Screening, Monitoring, and Treatment of Adenovirus Infections in Pediatric and Adult Recipients of Allogeneic Hematopoietic Cell Transplants: Multicenter Survey of European Transplant Centers

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BACKGROUND

Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients are at Risk of Life-Threatening Adenovirus (AdV) Viremia

- The risk is particularly high for pediatric patients, where mortality among those with disseminated AdV infection or high viral loads (for example, AdV viremia >10,000 copies/mL) has been reported to exceed 50% in single-center studies.[1, 2]
- There are currently few practice guidelines for the detection and management of AdV infection in patients who have recently received allo-HCT.[3, 4]
  - The 2011 European Conference of Infections in Leukemia (ECIL-4) guidelines recommend at least weekly blood screening for all allo-HCT recipients perceived to be at risk of AdV infection.[4]
  - The risk for AdV-associated disease is increased in children. Other risk factors for AdV disease are T-cell depletion, unrelated and cord blood HCT, Graft versus Host Disease (GvHD) grades III-IV, and lymphopenia.[4]
  - Pre-emptive treatment is recommended for asymptomatic patients with AdV viremia and at least 1 transplant-related risk factor.[4]
  - Currently, there are no defined AdV thresholds for treatment initiation.[4]
- There is a lack of multicenter data on the most commonly used practices regarding AdV screening and treatment in allo-HCT recipients.

OBJECTIVE

- To determine the practice patterns used by physicians to screen for and treat AdV infection in allo-HCT recipients in Europe.

METHODS

- AdVance is a multicenter, multinational study of the incidence, management, and clinical outcomes of AdV infections in European adult (age ≥18 years) and pediatric (age <18 years) allo-HCT recipients.
- As part of the AdVance study, physicians at the 50 participating institutions were asked to complete a survey outlining the current practices in use at their center for the management of AdV infections in allo-HCT recipients.
  - Questions specifically addressed screening and treatment practices.
- Analyses of the responses were stratified by those physicians who specifically treated pediatric or adult allo-HCT recipients.
  - The assessment of risk was per the physician's opinion.

RESULTS

Physician Characteristics

- The AdVance study included 50 centers in Spain (n=12), the UK (n=10), France (n=10), Italy (n=9), Germany (n=7), the Netherlands (n=1), and the Czech Republic (n=1).
- Practice surveys were completed during 2017. Among the responses, 28 were from physicians who treat pediatric patients and 14 who treat adult patients.
  - The majority of physicians who treat pediatric patients were transplant specialists (50%), and the median number of years managing allo-HCT recipients was 15.0 (range 4.0-30.0).
  - The majority of physicians who treat adult patients (79%) were hematology specialists, and the median number of years managing allo-HCT recipients was 16.5 (3.0-30.0).
- Physicians reported that their centers carried out a relatively high number of allo-HCT transplants per year.
  - Most (57%) physicians who treat pediatric patients reported managing between 26 and 50 allo-HCT recipients per year.
    - Approximately half (54%) of physicians reported seeing ≥10 cases of AdV infection a year (median 10.0).
  - Most (64%) physicians who treat adult patients reported managing over 50 allo-HCT recipients per year.
    - All reported seeing <10 cases of AdV infection a year (median 2.0).

PHYSICIANS WHO TREAT PEDIATRIC ALLO-HCT RECIPIENTS

Most Routinely Screen

- All of the 28 physicians who treat pediatric patients reported routine AdV screening practices at their center.
- 93% of physicians reported that they routinely screen all their pediatric allo-HCT recipients for AdV infection. Among the 7% of physicians who didn't, all screen patients they considered to be at high risk of AdV infection (**Figure 1**).
- For routine screening of pediatric patients for AdV, most physicians sampled blood and stools, with a frequency of weekly or more often (**Figure 2**).

FIGURE 1. ROUTINE ADV SCREENING FOR ALL PEDIATRIC ALLO-HCT RECIPIENTS IS COMMON

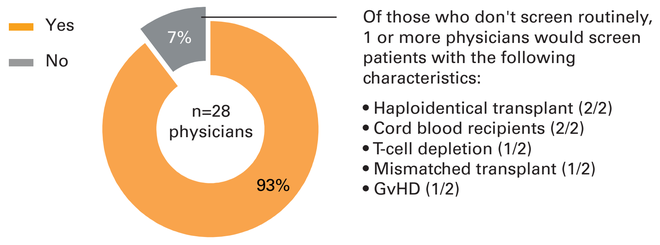
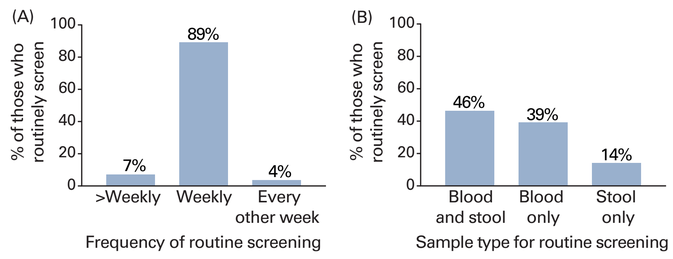


FIGURE 2. PHYSICIANS WHO TREAT PEDIATRIC ALLO-HCT RECIPIENTS SCREEN FOR ADV WEEKLY, IN BLOOD AND STOOL



AdV, adenovirus. Allo-HCT, allogeneic hematopoietic cell transplant; GvHD, Graft versus Host Disease.

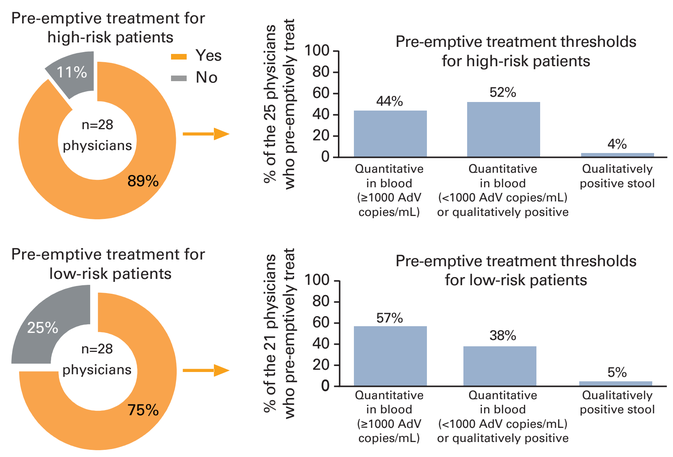
Pre-emptive Treatment is Common

- Nearly all (89% [25/28]) physicians took a pre-emptive approach to AdV infection after allo-HCT in high-risk pediatric patients (**Figure 3**).
  - Just less than half of pre-emptively treating physicians would wait for ≥1000 AdV copies/mL in a blood sample to initiate treatment.
  - More than half would treat at a quantitative threshold of <1000 AdV copies/mL or with a positive blood sample (qualitative positive).
  - Among the 13/25 pre-emptively treating physicians who specified a quantitative AdV trigger for treatment in blood, the median AdV threshold was 1000 copies/mL (range: 100-5000).
    - 11/13 had an AdV trigger threshold of ≥1000 copies/mL.
- Most (75% [21/28]) physicians took a pre-emptive approach for low-risk patients.
  - More than half of pre-emptively treating physicians would wait for ≥1000 AdV copies/mL in a blood sample to initiate treatment.
  - Over a third would treat at a quantitative threshold of <1000 AdV copies/mL or with a positive blood sample (qualitative positive).
  - Of the 13/21 pre-emptively treating physicians who specified a quantitative AdV trigger for treatment in blood, the median AdV threshold was 1500 copies/mL (range: 210-10,000).
    - 12/13 had an AdV trigger threshold of ≥1000 copies/mL.

There Are no Approved Treatments for AdV Infection

- Intravenous cidofovir is currently the first-line therapy specified in the European guidelines, at a suggested dose of 5 mg/kg/week.[4] It is often used to control AdV viremia but its usefulness is limited by nephrotoxicity.[5]
- Among physicians who treat pediatric patients, most (86%) reported the use of cidofovir as a first-line treatment for symptomatic AdV disease.
  - 5 mg/kg a week was the most common starting and maintenance dosages (**Table 1**).
- Brincidofovir (BCV) was the second most commonly used treatment. Cell-based therapy and ribavirin were less frequently used. BCV is an orally bioavailable, investigational, lipid conjugate of cidofovir, that has a lower risk of nephrotoxicity and is being investigated as a potential treatment for AdV infection.[6-9]

FIGURE 3. ADV VIREMIA (1000 COPIES/ML) IS A COMMON TREATMENT TRIGGER FOR PHYSICIANS WHO TREAT PEDIATRIC PATIENTS



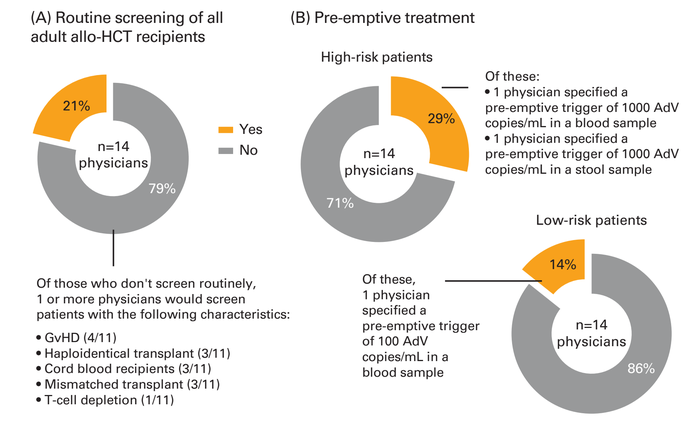
AdV, adenovirus.

PHYSICIANS WHO TREAT ADULT ALLO-HCT RECIPIENTS

Adults Are Screened Less Frequently and Pre-emptive Treatment Is Rarer

- A minority of physicians (36% [5/14]) who treat adult patients reported that they routinely screen for AdV.
- Even fewer reported that they routinely screen all of their adult allo-HCT recipients for AdV infection (21% [3/14]; **Figure 4**).
  - Among the 11/14 (79%) who did not routinely screen, some indicated that they would screen those deemed high risk (such as those with GvHD [4/11] or recipients of haploidentical, cord blood, or mismatched transplants [3/11]).
- Among those who did routinely screen, this was most commonly done weekly (80% [4/5]), using blood (80% [4/5]).
- A minority of physicians reported a pre-emptive treatment approach to AdV infection after allo-HCT in high- (29% [4/14]) and low-risk (14% [2/14]) adult patients.
  - Few pre-emptively treating physicians specified a quantitative AdV trigger for treatment.
- Physicians reported that cidofovir was the most commonly used first-line treatment for symptomatic AdV infection in adult patients (93% of physicians).
  - Of the physicians who used a standard cidofovir regimen, the most common standard regimen was 5 mg/kg per week for starting and maintenance dosages (**Table 1**).

FIGURE 4. FEW PHYSICIANS WHO TREAT ADULT PATIENTS SCREEN FOR, OR PRE-EMPTIVELY TREAT, ADV INFECTION



AdV, adenovirus; allo-HCT, allogeneic hematopoietic cell transplant; GvHD, Graft versus Host Disease.

Table 1: The typical treatment regimen for intravenous cidofovir in pediatric and adult patients is 5 mg/kg per week

	Physicians who treat pediatric patients n=28	Physicians who treat adult patients n=14
Use of a standard regimen	97%	86%
Comprising:		
Starting dose		
1 mg/kg 3 times a week	29%	7%
5 mg/kg per week	68%	79%
Maintenance dose		
1 mg/kg 3 times a week	36%	14%
5 mg/kg per week	61%	72%

CONCLUSIONS

- Current AdV screening practices among physicians who treat allo-HCT recipients are generally consistent with the ECIL-4 guidelines.[4]
  - Patients considered by their physicians to be at risk of AdV infection are monitored closely.
  - Pediatric allo-HCT patients are commonly screened weekly or more, using blood, or a combination of both blood and stool samples.
  - Adults are screened less routinely.
- Physicians who manage pediatric patients often treat AdV infections pre-emptively, using both qualitative and quantitative treatment thresholds. Pre-emptive treatment is less common for adult patients.
  - Off-label intravenous cidofovir is currently considered a first-line treatment in spite of toxicity concerns and lack of efficacy data.
  - Most physicians use cidofovir at 5 mg/kg per week, which is consistent with the ECIL-4 guidelines.[4]
  - Although there is no defined AdV threshold for treatment, AdV viremia ≥1000 copies/mL is a commonly used quantitative trigger for pre-emptive treatment.
- The use of routine screening and pre-emptive treatment for pediatric and adult allo-HCT patients may reflect how physicians perceive the risks and effects of AdV infection in these 2 distinct patient populations.

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ADVANCE

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