Clinical features and outcome of patients with respiratory virus infection

38th Annual Meeting of the European Group for Blood and Marrow Transplantation, Geneva

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Respiratory viruses

- Biological and clinical diversity
- Epidemiology in Hospitals
- Investigation in lung transplant recipients
- Nucleic acid detection and clinical impact
  - Association with symptoms/diseases
  - «common colds» viruses (Rhino-, corona-)
- HSCT recipients: clinical impact
- Antivirals in HSCT recipients: influenza and RSV
<table>
<thead>
<tr>
<th>Human Virus</th>
<th>Species/Sub-Sero-Genotypes</th>
<th>RNA/DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>A, B, C, &gt;140 serotypes</td>
<td>RNA</td>
</tr>
<tr>
<td>Influenza</td>
<td>A (H3N2,H1N1..), B, C</td>
<td>RNA</td>
</tr>
<tr>
<td>RSV</td>
<td>A and B</td>
<td>RNA</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>Type 1, 2, 3 and 4</td>
<td>RNA</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>A1, A2, B1, B2</td>
<td>RNA</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>OC43, E229, HKU1, NL63</td>
<td>RNA</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>&gt;100 serotypes</td>
<td>RNA</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>7 species, &gt; 50 serotypes</td>
<td>DNA</td>
</tr>
<tr>
<td>Bocavirus</td>
<td>4 species</td>
<td>DNA</td>
</tr>
<tr>
<td>Polyomaviruses</td>
<td>KI, WU, Merkel...</td>
<td>DNA</td>
</tr>
</tbody>
</table>
Immune response to respiratory viruses

- Protective immunity:
  - Not always present or can be of short duration
  - Serotype or subtype specific, cross reactions
    - Memory of previous infections impact disease pattern:
      - Influenza
      - RSV
- Antibody mediated vs. cellular: lack of « easy to use » and standardized assays
Upper vs. lower respiratory tract

Primary site of replication
Main site of viral screening
Pooled nasopharyngeal and pharyngeal swab

Lower respiratory infection and complications (BAL)
Respiratory viruses screening (panel)
University Hospital of Geneva, Nov. 2011- March 2012

Sensitive (nucleic acid detection)
Seasonal pattern and winter
Co-circulation
DNA viruses: reactivation vs 1st

Number of cases screened positive

Adeno Coronavirus Influenza A Influenza B hMPV Para1-3 Picorna RSV

November 11 December 11 January 12 February 12 March 12
Resp. viruses and lung transplant recipients

- Immunocompromised (anti-rejection therapy)
- Lack of lymphatic drainage and cough reflex
- The graft is directly exposed to viruses
- **Could promote graft dysfunction**

- *Frequent bronchoalveolar lavages and respiratory samples*

Garbino Thorax 2009, P Soccal CID 2010, DL Vu AJT 2011
Prospective cohort study (Geneva-Lausanne)

- 112 lung transplant recipients over 3 years
- Standardized CRF assessing respiratory symptoms + RT-PCR screening in the upper resp. tract (and BAL fluid if available)

1. Pre-scheduled screening visits, 3 times/year during 3 years
2. Emergency visits for acute respiratory disease with or without BALs
Mild respiratory symptoms during study specific pre-scheduled visits over 3 y.

Average positivity rate for any virus (URT): 16%
Viral screening during pre-scheduled study specific visits in absence of respiratory symptoms (n=297)

- Overall proportion of Positive: 80.0%
- Adenovirus: 3.3%
- Bocavirus: 10.0%
- Coronavirus: 6.7%
- Metapneumovirus: 10%
- Parainfluenza: 10%

N = 297
N = 30
Nasopharyngeal positivity (RT-PCR) rate and virus distribution during emergency visits (n=196)

- Overall proportion of Positive
  - Adenovirus
  - Bocavirus
  - Coronavirus
  - Metapneumovirus
  - Parainfluenza
  - Picornavirus
  - RSV

- or Negative (RT)-PCR
  - Influenza

N = 59 (30.1%)
Respiratory viruses and symptoms in lung transplant recipients: 34 studies, > 4000 cases

Study, year of publication

Garbino, 2004
Sumino, 2005
Larcher, 2005
Kumar, 2005
Gerna, 2006
Dare, 2007
Miyakis, 2008
Soccal, 2009
Gottlieb, 2009
Kumar, 2010

Odds ratio (95% CI) % Weight

30.36 (3.64-252.97) 8.0
4.91 (0.23-102.81) 5.3
2.10 (0.48-9.17) 10.7
22.32 (6.88-72.46) 12.1
33.33 (4.18-266.10) 8.1
8.38 (0.92-76.28) 7.7
11.47 (0.60-219.88) 5.5
1.71 (1.01-2.92) 14.8
3.10 (1.18-8.15) 13.1
0.88 (0.52-1.51) 14.8

Overall (95% CI)

4.97 (2.11-11.68)*

Risk of respiratory symptoms

DL. Vu et al. AJT, 2011;11:1071
Resp. viruses in bronchoalveolar lavage Hospital-based cohort study in adults (n=522) 17.4% of cases positive

Positive (RT)-PCR associated with:
• Respiratory symptoms
• Non response to previous antibiotic treatment
• Absence of chest X-ray infiltrate

J Garbino et al. Thorax 2009
Viral positivity rate in BAL according to symptoms (276 LTRs)

With clinical respiratory infection:
- Overall proportion of positive: 27.6%

Without clinical respiratory infection:
- Overall proportion of negative (RT)-PCR: 5.3%
Agreement between upper and lower resp. tract specimens

7% to 14% of negative nasopharyngeal specimens are BAL positive during the acute phase
H1N1 viral load in patients with pneumonia

- Upper respiratory tract (nasopharyngeal)
- Lower respiratory tract (BAL)
Resp. viruses in LTR recipients and in hospitalised patients

- Rhino- and coronavirus are the most frequent
- In presence of respiratory symptoms
  - $\geq 30$-60% positivity rate in the URT
  - Up to 30% positivity rate in the LRT
- Background positivity rate in $\sim 10\%$ the URT and $\sim 5\%$ in the LRT
- "RNA detection = infection = symptoms"
Cumulative incidence of upper respiratory viral infections in HSCT recipients (n=215)

100 days post transplantation
Rhinovirus incidence ~ 20%  
Paramyxovirus and influenza ~ 30%
« Common colds » viruses in HSCT recipients and symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Coronavirus OR (95% CI)</th>
<th>P</th>
<th>Rhinovirus OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinorrhea</td>
<td>1.4 (0.7-2.6)</td>
<td>.33</td>
<td>2.3 (1.3-4.1)</td>
<td>.004</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>0.9 (0.4-2.2)</td>
<td>.83</td>
<td>3.4 (1.8-6.9)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Postnasal drip</td>
<td>0.7 (0.3-1.6)</td>
<td>.38</td>
<td>2.4 (1.3-4.8)</td>
<td>.009</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0.9 (0.3-2.8)</td>
<td>.79</td>
<td>1.5 (0.7-3.3)</td>
<td>.32</td>
</tr>
<tr>
<td>Sputum</td>
<td>0.9 (0.4-2.0)</td>
<td>.74</td>
<td>1.9 (1.1-3.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0.8 (0.2-2.6)</td>
<td>.70</td>
<td>0.8 (0.4-1.7)</td>
<td>.61</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0.8 (0.2-2.4)</td>
<td>.63</td>
<td>0.9 (0.5-1.8)</td>
<td>.88</td>
</tr>
<tr>
<td>Cough</td>
<td>1.9 (0.9-4.1)</td>
<td>.12</td>
<td>2.3 (1.3-4.2)</td>
<td>.006</td>
</tr>
<tr>
<td>Wheezing*</td>
<td>—</td>
<td>—</td>
<td>2.0 (0.8-5.1)</td>
<td>.16</td>
</tr>
<tr>
<td>Fever</td>
<td>0.8 (0.3-1.8)</td>
<td>.58</td>
<td>0.7 (0.4-1.2)</td>
<td>.22</td>
</tr>
<tr>
<td>Headache</td>
<td>0.9 (0.5-1.9)</td>
<td>.85</td>
<td>1.0 (0.6-1.7)</td>
<td>.99</td>
</tr>
<tr>
<td>Myalgias</td>
<td>0.3 (0.1-0.8)</td>
<td>.02</td>
<td>0.6 (0.3-1.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.2 (0.6-2.5)</td>
<td>.55</td>
<td>0.7 (0.4-1.3)</td>
<td>.28</td>
</tr>
</tbody>
</table>
2008-2010: 193 HSCT recipients followed (65 allo- and 128 auto-)

Median of 3.5 specimens screened/pt (7.8 for alloHSCT recipients)

Median number of proven resp. viral infection =2.24 (range 1 to 10)

88% classified as URTI and 12% LRTI

Mortality: overall 5.7%, attributable 3.1%
Viral load

Peak of symptoms

~ 5 days

~ 10 days

Immunocompromised hosts

Immunocompetent adults

Rhinovirus shedding > 12 days: > 10% of cases
Influenza shedding > 14 days: 32% of cases
Viral shedding for weeks or months relatively common

Viral load in hematopoietic cell transplant recipients and pneumonia

- Viral load not associated with mechanical ventilation or death or other clinical outcomes
- RNA can be detected in serum in cases with high viral loads in BAL (~10% of RSV cases)
Respiratory viral infections complications in HSCT recipients

- Viral pneumonia
- Bacterial complications, antibiotic use
- Invasive aspergillosis (?)  
  R. Martino, BMT 2009:44:749
- Significant airflow decline (FEV1) one year after HSCT  
  V Erard JID 2006:193:1219
- Bronchiolitis Obliterans Syndrome  
  – Particularly in the first 100 following HSCT  
Respiratory virus: a spectrum of diseases

No or unnoticed symptoms  Mild diseases  Severe diseases

Rhinovirus

Coronavirus

Influenza

RSV
Rhinovirus A
Rhinovirus B
Rhinovirus C
Enterovirus A
Enterovirus B
Enterovirus C (Poliovirus)
Enterovirus D

PICORNAVIRUS

ENTEROVIRUS (genus)
(Rhinovirus and Enterovirus)
Rhinovirus genotyping (Geneva)

HRV-A: ~ 55%
HRV-B: ~ 8%
HRV-C: ~ 36%

HRVC: in humans since more than 250 years
... detected since less than 5 years

Taparel et al., PLoS ONE, June 2011; Volume 6, Issue 6:e21163
Rhinovirus as a cause of fatal lower respiratory tract infection in adult stem cell transplantation patients: a report of two cases

*Bone Marrow Transplantation* (2007) **40**, 809–811; doi:10.1038/sj.bmt.1705827; published online 20 August 2007
Rhinovirus: chronic infection and adaptation to the lower respiratory tract

C Tapparel et al PlosOne 2011
S Cordey et al PlosOne 2010
RSV complications in Allo-HSCT recipients

- Rate of progression from the upper to the lower respiratory tract
  - 0% to 60% (?), average ~ 30%
  - Higher when additional immunosuppressive conditions, lymphopenia... are present

- Established RSV LRTI or pneumonia
  - ICU/mortality rate, ≥ 30% (?)

- Respiratory dysfunction, bronchiolitis (?)

HSCT recipients
"pre-emptive ribavirin“ vs. placebo

- RSV: no lower respiratory tract symptoms, no infiltrate
- Aerosolized ribavirin (3x 2g at 600mg/mL) for 10 days

Trends toward a reduction of viral load. Proof of efficacy remains elusive.

\[\text{Table 2. Efficacy end points.}\]

<table>
<thead>
<tr>
<th>End points</th>
<th>Ribavirin treatment group (n = 9)</th>
<th>No treatment group (n = 5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pneumonia</td>
<td>1</td>
<td>2</td>
<td>.51</td>
</tr>
<tr>
<td>RSV pneumonia</td>
<td>0</td>
<td>2</td>
<td>.11</td>
</tr>
<tr>
<td>Survival at 28 days after randomization</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

\textbf{NOTE.} Data are no. of patients, unless otherwise indicated. RSV, respiratory syncytial virus.

M. Boeckh, CID 2007
Aerosolized ribavirin: HSCT patients treated early (« upper respiratory stage ») versus late

Review of retrospective and cohort studies

Risk of lower respiratory tract infection:
Treated early (n=44): 25% (n=11), 0-32%
Late treatment (n=116): 47% (n=54), 27-100%
P value < 0.01

Mortality:
Treated: 50% (28/56), 33-88%
Not treated: 89% (8/9), 50-100%
P value = 0.04

JN. Shah Blood 2011; 117:2755
Aerosolized ribavirin in children with LRT diseases due to RSV

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, 4 trials, n=158</td>
<td>9.7%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Resp. deterioration, n=116</td>
<td>18.3%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Days in ventilation, n=104</td>
<td>-1.8%</td>
<td>-</td>
</tr>
</tbody>
</table>

K. Ventre and Randolph A., Cochrane, 2010
Full course of aerosolized ribavirin

- 6 gr aerosolized over 18 hours each 24 hours periodes over 10 days.
  - Adapted to real-life: 2g over 2h., 3 times/day

- Geneva: ~ 23’000.- SFr. for 5 days.
Oral or iv ribavirin: case series, retrospective studies

แทบเป็นการรับรู้ว่า ยาribavirinจะมีประโยชน์ในการป้องกันความผิดปกติในกรณีที่ถูกให้ในระยะเริ่มต้น Avetisyan et al. 2009

ไม่พบประโยชน์ทางคลินิกที่ชัดเจน N Khanna et al. 2008

หลายกรณีที่มีผลที่บวกในผู้รับการผ่าตัดทางปอดต้องการให้ salida ที่มีประโยชน์ DL Vu AJT 2011

สำนักงานอาหารและยา (FDA) วิเคราะห์: ผลจุดประสงค์ทางคลินิกไม่ชัดเจน Riner et al, Postgraduate Medicine, 2009
Intravenous or oral ribavirin

- **iv:** loading dose 35 mg/kg in 3 doses for one day then 25 mg/kg in 3 doses every 8 hours for 6 days. ~ 15’000.- SFr.

- **Oral:** 15 to 20 mg/kg/day in 3 divided dose for 10 days. ~ 430.- SFr.

Biology of Blood and Marrow Transplantation 7:11S-15S (2001)
Palivizumab (?
Humanized monoclonal antibody directed against the RSV F protein
Figure: Summary of outcome data by type of regimen received

- Aerosolized ribavirin only
- Aerosolized ribavirin + immunoglobulins

For progression to LRI, AR alone vs. AR plus immunomodulators or IR or OR with or without immunomodulators; $P=0.13$.

J. N. Shah and R. R. Chemaly, Blood 2011
tract disease). Palivizumab did not prevent progression to lower respiratory infection and had no impact on the overall survival rate.

- 15 mg/Kg (for 3-4 weeks)
- Cost: ≥ 16’000 SFr- for one dose
Ribavirin and palivizumab in HSCT

- Evidence: insufficient to support strong recommendations
- Should generally not be used systematically for treatment
- Consider only in selected cases at risk
- Consensus guidelines not available…
- Further studies or better drugs needed…
Ribavirin and palivizumab (?)

- Risk assessment, nasopharyngeal positive cases
  - Early phase post-transplantation
  - Lymphopenia, GVH, steroids…
  - Predisposing lung conditions or bronchiolitis
  - Lower resp. tract symptoms, positive CT
  - Hypoxemia, ICU, ventilation
  - BAL screening positive
  - High viral load, positive culture
  - Protracted infection

- Ribavirin: aerosolized (reference), iv or oral
- Palivizumab: one infusion
RSV: future therapies

◆ Motavizumab
  – Greater affinity and virus neutralisation
  – Derived antibodies with extended half-life
◆ Hyperimmune IgG
◆ Fusion inhibitors
◆ Benzodiazepine derivatives (polymerase inhibitors)
◆ …
RNA interference therapy and RSV

- ALN-RSV01 targets the RSV capsid gene and in vivo reduces RSV viral load (mice)
- Phase II in 24 lung transplant recipients
- ~ 10 minutes nebulization
- No clear effect on acute symptoms and viral load
- Prevent BOS (?)
- Phase IIb ongoing, results in 2012 (?)

MR. Zamora, AJRCCM 2011: 183:531
Influenza in HSCT recipients

- Risk of LRT complications or pneumonia: ~30% to 50%
- ICU-mechanical ventilation: ~10% to 28%
- Risk of death: ~6% to 17%
- Risk factor: early post-Tx, lymphopenia, GVH...

AA. Boudreault, Biol. Blood Marrow Transplant 2010
Su-Mi Choi et al., Blood, March 3, 2011
P. Ljungman et al, Haematologica 2011
B. Mothy, BMT 2011
Could antiviral therapy prevent complications in immunocompetent adults?

- « No » randomized study has explored the ability of oseltamivir to prevent hospitalizations and complications as a primary end-point
- Pooled/meta-analysis of randomized studies in which lower respiratory tract complications / antibiotic use / hospitalizations were analyzed
- Size of the effect remains controversial

M. Hernan, CID 2011 / Cochrane, BMJ 2009 and 2012
Retrospective or case series: oseltamivir in pandemic H1N1

- Early oseltamivir treatment associated with
  - Decreased risk of hospitalization
  - Decreased risk of pneumonia
  - Decreased risks of ICU or death in severely ill
    - Pregnant women: ICU admission and mortality
    - SOT recipients: hospitalization and ICU death
  - Decrease viral load

Cao et al., NEJM 9 Dec 09; Li et al., Chest 137:759, 2010; Yu et al., Options abst P-208; Kumar et al., Lancet ID 9 July 2010; Siston et al., JAMA 303:1517, 2010; Yang et al., J Infect 2010; Jain et al., NEJM 8 Oct 09, BMJ 2011
Early antiviral therapy (<48h) associated with a reduction of lower respiratory tract diseases (OR 0.04; 95% CI 0.0 – 0.29, p < 0.001) and death (HR 0.21; 95% CI 0.0 – 1.0, p = 0.049)

Influenza outcome

- Early antiviral therapy seems beneficial to prevent lower respiratory disease and hypoxemia (similar results in SOT recipients)
- High dose steroids = prolonged viral shedding
- Influenza subtype: H1N1 p2009 more virulent?
- Resistance: can "easily" be selected in cases with prolonged viral shedding and can be transmitted

# Anti-influenza agents in clinical development 2012

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Route</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanamivir</td>
<td>NA</td>
<td>IV</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Peramivir</td>
<td>NA</td>
<td>IV</td>
<td>Phase 3*</td>
</tr>
<tr>
<td>Laninamivir</td>
<td>NA</td>
<td>Inhaled</td>
<td>Phase 3*</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Polymerase</td>
<td>Oral</td>
<td>Phase 3</td>
</tr>
<tr>
<td>DAS181</td>
<td>HA receptor</td>
<td>Inhaled</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Note: IV oseltamivir under study

Licensed in Japan*, S. Korea+

* Licensed in Japan, S. Korea
+ Licensed in S. Korea
Transfer of influenza vaccine-primed co-stimulated autologous T cells

E. Stadtmauer, Blood 117 (1), 6 January 2011
Laboratory of Virology and Division of Infectious Diseases
University Hospital of Geneva
  Caroline Tapparel
  Yves Thomas
  Lara Turin
  Sandra Van Belle
  Ghislaine Wagner

Division of Pulmonary Medicine, University Hospital of Geneva
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Swiss Institute of Bioinformatics, University of Geneva
  Evgeny Zdobnov
  Thomas Junier

Swiss National Foundation
Clinical Research Center of the University Hospital and the Faculty of Medicine, Geneva