



Pulmonary Complications in Pediatric and Adolescent Patients Following Allogeneic Hematopoietic Cell Transplantation



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Pulmonary complications after hematopoietic cell transplantation (HCT) can lead to significant morbidity and mortality. Limited evaluation of the true incidence of these complications in children and subsequent outcomes of these complications have not been evaluated recently. In April 2018, the National Heart, Lung, and Blood Institute; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and the National Cancer Institute cosponsored a meeting of experts to describe the status of pulmonary complications in children after HCT, identify critical gaps in knowledge, and explore avenues for research to advance care and optimize outcomes. The Center for International Blood and Marrow Transplant Research was used to evaluate the cumulative incidence of pulmonary complications in children and their respective survival. Of the 5022 children included in this analysis who received allogeneic HCT from 2010 to 2016, 606 developed pulmonary complications within the first year after HCT. Pneumonitis occurred in 388 patients, 125 patients developed pulmonary hemorrhage, and 200 patients had lung graft-versus-host disease (GVHD). For those developing pulmonary complications within 1 year, overall survival 100 days after diagnosis of pulmonary complications was 49% (95% confidence interval [CI], 43% to 54%) for patients with pneumonitis, 23% (95% CI, 16% to 31%) in patients with pulmonary hemorrhage, and 87% (95% CI, 81% to 91%) in patients with pulmonary GVHD. This study demonstrates the approximate incidence of these complications, as well as their significant effects on survival, and can serve as a baseline for future research.

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INTRODUCTION

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for pediatric patients with high-risk malignancies and nonmalignant diseases, with approximately 1600 children receiving HCT in the United States each year [1]. Outcomes for pediatric patients have continued to improve in recent years, with 5-year overall survival (OS) of 40% to 64% [2,3] for children with hematologic malignancies and 66% to 97% for children with nonmalignant diseases [4–8]. However, the effectiveness of this therapy is often limited by toxicities leading to morbidity and

mortality. Pulmonary complications are a significant cause of post-HCT complications and include infectious as well as noninfectious etiologies such as idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH), and chronic graft-versus-host disease (GVHD)/bronchiolitis obliterans syndrome.

Historically, 40% to 60% of adult patients experience pulmonary complications after HCT, and 30% of post-HCT deaths are attributed to pulmonary causes [9,10]. There are few data on the incidence and outcomes of pulmonary complications in pediatric patients, however. A single-center study from the 1990s described pulmonary complications in 25% of pediatric patients undergoing HCT, and this translated into a significantly increased risk of death [11]. Introduction of reduced-intensity regimens, improved supportive care, and targeted treatments for pulmonary complications have likely altered

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these statistics. However, the incidence and outcomes of pulmonary complications in pediatric patients have not been evaluated recently.

In April 2018, pediatric pulmonologists, intensivists, hematopoietic cell transplant physicians, and research scientists participated in a workshop sponsored by the National Heart, Lung, and Blood Institute (NHLBI); the Eunice Kennedy Shriver National Institute of Child Health and Human Development (HCHD); and the National Cancer Institute (NCI) on pulmonary complications in children after allogeneic HCT. The goals of this workshop were to identify critical gaps in existing knowledge of pulmonary complications in children after allogeneic HCT, as well as explore avenues for research to address these knowledge gaps to advance care and optimize outcomes. The lack of a multicenter description of the extent and impact of pulmonary complications in pediatric patients has limited the research efforts to further improve outcomes for these patients. Here, we present data from the Center for International Blood and Marrow Transplant Research (CIBMTR) database to help describe the incidence and outcomes of pediatric patients who develop pulmonary complications after allogeneic HCT. This knowledge will help guide future research into prevention and implementation of novel treatment strategies for these complications.

MATERIALS AND METHODS

The CIBMTR is a research affiliation of the Medical College of Wisconsin and the National Marrow Donor Program/Be the Match and collects longitudinal outcome data on HCTs from more than 450 centers worldwide. In the United States, a federal mandate requires all allogeneic HCTs to be reported to the Stem Cell Transplant Outcomes Database, which is managed by the CIBMTR. Data quality procedures are implemented at all phases of data collection, processing, and analysis. Transplant centers are encouraged to keep the data reporting up to date, and on-site data audits assist in minimizing errors. International allogeneic HCTs are reported on a voluntary basis, but data are also subject to audit. Observational studies are performed using the CIBMTR database, in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information is collected and maintained in the CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule.

All patients reported to the CIBMTR have transplant essential data forms completed that describe the indication for transplant and patient and transplant characteristics. In 2007, pretransplant comorbidities, as defined by the Hematopoietic Cell Transplantation Comorbidity Index, were added to the transplant essential data forms; this included reporting on pulmonary function with pulmonary dysfunction classified as moderate (Diffusing capacity of the lungs for carbon monoxide (DLCO) or Forced Expiratory Volume at 1 second (FEV1) 66% to 80% of normal) or severe (DLCO or FEV1 \leq 65% of normal or requiring oxygen supplementation) [12]. If patients did not fit these categories, they were considered to have normal pulmonary function. The assessment of pulmonary function was made by the reporting institution based on its evaluation of pulmonary symptoms and function.

A weighted algorithm is used to select approximately 25% of patients for additional data reporting, collected on comprehensive report forms (CRFs). CRFs supply more granular data on post-transplant complications, including data on whether a patient experienced noninfectious pneumonitis, bronchiolitis obliterans, cryptogenic organizing pneumonia, DAH, or chronic GVHD and, if present, the date of onset. The diagnosis of these pulmonary complications was based on the report from the individual centers. Follow-up data are collected at 100 days, 6 months, and yearly after HCT.

Patients were included in this study if they underwent first allogeneic HCT between 2010 and 2016 for any indication, were younger than 21 years at the time of HCT, and had CRF data reported to the CIBMTR. Patients who received a transplant from a syngeneic donor were excluded.

Statistical Analysis

Patient demographics, disease indications, HCT characteristics, and comorbidities were described using frequencies and percentages for discrete variables and median (range) for continuous variables. Cumulative incidences of pulmonary complications occurring in the first year after HCT were calculated, including pneumonitis (infection, idiopathic, or not otherwise specified), pulmonary hemorrhage, and lung GVHD (cryptogenic organizing pneumonia, bronchiolitis obliterans, both, or other). Death without a pulmonary event was considered a competing risk. Patients were censored at the

time of a subsequent HCT. Survival rates were calculated using Kaplan-Meier estimates. For landmark analysis, time started at 12 months post-transplant, and history of pulmonary toxicity determined to which group patients were assigned. Patients were followed until death or time of last follow-up. The χ^2 test was used to compare pretransplant pulmonary disease with post-transplant pulmonary outcomes. Analysis of cause of death after transplant was descriptive. All P values are 2-sided with a significance level defined as $P < .05$. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for all analyses.

RESULTS

Patient Characteristics

In total, 5022 children who received allogeneic HCT from 2010 to 2016 were included in the study. The median age at HCT was 8 years (range, <1 to 21 years), and 51% underwent HCT for nonmalignant diseases. Patient and transplant characteristics are noted in Table 1. Moderate pulmonary disease was present in 6% of children and severe pulmonary disease in 4% (Table 1).

Of the 606 children who reported pulmonary complications after HCT, 84% had no history of pulmonary disease, 8% had moderate pulmonary disease, 6% had severe pulmonary disease, and 1% did not report the pre-HCT pulmonary disease status (Table 2). A total of 509 patients had a single pulmonary event, whereas 97 patients had 2 or more pulmonary events.

Pneumonitis

Pneumonitis occurred in 388 patients with an incidence of 8% at 1 year post-HCT (Fig. 1A). The median time to onset was 1.6 months (range, 0 to 29 months). In these 388 patients, pneumonitis was described as idiopathic in 55%, infectious in 38%, and not otherwise specified in 7%. Survival after pneumonitis was poor, with OS of 49% (95% confidence interval [CI], 43% to 54%) at 100 days after diagnosis of pneumonitis and 38% (95% CI, 33% to 43%) at 1 year after diagnosis (Fig. 1B). Pneumonitis was more frequent in patients who underwent transplantation for malignant diseases ($P < .001$), received myeloablative conditioning ($P < .001$), and received cord blood grafts ($P < .001$, Table 3). Pneumonitis was more common in infants <1 year ($P = .04$, Table 4).

Diffuse Alveolar Hemorrhage

Pulmonary hemorrhage occurred early after HCT in 125 children, an incidence of 2% at day 100 after HCT (Table 3, Fig. 1A). The median time to onset was 1.7 months (range, 0 to 25 months). Outcomes for these patients were particularly poor, with only 23% (95% CI, 16% to 31%) surviving 100 days after developing DAH and only 16% (95% CI, 10% to 23%) surviving to 6 months (Fig. 1). The incidence of DAH was more frequent in patients who received cord blood grafts ($P < .001$) but was similar in patients with malignant and nonmalignant diseases ($P = .39$) and in patients with myeloablative and reduced-intensity conditioning ($P = .14$, Table 3). Pulmonary hemorrhage was more frequent in infants <1 year ($P = .001$, Table 4).

Lung GVHD

Two hundred patients developed lung GVHD after HCT, or 4% of the cohort. Two percent of children had lung GVHD reported within 1 year (Fig. 1A). The median time to onset was 5.7 months (range, 1 to 68 months). Lung GVHD was described as bronchiolitis obliterans in 52%, cryptogenic organizing pneumonia in 7%, both in 5%, and not specified in 36%. Outcomes were also poor for patients with chronic lung GVHD but less so than for those with pneumonitis or DAH; by 100 days after diagnosis of chronic lung GVHD, OS declined to 87% (95% CI, 81% to 91%) and decreased further to 72% (95% CI, 65% to 79%) OS by 1 year after diagnosis (Fig. 1B). Pulmonary GVHD

Table 1
Patient and Transplant Characteristics

Patient Characteristics	Value
Number of patients	5022
Number of centers	183
Age, median (range), yr	8 (<1–21)
Age group, yr, n (%)	
<1	623 (12)
1 to <2	382 (8)
2 to <5	816 (16)
5 to <10	1183 (24)
10 to <21	2018 (40)
Indication for transplant, n (%)	
Malignancies	
AML/MDS	1248 (25)
ALL	949 (19)
Other leukemia	128 (3)
Lymphomas	117 (2)
Other malignancies	10 (<1)
Nonmalignant diseases	
Aplastic anemia	449 (9)
Erythrocyte disorders	869 (17)
SCID and other immune deficiencies	752 (15)
Metabolic diseases	295 (6)
Histiocytic disorders	171 (3)
Other nonmalignant*	34 (<1)
Conditioning intensity, n (%)	
MAC	3552 (71)
RIC	579 (11)
NMA	566 (11)
No conditioning (nonmalignant only)	209 (4)
Missing	118 (2)
TBI used in conditioning, n (%)	
Yes	1662 (33)
No	3246 (65)
Missing	114 (2)
Donor type, n (%)	
HLA-identical sibling	973 (19)
Other related	662 (13)
Well-matched unrelated	860 (17)
Partially matched unrelated (partial and mismatched)	353 (7)
Unrelated match unknown	83 (2)
Cord blood	2089 (42)
Missing	2 (<1)
Graft type, n (%)	
Bone marrow	2070 (41)
Peripheral blood	863 (17)
Umbilical cord blood	2089 (42)
Donor/recipient CMV serostatus, n (%)	
+/+	1171 (23)
+/-	384 (8)
-/+	655 (13)
-/-	614 (12)
CB – recipient +	1128 (22)
CB – recipient –	909 (18)
CB – recipient CMV unknown	52 (1)
Missing	109 (2)
Pulmonary comorbidity, n (%)	
No pulmonary disease	4436 (88)

(continued)

Table 1 (Continued)

Patient Characteristics	Value
Moderate pulmonary disease	308 (6)
Severe pulmonary disease	217 (4)
Missing	61 (1)
Follow-up of survivors, median (range), mo	31 (1–96)

AML indicates acute myelogenous leukemia; MDS, myelodysplasia; ALL, acute lymphoblastic leukemia; SCID, severe combined immunodeficiency; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; NMA, non-myeloablative conditioning; TBI, total body irradiation; CMV, cytomegalovirus; CB, cord blood.

*Other nonmalignant: platelet disorder, n=24; autoimmune disorder, n=10.

was more frequent in patients who underwent transplantation for malignant diseases ($P < .001$) and in patients who received myeloablative conditioning ($P = .002$) but was similar among all graft types ($P = .48$, Table 3). The incidence of pulmonary GVHD increased with age ($P < .001$, Table 4). Twenty-four patients who were diagnosed with pneumonitis and 9 patients who were diagnosed with pulmonary hemorrhage survived and later developed chronic GVHD.

Cause of Death

A total of 1385 deaths occurred in this cohort. The most common causes of death were disease recurrence (33%) and infection (19%). Pulmonary disease, including lung GVHD, pulmonary failure, Acute Respiratory Distress Syndrome, pneumonitis, and DAH, were noted as the primary cause of death in 13% of deaths from related donors and 19% of deaths from unrelated donors.

Survival declined in the year following diagnosis of each pulmonary complication to 38% (95% CI, 33% to 43%) for patients with pneumonitis, 16% (95% CI, 10% to 23%) in patients with pulmonary hemorrhage, and 72% (95% CI, 65% to 79%) in patients with pulmonary GVHD (Fig. 1B).

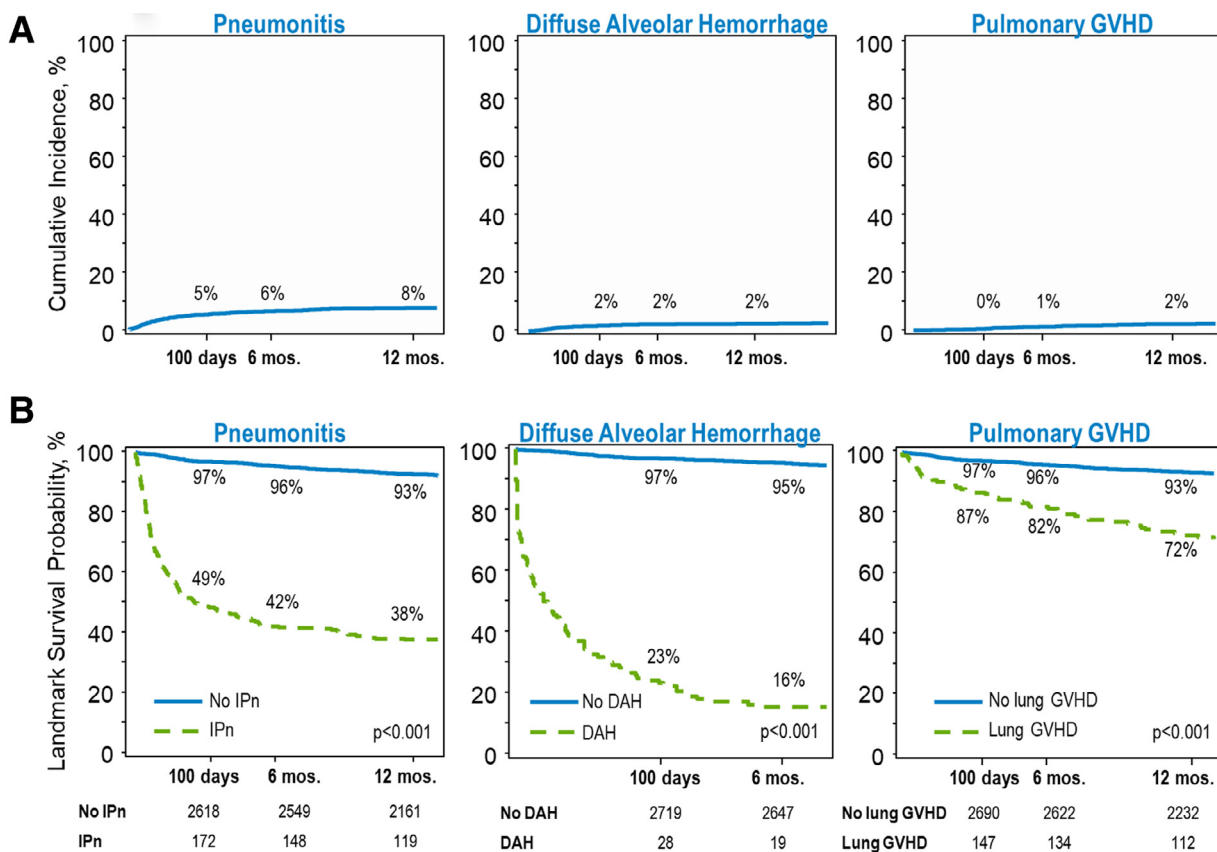
DISCUSSION

Outcomes for pediatric patients who develop pulmonary complications after allogeneic HCT have not been well described. We used the CIBMTR database to define the incidence and the outcomes of pediatric patients who developed pulmonary complications after allogeneic HCT. These analyses demonstrated that pulmonary complications are not infrequent and are associated with significant mortality.

The incidence of pneumonitis was 8% by 1 year after transplant. Previous reports have described IPS after HCT in 2% to 12% of children [13], and results presented here are consistent with this estimation. The introduction of etanercept as a targeted treatment for patients with IPS decreased early mortality from 50% to 80% to less than 20% in a multi-institutional, single-arm trial [13]. In addition, reduced-intensity conditioning regimens have been introduced for patients with nonmalignant diseases and those unable to tolerate myeloablative conditioning, in an attempt to decrease toxic complications [14]. Cytomegalovirus (CMV) and other viral prophylaxis measures have also decreased the incidence of CMV pneumonitis [15]. Mortality from pneumonitis was high in the current analysis, with survival of only 49% 100 days after diagnosis. Although etanercept may improve early outcomes, the long-term outcomes as demonstrated by our analysis and others suggest that these patients continue to have high rates of mortality after 1 year. It is possible that these patients have had pulmonary or other organ damage that makes them more susceptible to other complications [16]. This highlights that the

Table 2
Pulmonary History and Post-HCT Pulmonary Event Comparison

Characteristic	No Pulmonary Event, n (%)	Pulmonary Event, n (%)	Not Reported, n (%)	P Value
Pre-HCT pulmonary comorbidity				.0006
No pulmonary disease	3922 (89)	507 (84)	7 (88)	
Moderate pulmonary disease	256 (6)	51 (8)	1 (13)	
Severe pulmonary disease	178 (4)	39 (6)	0	
Not reported	52 (1)	9 (1)	0	



For those with pulmonary events, day 0 for survival curve is date of pulmonary event diagnosis. If pulmonary event did not occur within 12 months, case was not considered. For those without pulmonary events, day 0 is 12 months post-HCT.

Figure 1. Post-HCT pulmonary complications. (A) Cumulative incidence of pneumonitis, diffuse alveolar hemorrhage, and lung GVHD diagnosed by 1-year post-HCT. By 1 year after HCT, the incidence of pneumonitis was 8%, diffuse alveolar hemorrhage was 2%, and lung GVHD was 2%. (B) Twelve-month landmark survival analysis at 100 days, 6 months, and 1 year.

degree of long-term morbidity from pneumonitis is unknown, and further research and interventions are needed to improve outcomes for these patients.

Diffuse alveolar hemorrhage affected only 2% of pediatric patients but was associated with a dismal prognosis, with <20% of children surviving 6 months after diagnosis of pulmonary hemorrhage. Therapies such as high-dose steroids, cyclophosphamide, recombinant factor VII, and extracorporeal membrane oxygenation have been attempted as treatments for pulmonary hemorrhage [1,17–19]. Although case studies have described successes for a few patients, no treatment has reliably been shown to improve survival for patients with this complication.

Pulmonary chronic GVHD presented in 2% of patients before 1-year post-HCT. Other single-institution studies

have estimated an incidence of 8% [20]. The lower incidence found in this analysis is likely related to the limitation in assessment of pulmonary complications within the first year after HCT. Moreover, the mainstay of diagnosis is spirometry, which cannot be performed in young children and can be difficult even in teenagers who are unwell or uncooperative, leading to likely late diagnosis and underdiagnosis of this important complication. It is likely that incidence continues to increase over time. This analysis demonstrates that by 1 year after diagnosis of pulmonary GVHD, survival declines to 72%, highlighting a need for novel treatment approaches.

One might presume that patients with pulmonary dysfunction pre-HCT would be at increased risk of post-HCT

Table 3
Pulmonary Toxicity Incidences

Disease Type	No. of Evaluations	Probability (95% CI), %	No. of Evaluations	Probability (95% CI), %	P Value
	Malignant (n = 2452)		Nonmalignant (n = 2570)		
Pneumonitis	2375		2508		<.001
100 day		6 (5-7)		5 (4-5)	
6 months		8 (7-9)		5 (5-6)	
1 year		9 (8-10)		6 (5-7)	
DAH	2377		2509		.39
100 days		2 (1-2)		2 (1-2)	
6 months		2 (2-3)		2 (1-2)	
1 year		3 (2-3)		2 (2-3)	
Pulmonary GVHD	2394		2541		<.001
100 days		1 (0-1)		0 (0-0)	
6 months		2 (2-3)		1 (0-1)	
1 year		3 (3-4)		1 (1-2)	
Conditioning intensity	MAC (n = 3554)		RIC/NMA (n = 1143)		
Pneumonitis	3533		1136		<.001
100 days		6 (5-7)		3 (2-5)	
6 months		7 (7-8)		4 (3-5)	
1 year		9 (8-10)		5 (3-6)	
DAH	3535		1137		.14
100 days		2 (2-3)		1 (1-2)	
6 months		2 (2-3)		1 (1-2)	
1 year		3 (2-3)		2 (1-3)	
Pulmonary GVHD	3493		1123		.002
100 days		1 (0-1)		0 (0-1)	
6 months		2 (1-2)		1 (0-1)	
1 year		3 (2-3)		1 (1-2)	
Graft source	BM/PBSC graft (n = 2933)		Cord blood graft (n = 2089)		
Pneumonitis	2885		1998		<.001
100 days		4 (3-5)		7 (6-8)	
6 months		5 (4-6)		9 (7-10)	
1 year		6 (5-7)		10 (9-11)	
DAH	2887		1999		<.001
100 days		1 (1-1)		3 (2-4)	
6 months		1 (1-2)		3 (3-4)	
1 year		1 (1-2)		4 (3-5)	
Pulmonary GVHD	2869		2063		.48
100 days		0 (0-0)		1 (0-1)	
6 months		1 (1-2)		2 (1-2)	
1 year		2 (2-3)		2 (2-3)	

BM indicates bone marrow; PBSC, peripheral blood stem cell.

pulmonary complications. However, only 17% of patients with evidence of pre-HCT pulmonary disease later developed post-HCT pulmonary complications. The number of patients with pre-HCT pulmonary disease is likely an underestimation; this may be at least partly caused by the inability of many young patients to cooperate with standard pulmonary function testing. This highlights further that innovative approaches to assess pulmonary function in children are needed and that we need to better understand factors that affect a patient's risk for developing pulmonary complications.

We acknowledge the limitations in this analysis. The data rely on the diagnosis and report of pulmonary complications from individual centers, where variable methods of assessment of pulmonary function are used, and these methods or their results were reported. An important strength of this

analysis is the large data set and includes centers worldwide, adding to the generalizability of the findings.

The recent workshop sponsored by the NHLBI, NICHD, and NCI on pulmonary complications highlighted the need for a coordinated approach to post-HCT pulmonary complications in children. In addition, the results of these analysis emphasize the burden of pulmonary complications, which limits the success of HCT in pediatric patients. Moving forward, a dedicated research effort is needed to understand the mechanisms contributing to pulmonary complications, to design innovative approaches to pulmonary assessment in children, to identify patients most at risk, and to develop novel therapeutic approaches. A multidisciplinary approach to post-HCT pulmonary complications in children is needed to help decrease mortality and improve outcomes for these patients.

Table 4
Incidence of Pulmonary Toxicity

Outcomes	Less Than 1 (n = 623)		1 Year (n = 382)		2–4 Years (n = 816)		5–9 Years (n = 1183)		10–20 Years (n = 2018)		P Value
	No. of Evaluations	Probability (95% CI), %	No. of Evaluations	Probability (95% CI), %	No. of Evaluations	Probability (95% CI), %	No. of Evaluations	Probability (95% CI), %	No. of Evaluations	Probability (95% CI), %	
Pneumonitis	612		364		785		1158		1964		
100 days		8 (6–10)		6 (4–9)		4 (3–5)		4 (3–5)		6 (5–7)	.04
6 months		8 (6–10)		7 (5–10)		6 (4–7)		5 (4–6)		7 (6–8)	
1 year		9 (7–12)		9 (6–12)		6 (5–8)		6 (5–8)		8 (7–9)	
DAH	613		364		786		1159		1964		
100 days		4 (3–6)		2 (1–4)		1 (1–2)		1 (0–2)		2 (1–2)	.001
6 months		4 (3–6)		2 (1–4)		2 (1–3)		1 (1–2)		2 (1–3)	
1 year		5 (3–7)		3 (1–5)		2 (1–3)		1 (1–2)		2 (2–3)	
Pulmonary GVHD	617		379		808		1171		1957		
100 days		0 (0–1)		0 (0–1)		0 (0–0)		1 (0–1)		1 (0–1)	<.001
6 months		1 (0–1)		1 (0–3)		1 (0–1)		2 (1–3)		2 (1–2)	
1 year		1 (0–2)		2 (1–4)		1 (0–2)		2 (2–3)		3 (2–4)	

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