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ORIGINAL ARTICLE

Lung evaluation in 10 year survivors of pediatric allogeneic hematopoietic stem cell transplantation

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Abstract

There is little data on the long-term respiratory development of children after allogeneic hematopoietic stem cell transplantation (allo-HSCT). We describe the respiratory assessment 10 years after allo-HSCT of 35 children transplanted between 2000 and 2004. During this period, 90 children were transplanted at our center. Twenty-five children died, thirty were lost to follow-up, and thirty-five came to have a pulmonary investigation. The thirty-five participants answered a questionnaire asking if they had pulmonary symptoms, and pulmonary function tests (PFTs) were performed. The median age of these children 10 years after the transplant was 16 years old. Just over a third of them had pulmonary symptoms. Among them, 5/13 (38%) had bronchiolitis obliterans syndrome (BOS). The majority of children (62.8%) did not have respiratory symptoms. PFTs were abnormal in one-third of asymptomatic children, revealing restrictive lung disease that was always mild to moderate ($p = 0.02$).

Conclusion: In the long term, research at the time of the medical examination for the presence of chronic cough, shortness of breath on exertion, or wheezing helps to guide the clinician as to the need for further lung exploration. Similarly, informing patients and their families about these symptoms, which can be underestimated, should allow for more specific management.

What is Known:

- *Pulmonary complications are a major cause of hematopoietic stem cell transplantation (HSCT) morbidity and mortality.*
- *A long time after allogeneic HSCT, pulmonary function tests abnormalities may occur in children, but it is not always related to symptoms.*

What is New:

- *The occurrence of respiratory symptoms: cough, dyspnea on exertion, chronic bronchitis, and wheezing should be systematically investigated in the follow-up of allografted patients, even at a distance.*
- *The presence of respiratory symptoms should lead to a respiratory functional investigation to detect the presence of an obstructive syndrome.*

Keywords Hematopoietic stem cell transplantation · Long-term respiratory symptoms · Pulmonary function test · Bronchiolitis obliterans · Fibroelastosis

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Abbreviations

ATS	American thoracic society
BOS	Bronchiolitis obliterans syndrome
aGvHD	Acute graft-versus-host disease
cGvHD	Chronic graft-versus-host disease
ERS	European respiratory society
FEV1	Forced expiratory volume in 1 s
FVC	Full vital capacity
GLI	Global lung function initiative
GvHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplantation
PFTs	Pulmonary function tests
PPFE	Pleuroparenchymal fibroelastosis
TBI	Total body irradiation
TLC	Total lung capacity

Introduction

Few data exist on the long-term pulmonary evolution of children with allogeneic hematopoietic stem cell transplantation (allo-HSCT). Pulmonary complications are well-recognized consequences of allo-HSCT and are a major cause of posttransplant morbidity and mortality. In a retrospective review of 363 children undergoing HSCT over a 5-year period, Eikenberry et al. reported that those children with pulmonary complications had higher mortality rates than those who did not (65% versus 44%, $p = 0.01$) [9]. A long time after HSCT, pulmonary function tests (PFTs) abnormalities, such as restrictive lung disease, may occur in children, but it is not always related to symptoms [23, 25]. Respiratory symptoms appear in one-third of children 10 years after allo-HSCT for acute myeloid leukemia, and 17% of these children receive respiratory treatment [25]. Bronchiolitis obliterans syndrome (BOS) is the most common cause of long-term lung disease after allo-HSCT. It is a manifestation of chronic graft-versus-host disease (cGvHD) and occurs in 1.2 to 14.6% of HSCT recipients [24]. The objective of this work is to evaluate the frequency of respiratory symptoms and their long-term causes after allo-HSCT and to evaluate lung function in the children who received allo-HSCT in our institution between 2000 and 2004.

Patients and methods

A descriptive study including the patients who underwent allo-HSCT between 2000 and 2004 was conducted at Robert Debré Hospital. This study was approved by the hospital's ethics committee. For the survivors, patients and families were contacted by postal mail to perform clinical examination and PFTs. Respiratory symptoms were assessed in all patients. The age, sex, weight, height, current respiratory symptoms, pulmonary function, and radiological data were collected from April 1, 2014, through January 1, 2015. All patients responded to a questionnaire asking if they had experienced a wet or dry cough for more than 4 weeks per year in the past 2 years; if they had already presented in the past 2 years with dyspnea or limitation in sports activities; and if they had any wheezing, received bronchodilator treatment, or oral antibiotic therapy for a lower respiratory infection in the year preceding the evaluation. The questionnaire was inspired by the Childhood Cancer Survivor Study [11]. Patients were then classified as symptomatic or nonsymptomatic patients at the time of assessment. The indications for transplantation, HLA compatibility level, conditioning regimen, occurrence of acute graft-versus-host disease (aGvHD) and cGvHD, and presence of other long-term complications were also collected. The pretransplant and posttransplant histories of patients, including lung function tests, were studied according to the presence or absence of symptoms. Spirometry and whole-body plethysmography were performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [1, 14]. The results of PFTs were classified as restrictive, obstructive, and mixed defect based on the algorithm published by Pellegrino et al. [17]. The forced expiratory volume in 1 s (FEV1)% predicted was used to grade the severity of pulmonary defects [17]. The lung impairment was considered to be mild or moderate if it was associated with a FEV1 greater than 60% and severe or very severe if the FEV1 was below 49% [17]. Predicted values of spirometry were estimated using the race- and sex-specific equations developed by the Global Lung Function Initiative (GLI) [20]. The diagnosis of bronchiolitis obliterans syndrome (BOS) was based upon the consensus criteria from the National Institutes of Health established in 2014 [13]. BOS was defined as the absence of infection, and FEV1 < 75% predicted, and FEV1/FVC < 0.7, and RV > 120% or air trapping or bronchiectasis or small airways thickening on computed tomography [13]. Pleuroparenchymal fibroelastosis (PPFE) is characterized by intense elastic fibrosis involving the pleura and subpleural lung parenchyma predominantly in the upper lobes. It was defined as multiple subpleural foci of airspace consolidation with traction bronchiectasis located predominantly in the bilateral upper lobes on computed tomography [12].

Statistical analysis

Differences between groups were analyzed using Fischer's exact tests, nonparametric tests for paired (Wilcoxon) and unpaired (Mann-Whitney) groups. Two-sided p values < 0.05 were considered significant. Analyses were performed using Prism software v.6 (GraphPad).

Results

From 2000 to 2004, 90 children were treated with allogeneic bone marrow transplants at our institution. Of these, twenty-five children died, 16 during the first year after HSCT. Eight children died from or with infectious pulmonary complications or BOS. Beyond 1 year, the main cause of death was relapse (8/9, 89%). One patient died from BOS. Seventy patients were invited, and a total of 35 patients (50%) participated in this study (Fig. 1). When comparing the main characteristics, such as underlying disease, disease stage at time of transplantation, age at HSCT, donor and stem cell sources, total body irradiation (TBI)-based versus chemotherapy-based conditioning regimen, and occurrence of GvHD, the only statistically significant difference between participating and nonparticipating patients was the age at HSCT (5.4 ± 3.4 years versus 8.6 ± 4.1 years, respectively; $p = 0.002$).

The median age of patients at the evaluation for allo-HSCT was 16 years old (12–24 years old). Among the 35 children who responded to the questionnaire, 37% had respiratory symptoms: chronic cough during the past 2 years, dyspnea at exercise with a limitation in sports activities, and wheezing in the past year (Table 1). For five of them, these symptoms were secondary to BOS. PPFE was evidenced in one patient. For four of them, the symptoms were related to asthma. Two asthmatic patients also had an allergy to dust mites. Two patients had chronic bronchopathy associated with bronchiectasis. Finally, only one patient had isolated effort breathlessness. In the year previous to the assessment, 69% (9/13) of children with respiratory symptoms had received treatment related to their respiratory involvement. Eight of the symptomatic children developed symptoms within 2 years after allogeneic transplantation, but the others had symptoms later. Symptomatic children presented with more severe aGvHD compared with the asymptomatic children as well as more respiratory infections during the first year after HSCT (Table 1). They presented also with more cGvHD at the time of evaluation (Table 1). At the time of the lung assessment, ten patients (28.5%) had further signs of sequelae of cGvHD (eye, cardiac, skin, and gastrointestinal disorders), 19/35 (54%) presented with endocrine disorders, and one with a nervous system disorder. Echocardiography was done for all children 10 years after the transplantation; no arterial pulmonary hypertension was found.

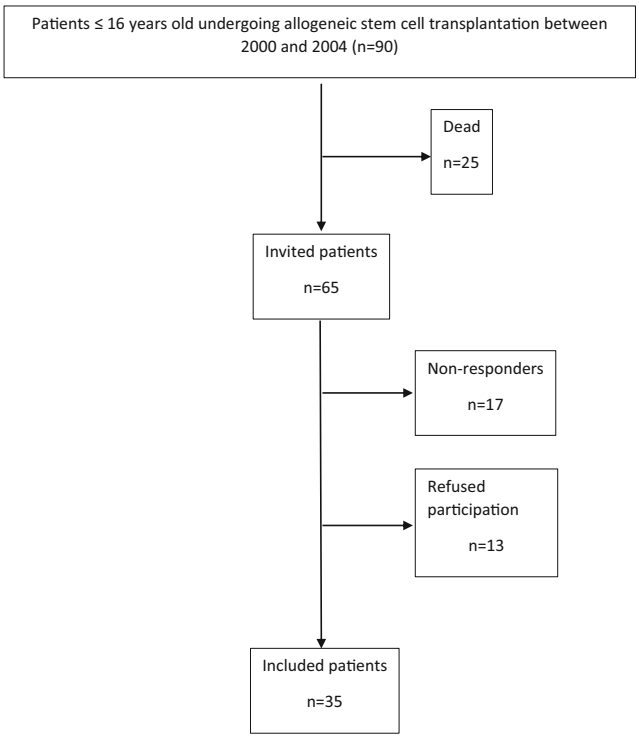

Fig. 1 Flowchart of the study population

Patients with respiratory symptoms had more lung function abnormalities (Table 1). Regarding the severity of lung function impairment, all the patients with severe or very severe lung function deficit were symptomatic ($p = 0.02$). The FEV1/FVC Z score, witness to an obstructive syndrome, was significantly different between symptomatic and nonsymptomatic patients (Fig. 2). Four of the five patients with respiratory symptoms and normal lung function had asthma. The last one had an isolated breathlessness at exercise. For this patient, the cardiopulmonary exercise testing highlighted the magnitude of muscle deconditioning.

When comparing children with ventilatory disorders, 15/35 (43%), with children with normal *lung* function, at 10 years after HSCT, there is no significant difference for subject age at HSCT (mean ± SD, 4.64 ± 2.1 vs 6.20 ± 3.9). Disease and treatment before transplantation, severity of acute GvHD, respiratory infection during the first-year posttransplantation, or nonrespiratory cGvHD do not appear to be predictive of lung function deficits in our cohort.

For 16 patients, eleven of which were nonsymptomatic, we had the lung function evolution over the last 5 years. The decline in FEV1 *Z* score (median, − 0.36 $IC_{95\%}$ [− 0.93; − 0.10]), FVC Z score (median, − 0.34 $IC_{95\%}$ [− 0.72; − 0.03]), and FEV1/FVC *Z* score (median, − 0.35 $IC_{95\%}$ [− 0.69; − 0.03]) was significant (Fig. 2).

Discussion

HSCT is being increasingly offered as a curative option for children with hematologic malignancies [2]. Although survival has improved, the long-term morbidity ascribed to the HSCT procedure is not well known. International recommendations for the follow-up of children with allo-HSCT focus on screening for respiratory symptoms: chronic cough, dyspnea, exercise discomfort [7]. If respiratory symptoms are present, it is recommended to perform a pulmonary function test [7]. For all these children, radiography should be considered based on clinical

Table 1 Clinical and lung characteristics of the 35 survivors with follow-up who received allogeneic transplantation between 2000 and 2004

Total	Asymptomatic ($n = 22$)	Symptomatic ($n = 13$)	p
Age at HSCT (years, mean ± SD)	5.54 ± 3.43	5.25 ± 3.57	0.77
Malignant disease	12 (54.5%)	11 (84.6%)	
Acute lymphoblastic leukemia	6	4	0.9
Acute myeloid leukemia	4	7	
Hodgkin's lymphoma	2		
Donor type			0.5
HLA identical sibling donor (n, %)	16	9	
Matched other relative	6	3	
Matched unrelated donor		1	
Total body irradiation (n, %)	6/22 (27%)	3/13 (23%)	1
Acute graft-versus-host disease grade 3–4	3/22 (13.6%)	8/13 (61.5%)	0.0069
Respiratory infection during the first year postallo-HSCT	0	5/13 (38.5%)	0.004
Nonrespiratory cGvHD present at the visit	3/22 (13.6%)	7/13 (53.8%)	0.0196
FVC GLI-2012 Z score (mean ± SD)	− 1.02 ± 1.59	− 2.63 ± 2.89	0.128
FEV1 GLI-2012 Z score (mean ± SD)	− 0.92 ± 1.5	− 2.8 ± 2.8	0.127
FEV1/FVC GLI-2012 Z score (mean ± SD)	0.17 ± 1.04	− 1.05 ± 1.82	0.042
Mixed or obstructive lung disease	0	4 (30.8%)	0.01
Restrictive lung disease	7 (31.8%)	4 (30.8%)	
Normal	15 (68.2%)	5 (38.4%)	
Degree of severity of lung function deficit*			0.02
Mild, moderate	7 (100%)	3 (37.5%)	
Severe, very severe	0	5 (62.5%)	

*The lung function deficit is considered to be mild or moderate if it is associated with a FEV1 greater than 60% and severe or very severe if the FEV1 is below 49%

presentation and with attention to avoiding unnecessary radiation exposure [7]. The origins of respiratory symptoms are many and diverse. A specialized follow-up allows the most appropriate therapeutic management. Wilhemson's study found one-third of children who underwent allo-HSCT for acute myeloid leukemia had respiratory symptoms [25]. In our study regarding more than 10 years of follow-up in transplanted pediatric patients, 37% of the children who received allo-HSCT had respiratory symptoms, with 8.5% having end-stage lung dysfunction. The occurrence of respiratory symptoms—cough, dyspnea on exertion, chronic bronchitis, and wheezing—should be systematically investigated in the follow-up of allografted patients, even at a distance [11]. These symptoms, while they may seem harmless, may reveal long-term lung complications related to allo-HSCT (obliterative bronchiolitis and bronchial dilation) or classic respiratory pathology such as asthma. In our cohort, lung infections during the first year after transplantation and severe aGvHD or presence of cGvHD were found more frequently in long-term respiratory symptomatic patients. The presence of these risk factors, also described in the literature, should lead to a more careful respiratory examination [15, 16]. In addition, the presence of respiratory symptoms should lead to a respiratory functional investigation to detect the presence of an obstructive syndrome. Recently, Uhlving et al. showed that small airway dysfunction was a common finding in the long term in children after allo-HSCT [23]. BOS typically occurs within the first 2 years following transplantation, but it may occur even several years afterward [6]. In our study, BOS was the most important explicative disease of respiratory symptoms (5/35, 14%; 95% CI, 3 to 26%). The recent reports suggest that BOS after allo-HSCT is five times more prevalent than previous estimates [3, 6]. The presence of respiratory symptoms, especially if associated with an obstructive syndrome, may require inhaled treatment to prevent decline in respiratory function [6]. After HSCT, stabilization of lung function with corticosteroids and other immunosuppressive treatments is first objective [10, 22]. Then, the treatment must focus on preventing the degradation of lung function. The use of inhaled corticosteroids in combination with long-acting bronchodilators and leukotriene receptor antagonists is useful [4, 27]. The early detection and the treatment of infections and vaccinations are essential to prevent the degradation of lung function [26]. Exercise therapy may improve quality of life especially for children with lung disorders [21]. Finally, prevention against inhalation of toxic substances may be done even long time after transplantation [7]. One-third of patients had a restrictive lung disease (11/35, 31%; 95% CI, 16 to 47%). As was the case in our study, restrictive lung disease had been

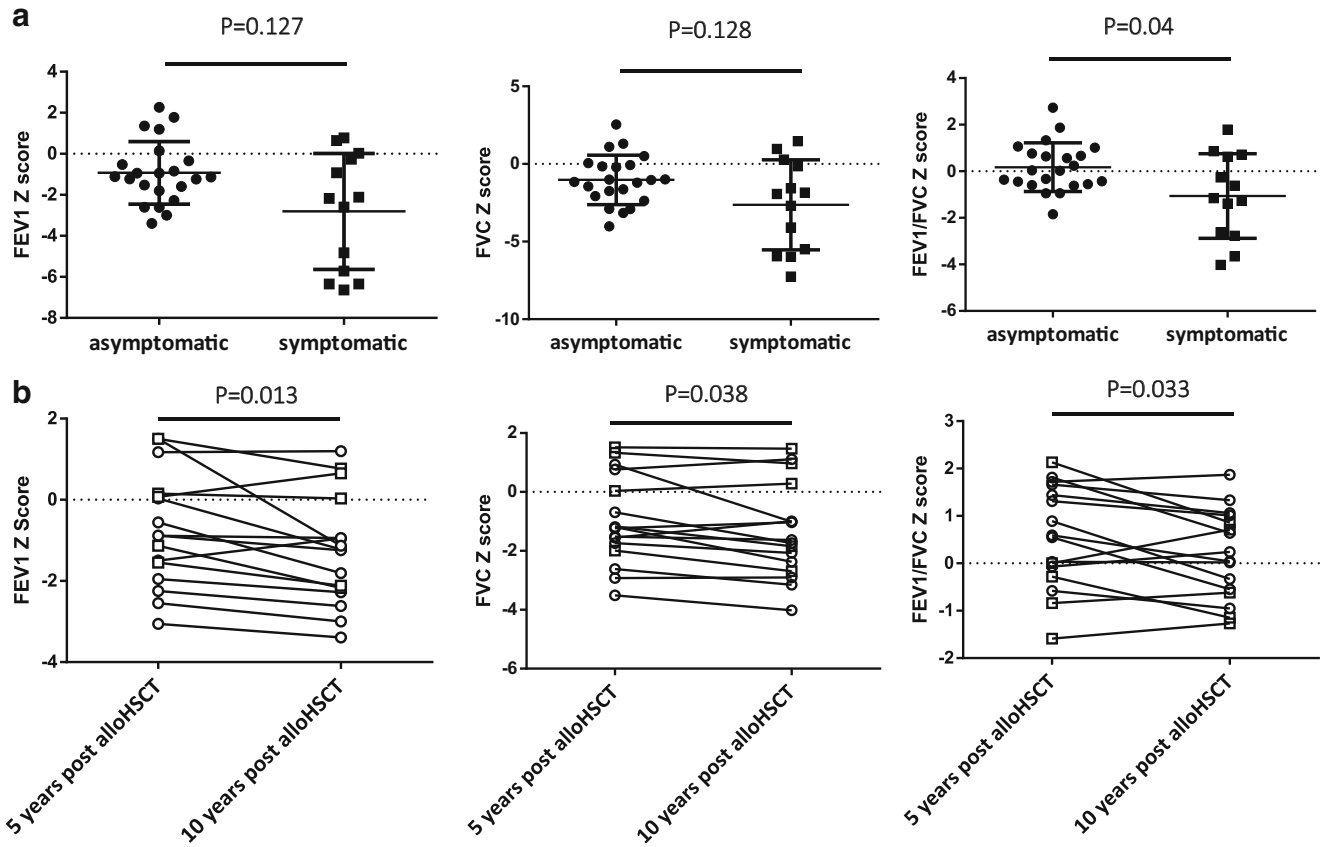

Fig. 2 Lung function between respiratory symptomatic and nonsymptomatic patients 10 years after allo-HSCT. **a** Statistical dot plots showing the FEV1, FCV, and FEV1/FCV expressed as *Z* scores according to the GLI 2012 standard in the 35 children 10 years after allo-HSCT. Geometric means (horizontal bars) and statistical significance (Mann-Whitney test) are indicated between nonsymptomatic (full circle) and symptomatic (full square) patients. **b** Evolution from left to right of FEV1, FCV, and FEV1/FCV expressed as *Z* scores according to the GLI 2012 standard at 5 and 10 years after allo-HSCT in 16 nonsymptomatic (circle) and symptomatic (square) children. Each point corresponds to 1 patient, and the lines connect matched samples. Statistical significance (Wilcoxon matched-pairs signed rank test) is indicated

reported to be the main abnormality after HSCT in children [18]. In our study, the majority of children with a restrictive syndrome were symptom-free, and the lung defect was mild or moderate. For asymptomatic patients, it is not recommended to systematically perform LFTs [19]. Nevertheless, in patients surviving longer than 2 years, Bathia et al. found a 15.1-fold increased risk of late mortality because of pulmonary dysfunction compared with the general population [5]. In addition, in our study, for the group of children who performed PFTs at 5 and 10 years after allo-HSCT, there was a significant decline in FEV1 *Z* score, FVC *Z* score, and FEV1/FVC *Z* score, regardless of the presence or absence of respiratory symptoms. Prais et al. showed that the deterioration of the pulmonary function precedes the symptoms and recommended a more systematic follow-up of the pulmonary function [18].

The weakness of this study is its retrospective nature. In addition, half of the children transplanted 10 years ago did not wish to perform the respiratory assessment or they were lost to follow-up. The significant difference of age at transplantation in the cohort (mean, 5.4 ± 3.4 years) compared with patients who did not wish to be evaluated at 10 years after transplantation (8.6 ± 4.1 years) might be important. Indeed, Dudek finds a higher prevalence of BOS at 3 years after HSCT among children transplanted between 10 and 19 years of age [8], but this is not consistently found in the literature. Finally, we do not have a follow-up of the respiratory function of these children but only an evaluation at a determined time. Nevertheless, this study highlights the importance of looking for respiratory symptoms in the daily follow-up of these children and questions the follow-up proposed for asymptomatic children.

In conclusion, at 10 years after transplantation, 37% of our cohort have respiratory symptoms and require specialized lung management. These children may be detected early if they have severe aGvHD, early respiratory infection, or cGvHD. For nonsymptomatic children, one-third have a restrictive syndrome at 10 years of transplantation. This raises questions about the long-term respiratory follow-up of these children and requires additional prospective studies to more accurately identify children at risk and requiring long-term follow-up. Vaccination, prevention against inhalation of toxic substances (environmental and professional), and appropriate physical activity must continue for adolescents or young adults.

Authors' contributions SL: collected the data and contribute to write the manuscript. KY: She is in charge of patient follow-up. CD: contribute to write the manuscript. J-HD: He is in charge of follow-up and helps the discussion. VH: in charge of lung evaluation and wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

1. (1995) Standardization of Spirometry, 1994 Update American Thoracic Society. Am J Respir Crit Care Med 152(3):1107–1136
2. Armenian SH, Sun C-L, Kawashima T, Arora M, Leisenring W, Sklar CA, Baker KS, Francisco L, Teh JB, Mills G, Wong FL, Rosenthal J, Diller LR, Hudson MM, Oeffinger KC, Forman SJ, Robison LL, Bhatia S (2011) Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). Blood 118(5):1413–1420
3. Au BKC, Au MA, Chien JW (2011) Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 17(7):1072–1078
4. Bergeron A, Chevret S, Chagnon K, Godet C, Bergot E, Peffault de Latour R, Dominique S, de Revel T, Juvin K, Maillard N, Reman O, Contentin N, Robin M, Buzyn A, Socié G, Tazi A (2015) Budesonide/formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation. Am J Respir Crit Care Med 191(11): 1242–1249
5. Bhatia S, Francisco L, Carter A, Sun CL, Baker KS, Gurney JG, McGlave PB, Nademanee A, O'Donnell M, Ramsay NKC, Robison LL, Snyder D, Stein A, Forman SJ, Weisdorf DJ (2007) Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. Blood 110(10):3784–3792
6. Chien JW (2011) Preventing and managing bronchiolitis obliterans syndrome after allogeneic hematopoietic cell transplantation. Expert Rev Respir Med 5(1):127–135
7. Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GMT, Huang JT, Pelletier W, Perkins JL, Rivard LS, Schechter T, Shah AJ, Wilson KD, Wong K, Grewal SS, Armenian SH, Meacham LR, Mulrooney DA, Castellino SM (2016) Late effects surveillance recommendations among survivors of childhood hematopoietic cell transplantation: a Children's Oncology Group report. Biol Blood Marrow Transplant 22(5):782–795
8. Dudek AZ, Mahaseth H, DeFor TE, Weisdorf DJ (2003) Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. Biol Blood Marrow Transplant 9(10):657–666
9. Eikenberry M, Bartakova H, Defor T, Haddad IY, Ramsay NKC, Blazar BR, Milla CE, Cornfield DN (2005) Natural history of pulmonary complications in children after bone marrow transplantation. Biol Blood Marrow Transplant 11(1):56–64
10. Even-Or E, Ghandourah H, Ali M, Krueger J, Sweezey NB, Schechter T (2018) Efficacy of high-dose steroids for bronchiolitis obliterans syndrome post pediatric hematopoietic stem cell transplantation. Pediatr Transplant 22(2):e13155. https://doi.org/10.1111/petr.13155
11. Geenen MM, Cardous-Ubbink MC, Kremer LCM, van den Bos C, van der Pal HJH, Heinen RC, Jaspers MWM, Koning CCE, Oldenburger F, Langeveld NE, Hart AAM, Bakker PJM, Caron HN, van Leeuwen FE (2007) Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297(24):2705–2715
12. Higo H, Miyahara N, Taniguchi A, Maeda Y, Kiura K (2019) Cause of pleuroparenchymal fibroelastosis following allogeneic hematopoietic stem cell transplantation. Respir Investig 57(4):321–324
13. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers MED (2015) National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 21(3):389–401.e1
14. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten C, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force (2005) General considerations for lung function testing. Eur Respir J 26(1):153–161
15. Nishio N, Yagasaki H, Takahashi Y, Muramatsu H, Hama A, Tanaka M, Yoshida N, Watanabe N, Kudo K, Yoshimi A, Kojima S (2009) Late-onset non-infectious pulmonary complications following allogeneic hematopoietic stem cell transplantation in children. Bone Marrow Transplant 44(5):303–308
16. Park M, Koh KN, Kim BE, Im HJ, Seo JJ (2011) Clinical features of late onset non-infectious pulmonary complications following pediatric allogeneic hematopoietic stem cell transplantation. Clin Transpl 25(2):E168–E176
17. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten C, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J (2005) Interpretative strategies for lung function tests. Eur Respir J 26(5):948–968
18. Prais D, Sinik MM, Stein J, Mei-Zahav M, Mussaffi H, Steuer G, Hananya S, Krauss A, Yaniv I, Blau H (2014) Effectiveness of long-term routine pulmonary function surveillance following pediatric hematopoietic stem cell transplantation. Pediatr Pulmonol 49(11):1124–1132
19. Pulsipher MA, Skinner R, McDonald GB et al (2012) National Cancer Institute, National Heart, Lung and Blood Institute/ Pediatric Blood and Marrow Transplantation Consortium First International Consensus Conference on late effects after pediatric hematopoietic cell transplantation: the need for pediatric-specific long-term follow-up guidelines. Biol Blood Marrow Transplant 18(3):334–347
20. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Stocks J, the ERS Global Lung Function Initiative (2012) Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 40(6):1324–1343
21. Senn-Malashonak A, Wallek S, Schmidt K, Rosenhagen A, Vogt L, Bader P, Banzer W (2019) Psychophysical effects of an exercise therapy during pediatric stem cell transplantation: a randomized controlled trial. Bone Marrow Transplant. https://doi.org/10.1038/s41409-019-0535-z

22. Uhlving HH, Buchvald F, Heilmann CJ, Nielsen KG, Gormsen M, Müller KG (2012) Bronchiolitis obliterans after allo-SCT: clinical criteria and treatment options. Bone Marrow Transplant 47(8): 1020–1029
23. Uhlving HH, Mathiesen S, Buchvald F, Green K, Heilmann C, Gustafsson P, Muller K, Nielsen KG (2015) Small airways dysfunction in long-term survivors of pediatric stem cell transplantation. Pediatr Pulmonol 50(7):704–712
24. Uhlving HH, Andersen CB, Christensen IJ, Gormsen M, Pedersen KD, Buchvald F, Heilmann C, Nielsen KG, Mortensen J, Moser C, Sengeløv H, Müller KG (2015) Biopsy-verified bronchiolitis obliterans and other noninfectious lung pathologies after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 21(3):531–538
25. Wilhelmsson M, Glosli H, Ifversen M, Abrahamsson J, Winiarski J, Jahnukainen K, Hasle H (2019) Long-term health outcomes in survivors of childhood AML treated with allogeneic HSCT: a NOPHO-AML Study. Bone Marrow Transplant 54(5):726–736
26. Williams KM (2017) How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Blood 129(4):448–455
27. Williams KM, Cheng G-S, Pusic I, Jagasia M, Burns L, Ho VT, Pidala J, Palmer J, Johnston L, Mayer S, Chien JW, Jacobsohn DA, Pavletic SZ, Martin PJ, Storer BE, Inamoto Y, Chai X, Flowers MED, Lee SJ (2016) Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transplant 22(4):710–716