Biol Blood Marrow Transplant 25 (2019) 810–818

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Incidence of Adenovirus Infection in Hematopoietic Stem Cell Transplantation Recipients: Findings from the AdVance Study

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Article history:
Received 14 November 2018
Accepted 14 December 2018

Key Words:
Allogeneic hematopoietic stem cell transplantation
Adenovirus
Screening
Diagnosis
Incidence
Viremia
Risk factors
Age
Immunosuppression
Donor

A B S T R A C T

Adenovirus (AdV) is an increasingly recognized threat to recipients of allogeneic hematopoietic stem cell transplantation (allo-HCT), particularly when infection is prolonged and unresolved. AdVance is the first multinational, multicenter study to evaluate the incidence of AdV infection in both pediatric and adult allo-HCT recipients across European transplantation centers. Medical records for patients undergoing first allo-HCT between January 2013 and September 2015 at 50 participating centers were reviewed. The cumulative incidence of AdV infection (in any sample using any assay) during the 6 months after allo-HCT was 32% (95% confidence interval [CI], 30.9% to 33.4%) among pediatric allo-HCT recipients (n = 1736) and 6% (95% CI, 4.7% to 6.4%) among adult allo-HCT recipients (n = 2540). The incidence of AdV viremia ≥1000 copies/mL (a common threshold for initiation of preemptive treatment) was 14% (95% CI, 13.0% to 14.8%) in pediatric recipients and 1.5% (95% CI, 1.1% to 2.0%) in adult recipients. Baseline risk factors for developing AdV viremia ≥1000 copies/mL included younger age, use of T cell depletion, and donor type other than matched related. Baseline demographic factors were broadly comparable across patients of all ages and identified by multivariate analyses. Notably, the incidence of AdV infection decreased stepwise with increasing age; younger adults (age 18 to 34 years) had a similar incidence as older pediatric patients (<18 years). This study provides a contemporary multicenter understanding of the incidence and risk factors for AdV infection following allo-HCT. Our findings may help optimize infection screening and intervention criteria, particularly for younger at-risk adults.

INTRODUCTION

Adenovirus (AdV) is an increasingly recognized threat to successful outcomes after allogeneic hematopoietic stem cell transplantation (allo-HCT). Infection or reactivation is common after allo-HCT, because of the immunosuppressive therapies required for transplant success [1–4]. In most cases, emergent AdV infection is first identified within 100 days after transplantation [1–4]. Several small-scale studies have shown that systemic AdV infection increases the risk of death, particularly in cases of prolonged and unresolved infection [5–16]. Higher AdV loads have been associated with a particularly poor prognosis [16]. Adenovirus viremia, defined as ≥1000 copies/mL, in a lymphopenic patient, or in a patient with stool positivity and rapidly rising quantitative results, are considered appropriate thresholds for the initiation of preemptive antiviral treatment [15].

Challenges in the management of AdV include the lack of validated criteria for identifying patients at risk of progression to life-threatening infection,the lack of treatments with a positive benefit:risk ratio, and the absence of systemic analyses of baseline risk factors for reactivated versus incident AdV infection from the gut or other tissues [17–20]. Current estimates for the incidence of clinically important AdV infection are variable and perhaps underestimates of the observed rates. The incidence reports of any AdV infection in allo-HCT recipients are generally from small or single-center studies and range from ~15% to 44%

Financial disclosure: See Acknowledgments on page 817.

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https://doi.org/10.1016/j.bbmt.2018.12.753

in pediatric patients, and from ~3% to 19% in adults [1–3,16,21–26].

Several previous studies have evaluated risk factors for AdV infection following allo-HCT, including younger age, graft-versus-host disease (GVHD) grade II-IV, myeloablative conditioning, T cell depletion/lymphopenia, cord blood or HLA-mismatched graft, and pretransplantation AdV infection [1,2,4,21–29]. However, these studies were conducted over varying time periods and in centers with variable surveillance techniques and immunosuppression protocols, posing a challenge to obtaining an accurate and generalizable estimate of the incidence of AdV infection in allo-HCT recipients.

The AdVance study was designed to examine the incidence, management, and outcomes of AdV infection following allo-HCT [30–33]. AdVance is the first multicenter study to evaluate AdV infection incidence across multiple European transplantation centers. The aim of this specific analysis was to evaluate the incidence of AdV infection in adult and pediatric allo-HCT recipients.

MATERIALS AND METHODS

The AdVance Study

AdVance was a retrospective, multicenter, multinational study of the incidence, management, and clinical outcomes of AdV infection in adult and pediatric patients undergoing first allo-HCT. Centers were initially selected for the potential to participate in the AdVance study if they were reported to conduct at least 30 allo-HCT procedures per year [34].

Fifty centers took part in the AdVance study, located in 7 European countries: the United Kingdom, France, Germany, Italy, Spain, The Netherlands, and Czech Republic.

Data Collection

An electronic registry of deidentified medical and laboratory data was compiled for patients who underwent a first allo-HCT procedure between January 1, 2013, and September 30, 2015, at a participating center. For each patient, the following information was entered into the registry: date of allo-HCT, patient age at allo-HCT, sex, stem cell source, graft manipulation, underlying disease for allo-HCT, donor type, type of induction/conditioning regimen, and vital status (alive or dead).

All patient records were also reviewed for any AdV-positive tests (ie, polymerase chain reaction, antigen, virus isolation) within the 6 months after allo-HCT, regardless of the biological specimen analyzed (ie, stool, blood, respiratory secretion, or urine). Separate and additional registries were created for patients with a positive AdV test result to capture detailed baseline and follow-up information, to examine the natural history of disease and the management of AdV infection for up to 1 year after transplantation. Data collated for these patients included: all AdV test results and the thresholds for AdV detection, demographic data, patient height and weight, other laboratory test findings including coinfections, AdV organ involvement, anti-AdV treatment or interventions received, hospitalizations during follow-up, clinical outcomes (eg, GVHD, relapse of underlying disease, graft failure, additional allo-HCT), and vital status.

Data extraction was done by a clinical research assistant at Analytica Laser (New York, NY) or by hospital personnel at each center. Analytica Laser oversaw the data collection process to minimize the possibility of missing or poor–quality data. Data collection and use were in accordance with local and national laws.

Statistical Analyses

Demographic and transplant characteristics were stratified by age (<18 years versus ≥18 years) and summarized for all allo-HCT recipients and those with AdV infection, AdV viremia, or AdV viremia ≥1000 copies/mL within the 6 months after allo-HCT. Definitions of AdV infection were from the ECIL-4 guidelines: AdV infection, as a positive AdV test from any biological sample; AdV viremia, as a positive PCR, antigen, or virus isolation test of peripheral blood [35].

Characteristics associated with incidence of AdV viremia ≥1000 copies/mL in the 6 months after allo-HCT, a threshold commonly used for the initiation of preemptive treatment, were assessed in a multivariate model using Cox proportional hazards analysis [15,16,30]. Factors collected for all patients and eligible for inclusion in the model were sex (male versus female), underlying disease (malignant, nonmalignant immunodeficient, or nonmalignant immunocompetent), age at the time of transplantation (pediatric: 0 to <2, 2 to 11, and 12 to 17 years; adult: 18 to 34, 35 to 49, 50 to 64, and ≥65 years), donor type (matched related, matched unrelated, mismatched, haploidentical, or cord blood), source of stem cells (bone marrow, peripheral blood stem cells, or cord blood), conditioning regimen intensity (myeloablative or nonmyeloablative, ie, reduced intensity), and T cell depletion method (ex vivo T cell depletion or serotherapy [alemtuzumab, antithymocyte globulin [ATG]], or none). In addition to a combined model including all patients, separate models were examined for pediatric and adult patients.

RESULTS

Pediatric Allo-HCT Recipients

Medical records were reviewed for 1736 pediatric patients who underwent a first allo-HCT between January 2013 and September 2015. Demographic and transplantation characteristics of these recipients are presented in Table 1. The median age among pediatric patients was 7 years, with a range of 0 to 17 years; 63% were male. Almost two-thirds (64%) had an underlying malignancy; the most common types were acute lymphocytic leukemia (30%) and acute myelogenous leukemia (17%). The most common stem cell source was the bone marrow (54%). The most prevalent donor type was matched unrelated (40%). The majority of patients received myeloablative conditioning (85%); 43% underwent T cell depletion using ATG serotherapy (Table 1).

In total, 558 of the 1736 pediatric allo-HCT recipients (32%; 95% confidence interval [CI], 30.9% to 33.4%) had a positive AdV test from blood, stool, urine or respiratory secretions in the 6 months after allo-HCT (Figure 1). AdV was commonly detected in stool (in 411 of the 588 patients; 74%). In 519 of the 558 patients (93%), AdV infection was identified as part of routine screening practices; the remainder were identified during syndromic workup (for, eg, pneumonia or cystitis). Most cases of AdV infection were identified in the first 100 days post-transplantation (in 503 of the 558 patients; 90%).

Table 1
Demographic, Clinical, and Transplantation Characteristics of the Pediatric and Adult Allo-HCT Recipients

Characteristic	Pediatric Patients (N = 1736)	Adult Patients (N = 2540)
Male sex, n (%)	1098 (63)	1463 (58)
Age, yr, median (range)	7 (<1-17)	51 (18-79)
Underlying condition, n (%)		
Malignant	1109 (64%)	2479 (97%)
Acute lymphocytic leukemia	519 (30)	330 (13%)
Acute myelogenous leukemia	299 (17)	996 (39%)
Other malignancy	131 (8)	355 (14%)
Myelodysplasia	103 (6)	299 (12%)
Non-Hodgkin's lymphoma	37 (2)	234 (9%)
Chronic myelogenous leukemia	19 (1)	77 (3%)
Multiple myeloma	1 (<1)	104 (4%)
Chronic lymphocytic leukemia	0	84 (3%)
Nonmalignant immunodeficient	427 (25)	19 (1%)
Congenital immunodeficiency	219 (13)	6 (<1%)
Other congenital	193 (11)	12 (<1%)
Autoimmune disease	15 (1)	1 (<1%)
Nonmalignant immunocompetent	200 (11)	42 (2%)
Aplastic anemia	87 (5)	34 (1)
Thalassemia	87 (5)	6 (<1)
Sickle cell anemia	26 (1)	2 (<1)
Stem cell source, n (%)		
Bone marrow	934 (54)	466 (18)
Peripheral blood stem cell	547 (31)	1882 (74)
Cord blood	255 (15)	192 (8)
Donor type*, n (%)		
Matched related	489 (28)	903 (36)
Matched unrelated	701 (40)	976 (38)
Mismatched	178 (10)	327 (13)
Haploidentical	269 (15)	291 (11)
Conditioning regimen, n (%)		
Myeloablative	1480 (85)	1711 (67)
Nonmyeloablative	256 (15)	829 (33)
T cell depletion, n (%)		
Ex vivo	283 (16)	737 (29)
Serotherapy (ATG)	752 (43)	729 (29)
Serotherapy (alemtuzumab)	252 (15)	228 (9)
None	449 (26)	846 (33)

*Nonexclusive categories. Cord blood units not included.
Pediatric patients defined as age <18 years. Mismatched donor type is any category other than fully aligned HLAs.

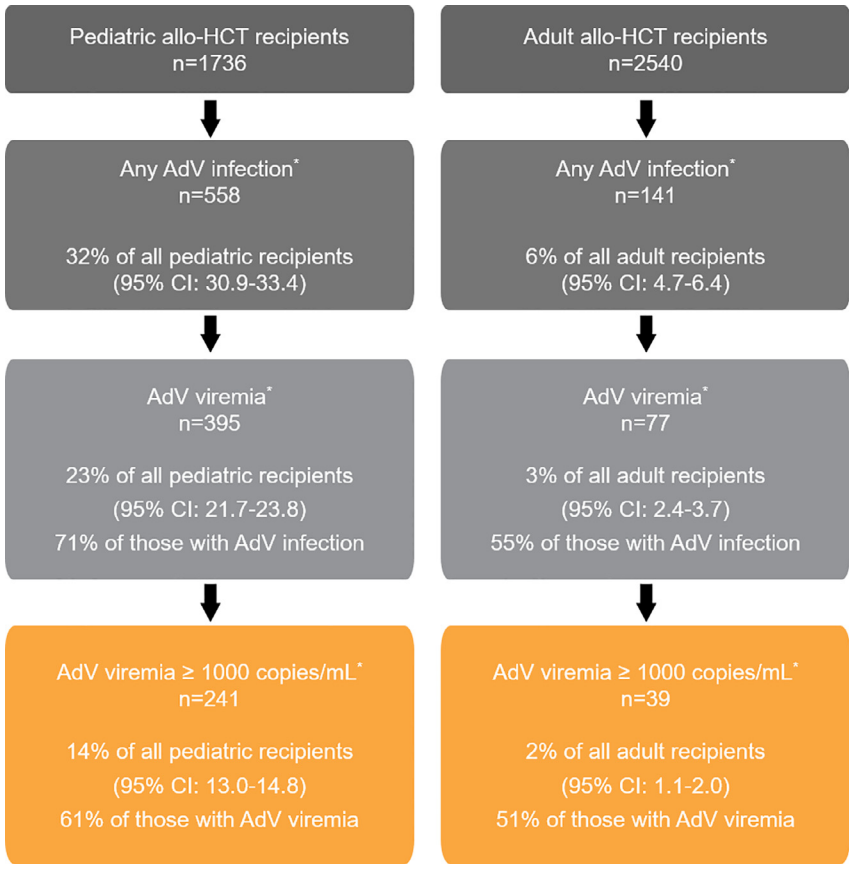

Figure 1. Incidence of AdV infection in allo-HCT recipients.
*In any assay of blood, stool, urine or respiratory secretions within 6 months of transplantation.
Note that incidence in pediatric and adult patients should not be compared directly.

Among those with an identified AdV infection, 395 of 558 (71%) developed AdV viremia within 6 months of allo-HCT (Figure 1). The cumulative incidence of AdV viremia among pediatric allo-HCT recipients was 23% (95% CI, 21.7% to 23.8%) (Table 2).

AdV disease was defined as AdV infection plus clinical symptoms (organ system involvement [cardiac/gastrointestinal/hepatic/central nervous system/renal/respiratory] with or without histological confirmation) [35]. Overall, 129 patients (23% of all those with AdV infection) developed AdV disease, most commonly in a single organ system (113 of 129; 88% of all patients with AdV disease), usually the gastrointestinal system (101 of 129; 78%). Of these, 97 patients (17% of those with AdV infection) developed disseminated AdV disease, defined as AdV disease in ≥1 organ system and AdV viremia, or in ≥2 organ systems without AdV viremia (with or without histological confirmation).

Among those with AdV viremia, 241 of 395 (61%) had AdV viremia ≥1000 copies/mL (Figure 1). The cumulative incidence of AdV viremia ≥1000 copies/mL in pediatric allo-HCT recipients was 14% (95% CI, 13.0% to 14.8%). AdV viremia ≥1000 copies/mL was detected at a median of 26 days (interquartile range [IQR], 13 to 56 days) after transplantation (Figure 2). Of these patients, 66% (158 of 241) had a bacterial, viral, and/or fungal coinfection at the time of first AdV detection. The median number of coinfections was 1 (range, 0 to 6). In total, 103 of the 241 patients with AdV viremia ≥1000 copies/ml (43%) had another dsDNA viral coinfection along with AdV: cytomegalovirus (27%), Epstein-Barr virus (17%), and/or BK virus (9%). Ten percent of the patients (24 of 241) had ≥2 dsDNA viral coinfections.

The incidence of AdV infection, AdV viremia, and AdV viremia ≥1000 copies/mL in pediatric patients with different demographic, clinical, and transplant characteristics are presented in Table 2. An age-dependent association was observed in which AdV infection appeared to be less common in older children. AdV viremia ≥1000 copies/mL was observed in 19% of patients aged 0-<2 years and in 10% of patients aged 12-17 years. Patients receiving allo-HCT from haploidentical or mismatched donors, ex vivo T-cell depletion, or alemtuzumab serotherapy, appeared to have the highest incidence of AdV infection. Among patients receiving alemtuzumab serotherapy, 44%, 33%, and 25%, developed AdV infection, AdV viremia, or AdV viremia ≥1000 copies/mL, respectively.

Multivariate analysis showed that patient age, donor type, and T cell depletion method were significant prognostic factors for the development of AdV viremia ≥1000 copies/mL. Significantly higher risk was associated with lower age, receipt of transplant from a non–HLA-matched related donor, and ex vivo T cell depletion or alemtuzumab serotherapy (versus none; Figure 3). Although stem cell source was a significant factor ($P < .05$) in the univariate analysis, it was excluded from the multivariate model as it was found to be highly correlated with type of donor.

Adult Allo-HCT Recipients

Medical records for 2540 adult recipients of allo-HCT performed between January 2013 and September 2015 were

Table 2
AdV Infection in Pediatric Patients (N = 1736) in the 6 Months after Allo-HCT by Demographic, Clinical, and Transplantation Characteristics

Characteristic	AdV Infection	AdV Viremia	AdV Viremia ≥1000 Copies/mL
Patients, n (%)	558 (32)	395 (23)	241 (14)
Sex, n/N (%)			
Male	364/1098 (33)	260/1098 (24)	159/1098 (14)
Female	194/638 (30)	135/638 (21)	82/638 (13)
Age group, n/N (%)			
0-<2 yr	101/320 (32)	80/320 (25)	61/320 (19)
2-5 yr	145/382 (38)	98/382 (26)	63/382 (16)
6-11 yr	191/564 (34)	125/564 (22)	72/564 (13)
12-17 yr	121/470 (26)	92/470 (20)	45/470 (10)
Underlying condition, n/N (%)			
Malignant	348/1109 (31)	258/1109 (23)	148/1109 (13)
Nonmalignant immunodeficient	152/427 (36)	101/427 (24)	72/427 (17)
Nonmalignant immunocompetent	58/200 (29)	36/200 (18)	21/200 (10)
Stem cell source, n/N (%)			
Bone marrow	275/934 (29)	182/934 (19)	116/934 (12)
Peripheral blood stem cells	198/547 (36)	157/547 (29)	92/547 (17)
Cord blood	85/255 (33)	56/255 (22)	33/255 (13)
Donor type*, n/N (%)			
Matched related	104/489 (21)	58/489 (12)	33/489 (7)
Matched unrelated	249/701 (36)	164/701 (23)	100/701 (14)
Mismatched	61/178 (34)	53/178 (30)	43/178 (24)
Haploidentical	109/269 (41)	90/269 (33)	49/269 (18)
Conditioning regimen, n/N (%)			
Myeloablative	478/1480 (32)	336/1480 (23)	202/1480 (14)
Nonmyeloablative	80/256 (31)	59/256 (23)	39/256 (15)
T cell depletion, n/N (%)			
Ex vivo	125/283 (44)	103/283 (36)	53/283 (19)
Serotherapy with ATG	230/752 (31)	151/752 (20)	95/752 (13)
Serotherapy with alemtuzumab	111/252 (44)	82/252 (33)	62/252 (25)
None	92/449 (20)	59/449 (13)	31/449 (7)

*Nonexclusive categories. Cord blood units not included.
Mismatched donor type is any category other than fully aligned HLAs.

reviewed. Their demographics and transplant characteristics are presented in Table 1. The median age was 51 years and 58% of the patients were male. Almost all patients (97%) had an underlying malignancy; the most common types were acute myelogenous leukemia (39%), acute lymphocytic leukemia (13%), and myelodysplasia (12%). Adult patients most commonly received a peripheral stem cell graft (74%) from a matched unrelated donor (38%) or a matched related donor (36%). Approximately two-thirds of patients received myeloablative conditioning (67%), and 29% received ex vivo T cell depletion or ATG serotherapy, respectively. One-third of the patients (33%) received no T cell depletion (Table 1).

In total, 141 of the 2540 adult allo-HCT recipients (6%; 95% CI, 4.7% to 6.4%) had a positive AdV test using blood, stool, urine, or secretions from the respiratory tract in the 6 months following their transplant (Figure 1). AdV was commonly detected in blood (141 patients) and stool (64 patients). In 101 of the 141 patients (72%), AdV infection was identified as part of routine screening practices; the remainder were identified during system-focused diagnostic workups. As in pediatric patients, most cases of AdV infection in adult patients were identified in the first 100 days after transplantation (96 of 141).

Among the 141 patients with an identified AdV infection, 77 (55%) developed AdV viremia (Figure 1). The cumulative incidence of AdV viremia adult allo-HCT recipients was 3% (95% CI, 2.4% to 3.7%) (Table 3).

Overall, 39 patients (28% of all patients with AdV infection) developed AdV disease, nearly always in a single organ system (32 of the 39 patients [82%] with AdV disease), usually the gastrointestinal system (28 of 39; 72%). Of these, 19 patients (13% of those with AdV infection) developed disseminated AdV disease.

Among the 77 patients with AdV viremia, 39 developed viremia with ≥1000 copies/mL (Figure 1). The cumulative incidence of AdV viremia ≥1000 copies/mL in adult allo-HCT recipients was 1.5% (95% CI, 1.1% to 2.0%). AdV viremia ≥1000 copies/mL was detected later in adults than in children, with a median of 61 days (IQR, 33 to 91 days) from transplantation to infection identification (Figure 2). Of these patients, 80% (31 of 39) had a bacterial, viral, and/or fungal coinfection at the time of detection of AdV infection. The median number of coinfections was 2 (range, 0 to 6). Twenty-six of the 39 patients (67%) had a dsDNA viral coinfection along with AdV: cytomegalovirus (51%), Epstein-Barr virus (23%), and/or BK virus (23%).

The incidence of AdV infection, AdV viremia, and AdV viremia ≥1000 copies/mL in adult patients with different demographic, clinical, and transplant characteristics are presented in Table 3. The highest incidence was noted in patients receiving alemtuzumab serotherapy, with AdV infection in 16%, AdV viremia in 12%, and AdV viremia ≥1000 copies/mL in 7%. These values were relatively higher in patients with a nonmalignant immunodeficient underlying condition (21%, 11%, and 5%, respectively).

Multivariate analysis identified patient age, donor type, and T cell depletion method as significant prognostic factors for the development of AdV viremia ≥1000 copies/mL. Significantly higher risk was associated with younger age, myeloablative conditioning, use of a mismatched donor (versus a matched related donor), and alemtuzumab T-cell depletion (versus none; Figure 4).

Findings from the Combined Multivariate Model

An exploratory multivariate model analysis was conducted including all pediatric and adult patients with AdV viremia ≥1000 copies/mL, despite differences in the patient populations. In this model (controlled for sex, conditioning regimen, underlying disease, donor type, and T cell depletion), a

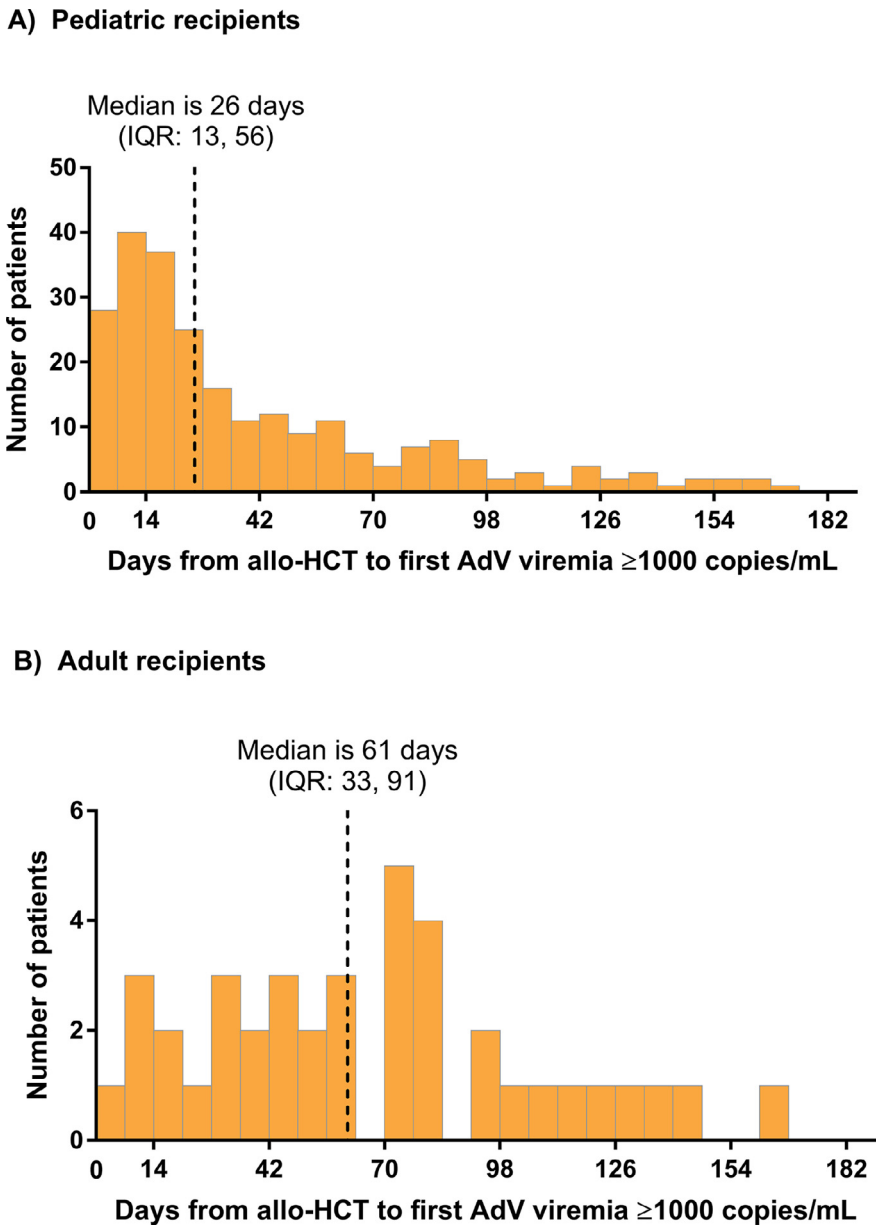

Figure 2. Time to first detection of AdV viremia with ≥1000 copies/mL following allo-HCT.

stepwise increase in risk was observed with younger patient age (versus 35 to 49 years as the reference group). The lowest risk (hazard ratio [HR], 0.20; 95% CI, 0.03 to 1.60) was associated with the oldest patients (age >65 years), and the risk increased stepwise with younger age: HR, 0.47 (95% CI, 0.18 to 1.21) for age 50 to 64 years, 2.34 (95% CI, 1.07 to 5.13) for age 18 to 34 years, 6.59 (95% CI, 3.2 to 13.58) for age 12 to 17 years, 10.16 (95% CI, 5.11 to 20.22) for age 2 to 11 years, and 13.32 (95% CI, 6.39 to 27.76) for age <2 years.

DISCUSSION

The multicenter AdVance study found higher incidences of AdV infection, viremia, and viremia ≥1000 copies/mL in pediatric allo-HCT recipients compared with adult allo-HCT recipients. This may be in part a product of the less frequent screening in adult patients, with many cases of AdV infection in adult transplant recipients identified only after clinical symptoms become apparent [30]. However, we found that the risk of AdV viremia ≥1000 copies/mL decreased stepwise with increasing age, suggesting that younger adults could particularly benefit from an increased intensity of AdV screening to allow preemptive treatment.

Published estimates for the incidence of AdV infection in allo-HCT recipients in previous single-center studies range from 15% to 44% in pediatric patients and 3% to 19% in adults [1–3,21–25]. This study reviewed medical records from over 4000 allo-HCT recipients treated between January 2013 and September 2015 at 50 European transplantation centers. Conducted as part of the larger AdVance study, this analysis represents a unique, large-scale, contemporary multicenter assessment of AdV infection incidence following allo-HCT [30–33]. Our findings showed that around 1 in 3 pediatric allo-HCT recipients (32%) had a detectable AdV infection in the 6 months following transplantation. A substantially smaller proportion (6%) of adult recipients had an AdV infection in the same period.

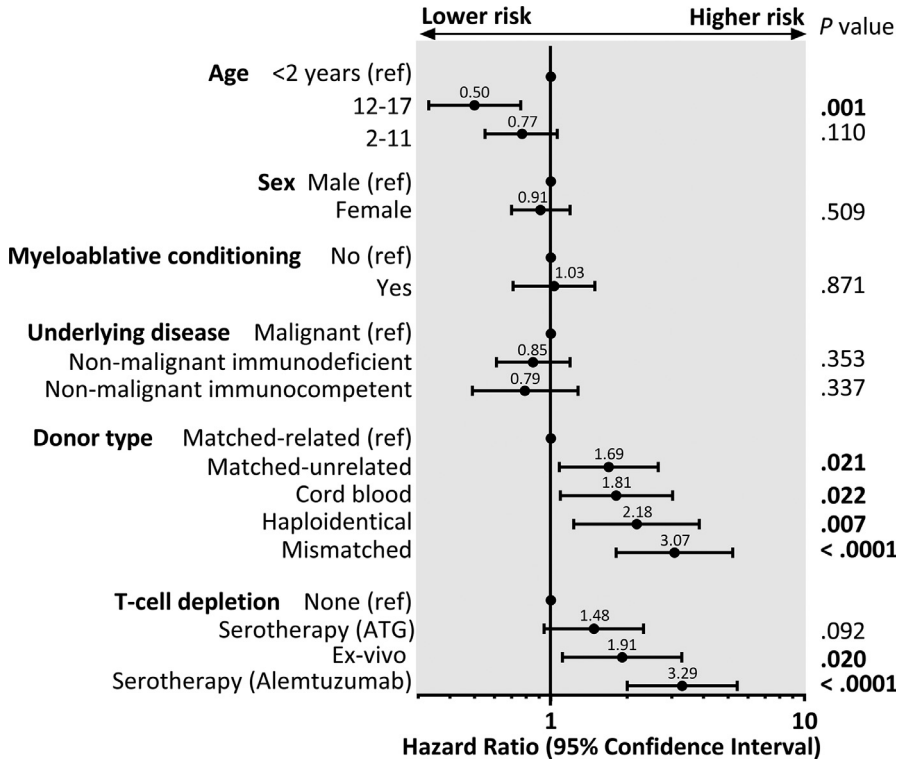

Figure 3. Prognostic factors for the development of AdV viremia ≥1000 copies/mL within 6 months of allo-HCT in pediatric patients.

Table 3
AdV Infection in Adult Patients (N = 2540) in the 6 Months after Allo-HCT by Demographic, Clinical, and Transplantation Characteristics

Characteristic	AdV Infection	AdV Viremia	AdV Viremia ≥1000 Copies/mL
Patients, n (%)	141 (6)	77 (3)	39 (2)
Sex, n/N (%)			
Male	79/1463 (5)	49/1463 (3)	26/1463 (2)
Female	62/1077 (6)	28/1077 (3)	13/1077 (1)
Age group, n/N (%)			
18-34 yr	63/566 (11)	39/566 (7)	21/566 (4)
35-49 yr	24/626 (4)	13/626 (2)	9/626 (1)
50- 64 yr	43/1086 (4)	19/1086 (2)	8/1086 (<1)
≥65 yr	11/262 (4)	6/262 (2)	1/262 (<1)
Underlying condition, n/N (%)			
Malignant	137/2479 (6)	75/2479 (3)	38/2479 (2)
Nonmalignant immunodeficient	4/19 (21)	2/19 (11)	1/19 (5)
Nonmalignant immunocompetent	0/42 (0)	0/42 (0)	0/42 (0)
Stem cell source, n/N (%)			
Bone marrow	16/466 (3)	10/466 (2)	6/466 (1)
Peripheral blood stem cells	104/1882 (6)	59/1882 (3)	29/1882 (2)
Cord blood	21/192 (11)	8/192 (4)	4/192 (2)
Donor type*, n/N (%)			
Matched related	29/903 (3)	16/903 (2)	8/903 (<1)
Matched unrelated	59/976 (6)	33/976 (3)	19/976 (2)
Mismatched	35/327 (11)	20/327 (6)	10/327 (3)
Haploidentical	11/291 (4)	6/291 (2)	0/291 (0)
Conditioning regimen, n/N (%)			
Myeloablative	97/1711 (6)	47/1711 (3)	21/1711 (1)
Nonmyeloablative	44/829 (5)	30/829 (4)	18/829 (2)
T cell depletion, n/N (%)			
Ex vivo	53/737 (7)	24/737 (3)	9/737 (1)
Serotherapy with ATG	29/729 (4)	15/729 (2)	8/729 (1)
Serotherapy with alemtuzumab	36/228 (16)	27/228 (12)	16/228 (7)
None	23/846 (3)	11/846 (1)	6/846 (<1)

*Nonexclusive categories. Cord blood units not included.
Mismatched donor type is any category other than fully aligned HLAs.

In our study, approximately three-quarters (71%) of pediatric patients with any AdV infection went on to develop viremia, with just over one-half of these (61%) developing viremia ≥1000 copies/mL. This corresponds to 14% of all pediatric allo-HCT recipients developing AdV viremia ≥1000 copies/mL, closely aligning with the 15% previously reported by Mynarek

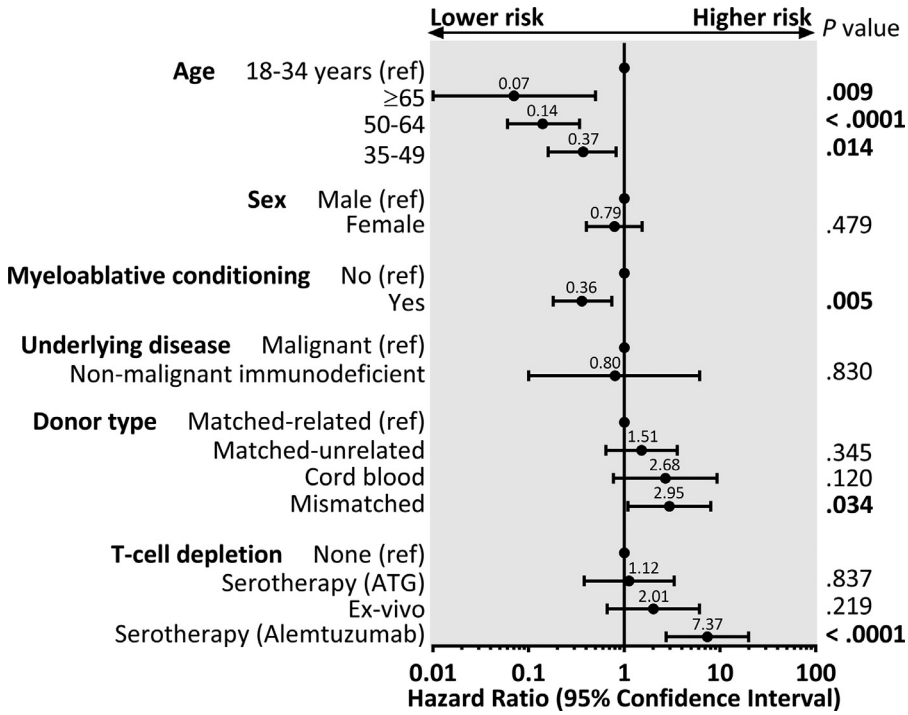

Figure 4. Prognostic factors for the development of AdV viremia ≥1000 copies/mL within 6 months of allo-HCT in adult patients.
No recipients with a haploidentical donor type or a nonmalignant immunocompetent underlying disease developed AdV viremia ≥1000 copies/mL. Mismatched donor type is any category other than fully aligned HLAs.

et al [16]. AdV loads of ≥1000 copies/mL in blood have been associated with a poor prognosis, and this threshold is becoming a point for considering preemptive antiviral therapy [15,16,30]. A similarly high proportion of adult patients with AdV infection also developed viremia (55%), with one-half of these developing AdV viremia ≥1000 copies/mL (51%; 2% of all patients) in our study. As this was a retrospective study of medical records, the identification of patients with AdV disease was challenging, but is expected to overlap with the population with AdV viremia ≥1000 copies/mL. These findings suggest that while the incidence of AdV infection is higher in pediatric compared with adult patients, the proportion who go on to develop more serious infection (viremia or viremia ≥1000 copies/mL) is similarly high. The lower incidence of initial AdV infection detection in adult patients may be in part a product of a less proactive approach to screening compared with in pediatric patients [30]. There also may be differences in the source of AdV infection in adults versus children after HCT, with AdV most commonly originating from persistent infection of gut mucosal lymphocytes in children. Replication to high levels within the gut commonly precedes dissemination of AdV in the blood [15]. The source of infection in adults is less well studied, but persistence of AdV in gut tissue may be less likely. The potential difference in pathogenesis is supported by recent publications encouraging stool screening as a way to detect early AdV infection in pediatric patients who would most benefit from preemptive antiviral treatment [15,18,21].

It is generally accepted that higher or more prolonged levels of AdV viremia are indicative of more clinically relevant infections [10–15,33]. We found similar prognostic factors for AdV viremia ≥1000 copies/mL in pediatric allo-HCT recipients (younger age, donor type other than matched related, and ex vivo T cell depletion or alemtuzumab serotherapy) and adult allo-HCT recipients (younger age, the use of nonmyeloablative conditioning, a mismatched donor type, and alemtuzumab serotherapy). It was of particular interest that younger age was a consistent risk factor in both pediatric and adult populations. A combined multivariate analysis of pediatric and adult patients revealed a clear stepwise reduction in risk of AdV viremia ≥1000 copies/mL with increasing age. Previous multivariate analyses have shown that gGVHD grade >II [21,23], cord blood donor source [21], ex vivo T cell depletion [21], and previous AdV infection [23] are significant predictive factors for AdV infection in pediatric allo-HCT recipients. Similar factors have been identified in adult allo-HCT recipients: GVHD grade ≥II [29], younger age [29], use of 50 to 100 mg alemtuzumab and low lymphocyte count [2], and GVHD or treatment with ≥2 immunosuppressive agents, have shown significant associations with AdV dissemination (ie, disease in ≥2 organ systems) [24]. Previously identified prognostic factors are from single-center studies in which patient profiles, transplant type, AdV surveillance frequency, sample type, testing protocol, definitions of AdV infection, and other transplantation-related factors, can vary widely. These differences in methodology make comparison of individual single-center studies challenging. We believe that our unique multicenter approach helps overcome these challenges.

Taken together with previously reported findings, our data confirm that similar prognostic factors can be used to assess the risk of AdV infection and significant AdV infection in allo-HCT recipients of all ages. The link between immunosuppressive therapy and AdV infection is well established in the literature and likely explains the increased infection risk seen in our allo-HCT patients receiving transplants from unrelated or unmatched donors, and particularly from mismatched donors, who may require more robust immunosuppression to decrease sequelae from GVHD. The first 100 days after allo-HCT is the period of lowest cellular immunity and greatest risk. This time frame is also the period during which most centers screen patients for AdV weekly [30]. Our findings suggest that the acknowledged higher risk of AdV infection in pediatric patients also should apply to younger adults, who are at much greater

risk of developing AdV viremia ≥1000 copies/mL than older adults and may benefit from preemptive treatment.

The reasons for the observed higher incidence of AdV infection in younger patients compared with older patients are unclear. One reason is perhaps the likelihood that younger patients have more severe *de novo* AdV infection or persistence of AdV in latent stores, particularly in the intestine, that can become reactivated during transplantation immunosuppression. Older adults are much more likely to have developed immunity and to have cleared this latent store. This factor also may help explain why the median time to AdV viremia ≥1000 copies/mL also appeared to be longer in adult patients than in pediatric patients. This is supported by recent publications encouraging stool screening to identify patients at risk for AdV infection who would most benefit from preemptive antiviral treatment [15,18,21]. Other factors could include the differences in the patient profiles between younger and adult patients, or the relatively underdeveloped acquired immunity in younger patients. Our study design limited the possible analyses in this study, as we were only able to evaluate the predictive power only of those factors prespecified in the data collection protocol. For example, because GVHD information was collected only in subjects with AdV infection, we could not include it as a potential prognostic factor for the incidence of AdV viremia with ≥1000 copies/mL. We also used historical medical record data; the quality and completeness of which cannot be confirmed. Centers may have used various AdV screening, analysis, and treatment protocols, as well as different post-transplant immunosuppressive regimens. Finally, although risk factors for AdV infection were identified, the scientific rationale driving the risk cannot be elucidated using the current analysis.

We believe that the foregoing limitations are outweighed by the relative benefits of our approach, in which we were able to combine data from several different centers with a variety of patients, all of whom underwent allo-HCT over the same time frame in a setting in which clinical practice was relatively stable.

In conclusion, results from this multicenter analysis, conducted as part of the AdVance study, confirm an incidence of AdV infection during the 6 months after allo-HCT of ~32% for the pediatric patients and ~6% for the adults. The proportion of patients with AdV infection who developed viremia or viremia with ≥1000 copies/mL was similar in adults and children. More than one-half of patients with AdV infection developed viremia, and more than one-half of those had viremia with ≥1000 copies/mL. Although the origin of infection may explain the lower incidence of AdV infection in adults, some of the age effect also could be related to less frequent AdV screening practices, and we suggest that more frequent screening should be considered for at-risk adults. The risk factors for developing AdV viremia with ≥1000 copies/mL are broadly comparable across patients of all ages. Most notably, our findings suggest that the risk of AdV infection is greatest in pediatric allo-HCT recipients but decreases in a stepwise fashion with age, with younger adults (ie, age 18 to 34 years) with risk more aligned with that of adolescents than with that of older adults. T cell depletion and donor type are also independent risk factors for AdV viremia with ≥1000 copies/mL. This study provides a contemporary and multicenter understanding of the incidence and risk factors for AdV infection following allo-HCT. These findings may help optimize AdV infection screening and treatment practices, particularly for younger and at-risk adults.

ACKNOWLEDGMENTS

The authors thank the patients and investigators at each of the AdVance study sites. Sites and principle investigators are listed in Supplemental Material 1.

Financial disclosure: This study was supported by Chimerix and conducted by Analytica Laser. Medical writing support for this manuscript was funded by Chimerix and provided by Jennifer Bodkin of Engage Scientific, Horsham, UK.

Conflict of interest statement: M.R. has previously received research grants from Neovii, Novartis, and Sanofi. A.C. is an employee of Analytica Laser. E.V., T.B., E.M., and G.N. are employees of Chimerix. P. Sedláček, T.P., P. Sivaprakasam, and S.V. have no conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.12.753.

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