XLVI Congresso Nazionale AMCLI

11 - 14 Novembre 2017

Palacongressi di Rimini

Corso Precongressuale

Le infezioni da non dimenticare nel paziente trapiantato

Adenovirus

Piralla Antonio

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Infections in Immunocompromised Hosts and Organ Transplant Recipients: Essentials

Jay A. Fishman
Transplant Center, Transplant Infectious Disease and Compromised Host Service, Infectious Disease Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA

17:S34-S37. 2011

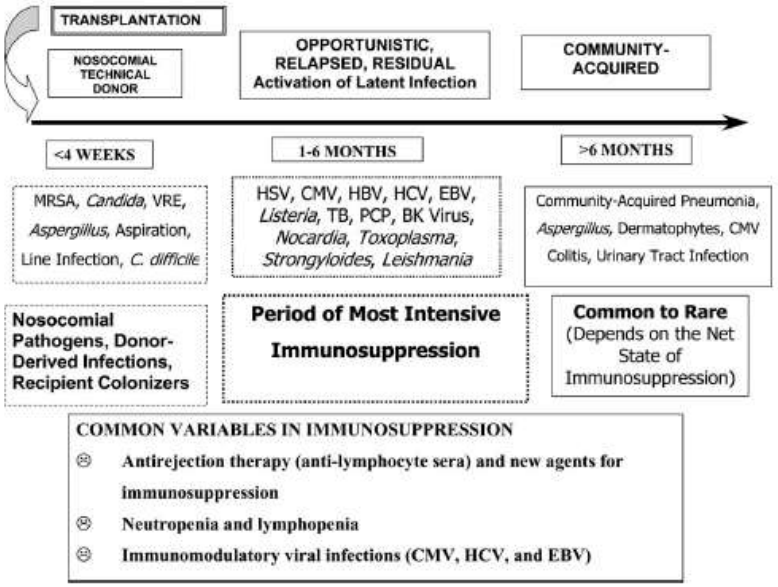
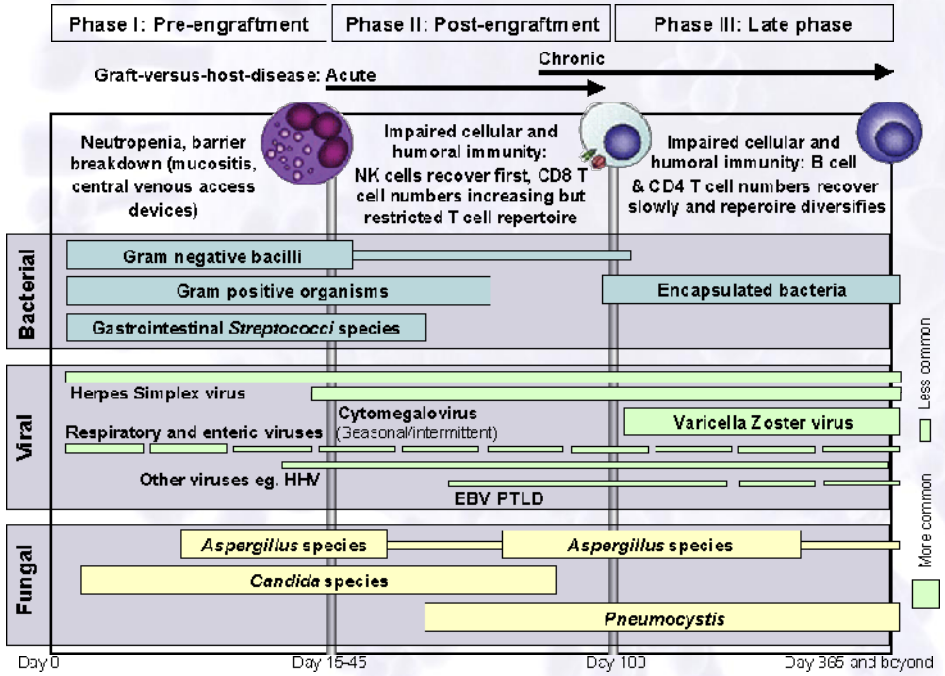


Figure 1. Timeline of posttransplant infections.

Stem Cell Research & Therapy
Kedia et al., J Stem Cell Res Ther 2013, S3
http://dx.doi.org/10.4172/2157-7633.S3-002
Review Article Open Access

Infectious Complications of Hematopoietic Stem Cell Transplantation

Shiksha Kedia[1], Pranab Sharma Acharya[1], Farhan Mohammad[1], Huy Nguyen[1], Deepak Asti[1], Suchita Mehta[1*], Manisha Pant[2] and Neville Mobarakai[3]



HAdV infections in HSCT and SOT: State of art

SOT

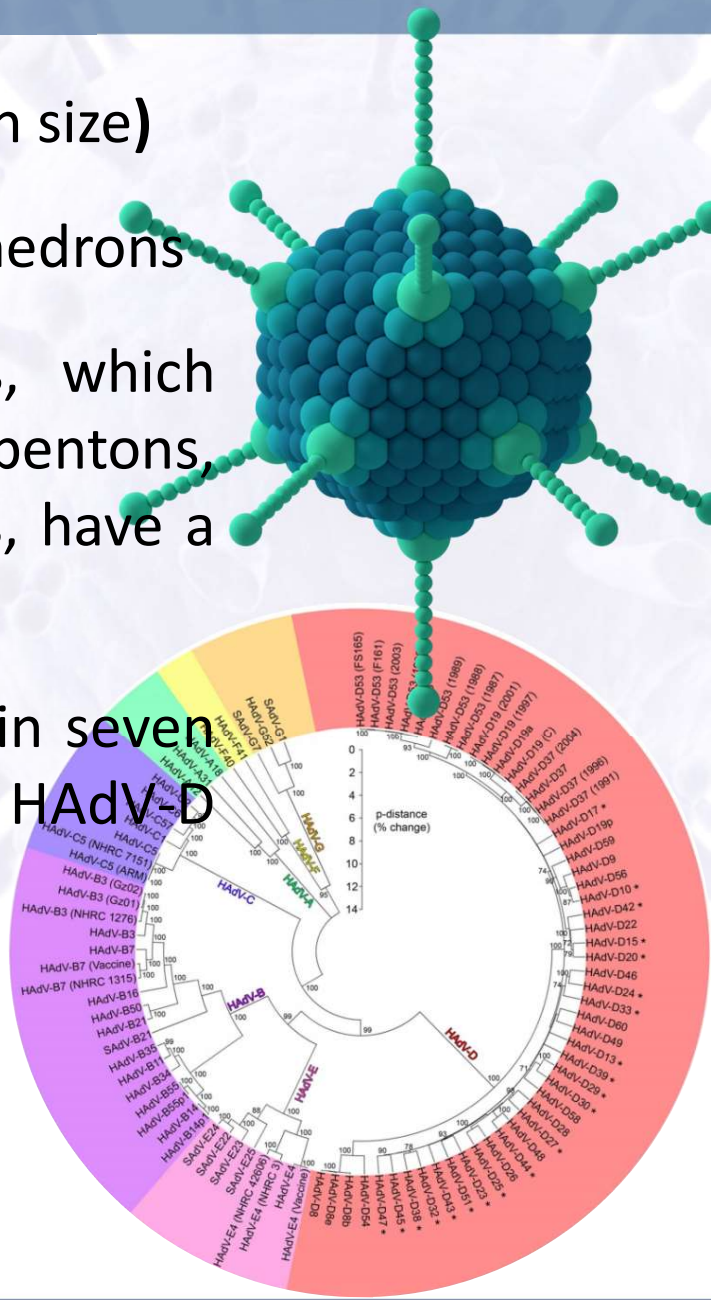
- ✓ Adenovirus (HAdV) infections have been reported in wide range of SOT population, including those receiving heart, lung, liver intestinal and kidney transplants. *(Hoffman JA, Ped Transpl 2006 10:17-25)*
- ✓ Asymptomatic HAdV DNA-emia is common among SOT recipients and generally is not associated with progression to symptomatic disease. *(Humar et al. Am J Transplant 2005; 5:2555-2559*)

HSCT

- ✓ HAdV has the highest impact on morbidity, graft survival, and mortality in profoundly T cell–depleted transplant recipients, especially in children and in patients after HSCT *(Florescu DF, Hoffman JA. Am J Transplant 2013; 13(Suppl 4): 206–211.)*
- ✓ Poor and late reconstitution is a factor associated with increased risk of adenovirus disease in HSCTR. (Moss and Rickinson *Nature Reviews Immunology* 2005; 5: 9–20)

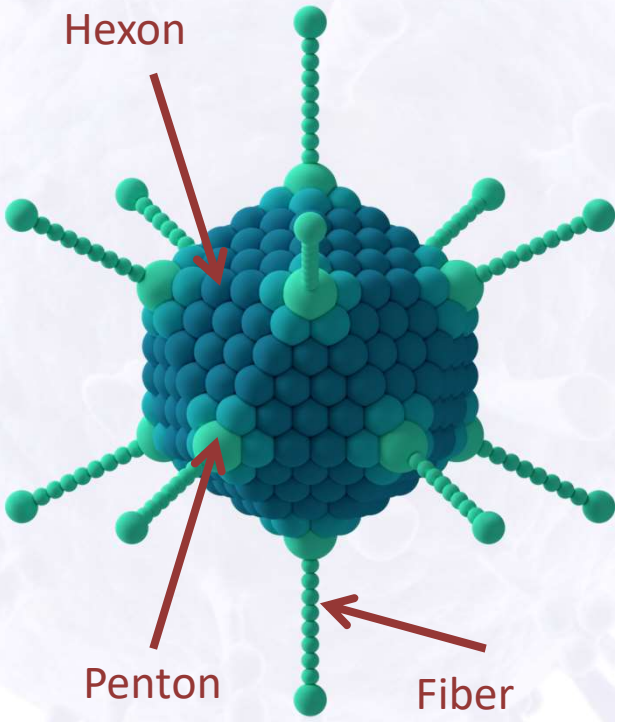
Viral structure and genome

- ✓ Linear, double-stranded DNA **(**≈34–36 kb in size**)**
- ✓ The virions are non-enveloped icosadeltahedrons
- ✓ The capsid comprises 240 capsomeres, which consist of hexons and pentons. The 12 pentons, which are located at each of the vertices, have a penton base and a fiber.
- ✓ There are currently over **60 HAdV types** in seven species (human adenovirus A–G), with HAdV-D containing the most members.



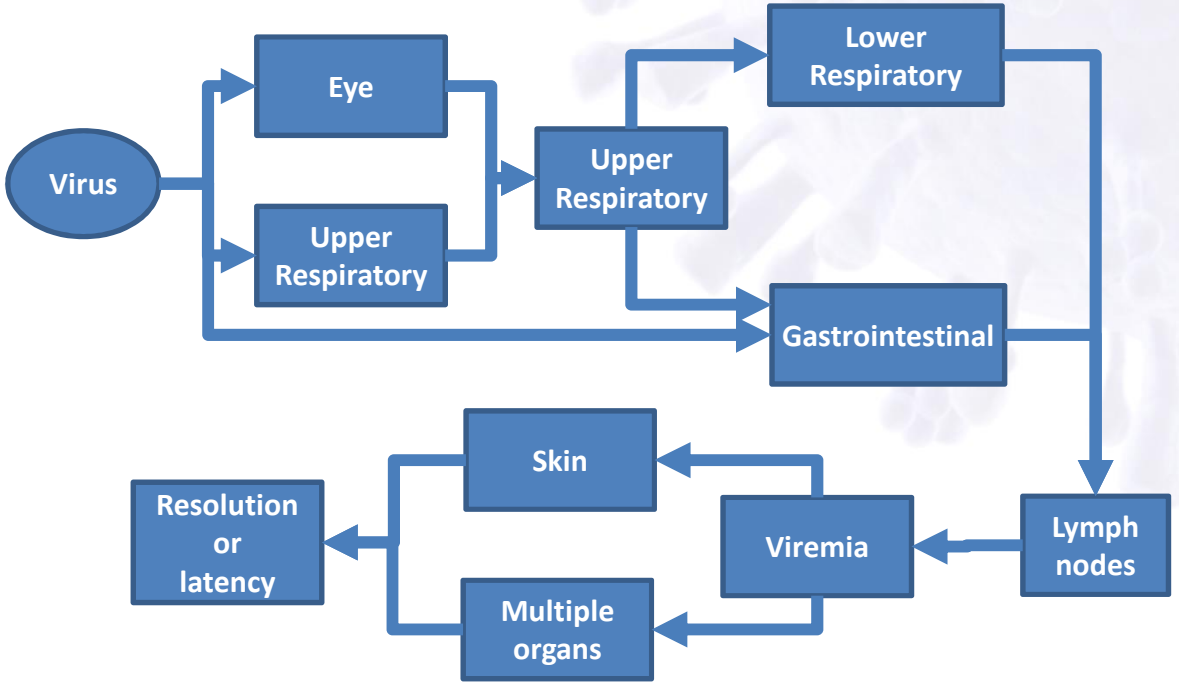
Antigenic sites

- ✓ Hexon, penton and fiber proteins are the most immunogenic parts of the HAdV capsid.
- ✓ Fiber and penton are targeted by neutralizing antibodies preventing viral entry, whereas antibodies directed to hexon prevent HAdV uncoating and genome delivery to the nucleus.
- ✓ Hexon is highly conserved across human HAdV species and has been used as an important antigen for monitoring of HAdV-specific T-cells.



HAdV pathogeneis

- ✓ Adenoviruses primarily infect children and less commonly infect adults.
- ✓ Spread by aerosol, close contact or oral-fecal route.
- ✓ Virus infects first mucoepithelial cells causing direct cell damage.
- ✓ Virus persist in lymphoid tissue
- ✓ Disease is determined by the tissue tropism of a HAdV type.



Clinical syndromes and HAdV types

- Acute respiratory disease (URTI and LRTI)
- Pharyngoconjunctival fever
- Epidemic keratoconjunctivitis
- Gastroenteritis and diarrhea

Subgroup	Serotype	Sites of infection
A	12, 18, 31	Gastrointestinal
B1	3, 7, 16, 21, 50	Respiratory
B2	11, 14, 34, 35	Urinary tract/renal
C	1, 2, 5, 6	Respiratory
D	8, 9, 10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36, 37, 38, 39, 42–48, 49, 51	Eye
E	4	Respiratory
F	40, 41	Gastrointestinal

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Case report

Acute respiratory distress syndrome in adenovirus type 4 pneumonia: A case report

R. Narra[a], P. Bono[a], A. Zoccoli[a], A. Orlandi[a], S. Piconi[b], G. Grasselli[c], S. Crotti[c], A. Girello[d], A. Piralla[d], F. Baldanti[d,e], G. Lunghi[a,*]

Clinical syndromes – Immunocompromised patients

Patients receiving stem cell transplantation and with T-cell deletion and lymphopenia are at risk for serious adenovirus infections.

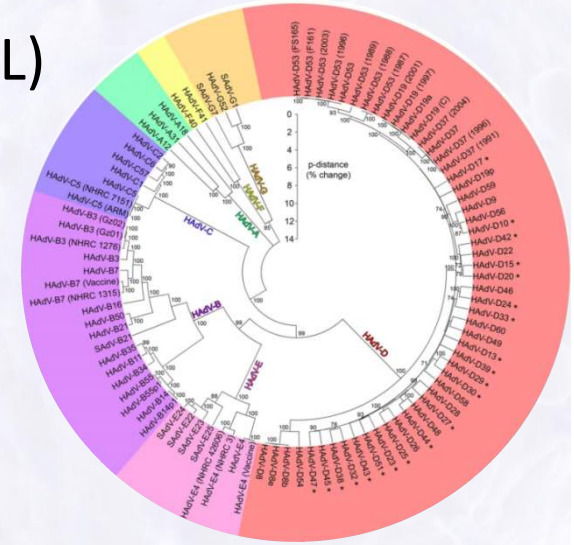
Infections in these patients may cause variable manifestations including:

- ✓ hemorrhagic cystitis
- ✓ pneumonia
- ✓ nephritis
- ✓ gastroenteritis
- ✓ Disseminated infection with organ localization preceded by viremia

Infection occurs either by reactivation of old infection or by exogenous transmission from other infected hosts.

Laboratory diagnosis

- ✓ Samples types should be collected from a site or secretion relevant to the disease symptoms.
  - Respiratory samples (NPA, nasal swabs, BAL)
  - Conjunctival swabs or scrapings
  - urine
  - Stool
  - Peripheral Blood
  - Biopsy (organ localization)

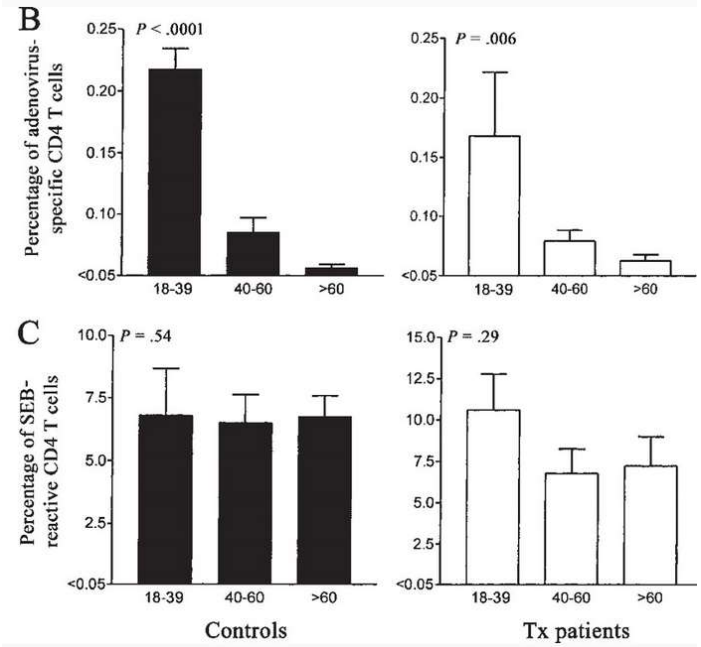


- ✓ qReal-time PCR can be used to detect and quantify HAdV.
- ✓ Sequencing of Hexon gene for typing.
- ✓ Serologic testing is rarely used except for epidemiologic purposes.

HAdV-specific Immunity decrease with older age

- ✓ IgG level reflects the exposure of young people at HAdV infections.
- ✓ HAdV-specific T cells did not differ between transplant recipients and control subjects.
- ✓ The absolute frequencies and the percentage of individuals with detectable virus-specific T cells were significantly higher in younger individuals, compared with those of the older individuals.

T-CD4



IgG

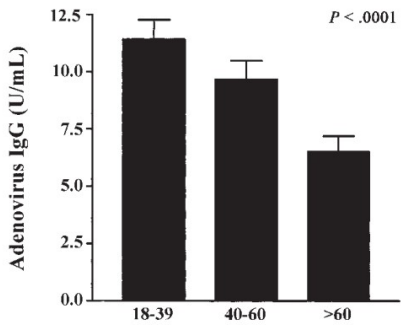


Table 1. Adenovirus-specific T cell frequencies, by control subject or transplant patient status and age group.

Group, T cell frequency	All individuals	Age group, years		
		18–39	40–60	>60
Control subjects, *n*	171	74	30	67
>0.05%	53.2 (91)	87.8 (65)	53.3 (16)	16.4 (11)[a]
≤0.05%	46.8 (80)	12.2 (9)	46.7 (14)	83.6 (56)[a]
Transplant recipients, *n*	59	16	27	16
>0.05%	55.9 (33)	87.5 (14)	48.2 (13)	37.5 (6)[b]
≤0.05%	44.1 (26)	12.5 (2)	51.9 (14)	62.5 (10)[b]

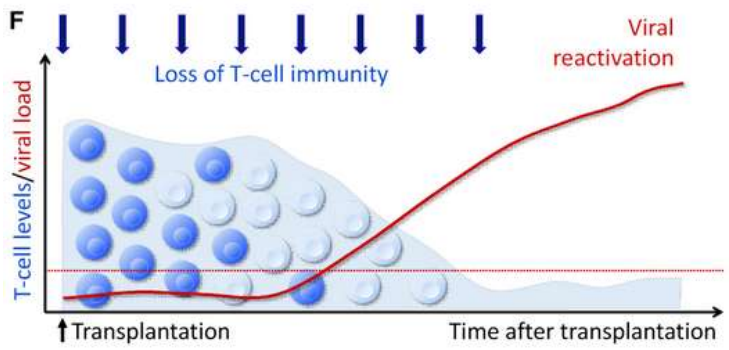
NOTE. Data are percentage (no.) of individuals with the indicated adenovirus-specific T cell frequency, unless otherwise indicated.
[a] $P < .0001$, χ^2 test.
[b] $P = .0094$, χ^2 test.

Sester et al., 2002 JID 185:1379-1387

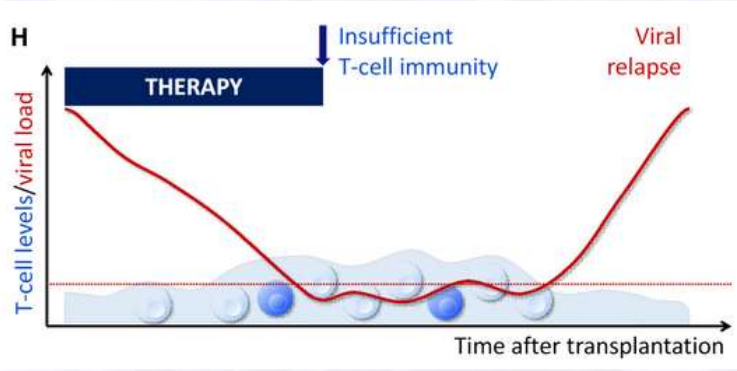
HAdV-specific Immunity (Sester et al. Am J Transpl 2016;16 (6):1697-1706.C

Absolute lymphocyte counts <300/µL predict poor outcome.

SOTR

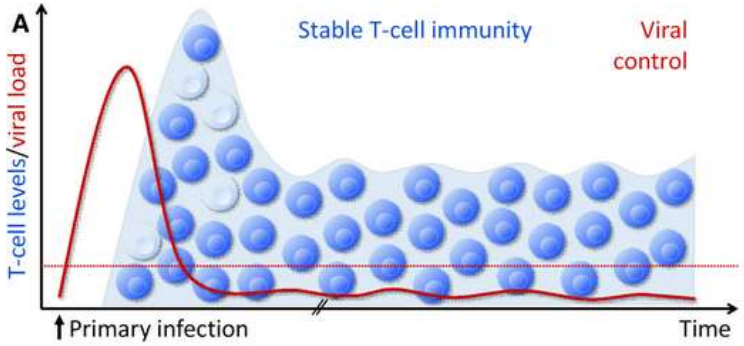


Chemotherapy or HSCTR

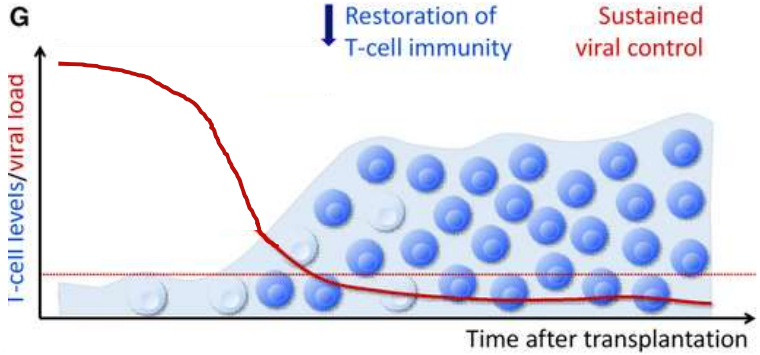


Increasing lymphocyte counts and the appearance of ADV-specific CD4 and CD8 T cells have been correlated with clearance of viremia.

immunocompetent



HSCTR



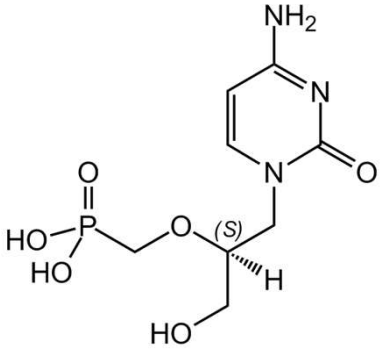
HAdV-specific Immunity

- ✓ Detectable immunity reflects ongoing viral exposure, explaining the particular susceptibility of immunocompromised children for infectious complications.
- ✓ **The functional role of HAdV-specific T-cells** is supported by results of adoptive HAdV-specific T-cell transfer that successfully **prevented** or **cleared** HAdV replication in pediatric HSCT recipients. (*Papadopoulou A et al. Sci Transl Med 2014; 6(242): 242–283.)*
- ✓ Little evidence supports surveillance for HAdV-specific T-cells after SOT, but its application would reasonably be focused on pediatric patients. (*Florescu DF, et al. Transplantation 2010; 90(2): 198–204.)*

Risk factor for HAdV disease

- ✓ Very young age (<5 years)
- ✓ T-cell depletion
- ✓ Immunosuppression

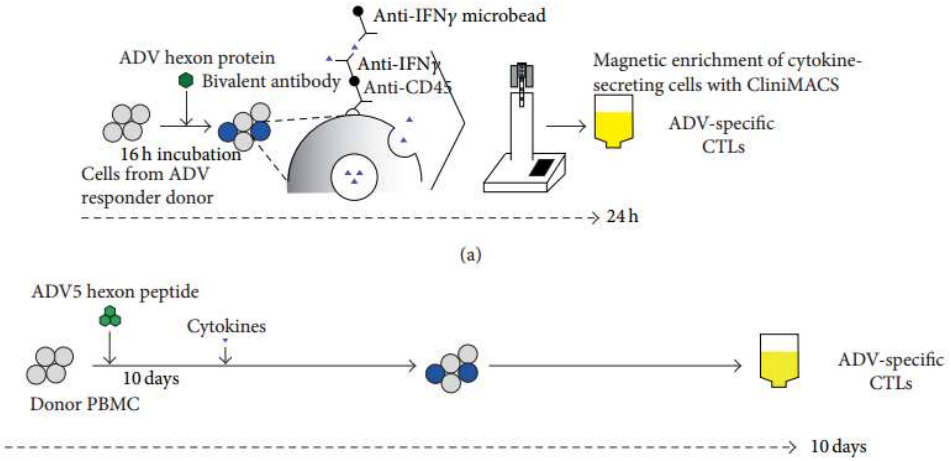
Treatment and Control



- ✓ Cidofovir (i.v) → (⚠ side effects on kidney)

Risk of renal toxicity was 26% in HSCTR and most of toxicity was mild (Ljungman et al., Bone Marrow Transp 2003;31:481-486)

- ✓ Infusion of donor derived HAdV-specific T-Cells (only in experienced centers)
- ✓ Reduce immunosoppression (if possibile)



Others

- ✓ Ribavirin (not reccomended)
- ✓ Brancidofovir ?? Only case reports so far

Because of toxicity and limited effectiveness, cidofovir is still not ideal, but, when used as a **preemptive therapy**, it is a reasonably safe option to buy time until immune recovery.

HAdV DNA load: Frequency of monitoring

Early detection of HAdV viremia is helpful for starting therapy within a certain timeframe before the occurrence of disease symptoms.

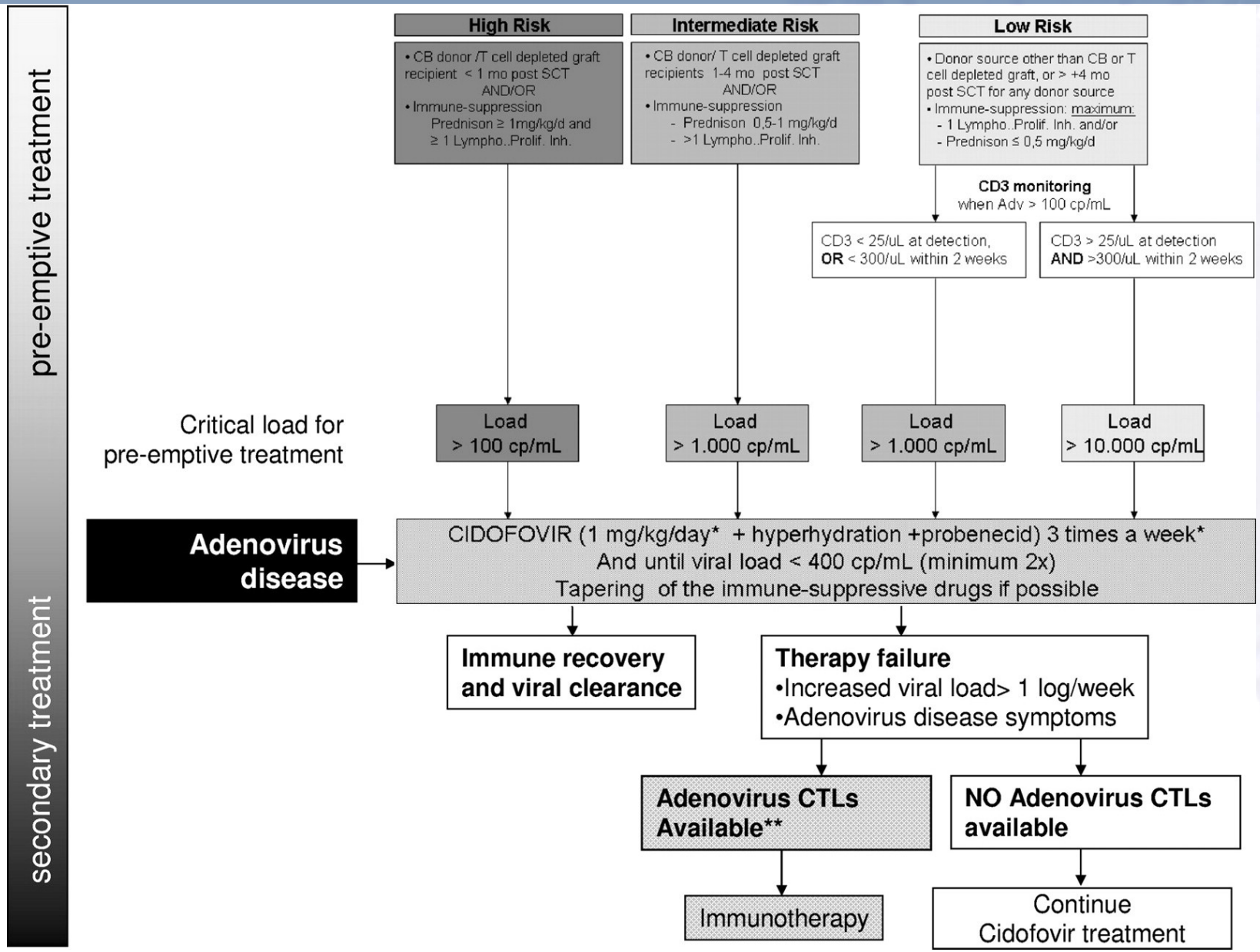
The monitoring of HAdV load is based on stratification of patients based on risk.

- ✓ Low risk – HSCT - family haploidentical donor
  No monitoring, only based on clinical signs

- ✓ Medium risk – HSCT – Match Unrelated Donor (MUD)
  Ones at month up to to 100 days after TX

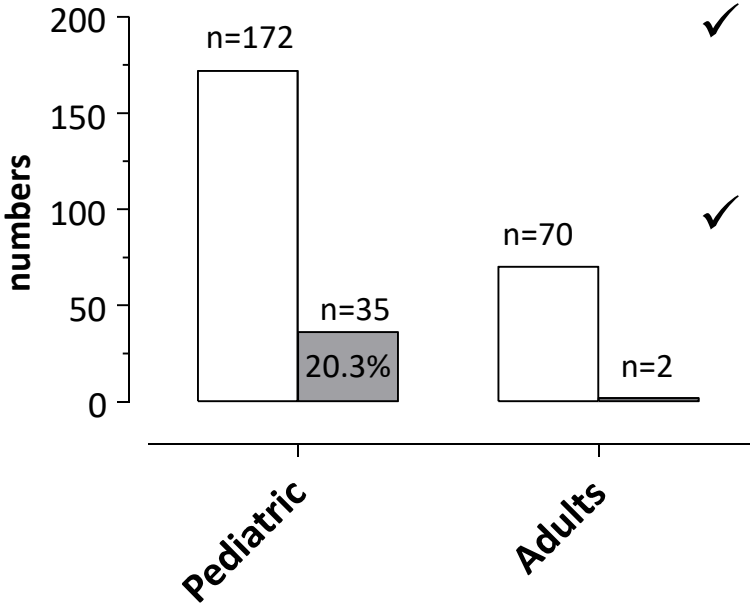
- ✓ High risk – HSCT- cord blood and T cell–depleted graft recipients
  Ones a week up to 100 days after TX and

Treatment guideline: HSCT recipients



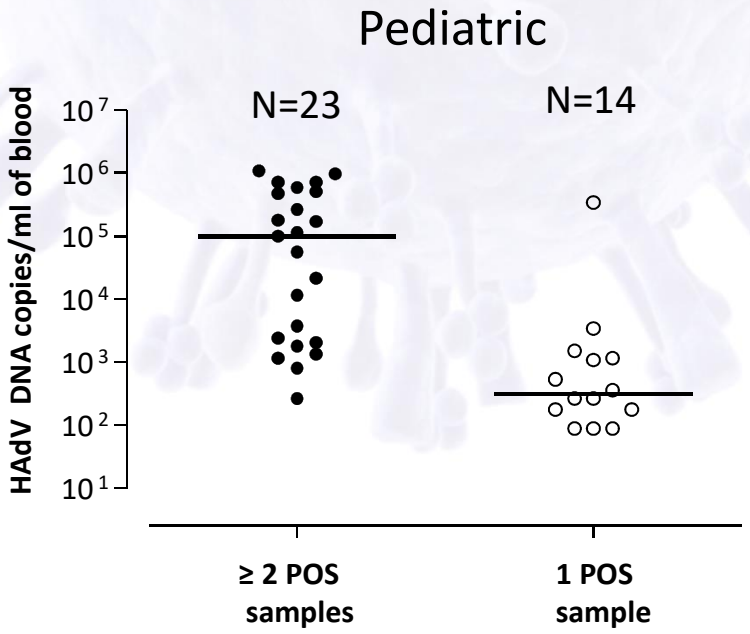
Caroline A. Lindemans et al. Blood 2010;116:5476-5485

Adenovirus infection in HSCTR or in chemotherapy: Our experience 2015-2017



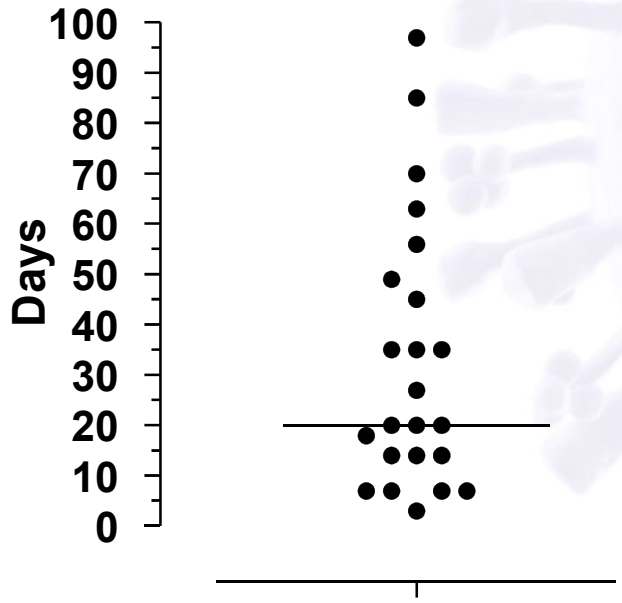
- ✓ A total of 35/172 (20.3%) pediatric patients and 2/70 (2.9%) adults patients had at least one positive blood sample.
- ✓ Among pediatric patients 33/35 (94.3%) had a single episode of HAdV infections, while 2/35 (5.3%) had two HAdV episodes.

In 14/37 (37.8%) HAdV episodes only one sample was positive, while in 23/37 (62.2%) episodes at least 2 samples were positive.



Adenovirus infection in HSCTR or in chemotherapy: Our experience 2015-2017

Median duration of HAdV episode: 20 days (range 3-90 days)

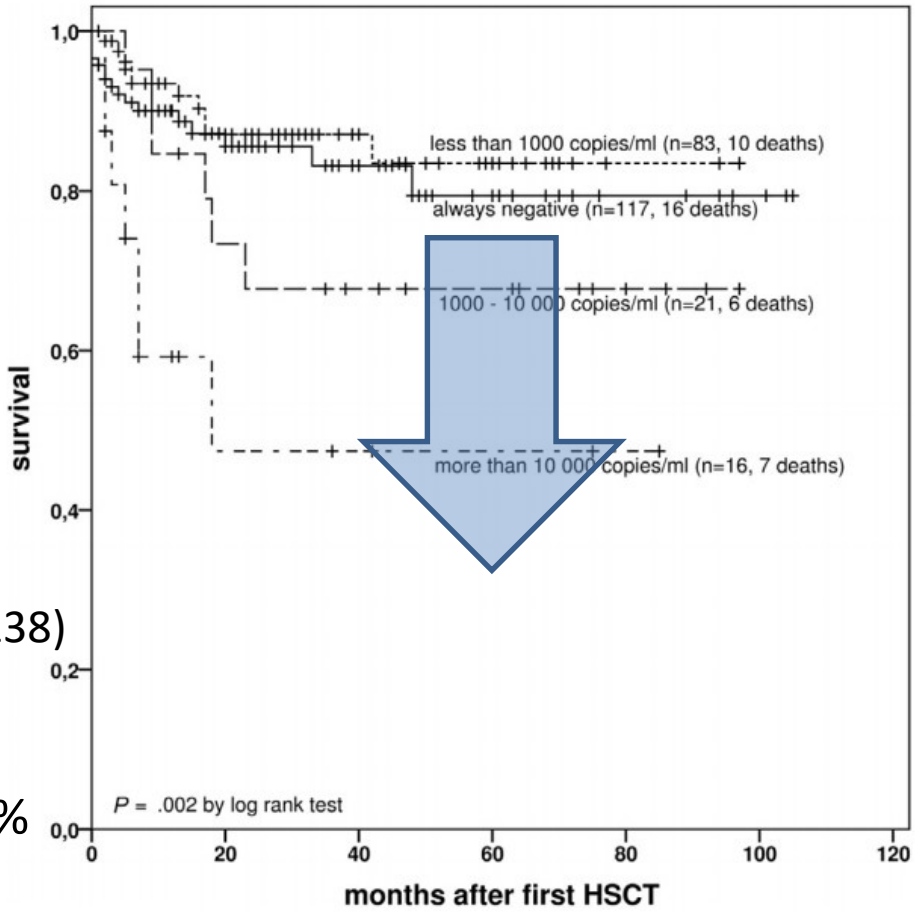


Adenovirus screening in pediatric HSCTR

Biol Blood Marrow Transplant 20 (2014) 250–256

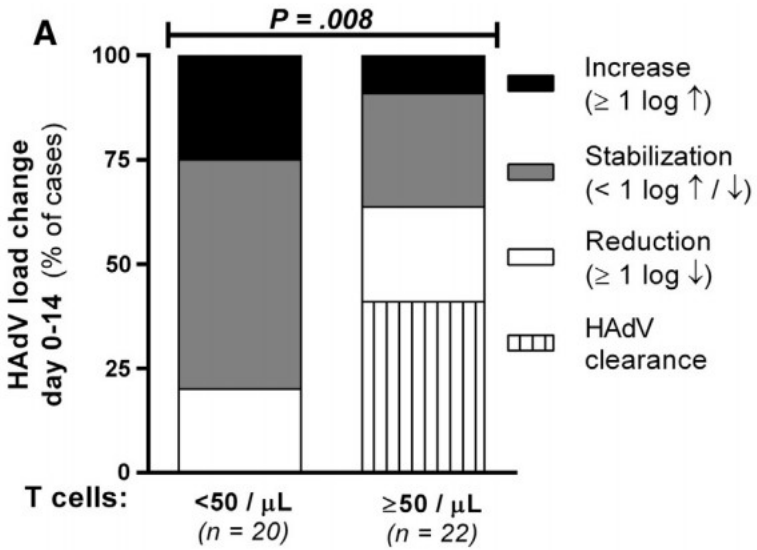
Patient, Virus, and Treatment-Related Risk Factors in Pediatric Adenovirus Infection after Stem Cell Transplantation: Results of a Routine Monitoring Program

Martin Mynarek [1,2], Tina Ganzenmueller [3], Annika Mueller-Heine [4], Christopher Mielke [1], Andrea Gonnermann [4], Rita Beier [1], Martin Sauer [1], Britta Eiz-Vesper [2,5], Ute Kohstall [6], Karl-Walter Sykora [1], Albert Heim [3], Britta Maecker-Kolhoff [1,2,*]



- ✓ Single center 2003-2012 (GER)
- ✓ Prospective weekly HAdV screening (n=238)
  - Mostly type A31, C1, C2
- ✓ HAdV load >1000 DNA copies/ml in 15.5%
- ✓ Limited direct mortality 0.84%
- ✓ peak HAdV blood levels of >10,000 copies/mL were an independent risk factor of poor overall survival.
- ✓ Cidofovir i.v. treatment – Possibily stabilized/decreased HaDV load by 1 $\log_{10}$

HAdV load with Cidofovir *vs* T-cell Recostitution



Biol Blood Marrow Transplant 21 (2015) 293–299

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Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

The Effect of Cidofovir on Adenovirus Plasma DNA Levels in Stem Cell Transplantation Recipients without T Cell Reconstitution

Gertjan Lugthart*, Marloes A. Oomen, Cornelia M. Jol-van der Zijde, Lynne M. Ball, Dorine Bresters, Wouter J.W. Kollen, Frans J. Smiers, Clementien L. Vermont, Robbert G.M. Bredius, Marco W. Schilham, Maarten J.D. van Tol, Arjan C. Lankester

- ✓ Children (n=36 4,5 yrs) – pediatric allo HCT in Leiden (NL) 2003-2012
- ✓ Monitor weekly: HAdV DNA load, T-cells (CD3+, CD14-) and NK cells (CD56+, CD14-)
- ✓ HAdV clearence correlated with ↑ T-cells
- ✓ Cidofovir at 1mg/kg 3x/wk only stabilizes HAdV load

Take home messages

- ✓ Children >>> Adult and HSCT >>>SOT
- ✓ T-cell reconstitution remains essential for viral clearance.
- ✓ Patients with HAdV viremia after HSCT might benefit from cidofovir treatment through a stabilization of the HAdV load but depending lymphocyte reconstitution for HAdV elimination.
- ✓ Therefore, adoptive T-cell therapy should be considered in patients not responding to cidofovir treatment.
- ✓ For clinical decision-making, the combined weekly monitoring of blood HAdV DNA levels and lymphocyte reconstitution provides an objective tool for the guidance of personalized antiviral treatment and prevention of unnecessary exposure to cidofovir.

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