Risks and Outcomes of Adenovirus Disease in Pediatric HSCT Recipients –Comparison of Current Antiviral Treatment Options

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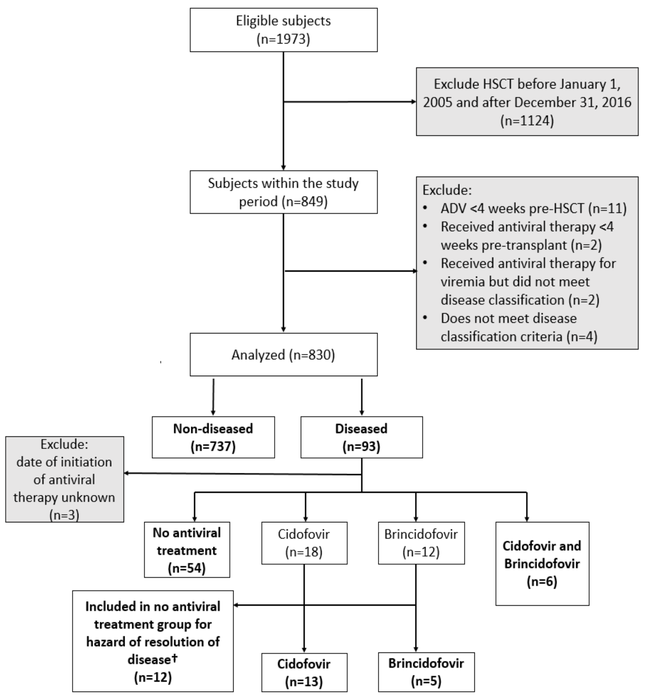
Introduction

- Adenovirus (ADV) infection in hematopoietic stem cell transplant (HSCT) recipients accounts for 22% of infection-associated mortality in pediatric umbilical cord transplant (UCT) recipients[1].
- ADV disease may present as upper respiratory infection, pharyngitis, conjunctivitis, meningoencephalitis, pneumonia, enteritis, myocarditis, hepatitis, and hemorrhagic cystitis[2].
- The current knowledge of the risk factors[3] associated with worse clinical outcome and the effectiveness of antiviral therapy in pediatric HSCT recipients have not been well described.
- This study determined the relationship between transplant characteristics and risk of ADV disease and also compared time to resolution of disease between pediatric patients who did and did not receive antiviral therapy.

Methods

- Retrospective cohort study.
- Pediatric HSCT recipients between January 1, 2005 and December 31, 2016.
- We identified cases of single end-organ and disseminated ADV disease[2] (2 or more organs) using a classification tool defined *a priori*.
- **Aim 1:** Determined the association between transplant characteristics and the risk of ADV disease.
  - Type of transplant: Allogeneic (non-cord) transplant (ALL), autologous transplant (AUT) and umbilical cord transplant (UCT).
  - Type of conditioning regimen: myeloablative or non-myeloablative.
- **Aim 2:** Compare clinical outcomes of ADV diseased patients who received antiviral therapy and those who did not.
  - Antiviral therapy: (1) intravenous cidofovir alone, (2) oral brincidofovir alone or (3) dual therapy with sequential intravenous cidofovir and oral brincidofovir.
- **Statistical analysis:** Time-varying cox proportional hazards regression model with robust sandwich estimate.



† These subjects had initiation of antiviral therapy after evidence of resolution of disease.

Figure 1. Study cohort diagram

Results

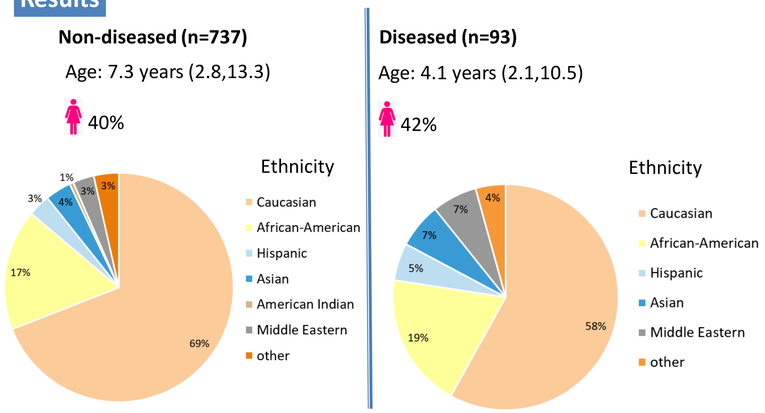
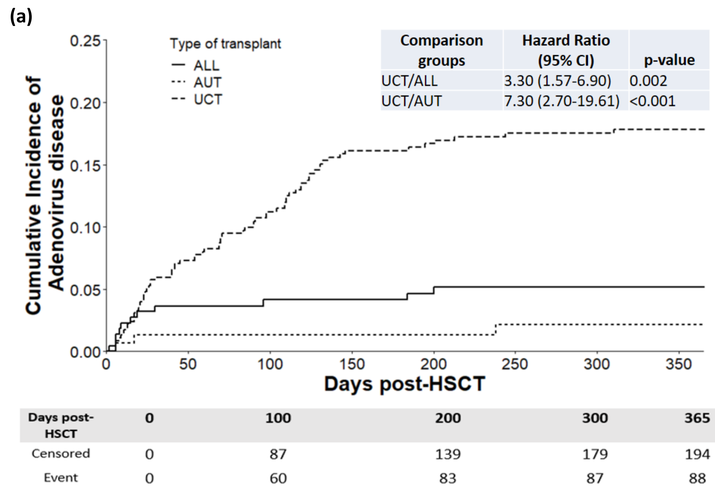
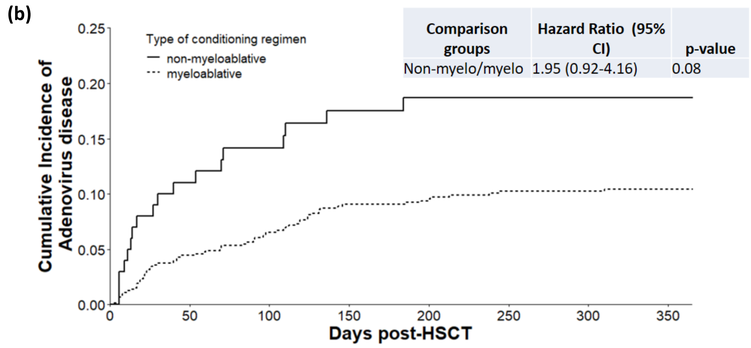


Figure 2. Characteristics of HSCT recipients (by transplants, n=830)



Comparison groups	Hazard Ratio (95% CI)	p-value
UCT/ALL	3.30 (1.57-6.90)	0.002
UCT/AUT	7.30 (2.70-19.61)	<0.001

Days post-HSCT	0	100	200	300	365
Censored	0	87	139	179	194
Event	0	60	83	87	88



Comparison groups	Hazard Ratio (95% CI)	p-value
Non-myelo/myelo	1.95 (0.92-4.16)	0.08

Days post-HSCT	0	100	200	300	365
Censored	0	87	139	179	194
Event	0	60	83	87	88

Cumulative incidence curves are not adjusted for covariates. ALL, Allogeneic (non-cord) transplants; AUT, autologous transplant; HSCT, hematopoietic stem cell transplants; UCT, umbilical cord transplants

Figure 3. Cumulative Incidence curve depicting cumulative incidence of adenovirus disease for the first year post-HSCT by (a) type of transplant and (b) conditioning regimen.

Table 1. Characteristics of HSCT recipients (by transplants, n=830)

	Non-diseased (n)	Non-diseased (%)	Diseased (n)	Diseased (%)
> 1 HSCT	63	9%	10	11%
Type of HSCT				
Autologous (AUT)	148	20%	3	3%
Allogeneic non-cord (ALL)	206	28%	13	14%
Allogeneic cord (UCT)	383	52%	77	83%
Conditioning regimen				
Myeloablative	656	89%	73	78%
Non-myeloablative	81	11%	20	22%
Primary diagnosis pre-transplant				
Hematologic Malignancy	290	39%	30	32%
Hematologic Non-malignancy	112	15%	18	19%
Solid Tumor	128	17%	2	2%
Genetic/Metabolic Disorder	126	17%	31	33%
Immunodeficiency	79	11%	11	12%
Other	2	0.3%	1	1%
Mortality	242	33%	47	51%
Death within first year of transplant (% of total mortality)	159	66%	35	74%

Table 2. Hazard of resolution of disease by presence or absence of antiviral therapy.

	ROD (n=78) (n (%))	No ROD (n=12) (n (%))	Comparison groups	Hazard Ratio (95% CI)	p-value
Antiviral therapy	14 (18)	10 (83)	Non-AT/AT	3.75 (1.57-8.93)	0.003
CID	5 (6)	8 (67)	Non-AT/CID	10.53 (3.69-30.30)	<0.001
CMX	4 (5)	1 (8)	Non-AT/CMX	5.92 (1.23-28.57)	0.03
Dual AT	5 (6)	1 (8)	Non-AT/Dual AT	1.22 (0.36-4.20)	0.75
No antiviral therapy	64 (82)	2 (17)	REF	REF	

AT, antiviral therapy; CID, intravenous cidofovir; CMX, oral brincidofovir; Dual AT, dual antiviral therapy (intravenous cidofovir and oral brincidofovir); LFTs, transaminases; REF, reference group.

Conclusions

- This is the first pediatric cohort study to report risk factors and clinical outcomes of ADV disease, irrespective of ADV-DNAemia.
- UCT recipients have a higher hazard of adenovirus disease compared to other HSCT recipients.
- Contrary to previous reports studying ADV-DNAemia, our study noted an earlier resolution of ADV disease in the absence of antiviral therapy even when adjusted for disseminated disease.

Limitations

- Analysis regarding efficacy of antiviral therapy is limited by lack of standard dosing or duration of therapy.
- Our study does not account for T-cell function, lymphocyte count, changes in immunosuppression during ADV disease and other co-morbidities such as graft-vs-host-disease that may limit the interpretation of the results for the resolution of disease.

Future Directions

- ADV disease should be considered on the differential diagnosis in the appropriate clinical scenario in UCT recipients.
- Given the lack of earlier resolution of disease with antiviral therapy, providers should weigh the risk of adverse effects against any potential benefit of antiviral therapy in the outcome of ADV disease post-HSCT.
- Future directions for therapeutic management should focus on T-cell and NK cell based therapies to define the role of T-cell reconstitution influencing ADV disease outcome.

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