

Current practices in the management of adenovirus infection in allogeneic hematopoietic stem cell transplant recipients in Europe: The AdVance study

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Abstract

Objective: Adenovirus (AdV) infections are potentially life-threatening for allogeneic hematopoietic stem cell transplant (allo-HCT) recipients. The AdVance study aimed to evaluate the incidence, management, and outcomes of AdV infections in European allo-HCT recipients.

Methods: As part of the study, physician surveys were conducted to determine current AdV screening and treatment practices at their center.

Results: All of the 28 respondents who treat pediatric patients reported routine AdV screening practices, with 93% screening all allo-HCT recipients and others screening those with transplant-related risk factors. Nearly all centers take a pre-emptive approach to AdV treatment in both high- (89%) and low-risk patients (75%). Among the 14 respondents who treat adult patients, 5 (36%) reported routine screening practices and few (21%) screen all allo-HCT recipients unless risk factors are present. In adults, pre-emptive AdV treatment is uncommon and quantitative AdV thresholds are rare. Typical treatment for all patients with symptomatic AdV infection is off-label intravenous cidofovir.

Conclusions: Our findings confirm that screening for AdV is more common in pediatric patients. Antiviral treatment is employed in both pediatric and adult patients, although adults are generally treated when AdV disease is diagnosed. The approach to AdV screening and treatment is risk-based and consistent with clinical guidelines.

KEYWORDS

adenoviridae, antiviral agents, DNA viruses, infection control, transplantation, virus diseases

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplant (allo-HCT) recipients are vulnerable to potentially life-threatening opportunistic infections. An important reason for a recent rise in risk is the more extensive use of T-cell depletion, which results in prolonged lymphopenia,^{1,2}

increasing the risk of viral infection or reactivation. As described with other double-stranded DNA viruses, high adenoviral loads in blood are predictive of a poor clinical outcome.³ Single-center studies have suggested that intense or disseminated adenovirus (AdV) infection following allo-HCT is associated with poorer clinical outcomes⁴⁻⁹ and that AdV viremia is an independent risk factor for mortality.^{10,11}

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In order to understand the outcomes associated with AdV infection in different subsets of allo-HCT recipients, it is important to understand the current approach to AdV detection and management. Due to the risks associated with AdV infection in allo-HCT recipients, guidelines have been developed to direct AdV screening and treatment practices, but the extent of adherence to these guidelines is unknown.^{1,9,12,13} The lack of consistently reported, contemporary, multicenter data on the current management practices for AdV infection limits the understanding of incidence and outcomes reporting and the ability to generalize outcomes data between patient groups. This includes the ability to differentiate the presentation, progression, and outcomes of AdV infection in children and adults. The AdVance practice patterns survey aimed to document the current screening and treatment paradigms for AdV infection in adult and pediatric allo-HCT recipients in Europe.

2 | PATIENTS AND METHODS

The practice pattern survey was a key part of the AdVance study, which was designed to collect retrospective data on the incidence and outcomes of AdV infection in allo-HCT recipients. One hundred and sixty-three transplant centers were identified from the 2014/2015 European Society for Blood and Marrow Transplantation (EBMT) registry as having conducted at least 30 allogeneic HCT procedures per year. Fifty centers took part in the AdVance study, including 28 of the 80 initially identified pediatric centers, 14 of the 56 adult centers, and eight of the 27 mixed-age centers. A higher number of pediatric centers were invited to participate as they perform a lower number of transplants per year when compared with adult centers. Sites were located in the Czech Republic, France, Germany, Italy, the Netherlands, Spain, and the United Kingdom. The study was managed by Analytica Laser (London, UK) and sponsored by Chimerix (Durham, NC, USA).

The practice patterns survey was completed by the lead AdVance investigator at each center. It included questions on the physician's experience, the annual number of transplants at the center, and the current clinical management of AdV infection in allo-HCT recipients at the centers. A copy of the survey is included in Appendix S1. Several questions asked about the screening and treatment approach for low- or high-risk patients, as defined locally.

The survey was distributed throughout 2017 and was completed on paper or directly via an electronic application within 2 weeks of receipt. Follow-up ensured that all centers responded. Results were summarized separately for physicians who reported that they manage pediatric patients (<18 years), and physicians who reported that they manage adult patients (≥18 years). As clinical practice was expected to differ significantly for pediatric and adult allo-HCT recipients, responses from the eight physicians who reported treating both pediatric and adult patients are not included. Data were compiled and analyzed by Analytica Laser using processes that adhered to good data management practices and data protection laws. All data management processes were conducted per standard operating procedures, ISO/IEC 27001/27002, and were CFR 21 part 11 compliant.

3 | RESULTS

AdVance practice pattern surveys were completed throughout 2017. Twenty-eight physician respondents reported that they manage pediatric patients (Table 1). Half of these physicians (14/28) were transplant specialists. Physicians had a median of 15.0 (interquartile range [IQR] 10-20) years of experience managing allo-HCT recipients; 57% managed between 26 and 50 allo-HCT recipients per year, and the median number of AdV infection cases managed per year was seven (IQR 4-14).

TABLE 1 Physician characteristics

	Physicians who manage	
	Pediatric patients	Adult patients
Number of physician responses	28	14
Country, n		
Spain	5	6
UK	9	1
France	4	3
Italy	4	3
Germany	4	1
The Netherlands	1	0
The Czech Republic	1	0
Specialty, n (%)		
Hematology	11 (39.3)	11 (78.6)
Transplant	14 (50.0)	3 (21.4)
Infectious diseases	1 (3.6)	0
Other	2 (7.1)	0
Years managing allo-HCT recipients, median (IQR)	15 (10-20)	17 (14-25)
Allo-HCT recipients managed/year ^a , n (%)		
<10	0	1 (7.1)
10-25	9 (32.1)	1 (7.1)
26-50	16 (57.1)	3 (21.4)
>50	3 (10.7)	9 (64.3)
AdV cases managed/year ^a , n (%)		
<10	15 (53.6)	14 (100.0)
10-25	12 (42.9)	0
26-50	1 (3.6)	0
>50	0	0
Median (IQR)	7 (4-14)	2 (0-3)

AdV, adenovirus; Allo-HCT, allogeneic hematopoietic stem cell transplant; IQR, interquartile range.

n (%), unless otherwise stated. Pediatric patients defined as <18 y.

Note that responses from physicians who manage pediatric patients and those who manage adult patients should not be directly compared.

^aAverage 2013-2016.



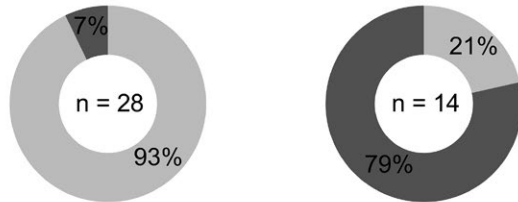
Physicians who manage pediatric patients Physicians who manage adult patients

■ Yes ■ No

(A) Availability of a routine screening protocol for allo-HCT recipients:



(B) Use of routine screening for ALL allo-HCT recipients:



If No, what type of allo-HCT recipients?

- Cord blood recipients (2/2)
- Haploidentical transplant (2/2)
- T-cell depletion (1/2)
- Mismatched transplant (1/2)
- GvHD (1/2)
- GvHD (4/11)
- Cord blood recipients (3/11)
- Haploidentical transplant (3/11)
- Mismatched transplant (3/11)
- T-cell depletion (1/11)

Allo-HCT, allogeneic hematopoietic stem cell transplant; GvHD, graft-vs-host disease
Note that responses from physicians who manage pediatric patients and those who manage adult patients should not be directly compared.

FIGURE 1 Routine screening practices for adenovirus in allogeneic hematopoietic stem cell transplant recipients

Fourteen physician respondents reported that they manage adult patients (Table 1). The majority were hematology specialists (79%). These physicians had a median of 17 (IQR 14-25) years of experience managing allo-HCT recipients; 64% managed more than 50 allo-HCT recipients per year, and the median number of AdV infection cases managed per year was two (IQR 0-3).

Eight respondents reported that they manage both pediatric and adult patients. Data from these surveys were not part of this analysis.

3.1 | Physicians who manage pediatric patients

3.1.1 | Screening

Each of the physicians who manage pediatric patients reported that there was a routine screening practice for the detection of AdV infection following allo-HCT at their center. Overall, 93% (26/28) conduct routine screening for all pediatric allo-HCT recipients. Regarding the 2 of 28 (7%) physicians who do not routinely screen all of their pediatric allo-HCT recipients, both reported that they screen high-risk patients with specific transplant characteristics that put them at high risk of AdV infection (ie, cord blood

recipient, haploidentical or mismatched donor, T-cell depletion, or graft-vs-host disease [GvHD]; Figure 1). Routine screening is generally conducted weekly (89%), in blood and stool samples (46%) or just blood samples (39%). Stool samples are not commonly used alone for screening (14%; Figure 2).

3.1.2 | Pre-emptive treatment

Among the 28 physicians who manage pediatric patients, 89% (25/28) utilize a pre-emptive approach to AdV infection after it is identified in a patient they perceive to be high-risk; 75% (21/28) utilize a pre-emptive approach to AdV infection after it is identified in a patient they perceive to be low-risk (Figures 3 and 4).

Twenty-five physicians reported using a virologic threshold for the initiation of pre-emptive antiviral therapy. Among the 13/25 physicians who pre-emptively treat high-risk patients and reported an AdV viremia threshold above which they initiate therapy, the median pre-emptive treatment threshold was 1000 AdV copies/mL (IQR: 1000-5000). Just over half (52%; 13/25) of physicians consider pre-emptive treatment when a high-risk pediatric patient has qualitatively detectable AdV or where AdV viremia is <1000 copies/mL, but 44% (11/25) wait for AdV viremia to reach ≥ 1000 copies/mL. Physicians reported waiting for higher levels of AdV viremia before initiating pre-emptive treatment in patients they felt to be at low risk vs those they felt to be at high risk. Among the 13/21 physicians who pre-emptively treat low-risk patients and reported an AdV viremia threshold above which they initiate therapy, the median threshold was 1500 copies/mL (IQR 1000-5000). Fifty-seven percent of physicians require AdV viremia ≥ 1000 copies/mL to initiate pre-emptive treatment, while 35% consider treatment at any detectable AdV viremia or for thresholds <1000 copies/mL.

When asked to indicate the types of pre-emptive treatment used, all physicians reported that they use off-label cidofovir for pre-emptive treatment in both high- and low-risk pediatric patients. Other pre-emptive treatment options considered for high-risk patients were the investigational drug brincidofovir (11/25; 44%), cell-based therapy (9/25; 36%), and off-label ribavirin (3/25; 12%). Similar options were identified for low-risk patients: the investigational drug brincidofovir (8/21; 38%), cell-based therapy (3/21; 14%), and off-label ribavirin (2/21; 10%).

3.1.3 | Treatment of symptomatic disease

Ninety-six percent of physicians reported that their center had a standard treatment regimen for AdV infection in pediatric allo-HCT patients. Although no treatments are indicated for AdV infection, when asked to rank their first-line treatments for symptomatic AdV disease, more than 85% of physicians picked intravenous off-label cidofovir as their first choice (Table 2). The investigational drug brincidofovir was a first or second choice for 57% of physicians, followed by cell-based therapy and off-label ribavirin.

Ninety-six percent of physicians reported that there was a standard protocol for the use of intravenous cidofovir at their center. For

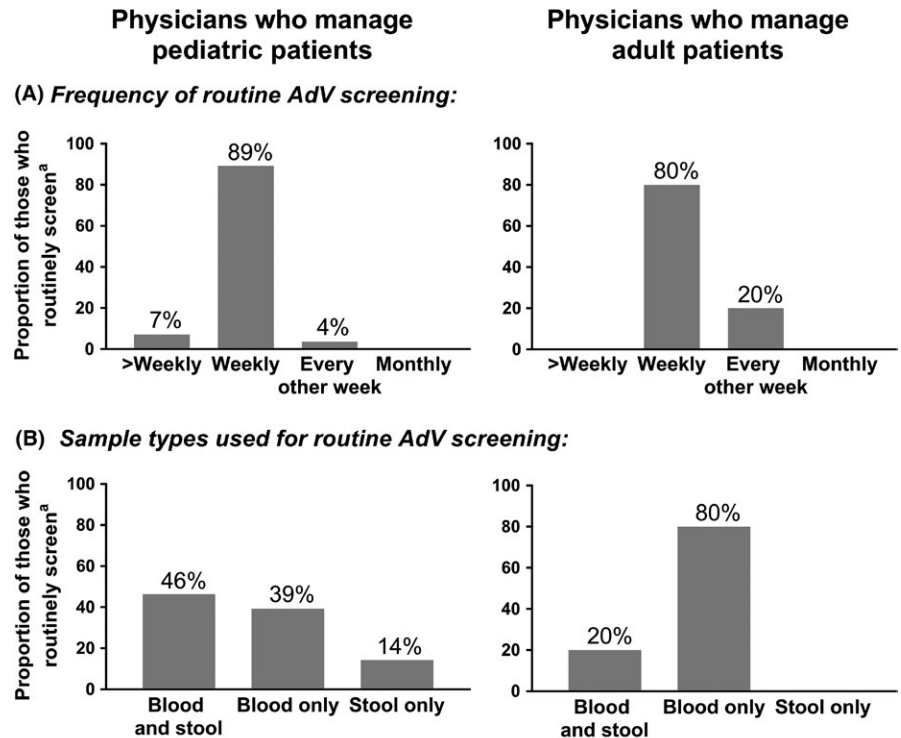


FIGURE 2 Frequency and sample type of routine screening for adenovirus in allogeneic hematopoietic stem cell transplant recipients

AdV, adenovirus.

^an of those who routinely screen = 28 pediatric physicians and five adult physicians.

Note that responses from physicians who manage pediatric patients and those who manage adult patients should not be directly compared.

typical pediatric patients, this most commonly consisted of a starting and maintenance dose of 5 mg/kg/wk (68% starting; 61% maintenance; others chose 1 mg/kg three times a wk; Table 2).

3.2 | Physicians who manage adult patients

3.2.1 | Screening

Of the 14 physician respondents who manage adult allo-HCT recipients, 36% (5/14) reported that their center had routine AdV screening practices for allo-HCT recipients (Figure 1). Routine screening is generally weekly (80%), using blood (80%) or blood and stool samples (20%). In adult patients, screening of only stool samples was not reported (Figure 2). Twenty-one percent (3/14) of physicians reported that their routine screening extended to all adult allo-HCT patients. Among the 11 physicians who do not screen all of their allo-HCT recipients as routine, some screen high-risk patients with specific transplant characteristics (ie, GvHD, cord blood recipients, or recipients of a haploidentical or mismatched transplant; Figure 1).

3.2.2 | Pre-emptive treatment

A pre-emptive treatment approach to AdV infection was reported for high-risk patients by 29% (4/14) of physicians, and for low-risk patients by 14% (2/14) of physicians (Figures 3 and 4). Among those physicians who reported pre-emptive treatment, all reported use of

off-label cidofovir therapy. Few physicians reported the use of quantitative AdV viremia thresholds for pre-emptive treatment initiation (Figures 3 and 4).

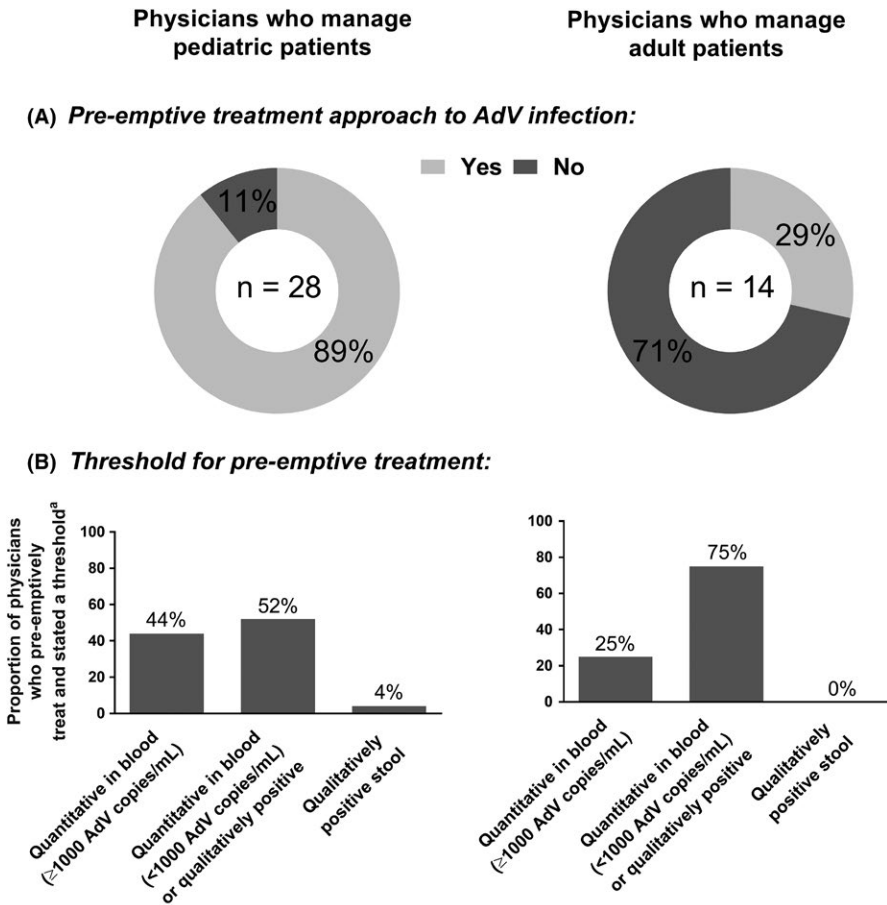
3.2.3 | Treatment of symptomatic disease

Seventy-one percent of physicians who manage adult allo-HCT recipients reported their center had a standard treatment regimen for AdV infection in adult patients. Similar to physicians who manage pediatric patients, 93% of physicians who treat adult patients reported off-label cidofovir as their first-line treatment for symptomatic AdV disease (Table 2). Off-label ribavirin (43%) and investigational brincidofovir (29%) were common second choices, followed by cell-based therapy.

Consistent with the responses from physicians who manage pediatric patients, 96% of physicians who manage adult patients reported that there was a standard protocol for intravenous cidofovir use at their center. For adult patients, this generally consisted of 5 mg/kg/wk as starting and maintenance dosages (Table 2).

4 | DISCUSSION

The AdVance practice patterns survey is the first to comprehensively summarize the current standard of care for AdV infection in allo-HCT recipients across multiple European transplant centers. Findings suggest that AdV screening and treatment practices are



AdV, adenovirus.

^an of those who pre-emptively treat and stated a threshold = 25 pediatric physicians and four adult physicians. Note that responses from physicians who manage pediatric patients and those who manage adult patients should not be directly compared.

FIGURE 3 Approach to pre-emptive treatment of adenovirus infection identified in allogeneic hematopoietic stem cell transplant recipients considered to be “high-risk”

aligned with contemporary guidelines and are predominantly based on physicians' perceptions of patient risk.

It is widely reported that the incidence of AdV infection is higher among pediatric allo-HCT recipients than adult allo-HCT recipients.^{7,8,14,15} In many cases, the source of AdV infection is thought to be persistent AdV in the gastrointestinal tract.^{16,17} Differences in patient risk likely led to the divergent surveillance and treatment approaches we observed: 93% of treating physicians routinely screen all pediatric allo-HCT recipients for AdV infection in blood and/or stool, whereas 21% screen all adult allo-HCT recipients. Moreover, those who would not routinely screen all allo-HCT recipients commonly reported that they would screen those with well-described risk factors for AdV infection, such as GvHD, cord blood or haploidentical transplant, or T-cell depletion. Differences in screening practices for pediatric and adult allo-HCT recipients may impact the identification of AdV infection in these distinct patient groups, with the likely delays in diagnosing adult patients. Likewise, the routine surveillance in pediatric allo-HCT recipients could also contribute to the higher incidence of AdV infection.^{4,7,18,19}

Although the definition of risk varies among previously published guidelines, a risk-based approach to screening has generally

been supported.^{1,9,12,13} ECIL-4 guidelines suggest patients at high risk are those who have received an unrelated cord blood, are severely lymphopenic (<200 lymphocytes/ μ L peripheral blood), or have grade 3 or 4 GvHD; pediatric patients who have undergone T-cell depletion (in vivo or ex vivo) or have received an unrelated transplant; or adults who have received alemtuzumab conditioning or a haploidentical transplant. Older guidelines propose broadly similar criteria: refractory GvHD, cord blood or a haploidentical transplant, T-cell depletion >2-3 \log_{10} , or use of T-cell depleting antibodies.^{9,12} The recently published Infectious Diseases Working Party (IDWP) of the EBMT position paper (2018)¹³ builds on ECIL-4 guidelines to suggest that pediatric patients with AdV shedding in their stool, or CD3+ T cells <300 per μ L of blood, should be screened at least weekly because of an increased risk of AdV infection. Those at high risk should be assessed for the presence of AdV-specific T cells.¹³ In this survey, the respondents' definition of risk was not interrogated; however, responses suggest that most physicians have criteria that broadly align with the ECIL-4 guidelines and where those with transplant-related risk factors are more likely to receive routine screening and pre-emptive treatment for AdV infection.

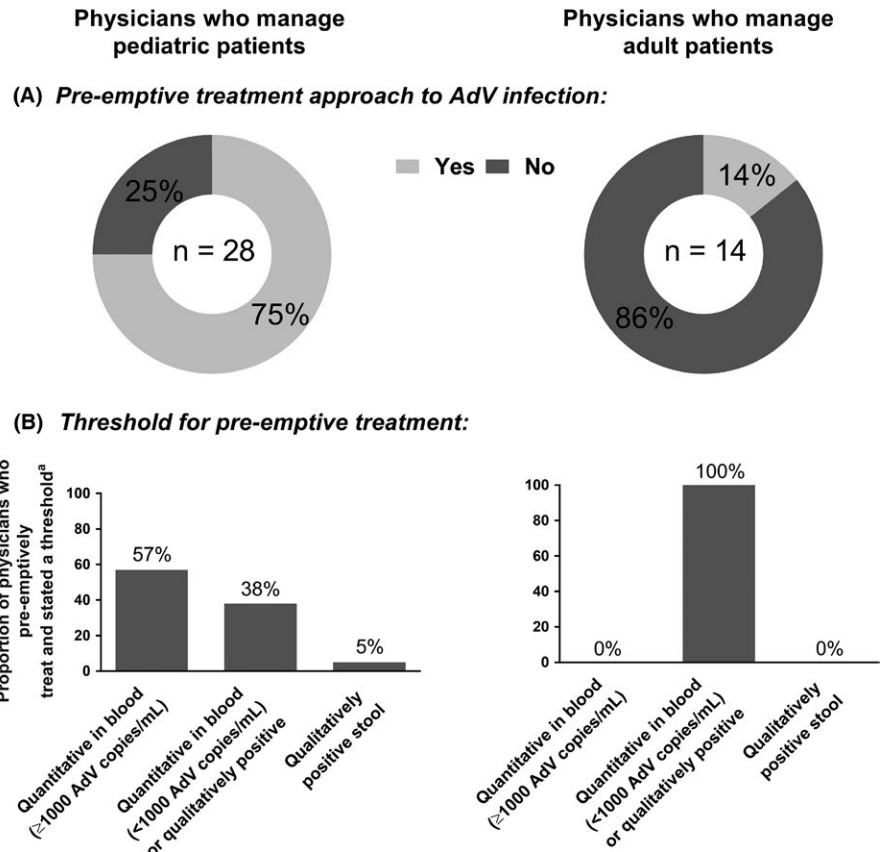


FIGURE 4 Approach to pre-emptive treatment of adenovirus infection identified in allogeneic hematopoietic stem cell transplant recipients considered to be “low-risk”

AdV, adenovirus.

^an of those who pre-emptively treat = 21 pediatric physicians and two adult physicians.

Note that responses from physicians who manage pediatric patients and those who manage adult patients should not be directly compared.

Results from the AdVance practice patterns survey suggest that physicians most commonly choose blood, or blood and stool, as their sample of choice for AdV screening. AdV viremia is widely considered to be an indicator of potential disease dissemination,^{4,5,20} and stool AdV positivity has been proposed in pediatric patients as an early predictor of viremia.²¹ The latest position statement from the IDWP EBMT reinforces the idea that the gastrointestinal tract is a common source of latent AdV and recommends stool screening in pediatric allo-HCT recipients both before conditioning and alongside blood screening until lymphocyte reconstitution.¹³

Survey responses showed that more than 75% of physicians who manage pediatric patients report pre-emptive AdV treatment for those considered to be at low or high risk, but this was the case for less than 30% of physicians who manage adult patients. The stated AdV treatment thresholds further confirmed that their readiness to treat was based on perceived risk (high or low). While ECIL-4 guidelines did not provide a threshold for pre-emptive treatment, the most recent position statement from the IDWP EBMT suggests that treatment should be considered for immunocompromised pediatric allo-HCT recipients when viremia reaches ≥ 1000 copies/mL or when AdV in stool is above 10^6 copies/g and is rapidly rising.¹³

When choosing a pre-emptive treatment for AdV infection or AdV disease, a high proportion of physicians currently utilize

off-label intravenous cidofovir. Use of investigational brincidofovir, cell-based therapies, or off-label ribavirin is currently rarer. The reported cidofovir dosage regimens were consistent with the 3-5 mg/kg/wk for 2-3 weeks, then every other week, as included in the ECIL-4 guidelines.¹ The AdVance practice patterns survey highlights the lack of approved treatments for AdV disease to accompany the withdrawal of immunosuppression.

The value of routine AdV screening and pre-emptive AdV treatment for allo-HCT recipients is clear for pediatric patients, as early detection and treatment can help prevent the development of highly lethal disseminated AdV disease.^{4,22,23} The relatively low incidence of AdV infection in adult allo-HCT recipients has been suggested as a reason to not screen prospectively; however, this means that infection is usually discovered later, often during the workup of AdV disease, which likely explains the poor outcomes associated with AdV infection in adults.^{4,17,18,24-26} The ECIL-4 guidelines represented the balance of opinion at the time, where screening is recommended for patients with the highest risk of AdV;¹ the perspective is also supported in the recent position statement from the IDWP EBMT.¹³

This study had limitations in common with all surveys. The fixed and limited number of questions meant that the reasoning behind each response could not be fully or freely explained by the reporting physician. In particular, this meant that aspects such as

**TABLE 2** First-line therapy for new cases of symptomatic adenovirus disease and standard protocols for the use of intravenous cidofovir

Ranked highest (1) to lowest (4) for first-line therapy n (%)	Cidofovir	Brincidofovir	Cell-based therapy	Ribavirin
Responses from physicians who manage pediatric patients; n = 28				
1	24 (85.7)	3 (10.7)	0	0
2	3 (10.7)	13 (46.4)	7 (25.0)	1 (3.6)
3	0	5 (17.9)	12 (42.9)	5 (17.9)
4	0	3 (10.7)	2 (7.1)	14 (50.0)
Not used	1 (3.6)	4 (14.3)	7 (25.0)	8 (28.6)
Responses from physicians who manage adult patients; n = 14				
1	13 (92.9)	0	0	1 (7.1)
2	1 (7.1)	4 (28.6)	1 (7.1)	6 (42.9)
3	0	4 (28.6)	5 (35.7)	1 (7.1)
4	0	2 (14.3)	5 (35.7)	2 (14.3)
Not used	0	4 (28.6)	3 (21.4)	4 (28.6)
Standard protocols for the use of intravenous cidofovir				
	Physicians who manage pediatric patients; n = 28		Physicians who manage adult patients; n = 14	
Availability of a standard protocol				
Yes	27 (96.4)		12 (85.7)	
No	1 (3.6)		2 (14.3)	
If yes; typical starting dose				
1 mg/kg three times a wk	8 (28.6)		1 (7.1)	
5 mg/kg/wk	19 (67.9)		11 (78.6)	
If yes; typical maintenance dose				
1 mg/kg three times a wk	10 (35.7)		2 (14.3)	
5 mg/kg/wk	17 (60.7)		10 (71.4)	

Note that responses from physicians who manage pediatric patients and those who manage adult patients should not be directly compared.

the assessment of patient risk and AdV testing protocols were not fully evaluated. These, and other interesting aspects such as the cost-benefit balance of screening, could be topics of future study. Additionally, although our findings are generally representative of major transplant centers in Europe, clinical practice may vary for a minority of patients treated at very small centers (with limited resources or experience), particularly for adults and other patient groups considered to be at low-risk of AdV infection.

Data gathered in this multicenter European survey, conducted as part of the wider AdVance study, provide a contemporary snapshot of current screening and treatment approaches in both pediatric and adult patients. Findings demonstrated that the current screening and treatment practices for AdV infection in allo-HCT recipients broadly align with current guidelines and are based on physicians' perception of patient risk. AdV is known to be a potentially serious complication following allo-HCT, particularly in pediatric patients. These perceptions appear to drive a more proactive screening and treatment approach in children than in adults.

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CONFLICT OF INTEREST

The AdVance study was supported by Chimerix, who are developing an investigational drug for the treatment of AdV infection in allo-HCT recipients. The AdVance practice pattern survey was conducted by Analytica Laser. Marta González-Vicent, Marta Verna, Cécile Pochon, and Kanchan Rao participated in the AdVance study. Aastha Chandak is an employee of Analytica Laser, and Enrikas Vainorius, Tom Brundage, Essy Mozaffari, and Garrett Nichols are employees of Chimerix.



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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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