COMPLICATIONS

Viral infections

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Viral infections after allogeneic HSCT

**Community acquired respiratory infections (CARVs)**
- **RNA viruses (predominantly)**
  - HRV  Human rhinovirus
  - PIV  Parainfluenza virus 1-3
  - RSV  Respiratory syncytial virus A/B
  - IFV  Influenza virus A/B
  - HCoV Human coronavirus
  - HMPV Human metapneumovirus
  - HBoV  *Human bocavirus*
  - HAdV  *Human adenovirus*

**„Classical“ infections**
- **DNA viruses**
  - HHV  Human herpes viruses 1-8
    - HHV1-HSV1  Herpes simplex virus 1
    - HHV2-HSV2  Herpes simplex virus 2
    - HHV3-VZV  Varicella-zoster virus
    - HHV4-EBV  Epstein-Barr virus
    - HHV5-CMV  Cytomegalovirus
  - BKV/JCV  Polyomaviruses I/II
  - PVB19  Parvovirus B19
  - HAdV  Human adenoviruses A-G/1-67

T.Lion ESH-EBMT 2014
Community acquired respiratory infections (CARVs)

Incidence in HSCT recipients


1-30%

≥50% in pediatric HSCT setting
median onset: +16 (range -7 to +100)

Verslyus AB et al. Biol Blood Marrow Transplant 2010, 16:783-791
Boelens JJ 2014 pers. comm.
### Community acquired respiratory infections (CARVs)

**Relative frequency in HSCT recipients**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>HRV</td>
<td>28%</td>
<td>43%</td>
</tr>
<tr>
<td>PIV1-3</td>
<td>25%</td>
<td>7%</td>
</tr>
<tr>
<td>RSVA/B</td>
<td>26%</td>
<td>3%</td>
</tr>
<tr>
<td>IFVA/B</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>HCoV</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>HMPV</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>HBoV</td>
<td>n.a.</td>
<td>2%</td>
</tr>
<tr>
<td>HAdV</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Multiple</td>
<td>10%</td>
<td>31%</td>
</tr>
</tbody>
</table>

55% detected by PCR in NPA/BAL prior to HSCT

* Data kindly provided by JJ Boelens, University Utrecht, Netherlands
Incidence and mortality of CARV-LRTI after allogeneic HSCT

Diagnosis and treatment of CARVs

**Diagnostic approaches**

- Viral culture: too slow in immunocompromised setting
- Direct immunofluorescence AG testing: rapid, inexpensive, but low sensitivity
- Real-time PCR (multiplex assays): preferred method (or pp65-antigen in CMV)

**Treatment options for RNA viruses**

- Primarily supportive care, few antivirals with well documented effect

<table>
<thead>
<tr>
<th>Virus</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFV</td>
<td>Neuraminidase inhibitors (oseltamivir, zanamivir) and/or M2 protein inhibitors (amantadine, rimantadine)</td>
</tr>
<tr>
<td>RSV</td>
<td>Ribavirine (aerosolized)-preemptive therapy particularly in high-risk patients*</td>
</tr>
<tr>
<td>PIV</td>
<td>Ribavirine?</td>
</tr>
<tr>
<td>HMPV</td>
<td>Ribavirine?</td>
</tr>
</tbody>
</table>

*High risk: LRTI and lymphopenia <300/µl; GvHD≥3, treatment with steroids

T.Lion ESH-EBMT 2014
Indirect effects of CARV infections after allogeneic HCT

Allo-immune lung syndromes (allo-LS)

Acute IPS: Idiopathic Pneumonia Syndrome
Chronic BOS: Bronchiolitis Obliterans Syndrome

BOOP: Bronchiolitis Obliterans Organizing Pneumonia

Definitions
IPS: acute, bilateral pulmonary infiltrates, with symptoms of cough, dyspnea and hypoxemia in the absence of infection
BO: typical HR-CT changes: bronchial wall thickening, air trapping, mosaic parenchymal attenuation, in the absence of infection signs; abnormal PFT
BOOP: restrictive pulmonary function test and consolidation of chest radiographs

Long-term persistence → damage → trigger immunologically mediated events

3-step process of alloreactivity development
1. Tissue damage (respiratory epithelium)
2. Release of inflammatory cytokines
3. Activation and influx of T-lymphocytes

Ferrara JL, 2006
CARV infections alter allo-HSCT and allo-immune lung syndromes

110 pediatric patients
30 allo-LS (18 IPS/12 BOS)

Verslyus AB et al, BBMT 2010;16(6):782-91

110 pediatric patients
30 allo-LS (18 IPS/12 BOS)

Verslyus AB et al, BBMT 2010;16(6):782-91

Reported incidence in adult studies:
IPS: 2-15%/BOS: 0-26%

CARV (any virus tested) early after allo-SCT

allo-LS (MVA: p<0.0001)

Higher mortality (MVA:0.004)

Probability of allo-LS

Cumulative survival

Hypothesis
CARV → lungs target for alloimmunity

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CARV infections after allogeneic HCT and allo-immune lung syndromes

Verslyus AB et al, BBMT 2010;16(6):782-91 and Boelens JJ 2014-personal communication

CARV: common in (pediatric) HSCT setting

30-50% prior to HSCT
long-term persistence: weeks-months

Increased risk for allo-LS
BAL+ more relevant than NPA+

Early detection important

Treatment for aGvHD was associated with lower incidence of allo-LS in patients with CARV
Antiviral treatment may not impact outcome (RSV? IFV?)

Current considerations

Postponement of elective transplantations
Prolongation /slower tapering of immunosuppression
Inhalation treatment with steroids?
Suspicion of allo-LS: Methylprednisolone pulse(s)-10mg/kg i.v. for 3 days
# DNA virus persistence and allogeneic HSCT

<table>
<thead>
<tr>
<th>Virus</th>
<th>Reported sites of persistence</th>
<th>References (exemplary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHV1 (HSV1)</td>
<td>Neuronal cells of sensory nerve ganglia (trigeminal)</td>
<td>Ryan KJ. Sherris Med Microbiol 2004</td>
</tr>
<tr>
<td>HHV2 (HSV2)</td>
<td>Neuronal cells of sensory nerve ganglia (sacral)</td>
<td>Ryan KJ. Sherris Med Microbiol 2004</td>
</tr>
<tr>
<td>HHV3 (VZV)</td>
<td>Dorsal root ganglia (spinal)</td>
<td>Steiner I. Lancet Neurol 2007</td>
</tr>
<tr>
<td>HHV5 (CMV)</td>
<td>Cells of myeloid lineage-macrophages, endothelial cells</td>
<td>Jarvis MA, Curr Opinion Microbiol 2002</td>
</tr>
<tr>
<td>HHV7</td>
<td>T-lymphocytes, salivary gland, (other organ tissues?)</td>
<td>Frenkel N, PNAS 1990</td>
</tr>
<tr>
<td>PVB19</td>
<td>Myocardium, BM (erythroid progenitors), kidney, liver</td>
<td>Aravindh R. Arch Virol 2014</td>
</tr>
<tr>
<td>HAdV</td>
<td>T-Lymphocytes, CNS, (other organ tissues?)</td>
<td>Lion T, Leukemia 2010; Kosulin K. J.Virol 2007</td>
</tr>
</tbody>
</table>

## Reactivation

Reactivation is the main source of viral disease after allo-HSCT.
# DNA virus infection/reactivation after allo-SCT: Clinical manifestations

<table>
<thead>
<tr>
<th>Virus</th>
<th>Manifestations</th>
<th>References (exemplary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHV1 (HSV1)</td>
<td>Mucocutaneous ulceration, pneumonitis, gastroenteritis, encephalitis</td>
<td>Nichols WG. J Inf Dis 2003; Styczynski J. BMT 2009</td>
</tr>
<tr>
<td>HHV3 (VZV)</td>
<td>Encephalitis, hepatitis, pneumonia</td>
<td>Breuer S. Mol Diagn Ther (MDT) 2012</td>
</tr>
<tr>
<td>HHV4 (EBV)</td>
<td>Post-transplantation lymphoproliferative disease (PTLD)</td>
<td>Ocheni S. Bone Marrow transplant (BMT) 2008</td>
</tr>
<tr>
<td>HHV5 (CMV)</td>
<td>Hepatitis, pneumonia, gastroenteritis, encephalitis, retinitis</td>
<td>Boeckh M. Blood 2012; Ljungman P. BMT 2008</td>
</tr>
<tr>
<td>HHV6A-B</td>
<td>Encephalitis, pneumonitis, hepatitis, thrombocytopenia</td>
<td>Bhanushali MJ, Neurology 2013</td>
</tr>
<tr>
<td>BKV</td>
<td>Hemorrhagic cystitis, meningitis, encephalitis, pneumonia, nephropathy</td>
<td>Hirsch H. Lancet Inf Dis 2003; Breuer S. MDT 2012</td>
</tr>
<tr>
<td>PVB19</td>
<td>Refractory anemia, leukopenia, thrombocytopenia, (hepatitis, myocarditis, pneumonitis)</td>
<td>Eid AJ, CID 2006</td>
</tr>
<tr>
<td>HAdV</td>
<td>Enteritis, hepatitis, nephritis, encephalitis, myocarditis, hemorrh. cystitis</td>
<td>Lion T. Blood 2003; Lion T. Leukemia 2010</td>
</tr>
</tbody>
</table>

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**Causal relationship?**
Broad molecular screening for DNA viruses in PB after allo-HSCT: Relative frequency of virus detection

Herpes viruses: > 70%

<table>
<thead>
<tr>
<th>Rank</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HHV6</td>
</tr>
<tr>
<td>2</td>
<td>EBV</td>
</tr>
<tr>
<td>3</td>
<td>CMV</td>
</tr>
<tr>
<td>4</td>
<td>AdV</td>
</tr>
<tr>
<td>5</td>
<td>HHV7</td>
</tr>
<tr>
<td>6</td>
<td>PVB19</td>
</tr>
<tr>
<td>7</td>
<td>BKV</td>
</tr>
<tr>
<td>8</td>
<td>HSV1</td>
</tr>
<tr>
<td>9</td>
<td>VZV</td>
</tr>
</tbody>
</table>
Frequency of virus detection after allo-SCT

77% of patients positive for \( \geq 1 \) virus

Up to 4 viruses present in PB
+ additional viruses at other sites

latent \leftrightarrow \text{active}

Reliable assignment of clinical manifestations to specific virus?
Restricted viral screening for specific virus cause? only cause?
Approaches to antiviral treatment in the HSCT setting

- Antiviral prophylaxis (> HSV, VZV, CMV)
- Preemptive treatment
- RQ-PCR monitoring of viral load in PB/serum

### Critical thresholds of viral load for preemptive therapy

<table>
<thead>
<tr>
<th>Virus</th>
<th>Threshold</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>&gt;10^2 virus copies/ml</td>
<td>Atkinson C. J Clin Virol 2011</td>
</tr>
<tr>
<td></td>
<td>&gt;10^3-10^5 virus copies/ml</td>
<td>Boeckh M. Blood 2009</td>
</tr>
<tr>
<td>EBV</td>
<td>&gt; 10^3/10^5 PBMCs</td>
<td>Coppoletta S. BBMT 2011</td>
</tr>
<tr>
<td></td>
<td>&gt;10^4 virus copies/ml</td>
<td>Omar H. Transpl Inf Dis 2009</td>
</tr>
<tr>
<td></td>
<td>4x10^4 virus copies/ml</td>
<td>Carpenter B. Transplant 2010</td>
</tr>
<tr>
<td>HHV6</td>
<td>&gt;5.5x10^5 cp (in SOT)</td>
<td>Le J. Gantt S. Am J Transpl 2013</td>
</tr>
<tr>
<td>AdV</td>
<td>10^2-10^4 virus copies/ml</td>
<td>Lindemans CA. Blood 2010</td>
</tr>
<tr>
<td></td>
<td>4x10^3 virus copies/ml</td>
<td>Teramura T. BMT 2004</td>
</tr>
<tr>
<td></td>
<td>10^4 virus copies/ml</td>
<td>Lee YJ. BBMT 2013</td>
</tr>
<tr>
<td></td>
<td>&gt; 1x10^6 copies/g stool</td>
<td>Lion T. Leukemia 2010</td>
</tr>
</tbody>
</table>

### Kinetics of viral load

- **CMV**
- **EBV**

[Graphs showing the kinetics of viral load for CMV and EBV]
Virus proliferation kinetics vs defined thresholds of viral load for preemptive antiviral therapy

## Antiviral (chemo)therapy

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Prophylactic Treatment</th>
<th>Preemptive Treatment</th>
<th>Symptomatic disease Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td>3x10 mg/kg/d</td>
<td>4x15 mg/kg/d</td>
<td>4x15 mg/kg/d</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>2x5mg/kg/d</td>
<td>2x5mg/kg/d</td>
<td>2x5mg/kg/d</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>2 x 10 mg/kg/d</td>
<td>2 x 10 mg/kg/d</td>
<td>No oral treatment</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>1x5 mg/kg/week or 3x1 mg/kg/week</td>
<td>1x5 mg/kg/week or 3x1 mg/kg/week</td>
<td>1x5 mg/kg/week or 3x1 mg/kg/week</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>2 x 40mg/kg/d</td>
<td>2 x 90 mg/kg/d</td>
<td>2 x 90-120 mg/kg/d</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>2 x 10 mg/kg</td>
<td>2 x 10 mg/kg</td>
<td>2 x 10 mg/kg</td>
</tr>
<tr>
<td>Brincidofovir</td>
<td></td>
<td>100 mg 2x/week* or 200 mg 1x/week*</td>
<td></td>
</tr>
<tr>
<td>Maribavir</td>
<td></td>
<td>100 mg/BID p.o.* or 400 mg/day or 400 mg BID*</td>
<td></td>
</tr>
<tr>
<td>Letermovir</td>
<td></td>
<td>80 of 120 or 240 mg 1x/day*</td>
<td></td>
</tr>
<tr>
<td>Rituximab (anti CD20)</td>
<td></td>
<td>375 mg/m² 1-4x</td>
<td></td>
</tr>
</tbody>
</table>

The indicated dosing reflects treatment in the pediatric setting  
* Not approved for use in children> dose from adult studies

### Genetic resistance in CMV to various antiviral agents (GCV, CDV, FOS, MBV)

#### UL 97: Protein kinase

<table>
<thead>
<tr>
<th>1</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>707</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### UL 54: DNA polymerase

<table>
<thead>
<tr>
<th>1</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>707</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Analysis by genotypic analysis (sequencing) and functional analysis (recombinant phenotyping)  
(James SH. Infect Disord Drug Targets 2011)

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## Human adenoviruses

### Double-stranded DNA-Virus

Genome size: ~36 kb

### 7 species (subgenera): A-G

<table>
<thead>
<tr>
<th>Species</th>
<th>Types (serotyping/computational analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12, 18, 31, 61</td>
</tr>
<tr>
<td>B</td>
<td>3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66, 68</td>
</tr>
<tr>
<td>C</td>
<td>1, 2, 5, 6, 57</td>
</tr>
<tr>
<td>D</td>
<td>8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, 53, 54, 56, 58, 59, 60, 63, 64, 65, 67, 69</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>40, 41</td>
</tr>
<tr>
<td>G</td>
<td>52</td>
</tr>
</tbody>
</table>

Most newly identified HAdV types resulted from homologous recombination events

HAdV infections in immunosuppressed patients

**Organ-Tropism of HAdV Species**

A  Intestinal tract; CNS
B  Respiratory tract; Eye; Intestinal tract; Genitourinary tract; CNS
C  Respiratory tract; Intestinal tract; Liver
D  Eye; Intestinal tract; CNS
E  Respiratory tract; Eye
F, G  Intestinal tract

**Clinical Manifestations**

- Gastro/enteritis
- Pneumonia
- Hämorrhagic cystitis
- Meningoencephalitis
- Hepatitis
- Keratoconjunctivitis
- Respiratory infections

**Multiorgan failure (MOF)**

T. Lion ESH-EBMT 2014
Lethal invasive HAdV infections in pediatric allo-SCT

Lion T et al. Leukemia 2010, 24(4):706-14

138 patients

- All pts: n=138, 6%
- All deaths: n=36, 22%
- TRM: n=26, 31%
Adenoviremia and transplant-related mortality

Lion T, Blood 102(3): 114-20, 2003

67% (+ 5%) 64% (+10%)
18% (+ 9%), (P< 0.001)

HAdV positivity in PB  TRM (p<0.001)

Quantification by RQ-PCR:
Rising virus load before onset of symptoms

Definition of critical HAdV threshold levels in PB for onset of treatment

Teramura T. BMT 2004, 33:87-92
4x10^3 cp/ml

10^4 cp/ml


> 10^2 cp/ml in high-risk patients
> 10^3 cp/ml in intermediate-risk patients
> 10^3 or > 10^4 cp/ml in low-risk patients

Any HAdV species (subgenus) may occur
Disseminated disease: species C, A, B

Diagnostics
Documented efficacy of antivirals in HAdV infections

**Cidofovir**
- Currently primary anti-HAdV agent for pre-emptive therapy
- Efficacy against all HAdV species > gain time for T-cell recovery
- Low bioavailability and nephrotoxicity


**Brincidofovir**
- Safe, but limited data in immunocompromised patients


**(CMX001-orally bioavailable lipid conjugate of cidofovir)**

**Ribavirin**
- Documented in vitro activity against HAdV-C only
- Questionable therapeutic effect in vivo > added value against HAdV-C?

(Morfin F. Antivir Ther 2009, 14:55-61; Lankester A. CID 2004, 38:1521-5) ;Abe S. BMT 2003, 32:1107-8

**Ganciclovir**
- Modest activity due to inefficient phosphorylation (lack of TK in HAdV)


**Foscarnet**
- No activity

(Naesens L. Antimicrob Agent Ther 2005, 49:1010-16)
## Incidence of HAdV viremia in patients after HSCT

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Viremia (lethal)</td>
<td>Viremia (lethal)</td>
</tr>
<tr>
<td>2013</td>
<td>Hiwarkar et al</td>
<td></td>
<td>15% (n.r.)</td>
</tr>
<tr>
<td>2012</td>
<td>Sive et al</td>
<td>12% (1/14)</td>
<td>16% (2/7)</td>
</tr>
<tr>
<td>2012</td>
<td>Taniguchi et al</td>
<td>9% (4/10)</td>
<td>15% (0/3)</td>
</tr>
<tr>
<td>2012</td>
<td>Watson et al</td>
<td></td>
<td>10% (8/16)</td>
</tr>
<tr>
<td>2011</td>
<td>Öhrmalm et al</td>
<td>3% (0/2)</td>
<td>11% (3/8)</td>
</tr>
<tr>
<td>2010</td>
<td>Lion et al</td>
<td></td>
<td>15% (1/2)</td>
</tr>
<tr>
<td>2009</td>
<td>de Pagter et al</td>
<td>15% (2/4)</td>
<td>14% (3/8)</td>
</tr>
<tr>
<td>2008</td>
<td>Gustafson et al</td>
<td></td>
<td>21% (1/37)</td>
</tr>
<tr>
<td>2007</td>
<td>Sivaprakasam et al</td>
<td></td>
<td>6% (7/21)</td>
</tr>
<tr>
<td>2007</td>
<td>Kalpoe et al</td>
<td>5% (1/5)</td>
<td>42% (2/7)</td>
</tr>
<tr>
<td>2006</td>
<td>Yusuf et al</td>
<td></td>
<td>14% (3/3)</td>
</tr>
<tr>
<td>2005</td>
<td>van Tol et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Walls et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Avivi et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Chakrabarti et al</td>
<td>3% (2/2)</td>
<td></td>
</tr>
</tbody>
</table>
Preemiptive treatment based on RQ-PCR screening in PB

Major risk factors for onset of HAdV viremia and disseminated disease

- Allo-HSCT with unrelatated donor or cord blood graft
- Allo-HSCT with in-vivo or ex-vivo T-cell depletion
- Severe GvHD (grade III-IV)
- Severe lymphopenia (<300 CD3-cells/µl PB)
- Treatment with alemtuzumab

Reduction of immunosuppression, if possible
Preemptive treatment based on RQ-PCR screening in PB

Cidofovir (± Ribavirin) at first HAdV positivity in PB

Treatment for ≥ 2 weeks

Adoptive transfer of donor-derived HAdV-specific T cells

(Feuchtinger T et al., BJH 134: 64-76, 2006)

Isolation of PBMC from donor by density gradient centrifugation

Stimulation ex vivo with HAdV antigen C
10^8-10^9 PBMC in RPMI for 16 h at 37°C

Magnetic enrichment of IFN-g secreting T-cells
(Cytokine Secretion System® and CliniMACS® device-Miltenyi®)

Transfer of HAdV-reactive T-cells without further in vitro expansion
(1x10^3-5x10^4 T-cells/kg recipient body weight)
Preemptive treatment based on RQ-PCR screening in PB

Cidofovir (± Ribavirin) at first AdV positivity in PB

Treatment for ≥ 2 weeks

Adoptive transfer of donor-derived AdV-specific T cells

(Feuchtinger et al., BJH 134: 64-76, 2006)

Preliminary conclusion:
Success ➡️ early onset of treatment

Rational basis for earlier initiation of treatment?
Adenoviruses and allogeneic HSCT

AdV-related disease

De novo infection

Reactivation

from latent/persistent infection
HAdV persistence in the gastrointestinal tract

Detection of HAdV in stool and viremia

Leukemia 2010, 24(4):706-14

Positivity in stool: 37%

- max. HAdV load ≤ $1 \times 10^6 / g$
- no/slow kinetics
- max. HAdV load $5 \times 10^6 - 10^{11} / g$
- rapid kinetics

No viremia (p < 0.001) >70% viremia

Types A31, B03, C01, C02, C06 and F41
Intestinal HAdV infection and viremia

Lion T. Leukemia 2010, 24(4):706-14

Monitoring of intestinal HAdV infection by RQ-PCR: basis for antiviral treatment

Intestinal infection

Viral load $> 1 \times 10^6 / \text{g}$ [confirmed by Jeulin H. Clin Microbiol Infect 2011]

Rapid proliferation kinetics

High risk of invasive infection

Preemptive treatment warranted
Screening by pan-HAdV PCR 
pre-transplant

**Recipient: stool**

Screening in stool
1x/week until day 28

- **AdV-negative w/o high-risk**
- **AdV-positive w/o high-risk**
- **AdV-negative + high-risk**
- **AdV-positive + high-risk**

**RQ-PCR testing discontinued**

- **RQ-PCR testing in stool 1x/~/2weeks**
  - **AdV positive: load <10^6 copies w/o high risk**
  - **AdV positive: rising load and/or load ≥ 10^6 copies/g**

- **RQ-PCR testing in stool 1x/~/month**

**RQ-PCR testing in PB 1x/week**

- **AdV-positive**

- **poor response****

**Adoptive T-cell transfer**

**Testing for presence of AdV-specific T-cells**

Donor: PB

Testing for presence of AdV-specific T-cells

- **present**

- **absent**

- Reduction of immunosuppression, if possible
- Treatment by Cidofovir/Ribavirin***

**Testing for HAdV-specific T-cells in recipient**

**AdV-positive**

Lion T et al. Leukemia 2010, 24(4):706-14
Future treatment strategies

Introduction of novel antiviral drugs
- ganciclovir triphosphate
- brincidofovir

Vaccination strategies
- lysate/peptide-loaded DCs

Improved adoptive T-cell transfer

Original stem cell donors
- Rapid in vitro expansion (< 2 weeks)

Donor registry
- Partially HLA-matched HAdV-specific cells from seropositive healthy donors

Third party donors
- Healthy donors with common HLA polymorphisms

Virus-specific T-cell line bank
- Multi-(Tri-) virus specific T-cells (CMV, HAdV, EBV...)


Moss, Nat Rev 2005


Leen AM. Blood 2013, 121: 5113-23;