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Adenoviral Infection – Common Complication Following Hematopoietic Stem Cell Transplantation

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1. Introduction

Allogeneic stem cell transplantations (allo-SCT) increase in recipients the risk of life-threatening opportunistic infections caused by different pathogens. In recent years, adenoviruses (AdV) have been recognized as an emerging pathogen causing serious post-transplant complications with very high mortality (Fowler et al., 2010). Hematopoietic stem cell transplantation is a standard treatment in malignant and non-malignant disorders of bone marrow, solid tumors, immunodeficiencies, and autoimmune disorders (Gyurkocza et al., 2010; Ljungman et al., 2010). Intensive immunosuppressive treatment for prevention both of graft rejection and graft-versus-host disease (GvHD) and the therapy of the latter one, makes the patients at risk of developing opportunistic infections. The immune reconstitution period following hematopoietic transplantation is therefore accompanied by high incidence of adenoviral infections due to profound immunodeficiency (Echavarri'a, 2008; Gyurkocza et al., 2010). Lack of immunological competence caused by invasive cancer therapy and conditioning procedures results mainly in lowering the number of CD3+ lymphocytes in peripheral blood. Lymphopenia increases patient's risk for de novo infection or reactivation of a latent virus that mainly occurs during the early post-transplantation period and usually leads to disseminated disease. The time of the infection onset is also vital, because AdV infections occurring after day +100 from the transplantation do not seem to be associated with life-threatening disease (Lion et al., 2003). According to different retrospective and prospective studies, adenovirus has been found to infect from just a few percent to a several dozen percent of patient post-HSCT (Akiyama et al., 2001; Arnberg et al., 2002; Benko et al., 2000; Ebner et al., 2005; Howard et al., 1999; Mahr & Gooding, 1999; Lauer et al., 2003; Robin et al., 2007; Rutala et al., 2006; Stone et al., 2003; Walls et al., 2003; Watzinger et al., 2004) with mortality in disseminated disease reaching even 80% (Akiyama et al., 2001; Mori et al., 2003; Russell, 2000; Walls et al., 2003; Watzinger et al., 2004). Adenoviruses are commonly detected in stool, pharyngeal swabs, urine and

whole blood in HSCT recipients usually causing limited infections of the respiratory tract, gastrointestinal system and urinary tract but sometimes progress to disseminated disease affecting many organs and whole systems, too (Watcharananan et al., 2010). The diagnosis of adenoviral infection can be difficult due to complexity of the multiorgan disease non-specific symptoms resembling other infections or acute graft versus host disease (aGvHD). This review describes adenoviral infections in recipients of hematopoietic stem cell transplantations and focuses attention on infection course, risk factors, possible complications, diagnostic methods for adenovirus identification and therapy strategies.

2. Human adenoviruses-general description

The original virus was isolated in 1953 from surgically removed adenoids from a child by Rowe et al. (Huebner et al., 1954; Rowe et al., 1953), thus it has been called adenovirus. Adenoviruses are ubiquitous in the environment contaminated with human feces or sewage. To date, 54 antigenic types of human adenoviruses belonging to genus *Mastadenovirus* and family *Adenoviridae* have been described, and over half of them have been recognized as pathogenic for humans. They have been divided into seven species (from A to G) on the basis of their morphological, hemagglutinating and oncogenic properties as well as their genome size, DNA sequence and electrophoretic mobility of virion polypeptides (Table 1). Adenoviruses from species B and D were further subdivided into subspecies: B1, B2 and D1, D2 and D3, respectively. In addition to this classification several AdV genotypes can be identified within previously mentioned serotypes (Echavarri'a, 2008, 2009; Ebner et al. 2005; Stone et al., 2003; Wadell et al., 1980).

Adenoviruses are non-enveloped, 70-90 nm in diameter particles with icosahedral symmetry. The capsid is composed of 252 capsomers: 240 hexamers and 12 pentons (Russell, 2009; Rux et al., 2003). Several different proteins in AdV particle can be distinguished, but three major proteins such as hexon, penton base and fiber protein create the main capsid structure. The hexon is a homotrimer of three identical polypeptide chains (pII) formulating a triangular vertex of surface loops. It is the most abundant protein in adenoviral particle (more than 80% of AdV2 capsid protein) formulating hexon molecules symmetrically distributed in the capsid (Burnett, 1999). The hexon possess the group- and type-specific determinants which are utilized in diagnostic procedures such as ELISA test, hemagglutination inhibition and serum neutralization. Occurrence of these specific antigen determinants on a viral surface is determined by the presence of variable and hypervariable regions (HVRs) in nucleotide sequence of the hexon gene. Since today, nine hypervariable regions (HVR1-HVR9) have been distinguished (Crawford-Miksza & Schnurr, 1996; Rux et al., 2003). They are situated within the loops at the top of the hexon molecule, hence can be utilized in diagnostic tests. The hexon protein is also an immunodominant T-cell target, however other structural components of the virion may also be immunogenic. Twelve penton bases (pIII) creating capsid vertex provide the basis for radially projecting trimeric fibers (pIV) of different lengths according to the AdV serotype (10-37 nm). The external end of the fiber is terminated with a C-terminal knob which posses several antigen determinants participating in cell receptors binding, hemagglutination in vitro and virus internalization into a host cell (Burmeister et al., 2004; Cusack, 2005; Echavarri'a, 2008). Genetic information of adenoviruses is encoded by about 34-36 kb double stranded linear DNA, containing more than 50 coding regions (Echavarri'a, 2008).

Species	Serotypes	Features#
A	12, 18, 31	Highly oncogenic GC%: 47-49 FL: 28-31nm HA: rat (incomplete)
B	B1: 3, 7, 16, 21, 50 [†] B2: 11, 14, 34, 35	Poorly oncogenic GC%: 48-52 FL: 9-11 nm HA: Rhesus
C	1, 2, 5, 6	Nononcogenic GC%: 55-59 FL: 23-31nm HA: rat (incomplete)
D	D1: 9, 19 D2: 15, 22 D3: 8, 10, 13, 17, 20, 23-30, 32, 33, 36-39, 42-49, 51 [†] , 53, 54 [*]	Nononcogenic GC%: 54-59 FL: 12-13 nm HA: rat, mouse, human, dog, pig, monkey
E	4	Nononcogenic GC%: 57 FL: 17 nm HA: Rat (incomplete)
F	40, 41	Nononcogenic GC%: 51-59 FL: 29 nm HA: rat (atypic)
G	52	ND

Data adopted from references: (Echavarria, 2006; Hierholzer, 1992; Kaneko et al., 2009; Wadell et al., 1980; Walsh et al., 2010; and from National Center for Biotechnology Information database (<http://www.ncbi.nlm.nih.gov>);

[†] according to Ebner et al. (2005) serotype 50 was reclassified into species D and serotype 51 into species B;

^{*} firstly described in year 2009, (proposal) (Kaneko et al., 2006);

ND- not determined, FL-fiber length, HA- hemagglutination;

Table 1. Adenovirus classification and general features.

3. Virus transmission in stem cell recipients

The most common source of adenoviral infection after haematopoietic stem cell transplantation is reactivation of a latent virus persisting in lymphocytes of peripheral blood, in adenoids, intestines and kidneys through low-grade replication. AdV1, AdV2 and AdV5 (C) are the most common serotypes remaining latent after primary exposure in the childhood (Lee et al., 2010; Malekshahi et al., 2010). They also play the significant role in development of AdV infections after SCT, therefore confirming the role of virus reactivation during an early post-transplant period. The next source of AdV infection in stem cell recipients might be the virus transmission from the positive donor to the negative recipient.

There are many reports confirming more than 4-fold increased risk of primary adenoviral infections in HSCT recipients grafted from previously infected (seropositive) donors in comparison to uninfected donors (Runde et al., 2001; Walls et al., 2003).

Adenoviruses can spread directly through respiratory droplets hence upper respiratory tract infections occur very often. They are able to replicate in the environment of the gastrointestinal tract due to their resistance to low pH of a stomach and proteolytic enzymes in gastrointestinal secretions, thus allowing the virus to achieve a high viral load in the gut. Because viral loads in stool samples of infected patients achieve the highest levels in comparison to other clinical materials, it can be suggested that fecal-oral transmission is the most common route of infection spread (Baldwin et al., 2000; Chakrabarti et al., 2002; Hale et al., 1999; Howard et al., 1999; Jeulin et al., 2011; Lion et al., 2010; Rutala et al., 2006).

There are also some reports suggesting possible virus spread via unsterile instruments and medical equipment, direct staff-to-patient transmission or inadequate air conditioning in the post-transplantation ward. Adenoviruses are strongly resistant to chemical or physical agents and adverse pH conditions and are able to remain infectious for a long period outside of the body, but this route of infection can be prevented by disinfection procedures in transplantation units (Artieda et al., 2010; Gerber et al., 2001; Gray, 2006; Leruez-Ville et al., 2006; Lessa et al., 2007; Romero et al., 2010).

4. Pathomechanism and clinical manifestations of adenoviral infections

Individual serotypes of *Adenoviridae* family show varied tissue tropism. They infect post-mitotic cells of even highly differentiated tissues such as skeletal muscles, lungs, brain and heart muscle (Russell, 2009; Zhang & Bergelson, 2005). The infection cycle is divided into two stages involving virus adsorption and internalization (Figure 1). Attachment to the host cell receptor and virus entry occurs via the fibre protein and penton base. Majority of adenoviruses (mainly those from species A, C, D, E and F) use the coxsackie-adenovirus receptor (CAR) which is a member of the immunoglobulin family and is situated on a surface of most human tissues such as heart muscle, brain, liver, pancreas, intestines, lungs and kidneys (Dehecchi et al., 2001; Raschperger et al., 2006; Russell, 2000, 2009; Rux et al., 2003; Zhang & Bergelson, 2005). In human cells lacking CAR receptor, other cell molecules are used for virus attachment. For example, AdV2 and AdV5 are able to bind the α -domain of MHC class I (*Major Histocompatibility Complex Class I*) molecule or heparan sulfate glycosaminoglycans (HS GAG). Additionally, these serotypes are capable to recognize and interact with vascular cell adhesion molecule-1 (VCAM-1) which is situated on atherosclerotic lesions of vascular endothelium. More rarely, $\alpha(2-3)$ - sialic acid, sBAR and sB2AR and CD46, CD80, CD86 are used (mainly serotypes: 3, 7, 8, 11, 14, 16, 19, 21, 37, 34, 35 and 50) (Benko et al., 2000; Burmeister et al., 2004; Chu et al., 2001; Sharma et al., 2009; Wang et al., 2007; Zhang & Bergelson, 2005). Virus binding to the cell receptor and interaction between penton base and integrins on the target cell induce internalization of the viral particle into the host cell by clathrin-coated vesicles and endosomes. Several proteins and intra-endosomal mechanisms lead to disintegration of virus particle and subsequently to viral core release. Viral DNA is transported to the cell nucleus by microtubule-mediated transport and undergoes DNA transcription and replication (Cusack, 2005; Kelkar et al., 2004; Russell, 2000). Replication process is divided into an early and late phase. Sometimes, an intermediate phase is also marked out. The early phase (6-8 hours) includes virus

penetration into the host cell, transport of viral DNA to cell nucleus and transcription/translation of the “early genes” such as E1A, E1B, E2, E3, E4. The products of the early genes act as regulatory factors. They change cell functions to facilitate further replication of the virus and transactivate other early transcription units. Second phase of AdV replication leads to transcription and translation of the “late genes” (L1-L5) encoding mainly structural proteins of the virion shell. Assembly and maturation of AdV particles take place in the nuclei of infected cells. The whole process usually takes only 4-6 hours (Greber et al. 1997, Gonçalves & de Vries, 2006; Matthews & Russell, 1998; Russell, 2000).

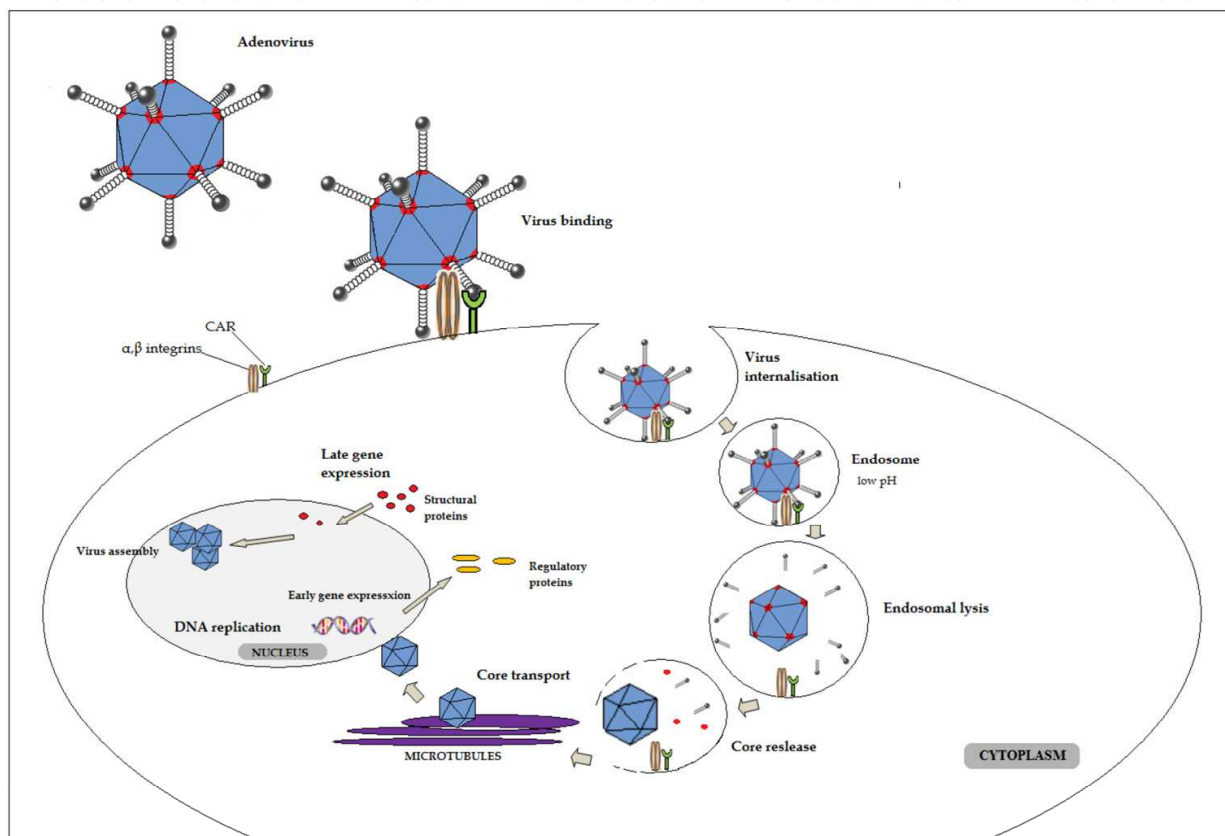


Fig. 1. AdV infection cycle. An interaction between penton base and α,β integrins induces internalization of viral particle into the host cell. Intra-endosomal mechanisms lead to disintegration of virion shell. Viral DNA is transported into the cell nucleus providing material for DNA replication. The early phase of replication includes expression of the “early genes” (E1-E4) acting as regulatory factors and facilitating virus replication. Second phase of AdV replication leads to expression of L1-L4 encoding mainly structural proteins determining virus assembly and maturation.

Adenoviral infection and active virus replication in the host cell can exert three different cytopathological effects. In most cases AdV infection leads to cell lysis. AdV genome contains at least four different coding regions (E1a, E4ORF4, E4ORF6/7 i ADP, which products can induce cell death and lysis (Braithwaite & Russell, 2001). Alternatively, after acute phase of the infection, the virus might remain in latent phase. Human adenoviruses, especially AdV1, AdV2, AdV5 from species C, possess the ability to prolonged persistence in adenoids, intestines, renal parenchyma and lymphocytes in peripheral blood with

periodic shedding of virus in feces and respiratory secretions (Akiyama et al., 2001; Braithwaite & Russell, 2001; Echavarría, 2008; Watzinger et al., 2004). The third possible outcome of adenoviral infection is an oncogenic transformation of infected cells, that is observed in animal models (Russell, 2009).

Primary adenoviral infections affect predominantly pediatric population with more than 50% of children infected before the age of five (Cooper et al., 2003). Children are often infected with adenovirus types 1, 2, 3, 4, 5, 7 and 30 which are the most common causes of tonsillopharyngitis and pneumonia (Carballal et al., 2002; Faden et al., 2005). These antigenic types are also the most frequent in recipients of SCT indicating virus reactivation or droplets transmission as most reliable routes of virus spread. AdV infections in immunocompetent humans are usually asymptomatic, localized and tend to be self-limited. They are restricted to the respiratory system, genitourinary and gastrointestinal tract infections, occasionally affecting conjunctiva and cornea. Recipients of HSCT and other immunocompromised patients present much broader spectrum of clinical manifestations. According to different studies, the estimated rate of AdV infection after HSCT ranges from 3–47% (Akiyama et al., 2001; Arnberg et al., 2002; Ebner et al., 2005; Howard et al., 1999; Lauer et al., 2004; Mahr & Gooding, 1999; Rutala et al., 2006; Stone et al., 2003; Walls et al., 2003; Watcharananan et al., 2010; Watzinger et al., 2004;) with mortality reaching up to 80% in patients with disseminated disease (Akiyama et al., 2001; Kaneko et al., 2009; Russell, 2000; Walls et al., 2003; Watzinger et al., 2004). The wide range in reported AdV incidence can result from different diagnostic methods, variety of body sites analyzed as well as demographic differences and lack of strict criteria for defining adenovirus infection or disease. AdV infections in immunocompromised patients tend to be invasive. The most common are infections of AdVs from subgroup C, followed by A, B and D. They cause exudative pharyngitis, acute respiratory disease epidemics, febrile laryngitis, conjunctivitis, keratoconjunctivitis, necrotizing enterocolitis, pharyngeal-conjunctival fever and hemorrhagic cystitis. Less frequent are testitis, nephritis, arthritis, myocarditis and pericarditis. Infections of the gastrointestinal tract are especially frequent in young children and include gastroenteritis, mesenteric lymphadenitis, intussusception, hepatitis, and appendicitis (Table 2) (Akiyama et al., 2001; Arnberg et al., 2002; Benko, 2000; Chakrabarti et al., 2000; Chmielewicz et al., 2005; Ebner et al., 2005; Echavarría, 2009; Ephros et al., 2009; Howard et al., 1999; Ison, 2006; Jones et al., 2007; Kaneko et al., 2009; Lim et al., 2005; Mori et al., 2003; Robin et al., 2007; Runde et al., 2001; Venard et al., 2000; Walsh et al., 2009). Most adenoviral infections in patients following HSCT occur during an early post-transplantation period, within 2-3 months (Ephros et al., 2009; Lion et al., 2010; Watcharananan et al., 2010). Adenovirus infections in patients after stem cell transplantations can occur throughout the year but there are some reports suggesting seasonal fluctuations of adenoviral infections indicating greater incidence in autumn and winter, 52-70% (Bil-Lula et al., 2010).

An intensity of virus replication depends on a site of infection. The highest viral loads are observed in gastrointestinal tract infections (even more than 10^8 copies/g of stool) and in upper respiratory tract infections (10^4 - 10^6 copies/ml). Whole blood viraemia remains at a moderate level and usually does not exceed 10^3 - 10^4 copies per ml, whereas in plasma samples only trace amounts of AdV particles can be detected ($< 10^2$ copies/ml). Some of patients with moderate viraemia are able to self-eliminate the virus within 2-4 weeks. However most patients presenting disseminated infections ($> 10^7$ copies/ml) die due to

adenoviral infection within short time (Ephros et al., 2009; Heim et al., 2003; Lion et al., 2003; Walls et al., 2005).

Clinical symptoms	Involved serotypes
Acute follicular conjunctivitis and keratoconjunctivitis	1, 3, 4, 5, 7, 8, 9, 11, 16, 19, 26, 27, 30, 37, 53, 54
Acute hemorrhagic cystitis (HC)	3, 7, 11, 21, 34, 35
Acute respiratory disease	1, 2, 3, 4, 5, 6, 7, 14, 21, 30
Exudative pharyngitis	1, 2, 3, 5, 7
Gastroenteritis	1, 2, 12, 16, 18, 31, 40, 41, 52
Hepatitis, appendicitis	1, 2, 3, 5, 7
Intussusception	1, 2, 5
Meningitis, encephalitis	2, 3, 7, 12, 32
Myocarditis	7, 21
Nephritis and kidney damage	11, 14, 34, 35
Pertussis-like syndrome	5
Pharyngitis	1, 2, 3, 5, 7
Pharyngoconjunctival fever (PCF)	3, 4, 7, 14
Pneumonia	1, 2, 3, 4, 7, 11, 14, 21, 30, 34, 35
Prolonged diarrhea	40, 41, 52
Ulcerative changes in the female genital organs, cervicitis	19, 37
Urethritis	1, 3, 4, 7, 14, 16, 19, 34, 35, 37, 50

Table 2. Clinical manifestations of adenoviral infection in stem cell transplant recipients (summary table).

5. Anti-viral response and viral immunoavoidance

Virus penetration into human organism induces both specific and non-specific response to infection. Firstly, virus by binding with the cell receptors activates congenital mechanisms of anti-viral defense. An induction of the inflammatory response stimulates interferon production by both immunocompetent and non-immunocompetent cells. Macrophages, natural killers (NK cells) and complement proteins are also involved in anti-adenovirus defense indirectly by killing infected cells or due to production of cytokins such as Il-1, Il-6 and TNF- α . Additionally, Smith et al. (2008) confirmed the role of the epithelial defensins which coat the capsid vertex of adenoviral particle and inhibit virus uncoating in cytoplasm of infected cell (Smith & Nemerow, 2008). Another way of virus elimination from the organism is induction of pro-apoptotic mechanisms in infected cells due to e.g. p53, TNF α and Bax proteins (Randall & Goodbourn, 2008; Russell, 2000, 2009; Smith & Nemerow, 2008). Very important role in viral clearance is played by acquired immunity mechanisms. The cellular response is limited to CD3+ cells activation (both helper and cytotoxic lymphocytes) which also produce TNF α and INF γ . Activation of CD8+ cells due to presentation of hexon determinants in MHC I complex leads to eradication of infected cells by means of cell perforation and lyses. This mechanism prevents virus replication and further spread of viral particles. The humoral response is focused on production of

neutralizing antibodies. The neutralizing antibodies recognize HVRs and the fiber determinants leading to agglutination of virus particles and interrupting infection of new cells. The presence of anti-adenoviral antibodies in patient serum grants permanent immunity against AdV (Baldwin et al., 2000; Crawford-Miksza & Schnurr, 1994; Leen et al., 2008; Russel, 2009; Rux et al., 2003; Schilham et al., 2002; Walls et al., 2003).

Intensity and length of immunosuppressive therapy are tailored to the risk of graft-rejection or graft versus host disease.

The prevention and therapy of GvHD is crucial in allogeneic HSCT recipients, which explains its intensity and diversity by combining drugs (cyclosporine, tacrolimus, mycophenolate mofetil) with biological agents (OKT-3, alemtuzumab, ATG) or graft engineering methods like T-cell depletion/CD34+ positive selection. Immunosuppression determines stable engraftment and prevents from GvHD, but increases risk of disease relapse or opportunistic infections, due to depletion of donor lymphocytes necessary for graft-versus-tumor (GVT) effects and delayed immune reconstitution (Gyurkocza et al., 2010).

Immune defense against adenoviral infections is hampered by viral abilities for avoidance of both humoral and cellular host immune response. By means of E1A (early region 1A) and VARNAs (virally associated RNAs) they developed the ability to inhibit human interferons α and β . The product of E1B inhibits apoptosis of infected cells. Moreover, product of E3 coding region can inhibit a transport of MHC I particles to the cell membrane disturbing viral antigens presentation to the cytotoxic lymphocytes (CLS) (Braithwaite & Russell, 2001; Lauer et al., 2004; Mahr & Gooding, 1999; Russell, 2000; Stone et al., 2003). Some of E3 products interfere with pro-inflammatory and cytolytic activity of TNF or remove Fas and TRAIL receptors from cell surface (Echavarria, 2009). The fact, that these proteins are expressed during early stage of transcription, protects infected cells from immune surveillance.

6. Risk factors for development of adenoviral infection after HSCT

The hematopoietic stem cell transplantation recipients constitute a group of patients with an extremely high risk of death due to opportunistic infections, and among them the AdVs are accounted to most challenging pathogens responsible for fatal outcome. The problem of AdV infections after HSCT is a consequence of different factors affecting recipient's immunity. Development of graft versus host disease and its prophylaxis or therapy with potent immunosuppressants are the reasons for numerous opportunistic infections. The anti-leukemic efficacy and early complications of HSCT result from both intensity of the conditioning regimen and the graft-versus-leukaemia (GVL) effect. However, conditioning strategies with high doses of cytotoxic and immunosuppressive drugs lead to tissue damage, cytokine storm and profound impairment of patients immunity, thus increasing patient's risk of de novo infection or reactivation of latent adenovirus during a post-transplantation period. Reduced-intensity conditioning (RIC) regimens lower the risk for AdV infection due decreased organ damage and lower proinflammatory cytokines secretion, hence protecting the patient from aGvHD but maintaining an effect of GVL (Couriel et al., 2004; Gyurkocza et al., 2010; Hill & Ferrara, 2000; Pérez-Simón et al., 2002, 2005). The clinical course of AdV infection after HSCT is different from the one observed in immunocompetent individuals. AdVs usually cause permanent and stubborn infections in those patients because immunological response to adenoviruses following SCT is very poor. In rare situations, AdV

can be responsible for graft rejection or delayed implantation of stem cells (Hierholzer, 1992; Ison, 2006).

Risk factors affecting patient's susceptibility to adenovirus infections after stem cells transplantation are well known (Figure 2). Many reports indicate increased morbidity among recipients of allogeneic grafts from matched unrelated donors (MUD) in comparison to partially matched family donors (PMFD) (Baldwin et al. 2000; Bruno et al., 2003; Ebner et al., 2005; Gu et al., 2003; Hale et al., 1999; Howard et al., 1999; Ison, 2006; Legrand et al., 2001; Lion et al., 2003). An incidence of AdV infections and patient's mortality due to infection in this group reach about 5-47% and 60%, respectively (Hierholzer, 1992; Howard et al., 1999; Leruez-Ville et al., 2006; Lim et al., 2005; Robin et al., 2007; Runde et al., 2001; Venard et al., 2000; Walls et al., 2005). In recipients of autologous transplantations AdV infections prevalence is much lower, about 1-14% (Baldwin et al., 2000; Bruno et al., 2003; Hale et al., 1999; Howard et al., 1999; Teramura et al., 2004). Significant differences in occurrence of adenoviral infections are believed to result from more aggressive and longer immunosuppressive therapy after allogeneic transplantations (Walls et al., 2003). Lack of endogenous T-cell immunity makes patient more predisposing to development of adenoviral infection and disseminated disease with fatal outcome (Bil-Lula et al., 2010; Feuchtinger et al., 2008; Watcharananan et al., 2010). Therefore, delayed immune recovery after stem cell transplantation has critical impact on progression of adenoviral infections. Moreover, second allotransplantation also increases patient's susceptibility to AdV infection (Bruno et al., 2003).

Another risk factor for development of adenoviral infections in HSCT recipients is patient's age. There are many reports confirming that children and adolescents are at greater risk of adenovirus infection than adults (Robin et al., 2007; Walls et al., 2005). Greater susceptibility of younger patients may results from immaturity and worse efficiency of immune system in comparison to older recipients. Moreover, persistent infections are predominantly caused by AdV from species C, which are common etiological factor of adenoviral infections in a childhood. Combination of immunosuppression and young age of graft recipients can lead to intensified replication of adenoviruses and to greater viral load in clinical samples (more than 10^5 copies /ml) in comparison to adult recipient (viral load usually not exceeds 10^3 copies /ml) (Baldwin et al., 2000; Bruno et al., 2003; Chakrabarti et al., 2002; Howard et al., 1999; Heim et al., 2003; Ison, 2006; Robin et al., 2007; Walls et al., 2003).

The role of T-cells in controlling the AdV infection is unquestionable. The graft engineering methods involving ex-vivo removal of T-cells by CD34+ positive selection or by lymphocyte depletion are very effective in respect of GvHD reduction but cause profound long-term T-cell deficiency and function impairment. Adenoviral infections due to reactivation of latent virus are also reported more frequently (more than 70%) in recipients of manipulated grafts in comparison to those who received graft containing donor's lymphocytes (25%). Moreover, some reports suggested delayed recovery and lower overall survival in patients undergoing T-cells depletion (Chakrabarti et al, 2002; Ison, 2006; Lion et al., 2003; Venard et al., 2000; Walls et al., 2003, 2005).

The development and severity of graft versus host disease are typically identified independent risk factors for progression of adenoviral infection after stem cell transplantation. The mechanism of GvHD induction is multifactorial and despite intensive research only moderately understood, the incompatibilities in HLA and in minor histocompatibility antigens (mHA) are generally recognized causes for its occurrence

(Gyurkocza et al., 2010). It was reported that moderate to severe aGvHD and its therapy may facilitate virus replication in recipients of SCT (Baldwin et al., 2000; Bil-Lula et al, 2010; Bruno et al., 2003; Ison, 2006; Robin et al., 2007; Runde et al., 2001; Watcharananan et al., 2010). GvHD requires immunosuppressive therapy which lowers the number of lymphocytes and hampers the immunity of the recipient, thus enabling adenoviral infections. A low lymphocyte count due to non-specific T-cell depletion or delayed T-cell reconstitution is considered as important predictor for detection of adenoviral infections. An inadequate humoral response due to B lymphocyte impairment contributes to greater susceptibility to AdV infection (Chakrabarti et al., 2000, 2002; Heemskerk et al., 2005). Some authors emphasize that presence of adenovirus in peripheral blood or plasma is an indicator of impending symptomatic adenoviral disease and multiorgan failure in patients undergoing HSCT. Chakrabarti et al. (2002) and others confirmed a strong correlation between the presence of adenovirus in whole blood/plasma and an increased mortality due to infection (9-86%) (Chakrabarti et al., 2002; Ebner et al., 2005; Echavarria et al, 2001; Lion

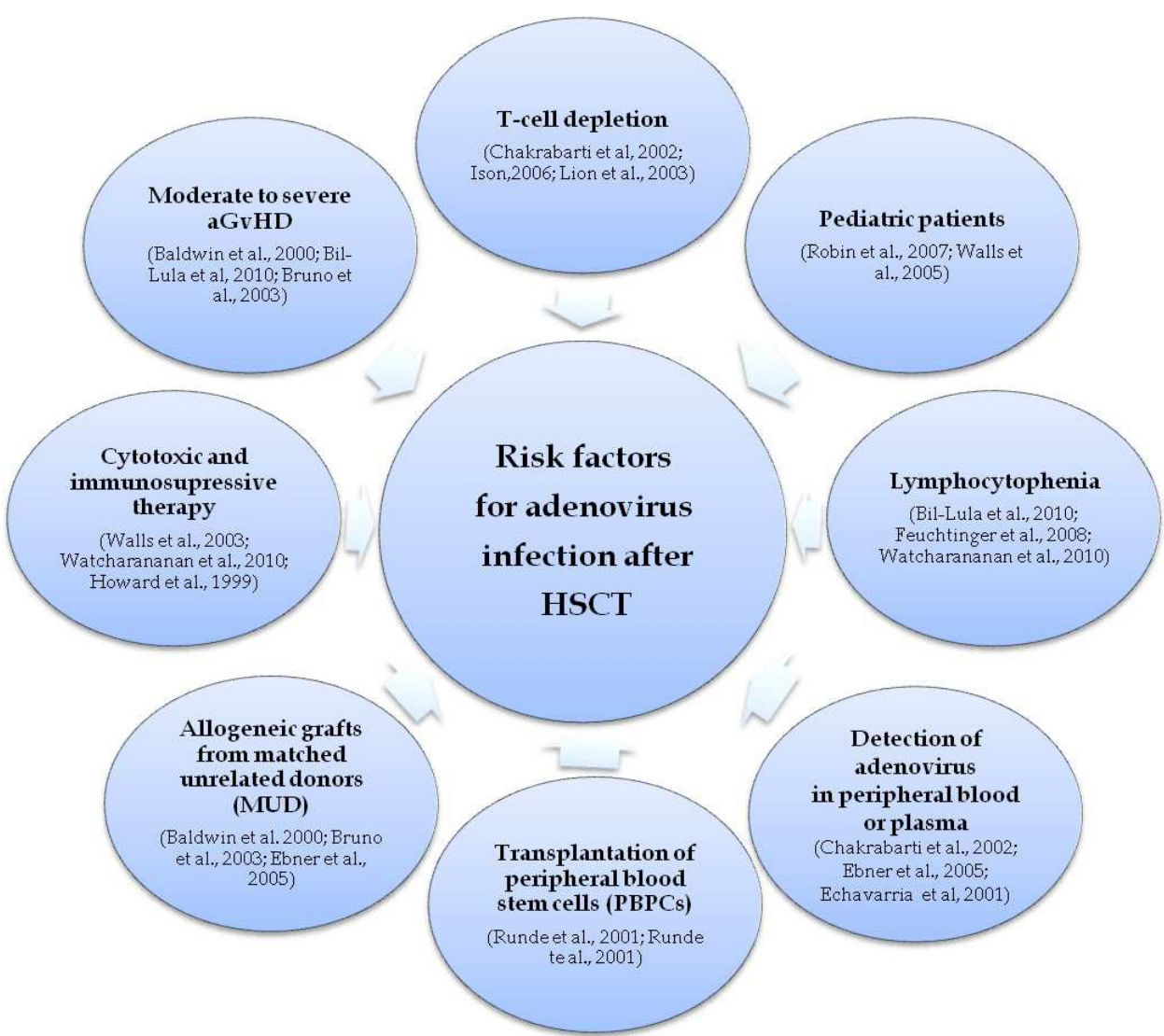


Fig. 2. Risk factors for adenoviral infections in patients after haematopoietic stem cell transplantation.

et al., 2003; Robin et al., 2007; Schilham et al., 2002; Watcharananan et al., 2010). High viral load in plasma samples (10^6 - 10^7 copies/ml) should be considered as a risk factor for serious post-transplantation complications (Ison, 2006; Claas et al., 2005), but the issue is still controversial because other authors did not confirm the relationship between viral load and severity of infection (Walls et al., 2005). In some studies were reported patients who despite high viral load in blood recovered from adenoviral infection without any treatment. It suggests that not each adenoviral infection needs antiviral treatment (Lankester et al., 2002; Schilham et al., 2002).

It needs to be mentioned that the source of progenitor cells also plays a significant role in development of adenoviral infection. It was confirmed that transplantation of peripheral blood progenitor cells (PBPCs) increases an incidence of AdV infections in hematological patients in comparison to bone marrow transplantations (BMT) due to high number of lymphocytes transferred with the graft. Adenovirus latency in peripheral lymphocytes may be a source of infection in those patients (Runde et al., 2001). On the other hand, unrelated cord blood transplantations (UCB) are suggested to be an independent risk factor for AdV infections (Robin et al., 2007) due to lack of mature lymphocytes in CB regarded as the major component of antiviral defense. Therefore it is still controversial issue.

7. Co-infections in patients undergoing stem cell transplantation

Recipients of stem cell transplantations with AdV infection are prone to life-threatening multiple opportunistic infections. Simultaneous infections of adenoviruses and CMV (4,3-73%), EBV (2,8-34%), polyoma BK (BKV) (1,7-20%), HSV (6,7-26,6%) or RSV (3,8-13%) are most frequently reported (Baldwin et al., 2000; Bruno et al., 2003; Chakrabarti et al., 2002; Leruez-Ville et al., 2006; Lion et al., 2003; Myers et al., 2005; Watcharananan et al., 2010). Co-infections of AdV and BKV are usually detected in urinary tract of immunocompromised patients leading to intensification of hemorrhagic cystitis symptoms (Akiyama et al., 2001). It was also found that CMV viraemia leads to more than 4-fold increase in patient's risk for development of AdV infection (Baldwin et al., 2000; Watcharananan et al., 2010). In rare cases, co-infections of AdV and other viruses such as: HSV1, RSV, EBV and rotaviruses were observed (Legrand et al., 2001; Robin et al., 2007). Many reports suggested that infection of one AdV serotype increases patient's risk for co-infection with second type of human adenovirus leading to extensive organ and whole system involvement (Echavarria et al., 2006; Kroes et al., 2007; Watcharananan et al., 2010).

8. Diagnostic methods for adenovirus detection and identification

Permanently growing number of hematopoietic transplantations in recent years and high risk of viral complications following this procedure demands an implementation of better and more effective diagnostics methods for detection and monitoring of viral infections. There are several methods commonly used for adenovirus detection and identification in clinical samples. Serological tests, virus isolation in cell culture, microscopic techniques and molecular methods found their way into clinical practice.

Virus isolation in cell culture is still considered a "gold standard" for detection of adenoviral infection. Different cell lines like A549, Graham 293 and HEp-2 can be used for virus isolation from clinical samples such as stool, throat swabs, conjunctival swabs, urine and biopsy specimens. Within several days of culturing, cytopathic effect as clumping and cell rounding can be observed (Figure 3).

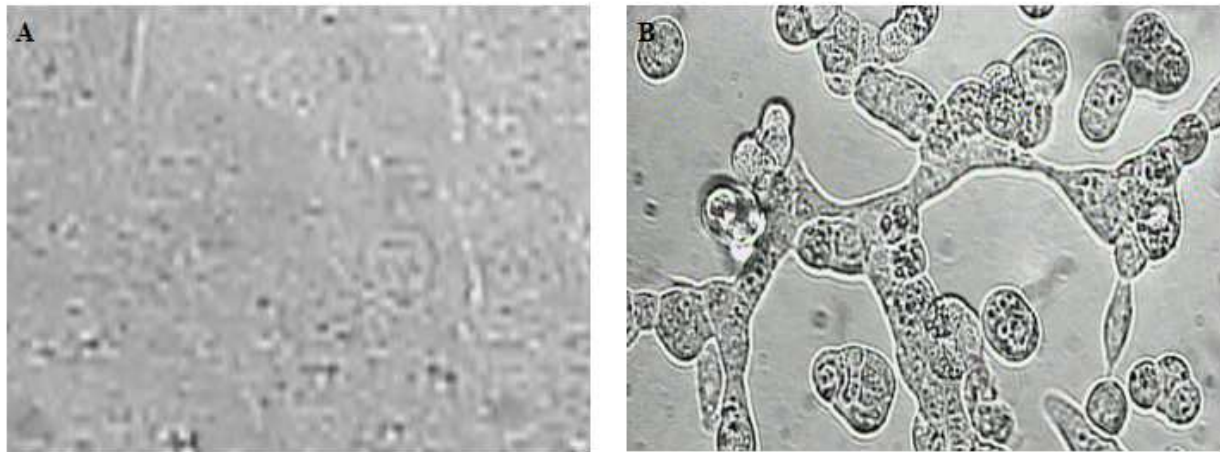


Fig. 3. Microscope image of A549 cells. (A) native culture; (B) cythopatic effect occurring within 48 hours since AdV21 infection (species B). Own collection.

This reference method provides virus identification and typing by means of serum neutralization (SN), hemagglutination inhibition (HI) and complement fixation tests. Unfortunately, the culture technique is laborious, time-consuming and lacks sensitivity to detect virus in the early phase of infection. It can also be inhibited by neutralizing antibodies or other interfering substances (Echavarria, 2009; Huang & Turchek, 2000; Raboni et al., 2003). Nowadays, due to its disadvantages it is replaced by new, more reliable methods like molecular tests.

The next conventional methods for detection of adenoviral infection are serological tests. They are used for indirect antigen detection on capsid surface (IFA, RIA) allowing for virus identification in highly concentrated samples of respiratory secretion, pharyngeal swabs and stool or to confirm AdV infection on the basis of specific antibodies detection. ELISA tests are also used for identification of AdV-antibodies in patient's serum (Echavarria, 2009; Hierholzer et al., 1993; Madisch et al., 2005; Raboni et al., 2003). Although serological tests are commonly used in routine diagnostics of viral infections they are not recommended in adenoviral infections due to their insensitivity, low specificity, false negative results during the window period and difficulties arising from virus variability (Chirmule et al., 1999; Chmielewicz et al., 2005; Crawford-Miksza & Schnurr, 1994; Echavarria, 2009; Raboni et al., 2003). Furthermore, serological tests are useless in recipients of SCT due to profound immunosuppression and using of anti-viral drugs.

The characteristic icosahedral morphology of adenoviruses can be utilized in virus detection by use of electron microscopy (EM) and other microscopic techniques. Infected cell are characterized by presence of enlarged nuclei containing crystalline inclusions of adenoviral particles. Nonetheless, this method is limited by access to unique equipment and EM requires a large number of viral particles in clinical sample hence it can be mainly used in diagnostics of acute gastroenteritis and upper respiratory tract infections (Chirmule et al., 1999; Roingeard, 2008).

Numerous limitations of conventional methods make these techniques impractical in routine diagnostics. The culture collection, serological tests and microscopic techniques are laborious, time-consuming, and insensitive especially in an early phase of the infection. Hence in recent years, molecular methods dominate virus detection and identification in clinical practice. Identification of adenovirus by polymerase chain reaction (PCR) facilitates

accurate and rapid diagnostics and surveillance. PCR is currently the most widespread method used for detection of microbial infections. In comparison to conventional techniques it offers high sensitivity and specificity as well as possibility to obtain a reliable result within several hours. This method allows detecting even small number of viral particles in largely cell-free fluids such as plasma, serum, urine (centrifuged), cerebrospinal fluids and others, preferably before clinical manifestation and tissue damage (Ephros et al., 2009). It can also be implemented for detection of AdV serotypes which are potentially considered as not growing in routine cell culture. Moreover, polymerase chain reaction may be employed for detection of variance and mutations in virus genome (Powledge, 2004). In combination with other methods such as sequencing of hyper variation regions (HVRs) or restriction fragment length analysis, PCR may be used for AdV typing. During last years, the quantitative real-time PCR (RQ-PCR) technique has been successfully implemented more often in viral diagnostics (Bil-Lula et al., 2010; Claas et al., 2005; Echavarria et al., 1999, 2001; Gu et al., 2003; Heim et al., 2003; Hierholzer et al., 1993; Lankester et al., 2002; Lion et al., 2003; Watzinger et al., 2004). Use of highly specific probes allows sensitive detection and quantification of viral equivalents in clinical samples. Sensitive and reliable monitoring of viral replication in immunocompromised patient is extremely important due to possibility for dissemination of infection and poor outcome. It has also a prognostic significance for the patient. Moreover, monitoring of active replication and increasing viral load in clinical samples constitutes the basis for differentiation of active and latent infection in recipients of stem cell transplantations. On the other hand, an early detection of adenovirus due to highly sensitive RQ-PCR creates the opportunity for reduction of immunosuppressive therapy or early initiation of preemptive anti-viral agents before onset of fulminant disease, simultaneously determining therapy effectiveness (Mori et al., 2003). It was confirmed that weekly surveillance of samples for AdVs and early intervention with anti-AdV agents results in significant reduction in the disseminated disease rate and fatal outcomes (Sivaprakasam et al., 2007; Yusuf et al., 2006).

9. Treatment strategies for adenoviral infections

There are many reports describing treatment trials of adenoviral infections in recent years. However, treatment of AdV infections remains a serious problem due to lack of unequivocally proven effectiveness of used drugs. Therefore adenoviral infections in immunocompromised patients should be considered as a serious, life-threatening complication.

Due to numerous toxicities and limitations, administration of anti-AdV drugs should be tailored to the patients situation and risk of dismal outcome. In severe AdV infections usually cidofovir (CDV) or ganciclovir are administered (Bordigoni et al., 2001; Hoffman et al., 2001; Legrand et al., 2001). Other anti-viral drugs such as vidarabine and ribavirine may be implemented (Bordigoni et al., 2001; Miyamura et al., 2000). It was demonstrated that ribavirin (usually used in treatment of HCV and RSV infections) is highly effective in treatment of localized AdV infections in urinary tract but is of limited efficacy in disseminated infections (Bordigoni et al., 2001; Gavin & Katz, 2002; Hoffman et al., 2000; Lankester et al., 2004). Some studies also confirmed partially the ability to virus elimination from urine samples after cidofovir administration in patients suffering from hemorrhagic cystitis. Unfortunately, CDV shows numerous side effects such as renal toxicity, carcinogenicity and toxic injury of muscles (Bordigoni et al., 2001; Feuchtinger et al., 2006,

2008). Despite all these side effects, lack of other more effective medicaments dictates the application of these drugs in therapy of adenoviral infections of urinary tract, gastroenteritis and pneumonia (Bruno et al., 2003; Ebner et al., 2006; Heim et al., 2003; Hoffman et al., 2001; Legrand et al., 2001; Uchio et al., 2007). New antiviral agents are under development. CMX001 is a new formulation of cidofovir. It is oral lipid conjugate of CDV, potentially highly effective against all dsDNA viruses, including adenoviruses (Fowler et al., 2010; Randhawa et al., 2006). Novel form of cidofovir is characterized by convenient oral supply, decreased dose and lack of affinity to kidney tissue. Due to insufficient effectiveness of previously used drugs, new clinical trials are still carrying on. New candidates for treatment of adenoviral infections are also zalcitabine and stavudine, commonly used as anti-HIV agents (Inoue et al., 2009; Romanowski et al., 2009). Zalcitabine is a reverse transcriptase inhibitor which may be used in treatment of AdV infections caused by serotypes: 2, 3, 4, 8, 19 and 37. Unfortunately, only low doses of zalcitabine may be administered because of its mitochondrial toxicity and possibility of peripheral neuropathy and esophageal varices. Stavudine, in turn, is an analogue of pyrimidine nucleoside which inhibits the activity of reverse transcription. It may be potentially used in treatment of AdV3 and AdV4 infections (Inoue et al., 2009; Romanowski et al., 2009; Uchio et al., 2007).

Timing of therapeutical intervention plays important role, too. There are many reports confirming the significant role of early detection of viraemia before the appearance of clinical symptoms (Legrand et al., 2001; Teramura et al., 2004; Watzinger et al., 2004). Initiation of antiviral treatment before the onset of invasive disease is beneficial. It was documented that even intravenous supplementation of antiviral agent during active virus replication does not result in recovery in some patients (Chakrabarti et al., 1999). Therefore, an early diagnosis of infection and adequately early implementation of antiviral therapy can significantly reduce the effects of AdV infections (Chakrabarti et al., 2002; Gavin & Katz, 2002; Sivaprakasam et al., 2007; Walls et al., 2003). Drug cytotoxicity and its limited efficacy in adenoviral infections should encourage clinicians to focus on an earlier diagnostics and monitoring of adenoviral infections.

In recent years, immunomodulation has been most frequently proposed as a new therapeutic strategy. Adoptive transfer of T-cell immunity from the donor to the recipient (DLI) and infusion of donor immunoglobulins (IVIG) combined with reduced immunosuppression has become a new treatment option for patients with an insufficient number of AdV-specific T-cells. It was demonstrated that infusion of donor AdV-specific lymphocytes T is well tolerated and may lead to partial reconstruction of recipient's immune system leading to prophylaxis or treatment of adenoviral infections (Amrolia et al., 2006; Bordigoni et al., 2001; Feuchtinger et al., 2008; Fujita et al., 2008; Ison, 2006; Lion et al., 2010). Successful reduction of AdV replication is achieved mainly due to infusion of selected AdV-specific lymphocytes. Infusion of unselected donor lymphocytes is associated with higher risk of aGvHD due to high alloreactivity which requires more aggressive immunosuppressive therapy conducting development of viral infections (Walter et al., 1995). The sufficient immune response is achieved mainly due to infusion of combined CD4⁺/CD8⁺ (60%) or solely CD4⁺ (40%) cells (Feuchtinger et al., 2008). However, heterogeneity of *Adenoviridae* family in the context of immunomodulation is questionable. Human immune system recognizes the surface determinants of AdV capsid which are highly variable between AdV serotypes. Hence, the success of T-cells administration may be dependent on infecting serotype (Ebner et al., 2006). On the other hand, human adenoviruses exhibit high cross-reactivity against different clinically relevant species of AdV

and therefore there is a large chance that successful DLI may become a new therapeutic strategy for treatment of adenoviral infections after SCT, as antiviral therapy has revealed limited success (Bordigoni et al, 2001; Feuchtinger et al., 2008; Lion et al., 2010). Lion et al. (2010) suggested that initiation of cidofovir/adoptive transfer of AdV-specific T cells may reduce proliferation of adenovirus until recovery of host immune system. These considerations suggest that simultaneous detection and treatment of adenoviral infection at early stage might prevent life-threatening disseminated infections in recipients of hematopoietic stem cell.

Anti-adenovirus treatment needs careful consideration in many clinical aspects. The knowledge on AdV pathogenicity needs more elucidation. The retrospective studies of Wall et al. (2005), Hale et al. (2003) and others proved that there is a possibility for elimination of high viraemia without any treatment due to sufficient host T-cell response (Ephros et al., 2009). The opportunity for 'watch and wait' strategy is a new unexplored clinical option, but the identification of patients with benign clinical course is impossible yet.

10. Conclusion

Taking into account that more than 50000 of hematopoietic stem cell transplantations are performed every year and nearly 10000 originate from unrelated donors, the number of patients who may be affected from adenoviral infections seems to be significant. In view of worldwide distribution of adenoviruses, numerous routes of infection and limited effectiveness of anti-AdV treatment, adenoviral infections in patients undergoing hematopoietic stem cell transplantations should be always considered as serious, life-threatening post-transplant complication which demands rapid and unequivocal diagnosis defining patient's outcome.

11. References

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