Management of adenovirus (ADV) infections

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ADV: Definitions I

- **Primary infection:** First infection in infancy and childhood
- **Reactivation:** Endogenous reactivation in immunocompromized patients
- **Reinfection:** Infection with a new subtype.
- **Systemic infection / viremia:** Positive PCR, virus isolation or Ag detection in blood
- **Local infection:** Positive PCR, virus isolation or Ag detection in body fluids.

ADV: Definitions II

- **Probable disease** — **Infection plus symptoms and signs without histological confirmation**

  - Detection of ADV in stool + enteritis
  - Detection of ADV in urine + nephritis
  - Detection of ADV in PB +
    - fever
    - enteritis
    - hepathopathy
    - nephritis

    } together with negative diagnostic tests indicative for bacterial or fungal infection

- **Proven disease:** — **Infection plus symptoms related to the infection and histological confirmation**

  - Detection of ADV in organ biopsy
  - Detection of ADV in cerebrospinal fluid
  - Multiple organ failure, high viral load in PB and detection of ADV in autoppsy

ADV Infection: high risk patients

Children:

- allo-SCT with in-vivo or ex-vivo T-cell depletion
- allo-SCT with unrelated donor graft
- allo-SCT with unrelated cord blood graft
- severe (Gr III-IV) Graft versus Host Disease
- severe lymphopenia (< 300 CD3+ cells/µl PB)

Adults:

- post allo-SCT haploidentical donor or unrelated cord blood graft
- severe (Gr III-IV) Graft versus Host Disease
- treatment with Alemtuzumab

ADV Infection in the immunocompromized host: sings and symptoms

- Fever
- Enteritis
- Hepathopathy
- Nephritis
- Retinitis
- Encephalitis

Recommendation ADV: diagnostic techniques

- PCR is fast and has higher sensitivity and specificity compared to culture or IF (AII)

- Quantitative PCR is more predictive for lethal disease (AII)

- Quantification in stool samples helps to identify patients (primarily children) at risk for viremia (BIII)

- Subtyping of adenovirus might yield additional information

- Quantitative PCR - either commercial or in-house (validated by round-robin tests) is the current gold standard and should be used (A II)

ADV: diagnostic studies

- High incidence of ADV-infection post allo-SCT in children
- Low incidence of ADV-infection post allo-SCT in adults.
- Incidence increases with degree of immunosuppression both in adults and children
- High mortality in case of ADV-viremia
- ADV infection is a rare event following autologous SCT
- No screening studies available for children with chemotherapy
- Single cases of lethal ADV hepatitis in children with ALL

Recommendation ADV-screening in allo SCT (children):

- Quantitative PCR-screening on PB is recommended on an at least weekly basis to patients at risk (AII)
- Screening is not routinely recommended in patients receiving matched sibling grafts (BII)
- Length of screening should be adapted according to degree of immune reconstitution (BIII)

Recommendation ADV-screening in allo SCT (adults):

- Routine screening is not routinely recommended in standard risk patients (BII)
- For high risk patients screening should be considered (BIII)
- Length of screening should be adapted according to degree of immune reconstitution (CIII)

Recommendation ADV-screening in auto SCT and chemotherapy:

- no viral screening warranted (BII)
- quantitative PCR in case of clinical suspicion (BIII)

Recommendation ADV-monitoring in case of viremia:

- In patients with ADV-viremia viral load should be monitored by quantitative PCR at least once weekly (AII)

ADV: Prophylactic virostatic treatment

No data on cidofovir or ribavirin

Ganciclovir:

Bruno et al 2003	lower incidence of ADV infection in patients receiving prophylactic ganciclovir
Avivi et al 2004	trend towards lower incidence

Recommendation prophylactic treatment:

Prophylactic antiviral therapy is not recommended (BIII)

ADV recommendation for preemptive treatment of asymptomatic viremia:

Goal: To prevent ADV disesase

Indication to start preemptive treatment:

ADV viremia plus presence of at least one risk factor

Children: **(BII)**

- allo-SCT with in-vivo or ex-vivo T-cell depletion
- allo-SCT with unrelated donor graft
- allo-SCT with unrelated cord blood graft
- severe (> Gr II) Graft versus Host Disease
- severe lymphopenia (< 300 CD3+ cells/µl PB)

Adults: **(BIII)**

- post allo-SCT haploidentical donor or unrelated cord blood graft
- Gr III-IV acute Graft versus Host Disease
- following treatment with Alemtuzumab

Viral loads should be monitored during therapy **(BIII)**

ADV recommendation for treatment indication:

Indication to start treatment: **(BIII)**

- Proven ADV disease

- Probable ADV disease

Adenovirus – treatment options

- Antiviral drugs
  - Cidofovir
  - Ribavirin
  - Ganciclovir
  - CMX001 (oral lipid derivate of cidofovir; non-licensed)
- Other options
  - Iv Ig
  - Transfer of adenovirus specific T-cells (experimental)
  - Reduction/withdrawal of immunosuppression

ADV recommendation for treatment I:

- Iv. cidofovir is recommended as first line therapy (BIII)
  - Studies of preemptively given cidofovir suggests efficacy in reducing viral load
  - No clear data to support that preemptive cidofovir reduces the incidence of ADV disease
  - No clear data regarding efficacy in treating adenovirus disease
  - Varying doses and schedules have been used most commonly 5 mg/kg weekly (2-3 doses) thereafter every other week. There is no evidence supporting one particular schedule
- Supportive measures should be taken with oral probenecid hyperhydration, and if possible avoidance of other nephrotoxic drugs at day of cidofovir administration (BIII)

ADV recommendation for treatment II:

- Ribavirin is not generally recommended for adenovirus infection but can be considered in cases with type C infections especially in patients with decreased renal function (CIII)
- Consider the addition of iv Ig (BIII)
- Immunosupression should be reduced whenever possible (AII)

- For systemic adenovirus disease, virus specific CTLs can be considered if available (B III)

Future developments

- Lower risk for ADV-associated disease and ADV-associated mortality has been shown in the presence of ADV-specific T-cells

- Safety and feasibility of adenospecific T-cell transfer has been shown (Feuchtinger et al BJH 2006; Leen et al, Nature Medicine 2006)

- Adenospecific T-cell transfer is a promising strategy but there are still limited data on efficacy and further studies are neded (Leen et al Blood 2009; Feuchtinger et al. 2009)

- Multispecific CTLs are in development

- CMX001, a cidofovir lipid conjugate, has shown efficacy in a phase II study