Virus infections – emerging threats and management strategies

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Stockholm, Sweden
### 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>
</tr>
<tr>
<td>Measles</td>
<td>JCV</td>
<td>HAV</td>
<td>Noroviruses</td>
</tr>
<tr>
<td>VZV</td>
<td>EBV</td>
<td>HSV</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Rabies</td>
<td>HHV-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 (??)
Prevention of disease

- Early diagnosis
- Monitoring of patients
- Antiviral prophylaxis
- Vaccination
How to diagnose a viral infection!
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
Timing of management options

Viral replication

Grafting

Time

Pre-emptive therapy

Prophylaxis

Treatment of established disease

viral disease

Diagnosis of viral infection

Alain, ILTS 2008
A virological "smorgasbord"
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)
What is the influence of CMV on outcome of a HSCT?

- Being CMV seropositive is associated with decreased survival
- Having a CMV seropositive donor for a CMV seronegative patient is associated with decreased survival
- Having a CMV seronegative unrelated donor for a CMV seropositive patient is associated with decreased survival
Effect of donor status – CMV seropositive patients

The protective effect of a CMV matched unrelated donor is seen only in patients receiving myeloablative conditioning

<table>
<thead>
<tr>
<th></th>
<th>MAC</th>
<th>RIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>0.91 (0.86-0.97; p = .01)</td>
<td>1.06 (0.96-1.17; p = ns)</td>
</tr>
<tr>
<td>RFS</td>
<td>0.94 (0.88-1.00; p = .05)</td>
<td>1.08 (0.99-1.19; p = .08)</td>
</tr>
<tr>
<td>NRM</td>
<td>0.87 (0.81-0.95; p = .01)</td>
<td>1.09 (0.96-1.23; p = ns)</td>
</tr>
<tr>
<td>RI</td>
<td>1.05 (p = ns)</td>
<td>1.05 (p = ns)</td>
</tr>
</tbody>
</table>
Treatment of CMV

- Ganciclovir = foscarinet
- Valganciclovir = ganciclovir

- Effects are the similar
- Side effects are different
There might therefore be at least a week before the DNA levels decrease.
Repeated CMV reactivations

- Common in high risk patients
- Associated with poor T-cell control of CMV
- Increased risk for antiviral resistance
- Increased risk for toxicity from antiviral drugs
New drugs/options

- Maribavir
- Letermovir
- CMX001
- CMV specific T-cell infusions
- CMV vaccines
Adoptive T-cell therapy

- In development for > 20 years
- Major advances in technology have been achieved over the last few years
- However, still far away from routine therapy in most centers
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
VZV

- 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
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 (rituximab)
- Reduced immunosuppression
- Cell therapy (CTL or donor lymphocytes)
- Antiviral therapy – most likely not
Results of rituximab therapy of established PTLD

Mortality from PTLD

Overall survival

Styczynski et al, EBMT 2012
Adenovirus infections

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

- Upper and lower respiratory infections
- Renal infections / hemorrhagic cystitis
- Gastrointestinal infections
- Hepatitis
- CNS disease
Possible sources of adenovirus in SCT patients

- Infection from an outside source
  - Respiratory route
  - GI-route
- There are described outbreaks within units
- Activation/reactivation of persistent/latent virus
Frequency of adenovirus disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (summary of studies)</td>
<td>144/1370</td>
<td></td>
<td>10.5%</td>
</tr>
<tr>
<td>Adults (summary of studies)</td>
<td>7/198</td>
<td></td>
<td>3.5%</td>
</tr>
</tbody>
</table>
Diagnostic procedures

- qPCR for monitoring

- Important to detect in tissue for diagnosis of visceral infections (not PCR)

- Presumed infections (GI disease, HC) with adenovirus detected in stools or urine in symptomatic patients
Outcome of antiviral therapy (mortality)

Children (summary of studies)  
84/234  37%

Adults (summary of studies)  
13/56  23%
Possible antiviral agents

Cidofovir
(Ribavirin)
(Ganciclovir)
CMX001
Specific T-cells
Cidofovir and viral load

Neofytos et al BBMT 2007
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
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
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
Allogeneic Hematopoietic Stem Cell Transplantation and Norovirus Gastroenteritis: A Previously Unrecognized Cause of Morbidity

C. Roddie,1 J. P. V. Paul,2 R. Benjamin,1 C. I. Gallimore,3 J. Xerry,3 J. J. Gray,3 K. S. Peggs,1 E. C. Morris,4 K. J. Thomson,1 and K. N. Ward2

1Department of Haematology, University College London Medical School, 2Centre for Virology, Division of Infection and Immunity, University College London Medical School, Windeyer Institute of Medical Sciences, 3Enteric Virus Unit, Virus Reference Department, Centre for Infections, Health Protection Agency, and 4Department of Immunology, University College London Medical School, Royal Free Hospital, London, England

- 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
<table>
<thead>
<tr>
<th>&quot;Old&quot;</th>
<th>&quot;New&quot;</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>SARS</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
Community Acquired Respiratory Viruses
Recommendations

Prevention

- Good personal hygiene should be observed including frequent hand washing, cover the mouth when coughing & sneezing, and safe disposal of oral & nasal secretions. (*II-A*)

- Leukaemia patients and HCT patients should avoid contact with individuals with RTI in the hospital and in the community. (*II-A*)

- Young children should be restricted from visiting to patients and wards because of the higher risk of CARV exposure and transmission. (*II-B*)

- All visitors and health care workers (HCW) with RTI should be restricted from access to patients and wards. (*II-A*)
<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>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>LTI</td>
<td>10</td>
<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
- New drugs?
## RSV Treatment

- **Review of outcome of *any* ribavirin combinations**

<table>
<thead>
<tr>
<th></th>
<th>Percentage (%)</th>
<th>P-value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>URTI treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to LRTID (n=26)</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>URTI untreated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression to LRTID (n=150)</td>
<td>44</td>
<td>&lt;.001</td>
<td>4.1 (2.5 – 6.5)</td>
</tr>
<tr>
<td><strong>LRTI treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (n=87)</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LRTI untreated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (n=28)</td>
<td>80</td>
<td>&lt;.001</td>
<td>7.0 (2.9 – 16.8)</td>
</tr>
</tbody>
</table>

(Shah & Chemaly 2011, Blood 117: 2755; see Table 4)
## Data on influenza in transplant recipients

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</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>
<td>17%</td>
</tr>
<tr>
<td>Ljungman 2001</td>
<td>HSCT</td>
<td>No</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Nicholls 2004</td>
<td>HSCT</td>
<td>Yes</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td>Machado 2004</td>
<td>HSCT</td>
<td>Yes</td>
<td>5.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Kumar 2010</td>
<td>SOT</td>
<td>Yes</td>
<td>31.7%</td>
<td>4%</td>
</tr>
<tr>
<td>Tramontana 2010</td>
<td>HSCT+HM</td>
<td>Yes</td>
<td></td>
<td>22%</td>
</tr>
</tbody>
</table>
H1N1 characteristics, prevention, and therapy

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 not earlier than 3 months after HSCT

Are there any risks?
No evident risks with the seasonal vaccine
Staff vaccination is strongly recommended!

Data in nursing home residents show that staff vaccination works!

No negative effects of repeated vaccinations with the seasonal vaccine
Metapneumovirus

- Paramyxovirus

- 5-10 or respiratory virus infections in children

- Similar outcome as RSV if pneumonia develops

- Ribavirin???
Human Rhinovirus (HRhV)

HRhV are throughout the year the most common cause of URTID (rhinorhoea, postnasal drip, cough) and occasionally bronchitis.

In allogeneic HCT recipient, HRhVs are the most frequent CARV reaching a cumulative incidence of 22.3% by day 100.

LRTID in allogeneic HCT is rare (<10%).

The role of treatment is limited by the lack of agents and RCTs.
Rhinovirus pneumonia; overall survival

Seo et al Tandem 2013
New threats

- New viruses are emerging usually from animals and crossing over to humans:
  - What will be the impact on transplant patients?
    - Might appear in the donor and transferred to the patient
    - Might appear in the patient
    - Might appear in contacts and transmitted to the patient
Some examples

- New respiratory viruses - Boca, papova
- New coronaviruses - last year in the middle east
- New influenza viruses - just now in China (H7N9)
- West Nile virus - increasing in some areas
- Dengue virus - Outbreak in Madeira

Travel to endemic areas
A common practical question

What do I do with a HSCT patient travelling to
............... ?
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Risk/Benefit</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!