (1.1-17.3)	.04
Unrelated adult donor	0.62 (0.3-1.5)	.30	NA	NA
ATG	4.68 (1.8-11.9)	.001	NA	NA
Acute GVHD: grades II-IV‡	8.07 (3.08-21.2)	<.0001	7.5 (2.8-19.8)	<.0001

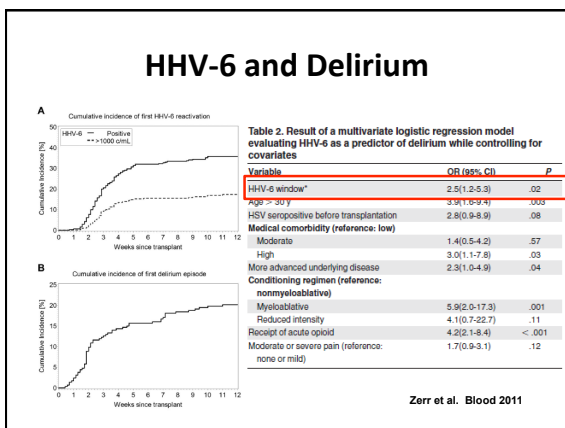
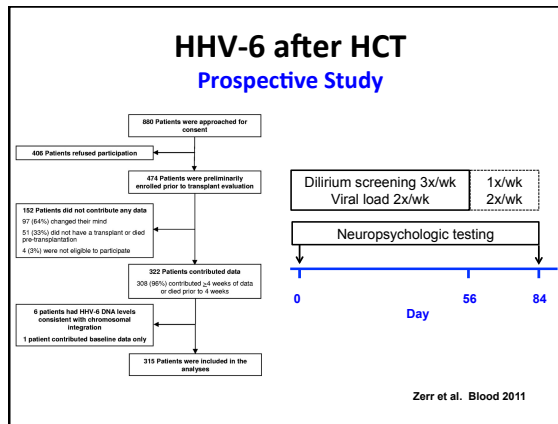
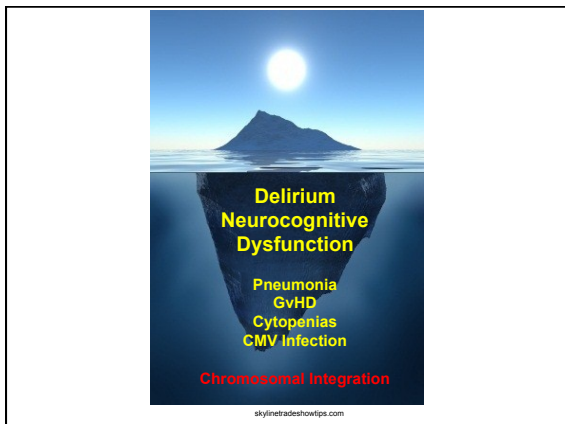
Outcome:

- UCBT: 5/5 died (median 45 days after onset)
- Adult donors: no death
- Long-term neurologic dysfunction in 9/13 long-term survivors

Hill et al., Biol Blood Marrow Transplant 2012



sky@metacoshowtips.com



HHV-6: Neurocognitive Decline

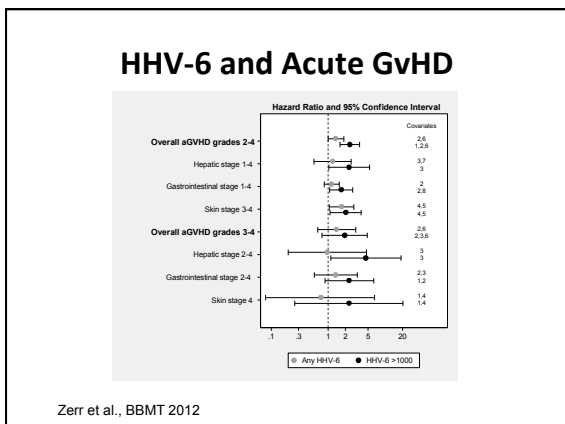
Table 3. Patients with and without HHV-6 reactivation who had > 0.75 SD decline in neurocognitive assessment score from baseline to 12-week follow-up

Domain (specific tests used for different ages)	HHV-6, no. (%) (n = 101)	No HHV-6, no. (%) (n = 189)	P
Cognitive flexibility and divided attention (Trail Making Test B, NEPSY Visual Attention)	19 (40)	23 (25)	.08
Attention and processing speed (Digit Symbol Coding Test, WISC-IV coding B, WPPSI Coding)	11 (22)	3 (3)	< .001
Concentration (Stroop color/words, NEPSY Speeded Concentration)	7 (15)	4 (4)	.05
Voice fluency (LOWAT, NEPSY Verbal Fluency)	13 (27)	14 (15)	.56
Visual memory (Faces WMSIII and Faces CMS)	6 (13)	6 (7)	.23
Verbal memory (WRAL2, 2)	5 (10)	9 (9)	.44
Visuospatial perception (Judgment of Line Orientation, NEPSY Arrows)	9 (18)	14 (15)	.61
Fine motor speed and coordination (Grooved Peg Board)	9 (18)	25 (27)	.23

Table 4. Multivariate models examining any level and high-level HHV-6 reactivation and their association with 0.75 SD decline in cognitive flexibility and divided attention between baseline and the 12-week follow-up

Model	OR (95% CI)	P
HHV-6, any level viral DNA*	2.6(1.1-6.2)	.03
HHV-6, > 1000 copies DNA/mL†	3.4(1.0-11.0)	.04

Zerr et al. Blood 2011



- ### HHV-6 Take Home Points
- HHV-6 can cause severe encephalitis. The risk appears to be higher after cord blood transplantation.
 - HHV-6 has been associated with delirium.
 - HHV-6 has been associated with early mortality and GvHD.
 - Both ganciclovir and foscarnet have been used to treat HHV-6 disease.
 - Prevention strategies have not been studied in randomized trials
 - Preemptive therapy
 - Prophylaxis
 - New drugs on the horizon: CMX-001



Respiratory Virus Infections in Immunocompetent Hosts

- Substantial impact on:
 - Quality of life
 - Economic burden on society
 - Healthcare visits (>25 million in U.S.)
 - Unnecessary use of antibiotics
 - School/work absenteeism (>20 million days)
- Death and hospitalization uncommon in older children adults



Heikkinen and Jarvinen, Lancet 2003;361:51-9

Respiratory Viruses after Transplantation

Significance

Documented morbidity	RSV PIV Influenza HMPV
Uncertain significance	Rhinovirus Coronaviruses Bocavirus Polyomaviruses (Wu, Ki)

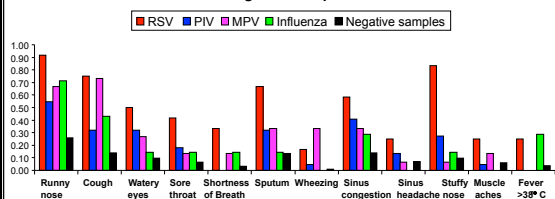
Respiratory Virus Infections in Transplant Recipients

Clinical features:

- High frequency of pneumonia and death
- Rapid clinical progression
- Atypical presentations
- Prolonged viral shedding
- Frequent asymptomatic infection
 - 10-40% of patients are asymptomatic at some point while positive for an RV
- High rates of nosocomial acquisition

Symptoms in HCT Recipients

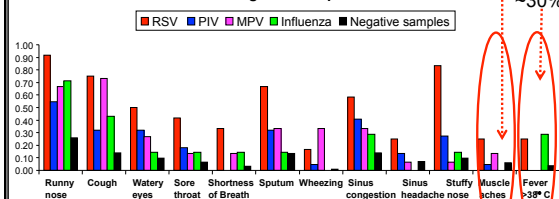
Proportion of Sample with Symptoms Reported: Virus-Positive versus Virus-Negative Samples



Peck, et al. Blood 2007;110:1681-88

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Clinical Course in Transplant Recipients

Upper Respiratory Infection
↓ Median 7 days
Lower Respiratory Infection

Clinical Course is often difficult to predict in immunosuppressed subjects.
Clinical signs unreliable.
Mild URIs can progress rapidly to the lower tract disease.

Therapeutic Strategies Respiratory Viruses

Prophylaxis
Pre-emptive
Rx of Disease

Upper respiratory Virus Detection: DFA, SV, PCR

BAL, histopathology SV, culture, PCR, IHC

Lymphocytes
Days after Transplantation

Progression to RSV LRD Lymphopenia

- 150 HCT patients with RSV URI
- All ages
- Progression to LRD: 25%

Significant
- Lymphopenia

Not significant
- Stem cell source
- Donor type/match
- Age
- Gender
- Smoking status
- FEV-1
- Time after HCT
- GVHD
- RSV type
- Neutralizing antibody titer
- donor/recipient pretransplant
- recipient at the time of URI

Boeckh & Kim, unpublished

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Boeckh & Kim, unpublished

Progression to RSV LRD Ribavirin and steroids

Ribavirin
ALC < 300/mm³

Multivariable Model

	OR (95% CI)	p-value
Age in years		
< 25	1.0	
≥ 25	1.8 (0.6 – 5.5)	0.30
Lymphocyte count at URI		
> 500	1.0	
101 – 500	2.4 (0.7 – 8.1)	0.15
≤ 100	7.4 (2.1 – 26.4)	0.002
Ribavirin		
None or low dose	1.0	
High dose	0.3 (0.1 – 1.2)	0.09
Steroids		
No	1.0	
Yes	1.7 (0.6 – 4.3)	0.30

ALC > 300/mm³

Boeckh & Kim, unpublished

Preemptive Aerosolized Ribavirin and RSV Pneumonia after HCT

Infection	Total	Treated for URI		Not Treated for URI		p Value*
		No.	Pneumonia No. (%)	No.	Pneumonia No. (%)	
Influenza	112	41	4 (10)	71	30 (42)	<0.005
A	72	26	3 (12)	46	22 (48)	<0.005
B	40	15	1 (7)	25	8 (32)	0.06
RSV	107	61	12 (20)	46	27 (59)	<0.005
Parainfluenza	92	49 (53)	3 (6)	43 (47)	30 (70)	0.22
Total	311	109	20 (18)	202	87 (43)	<0.005

*p value by chi-square test or Fisher exact test where appropriate.

Chemaly et al. Medicine 2006

All RSV LTD Cohort: Multivariate analysis N=118

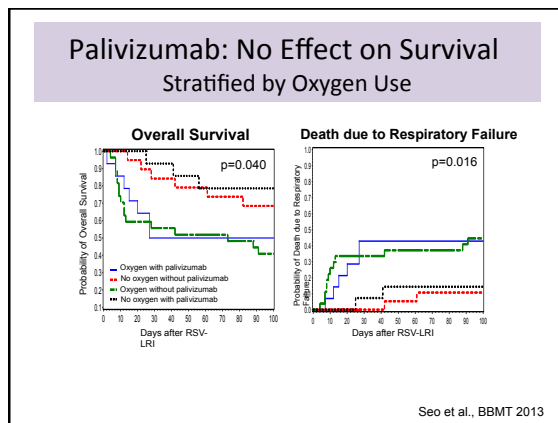
Overall mortality at 90 days

Covariates	HR 95% CI	P-value
Ribavirin: Systemic vs. None	0.71 (0.28-1.76)	0.454
Aero vs. None	0.33 (0.17-0.64)	0.001
Oxygen at Dx: >2L/Ventilator vs. None/<2L	2.73 (1.58-4.71)	<.001
Cell source: BM/Cord vs. PBMC	2.44 (1.28-4.64)	0.006
Steroid pre DX: >2 mg/kg vs. <=2 mg/kg	2.46 (1.24-4.92)	0.010

Pulmonary death at 90 days

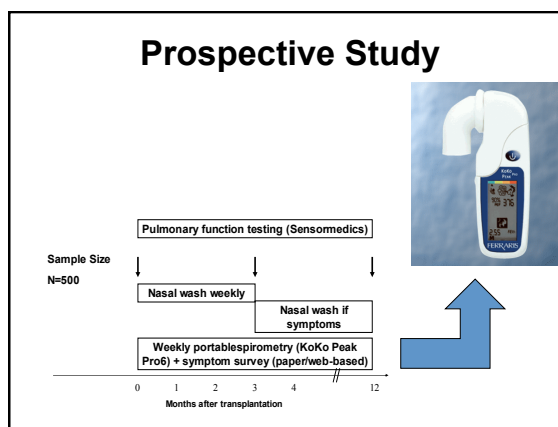
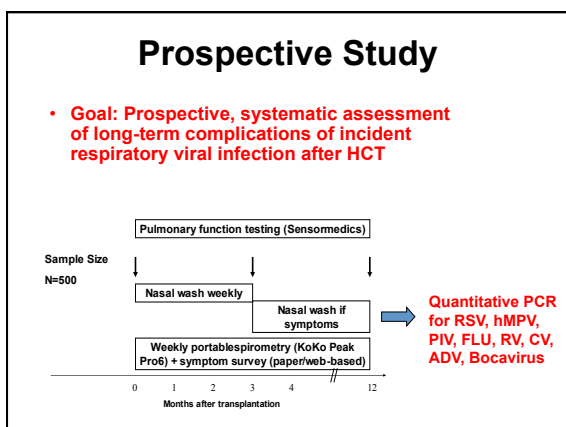
Covariates	HR 95% CI	P-value
Ribavirin: Systemic vs. None	0.55 (0.18-1.68)	0.296
Aero vs. None	0.26 (0.12-0.55)	<.001
Oxygen at Dx: >2L/Ventilator vs. None/<2L	3.42 (1.78-6.57)	<.001
Cell source: BM/Cord vs. PBMC	2.48 (1.15-5.31)	0.020

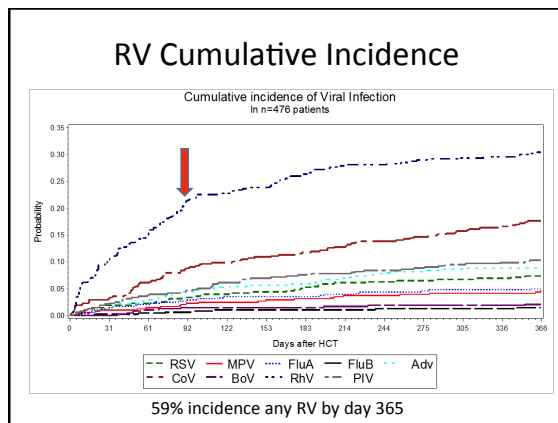
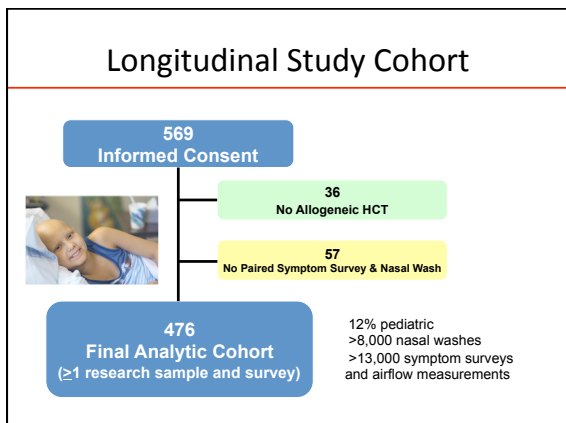
Waghmare et al., IDSA, 2012



- ### Management of RSV in HCT Recipients at FHCRC (2/2013)
- RSV URI
 - Lymphocyte count > 300
 - No radiographic and clinical findings of LRI
 - Observation with daily exam, clinical trial being developed
 - Lymphocyte count < 300
 - No radiographic and clinical findings of LRI
 - Aerosolized ribavirin 6 g per day (divided in 3 doses) for 7 days
 - RSV LRI
 - Radiographic and/or clinical findings of LRI
 - Aerosolized ribavirin 6 g per day (divided in 3 doses) for 10-14 days

Human Rhinovirus





- ### Early Studies of HRV in HCT Recipients
- 1990–96: 29 HRV-positive patients; 1 in BAL
 - 1992–97: 22 patients with HRV (viral culture)
 - 7 had fatal HRV-associated pneumonia; 4 with co-pathogens
 - 1999: Consecutive BALs samples from 77
 - 6 positive by RT-PCR (culture negative)
 - 5/6 died of pneumonia
 - All 6 had co-pathogens detected in BAL
- Bowden. Am J Med 1997;103:27-30
Ison et al. CID 2003;36:1139-43
- Ghosh et al. CID 1999;29:528-32

HRV Fatal Cases

Bone Marrow Transplantation (2007) 40, 809–811
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www.nature.com/bmt

LETTER TO THE EDITOR

Rhinovirus as a cause of fatal lower respiratory tract infection in adult stem cell transplantation patients: a report of two cases

Of 52 LRTI cases (RSV, PIV, FLU, HRV), case #2 was the only one with nonmyeloablative conditioning

Gulman, et al. BMT 2007;40:809-11

Rhinovirus & Coronavirus Detection and Associated Symptoms (N=215 patients, 62 positive)

Symptom	Coronavirus (n=22)		Rhinovirus (n=45)	
	OR (95% CI)	p	OR (95% CI)	p
Rhinorrhea	1.4 (0.7–2.6)	0.33	2.3 (1.3–4.1)	0.004
Sinus congestion	0.9 (0.4–2.2)	0.83	3.4 (1.8–6.9)	<0.001
Post-nasal drip	0.7 (0.3–1.6)	0.38	2.4 (1.3–4.8)	0.009
Shortness of breath	0.9 (0.3–2.8)	0.79	1.5 (0.7–3.3)	0.32
Sputum	0.9 (0.4–2.0)	0.74	1.9 (1.1–3.3)	0.03
Cough	1.9 (0.9–4.1)	0.12	2.3 (1.3–4.2)	0.006
Wheezing	–	–	2.0 (0.8–5.1)	0.16
Fever	0.8 (0.3–1.8)	0.58	0.7 (0.4–1.2)	0.22

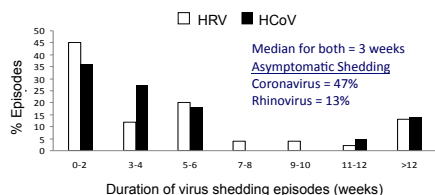
Milano/Campbell, et al. Blood 2010;115:2088-94

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Milano/Campbell, et al. Blood 2010;115:2088-94

Prolonged Viral Shedding



56 patients with HRV >1 month: 82% same strain
– 26 A, 7 B, and 10 C

Milano/Campbell, et al. Blood 2010;115:2088-94

HRV Morbidity and Mortality

Severity of HRV infection in immunocompromised adults similar to that of 2009 pH1N1 influenza

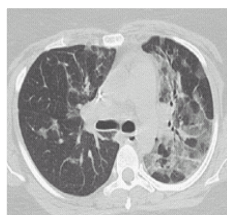
TABLE 3 Clinical outcomes of pH1N1 and HRV groups in the study population

Characteristic	Result (no. [%]) for group		P value ^a
	pH1N1	HRV	
Death	2 (2.0)	2 (3.2)	NS
Hospitalization	36 (36.4)	24 (38.7)	NS
ICU admission	7 (7.1)	7 (11.3)	NS

^a Statistically significant findings are presented in bold. NS, no statistical significance.

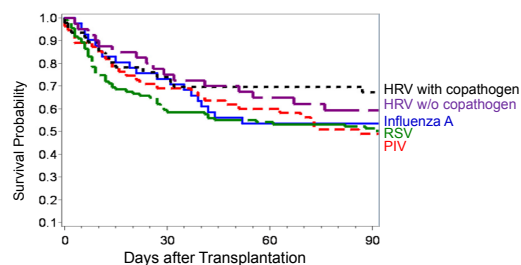
Kraft, et al. J Clin Micro 2012;50:1061-3

Is HRhV a Pulmonary Pathogen?



Gutman, et al. BMT 2007;40:809-11

Overall Survival in HCT Recipients with Respiratory Virus Detection in Lower Respiratory Tract Samples



Seo et al. ASBMT 2013

HRV Treatment

- No agent available, no studies in transplant
- Pleconaril (capsid binder)
 - Decreased symptoms by median of 1 day, associated with loss of culturable virus
- BTA798 (vapendavir, oral capsid binder)
 - Phase 2b study achieved primary endpoint: statistically significant reduction of cold symptoms in asthmatics
- SNG001 (inhaled beta-interferon)
 - Phase 2 study: in patients with difficult to treat asthma, reduced asthma symptom severity and improved lung function

Hayden, et al. CID 2003;36:1523-32

Pevear, et al. AAC 2005;49:4492-99

Respiratory Viruses

Take Home Points

- Highly immunosuppressed patients with CRV infections have a high risk of
 - Pneumonia
 - Late airflow obstruction
 - Death
- Risk factor for progression from upper to lower tract disease include
 - Early after transplantation: lymphopenia
 - Late after transplantation: unknown (preexisting lung conditions ?)
- Rhinovirus
 - More evidence that it is a true pulmonary pathogen
- RSV
 - Aerosolized ribavirin is most effective when used early in the course of pneumonia
 - Recent data suggest no major effect of palivizumab
- Influenza: treatment of choice are neuraminidase inhibitors (e.g. oseltamivir, zanamivir)
- Infection control remains critical
 - Handwashing
 - Influenza vaccination of all contacts including healthcare workers
 - Restriction of infected healthcare workers from work while sick with a respiratory virus illness

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