The challenges of viral infections – from prophylaxis to vaccination

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Therapies increasing the risk for viral infections

- Allogeneic SCT
- anti-CD52 treatment
- Fludarabine / CDA
- Anti-T-cellsantibodies (ATG, OKT-3)
- TBI
Some viruses important for differential diagnoses in SCT patients

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Encephalitis</th>
<th>Hepatitis</th>
<th>GI disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>CMV</td>
<td>CMV</td>
<td>CMV</td>
</tr>
<tr>
<td>Influenza</td>
<td>Adenovirus</td>
<td>EBV</td>
<td>HSV</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>HSV</td>
<td>Adenovirus</td>
<td>Adenovirus</td>
</tr>
<tr>
<td>RSV</td>
<td>VZV</td>
<td>HBV</td>
<td>EBV</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>HHV-6</td>
<td>HCV</td>
<td>VZV</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>Measles</td>
<td>VZV</td>
<td>Rotaviruses</td>
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<tr>
<td>Measles</td>
<td>JCV</td>
<td>HAV</td>
<td>Noroviruses</td>
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<tr>
<td>VZV</td>
<td>EBV</td>
<td>HSV</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Rabies</td>
<td>HIV-6 (?)</td>
<td></td>
</tr>
<tr>
<td>New respiratory viruses</td>
<td>West Nile virus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Protection against viral infection is different from protection from viral disease!

Antibodies protect against primary infection

The innate and adaptive cell-mediated immunity protect against disease (T-cells, NK-cells)
How can we manage viral infections?

- Prevent a patient being infected
- Prevent an infected patient to develop disease
- Treat an established viral disease
Prevention of infection

- Select the right donor
- Safe blood products
- Infection control
- Antiviral prophylaxis
- Vaccination
Select the right donor

Viral infection possibly transmitted through the donor:

- CMV
- HIV
- EBV
- HBV
- HHV-6
- HCV
- West Nile virus
- HTLV-1/2

Other viruses that give viremia
- Influenza (?), adeno (?)
Safe blood products

- Leukocyte depleted
- HBV, HCV, HIV negative
- CMV negative (?)
Infection control

- Hygienic standards
- Isolation
- Avoiding infected persons.
- Restrictions for visitors
  - Always? Age limit? Epidemiological situations?
Prevention of disease

- Early diagnosis
- Monitoring of patients
- Antiviral prophylaxis
- Vaccination
General points

- What is the question?
- Do you suspect a specific virus?
- Where should you look for the virus?
Diagnostic techniques

Detection of an immune response
  Serology / antibody detection

Detection of virus or virus components
  Isolation
  Antigen
  Nucleic acid(s) – DNA, RNA
  Quantification of viral load
Serology

- Not very useful for diagnosing active virus infection
- Can be used for determining risk status
Antigen detection

- **Pro**
  - Rapid
  - Specific
  - Usually quite cheap
  - Detects proteins

- **Con**
  - Variable sensitivity
  - Sample quality dependent
Nucleic acid testing (NAT); PCR

- **Pro**
  - Very sensitive
  - Rapid
  - Allows quantitation (viral load)

- **Con**
  - Relatively expensive
  - Can be sensitive to transport conditions (RNA)
  - Can be too sensitive (poor predictive value)
Timing of management options

- Viral replication
- Time
- Grafting
- Prophylaxis
- Pre-emptive therapy
- Treatment of established disease
- Diagnosis of viral infection
- Viral disease

Alain, ILTS 2008
CMV

The "troll" of transplantation
CMV

- Usually asymptomatic primary infection in healthy individuals

- Can be transmitted different ways
  - From infected individuals (children)
  - Sexually
  - Transfusions
CMV pneumonia
Other forms of disease

- Gastrointestinal disease (frequently together with GVHD)
- Encephalitis
- Hepatitis
- Bone marrow suppression.
- Retinitis
Risk factors for CMV disease.

The patient’s serological status

The donor’s serological status

The type of stem cell donor (sibling, unrelated, haplo)

The type of transplant (allogeneic, autologous, reduced conditioning)
Probability of CMV disease

- Rec pos
- Don pos / rec neg
- Don neg / rec neg

Days after SCT
Donor influence in CMV pos patients

Negative donors:

Higher transplant related mortality

- 39% CMV + donor \( p = 0.006 \)
- 52% CMV – donor

More repeated CMV reactivations

More courses of antiviral therapy

More CMV disease
Antiviral therapy

- Iv ganciclovir
- Oral vanganciclovir
- Iv foscarnet
- Iv cidofovir
Days after randomization

Ganciclovir vs. Foscarnet
EBMT randomized study

Foscarnet
Ganciclovir

Days after randomization
Achievement of CMV PCR negativity

Proportion

Duration of treatment (days)

p = 0.257

n = 50

n = 51

VGCV

Iv GCV
Repeated CMV reactivations

- Common in high risk patients
- Associated with poor T-cell control of CMV
- How shall we manage these patients?
Cidofovir for CMV pneumonia

<table>
<thead>
<tr>
<th>CMV pneumonia</th>
<th>Failed previous antiviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Success / possible success</td>
<td>7</td>
</tr>
<tr>
<td>Failure / not evaluable</td>
<td>4</td>
</tr>
</tbody>
</table>

Ljungman et al Blood 2001
New drugs/options

- Maribavir
- AiCuris (AIC247)
- CMX001

- CMV specific T-cell infusions
- CMV vaccines
HSV virus

- Common

- Can give “uncharacteristic” signs and symptoms in SCT recipients

- Prophylaxis usually effective

- Visceral and CNS manifestations are rare
Aciclovir resistance

- Usually mediated through mutations in the HSV TK
- Usually less pathogenic than wild type
- Reported in up to 12% of HSCT recipients
- Foscarnet or cidofovir is possible alternatives
Both primary and reactivated infections can cause severe disease.

Primary infection (usually children) is a serious complication.

VZV disease without skin lesions can occur (GI, liver, CNS)
- Severe abdominal pains
- Increasing liver function tests
- Neurological symptoms

VZV visceral disease has high mortality.
Herpes zoster
All varicella-zoster infections should be treated in HSCT patients!

IV acyclovir for varicella and disseminated zoster
PO acyclovir, valacyclovir, or famciclovir can be used for local HZ
Long term ACV/VCV prophylaxis; probability of VZV disease

Group 1: 30 days
Group 2: 1 year
Group 3: > 1 year

Erard et al  Blood 2007
EBV

Might cause symptoms of various types after SCT

- Encephalitis
- Pneumonia
- Hepatitis

However, these symptoms are rare!
Where does the EBV come from?

From the patient (reactivation/increased replication)

From the outside

a) The stem cell donor (both in pretransplant seropositive and seronegative patients)

b) Blood transfusions

c) ”True” primary infection – oral transmission
EBV PTLD

Important complication in SCT patients
EBV-driven B-cell proliferation
Increasing frequency over the last decade
High mortality
What can we do to prevent PTLD?

- Anti-CD20 monoclonal antibody
- Cell therapy (CTL or donor lymphocytes)
- Antiviral therapy?
- Reduced immunosuppression?
Adenovirus infections

- DNA virus.
- Many subtypes (currently 51)
- Divided into 6 subgenuses (A-F)

- Upper and lower respiratory infections
- Renal infections / hemorrhagic cystitis
- Gastrointestinal infections
- Hepatitis
- CNS disease
<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>Pts. No.</th>
<th>% T-cell-depletion</th>
<th>Diagnostics</th>
<th>Material</th>
<th>% ADV-infection</th>
<th>ADV-disease % of pos. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venard</td>
<td>2000</td>
<td>65 (nr)</td>
<td>nr</td>
<td>C</td>
<td>U/S/T</td>
<td>20</td>
<td>nr</td>
</tr>
<tr>
<td>Runde</td>
<td>2001</td>
<td>130 (nr)</td>
<td>5</td>
<td>C +/- PCR</td>
<td>U/T/B</td>
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<td>14</td>
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<tr>
<td>Bordigoni</td>
<td>2001</td>
<td>303 (30)</td>
<td>50</td>
<td>C</td>
<td>U/S/T/C</td>
<td>12</td>
<td>48</td>
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<tr>
<td>Echavarria</td>
<td>2001</td>
<td>14 (nr)</td>
<td>nr</td>
<td>+ PCR</td>
<td>U/S/T/B</td>
<td>71</td>
<td>80</td>
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<td>Hoffmann</td>
<td>2001</td>
<td>36 (100)</td>
<td>nr</td>
<td>C</td>
<td>S/T/B</td>
<td>47</td>
<td>59</td>
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<td>Chakrabarti</td>
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<td>41</td>
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<td>U/S/T/B</td>
<td>20</td>
<td>40</td>
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<tr>
<td>Walls</td>
<td>2002</td>
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<td>nr</td>
<td>+ PCR</td>
<td>B</td>
<td>42</td>
<td>72</td>
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<tr>
<td>Lion</td>
<td>2003</td>
<td>13 (30)</td>
<td>nr</td>
<td>+ PCR</td>
<td>U/S/T</td>
<td>12</td>
<td>55</td>
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<tr>
<td>Leruez-Ville</td>
<td>2004</td>
<td>54 (100)</td>
<td>nr</td>
<td>+ PCR</td>
<td>B</td>
<td>32</td>
<td>50</td>
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<tr>
<td>Kampmann</td>
<td>2005</td>
<td>156 (100)</td>
<td>nr</td>
<td>+ PCR</td>
<td>U/S/T/B</td>
<td>32</td>
<td>41</td>
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<tr>
<td>Myers</td>
<td>2005</td>
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<td>nr</td>
<td>+ PCR</td>
<td>U/S/T/B</td>
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<td>26</td>
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<tr>
<td>van Tol</td>
<td>2005</td>
<td>328 (100)</td>
<td>75</td>
<td>C + PCR</td>
<td>U/S/T/B</td>
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<td>46</td>
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<tr>
<td>Yusuf</td>
<td>2006</td>
<td>169 (100)</td>
<td>nr</td>
<td>PCR</td>
<td>B</td>
<td>32</td>
<td>62</td>
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<tr>
<td>Sivaprakasam</td>
<td>2007</td>
<td>71 (100)</td>
<td>66</td>
<td>PCR</td>
<td>S/B</td>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>Anderson</td>
<td>2007</td>
<td>38 (100)</td>
<td>0</td>
<td>C + PCR</td>
<td>U/S/T/B</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

Diagnostics: C = culture, PCR = polymerase chain reaction.
Material: U = urine, S = stool, T = throat and/or upper respiratory tract, B = peripheral blood

Adults 6.0%
Adults and children 7.3%
Children 10.1%

Matthes-Martin, 2009
Possible sources of adenovirus in SCT patients

- Infection from an outside source
  - Respiratory route
  - GI-route
  - From blood products or the donor (?)

- Activation/reactivation of persistent/latent virus
Possible antiviral agents

Ribavirin
Ganciclovir
Cidofovir
CMX001
Specific T-cells
# Outcome of antiviral therapy; Adv disease (enteritis alone excluded)

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>No Pts</th>
<th>T-cell- depletion No (%)</th>
<th>Therapy</th>
<th>ADV-related death No (%)</th>
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</thead>
<tbody>
<tr>
<td>Bordigoni</td>
<td>2001</td>
<td>14</td>
<td>11 (78)</td>
<td>rbv +/- DLI</td>
<td>9 (64)</td>
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<tr>
<td>Legrand</td>
<td>2001</td>
<td>1</td>
<td>0</td>
<td>cdv</td>
<td>1 (100)</td>
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<tr>
<td>Hoffman</td>
<td>2001</td>
<td>7</td>
<td>nr</td>
<td>cdv</td>
<td>1 (14)</td>
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<tr>
<td>Chakrabati</td>
<td>2002</td>
<td>4</td>
<td>4 (100)</td>
<td>rbv or cdv</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Ljungman</td>
<td>2003</td>
<td>7</td>
<td>nr</td>
<td>cdv</td>
<td>8 (50)</td>
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<tr>
<td>Lion</td>
<td>2003</td>
<td>10</td>
<td>2 (20)</td>
<td>cdv</td>
<td>8 (80)</td>
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<tr>
<td>Lankester</td>
<td>2004</td>
<td>4</td>
<td>nr</td>
<td>cdv</td>
<td>4 (100)</td>
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<td>Leruez-Ville</td>
<td>2004</td>
<td>26</td>
<td>11 (42)</td>
<td>rbv +/- cdv</td>
<td>5 (19)</td>
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<tr>
<td>Muller</td>
<td>2005</td>
<td>16</td>
<td>1 (6)</td>
<td>cdv</td>
<td>8 (50)</td>
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<td>Kampmann</td>
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<td>2 (20)</td>
<td>cdv</td>
<td>8 (80)</td>
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<td>Symeonidis</td>
<td>2006</td>
<td>11</td>
<td>8 (73)</td>
<td>cdv</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Yusuf</td>
<td>2006</td>
<td>57</td>
<td>35 (61)</td>
<td>cdv</td>
<td>1 (2)</td>
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<td>Neofytos</td>
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<td>5</td>
<td>3 (60)</td>
<td>cdv</td>
<td>2 (40)</td>
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<tr>
<td>Anderson</td>
<td>2007</td>
<td>7</td>
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<td>cdv</td>
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<tr>
<td>Sivaprakasam</td>
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<td>Robin</td>
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<td>25</td>
<td>0</td>
<td>cdv</td>
<td>8 (32)</td>
</tr>
</tbody>
</table>

Total ADV related death 57/204 (27.9%)
Papovaviruses

- BK-, JC-virus and two new respiratory viruses
- DNA viruses
- Ubiquitous viruses in the population
  - Symptoms from the primary infections are mild and uncharacteristic
  - Reactivates in severely immunocompromised patients
Symptoms in transplant patients

JC-virus   PML (rare)

BK-virus   Nephropathy in renal tx patients
           Hemorrhagic cystitis in SCT patients(?)

Hemorrhagic cystitis in SCT patients(?)
Many interventions to treat the symptoms have been proposed and tried.

- Low dose cidofovir has been used
- Some encouraging results
Hepatitis viruses and HSCT patients

Before HSCT
- latent infection with no liver disease
- chronic asymptomatic hepatitis
- acute, clinically overt hepatitis (rare)

Following HSCT
- reactivation of latent infection ± LD
- de novo infection ± LD
- unmodified ongoing chronic hepatitis
Post-SCT liver disease in ALLO SCT with HBV or HCV infection

Liver disease (%): no LD = absent or resolved; unchang = unmodified by SCT; reactiv = acute flare; F/subAH = fulminant or subacute
Post-SCT liver disease in ALLO SCT with donor HBV or HCV infection

liver disease (%): no LD = absent or resolved; unchang= unmodified by SCT; de novo = new post-SCT infection; F/subAH = fulminant or subacute
HBV reactivation/ seroreversion

Development of acute hepatitis /rising HBV DNA levels in patients who are HBsAg +

Development of HBV DNA positivity, HBsAg positivity in patients who are HBsAb+ with or without anti-HBcAb

SCT
Rituximab
Alemtuzumab
Norovirus – a nuisance or an important pathogen?

- **Family:** Caliciviridae
- **Genus:** Norovirus

- Different subtypes
- **Liknande virus:** sapovirus
- **Single stranded RNA viruses**

- **Diagnosis:** PCR or elektronemicroskopy

- **Incubation time:** 12-48 hs
12 patients
All had prolonged diarrhoea (0.5 – 14 mths)
6 required nutritional support
Karolinska experience

- 67 patients (42 hematology, 25 SCT)
- PCR positivity – median 2 d (1-216)
  - 42% positive > 1 week
  - 32% positive > 2 weeks
  - 18% positive > 4 weeks

Ljungman et al poster ASH 2009
Clinical outcome

- All but one SCT patients had mild symptoms also the long-term excreters.
- One died of GI bleed but had also CMV enteritis and GVHD of the gut
- Four hematology patients died in close association to the infection
  - Three of these with significant fluid balance and electrolyte disturbances
  - One patient entered renal failure
- 11% had to postpone planned chemotherapy including one allo SCT
Respiratory viruses

<table>
<thead>
<tr>
<th>“Old”</th>
<th>“New”</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>Metapneumo</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>Boca</td>
</tr>
<tr>
<td>Influenza</td>
<td>Papova</td>
</tr>
<tr>
<td>Rhino</td>
<td>Avian influenza</td>
</tr>
<tr>
<td>Corona</td>
<td>Mimi</td>
</tr>
</tbody>
</table>
Respiratory virus infections

Frequency of infections associated to the epidemiological situation in the community

Major risk for nosocomial transmission within units (RSV, parainfluenza, influenza)

No controlled studies

Varying treatment schedules and combinations
Infection control measures

Handwashing

Avoidance of infected persons

Vaccination against influenza
  Patients
  Family
  Staff
RSV infection

<table>
<thead>
<tr>
<th></th>
<th>Severe immunodef.</th>
<th>Moderate immunodef</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Treatment</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Progression</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>LTI</th>
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</tr>
</thead>
<tbody>
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<td>UTI</td>
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<td>2</td>
</tr>
<tr>
<td>Treatment</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Khanna et al CID 2008
Treatment options

- Ribavirin iv, po or inhaled
- Palivizumab
- Immune globulin
- Two new drugs
H1N1 "Swine flu"
Previous data on influenza in transplant recipients

<table>
<thead>
<tr>
<th>Study</th>
<th>Neuramidase inhibitors</th>
<th>LRT</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whimbey 1994</td>
<td>HSCT</td>
<td>No</td>
<td>75%</td>
</tr>
<tr>
<td>Ljungman 2001</td>
<td>HSCT</td>
<td>No</td>
<td>0%</td>
</tr>
<tr>
<td>Nicholls 2004</td>
<td>HSCT</td>
<td>Yes</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>28%</td>
</tr>
<tr>
<td>Machado 2004</td>
<td>HSCT</td>
<td>Yes</td>
<td>5.1%</td>
</tr>
<tr>
<td>Kumar 2010</td>
<td>SOT</td>
<td>Yes</td>
<td>31.7%</td>
</tr>
<tr>
<td>Tramontana 2010</td>
<td>HSCT+HM</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Median time to H1N1 from HSCT was 19.4 months (0-204.9)

92 patients were hospitalized due to H1N1 infection

33 patients (11.%) became infected while in hospital (nosocomial infection)
## Symptoms of H1N1 infection

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>232</td>
<td>81.1</td>
</tr>
<tr>
<td>Cough</td>
<td>242</td>
<td>85.0</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>141</td>
<td>49.3</td>
</tr>
<tr>
<td>Muscle ache</td>
<td>82</td>
<td>28.7</td>
</tr>
<tr>
<td>Sore throat</td>
<td>65</td>
<td>22.7</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>71</td>
<td>24.8</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>33</td>
<td>11.5</td>
</tr>
</tbody>
</table>
### Outcome of H1N1 infection

**EBMT/GETH survey (n=286)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRT disease</td>
<td>93</td>
<td>32.5</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>33</td>
<td>11.5</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>Death from H1N1</td>
<td>18</td>
<td>6.3</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Time to H1N1 from HSCT in fatal cases: Median 1.1 years (0 – 15.3)
Influenza vaccination

Recommended to HSCT patients
Clinical support for a protective effect (Machado)

When after HSCT is it meaningful to vaccinate?
Better immune responses later after HSCT

Current recommendations are to start when the season arrives but earliest at 3 months after HSCT

Are there any risks?
No evident risks with the seasonal vaccine
Why take the flu shot (hospital staff)?

- You will protect your patients
- Less time away from work
- You will not get sick

Me!
Why do staff not take the flu shot?

- It does not work
- I will get sick from the shot
- I never get the flu anyway
- Flu is a mild infection
- I will get sick from the shot
Strongly recommended!

Data in nursing home residents show that staff vaccination works!

No negative effects of repeated vaccinations with the seasonal vaccine
A common practical question

What do I do with a HSCT patient travelling to

..................?
### What vaccines might come up?

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Risk description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>No risk / data exist</td>
</tr>
<tr>
<td>HAV</td>
<td>No risk / limited data</td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>No risk / data exist</td>
</tr>
<tr>
<td>Measles</td>
<td>Some risks? / some data exist</td>
</tr>
<tr>
<td>BCG</td>
<td>Poor risk / benefit ratio?</td>
</tr>
<tr>
<td>Typhoid</td>
<td>No data / should be no risk</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>No data / should be no risk</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Limited data / risk?</td>
</tr>
</tbody>
</table>
Thank you for your attention!