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# Diagnosis and treatment of human adenovirus infection following allogeneic stem cell transplantation

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## Summary

**Background** Human adenovirus (HAdV) infections are increasingly recognized as a frequent cause of potentially fatal infections in paediatric allogeneic stem cell transplantation (SCT) recipients.

**Aim** To analyse data in the field of diagnosis and treatment of human adenovirus infection following allogeneic haematopoietic stem cell transplantation.

**Materials/Methods** A review of PubMed references based on evidence-based recommendations and own experience.

**Results** Incidence of HAdV infections is higher in paediatric than in adult SCT recipients, which might be related to the high exposure to HAdV at young age, while HAdV-specific immunity has still to be mounted, especially in children receiving a T-cell depleted graft and/or a graft of another than an HLA-genotypically identical related donor. In subsequent retrospective and prospective studies evidence has been provided that monitoring of serum/plasma by RQ-PCR is a sensitive tool for the recognition of patients at risk of potentially fatal infection, and that quantification of HAdV DNA is instrumental to make decisions on clinical intervention, and to accurately monitor the response to antiviral therapy. Several antiviral drugs (ribavirin and cidofovir) are being used to treat HAdV infections and variable efficacy has been reported. Reports on possible clinical efficacy of drugs are often biased, because of the heterogeneity of patients and lack of information about the level of simultaneous immune reconstitution. Data from several retrospective and prospective studies have demonstrated that lymphocyte recovery is essential for the elimination of HAdV infection.

**Conclusions** Based on current knowledge, boosting of immunity by tapering of immunosuppression or infusion of lymphocytes from the donor seems to be an essential element in treatment of patients at risk of HAdV viraemia. Simultaneous analysis of lymphocyte reconstitution will further improve the identification of individuals that will require and benefit most from the immunotherapeutic interventions.

**Key words** **human adenovirus infection • allogeneic HSCT**

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## Background

Human adenovirus (HAdV) infections are increasingly recognized as a frequent cause of potentially fatal infections in paediatric allogeneic stem cell transplantation (SCT) recipients. Currently, 51 serotypes of HAdV are known which are grouped into six species (A–F). In normal individuals HAdV infections may present in various ways, affecting mainly the respiratory and intestinal tract. Generally, these HAdV infections are well controlled by the innate and adaptive immune system. The incidence of HAdV infections is higher in paediatric than in adult SCT recipients, which might be related to the high exposure to HAdV at young age, while HAdV-specific immunity has still to be mounted. The highest incidence of HAdV infections following SCT was found in children receiving a T-cell depleted graft and/or a graft of another than an HLA-genotypically identical related donor [1].

HAdV infections are not easily diagnosed and the development of a severe infection cannot be predicted by standard culture techniques. Similar to what has been demonstrated for several human herpes viruses, it was first shown several years ago that the appearance of HAdV DNA in serum preceded the development of a severe or fatal HAdV infection [2]. In subsequent retrospective as well as prospective studies evidence has been provided that monitoring of serum/plasma by real-time quantitative PCR (RQ-PCR) is a sensitive tool for the recognition of patients at risk of a potentially fatal infection.[3–5] In addition, evidence has been provided that quantification of HAdV DNA is instrumental to make decisions on clinical intervention, and to accurately monitor the response to antiviral therapy.

Several antiviral drugs (esp. ribavirin and cidofovir) are being used to treat HAdV infections and variable efficacy has been reported. Susceptibility of clinical isolates to both antiviral drugs has been demonstrated *in vitro*. However, in the case of ribavirin susceptibility *in vitro* was restricted to subgroup C viruses only [6]. Reports on the possible clinical efficacy of the drugs are often biased because of the heterogeneity of the patients and the lack of information about the level of simultaneous immune reconstitution. In our experience, ribavirin, when started in the early phase of viraemia, lacks the potential to effectively control disseminating HAdV (including subgroup C) infections [7]. In the case of cidofovir treatment, temporary control of HAdV dissemination has been observed. In our experience, persistent control and subsequent clearance of HAdV infection in cidofovir treated patients has only been documented in those SCT recipients with stable lymphocyte reconstitution.

## Aim

To analyse data in the field of diagnosis and treatment of human adenovirus infection following allogeneic haematopoietic stem cell transplantation.

## Materials and Methods

References were retrieved using the online database of the National Library of Medicine (PubMed; *http://www.ncbi.nlm.nih.gov/PubMed*). Terms used included: human adenovirus infection, allogeneic HSCT. The retrieved references were supplemented by references from the author's own database.

## Results

Data from several retrospective and prospective studies have demonstrated that lymphocyte recovery is essential for the elimination of HAdV infection [8,9]. Low lymphocyte counts at the onset of infection were predictive of HAdV viraemia. Survival of patients with HAdV viraemia was associated with an increase in lymphocyte counts during the first weeks after infection. In these patients, HAdV-specific CD4+ T cell responses, as well as increases in titres of neutralizing antibody, were detected after clearance of

HAdV. Notably, in a significant number of patients lymphocyte recovery during HAdV infection and subsequent clearance was exclusively represented by expansion of NK cells (Verhoeven et al, manuscript submitted). These NK cells displayed an activated phenotype indicating that the NK cells might have contributed to the control of HAdV infection.

## Discussion

Based on current knowledge, boosting of immunity by tapering of immunosuppression or infusion of lymphocytes from the donor seems to be an essential element in the treatment of patients at risk of HAdV viraemia. Obviously, infusion of unmanipulated donor lymphocytes will bear a significant risk of inducing serious graft-versus-host disease (GvHD). To lower the risk of alloreactivity, infusion of allodepleted donor T cells has been studied in HLA-mismatched haploidentical SCT, although so far with limited efficacy against HadV infection [10]. Enrichment for HAdV-specific T cells using *in vitro* culture systems appears to be a promising and feasible alternative approach. Recently, several of these methods have been reported. These include the generation of HAdV specific T cells using 1) HAdV lysate [11], 2) genetically modified antigen-presenting cells expressing several viral epitopes including HAdV [12], and 3) a pool of conserved HAdV peptides [13]. Clinical experience with the first two methods seems promising. We are currently preparing the clinical use of HAdV-specific T cells obtained after enrichment by the peptide stimulation procedure. In addition to the adoptive transfer of HAdV-specific T cells it cannot be excluded that infusion of purified NK cells may exert a beneficial antiviral effect without the concomitant risk of inducing GvHD.

Similar to what has been reported for human herpes viruses, monitoring of HAdV infection by RQ-PCR analyses on serum/plasma samples seem to be a reliable and sensitive tool to identify individuals at risk for progressive infection.

## Conclusions

Data from several retrospective and prospective studies have demonstrated that lymphocyte recovery is essential for the elimination of HAdV infection. Simultaneous analysis of lymphocyte reconstitution in these patients will further improve the identification of individuals that will require and benefit most from the aforementioned immunotherapeutic interventions.

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