Received: 9 September 2019 | Accepted: 16 April 2020

DOI: 10.1002/ppul.24801

PEDIATRIC PULMONOLOGY WILEY

Long-term pulmonary function testing in pediatric bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation

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Funding information
Foundation Stiftung Starke Lunge, Grant/Award Number: Regierungspräsidium Darmstadt: AZ: I 13-25d 04/11-(6)-78

Abstract

Rationale: Bronchiolitis obliterans syndrome (BOS) is a severe, chronic inflammation of the airways leading to an obstruction of the bronchioles. So far, there are only a few studies looking at the long-term development of pulmonary impairment in children with BOS.

Objective: The objective of this study was to investigate the incidence and long-term outcome of BOS in children who underwent allogeneic hematopoietic stem cell transplantation (HSCT).

Methods: Medical charts of 526 children undergoing HSCT in Frankfurt/Main, Germany between 2000 and 2017 were analyzed retrospectively and as a result, 14 patients with BOS were identified. A total of 271 lung functions (spirometry and body plethysmography), 26 lung clearance indices (LCI), and 46 chest high-resolution computed tomography (HRCT) of these 14 patients with BOS were evaluated.

Results: Fourteen patients suffered from BOS after HSCT (2.7%), whereby three distinctive patterns of lung function impairment were observed: three out of 14 patients showed a progressive lung function decline; two died and one received a lung transplant. In five out of 14 patients with BOS persisted with a severe obstructive and secondarily restrictive pattern in lung function (forced vital capacity [FVC] < 60%, forced expiratory volume in 1 second [FEV1] < 50%, and FEV1/FVC < 0.7) and increased LCI (11.67-20.9), six out of 14 patients recovered completely after moderate lung function impairment and signs of BOS on HRCT. Long-term FVC in absolute numbers was increased indicating that the children still have lung growth.

Abbreviations: BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; CT, computed tomography; FAM, fluticasone, montelukast, and azithromycin; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GvHD, graft vs host disease; HRCT, high-resolution computed tomography; HSCT, hematopoietic stem cell transplantation; LCI, lung clearance index; MTX, methotrexate; OS, oral corticosteroids; PFT, pulmonary function test; RV, residual volume; RV/TLC, functional residual capacity; TLC, total lung capacity.

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Conclusion: Our results showed that the incidence of BOS in children is low. BOS was associated with high mortality and may lead to persistent obstructive lung disease; although, lung growth continued to exist.

KEYWORDS
body plethysmography, bronchiolitis obliterans syndrome, lung function, spirometry

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (aHSCT) is widely used to treat hematological disorders, relapsing malignant, and rarely benign conditions.[1-3] Since there is a global increase of aHSCTs,[4] the importance of complications such as graft vs host diseases (GvHD) is growing.[5,6] The pathophysiology is poorly understood but it can be described as an exaggerated inflammatory response due to a mismatch between histocompatibility antigens between donor and recipient.[7-9]

GvHD of the lung, clinically described as bronchiolitis obliterans syndrome (BOS), is a relatively rare condition with an incidence of 4.8% to 6.5%,[9-11] which is associated with significant morbidity and mortality.[8,12,13] BOS after aHSCT is often a progressive, chronic lung disease in which a persistent inflammation leads to obstruction of the small airways. In histopathology, the persistent noninfectious inflammation involving lymphocytes and neutrophils leads to obliteration of the airway lumen of terminal bronchioles and results in the proliferation of fibroblasts and smooth muscle cells.[8,13]

The condition often starts insidiously with mild symptoms like dry cough and wheezing,[14,15] typically within the first 2 years after transplantation.[9,16] Severe progression or complications, such as respiratory failure and opportunistic infections, may lead to death. Mortality rates between 21% and 100% have been reported,[17] and the survival rate has not improved significantly over the last 20 years.[18] Treatment options are scarce and are often based on personal experiences or on small trials in adults.[19,20] Current therapeutic regimes consist of high-dose systemic intravenous corticosteroid pulses, oral macrolides, montelukast, inhaled corticosteroids, and bronchodilators.[7]

In most centers, BOS is diagnosed noninvasively by a joint clinical assessment considering typical clinical findings, pulmonary function testings (PFTs) and HRCT abnormalities.[5,15] According to the recent consensus criteria, PFTs are an important tool to establish the diagnosis of BOS and are recommended routinely after aHSCT. The National Institutes of Health Clinical Center (NIH-CC) propose that the clinical diagnosis of BOS post aHSCT is made when forced expiratory volume in 1 second (FEV1)/VC is less than 0.7, FEV1 less than 75% of predicted with greater than 10% decline over less than 2 years,in addition to the absence of infection and evidence of air trapping by HRCT or PFTs.[15]

Still, the long-term follow-up of lung function in children with BOS is poorly characterized. A recent study in adult patients with BOS has shown distinctive patterns of lung function decline which were associated with the survival outcome.[11] Patients with a rapid lung function decline within 3 months after BOS was diagnosed, had a significantly poorer lung function and worse overall survival outcome compared with those with a gradual decline in lung function.

Current guidelines for BOS point out the need to find new sensitive lung function indices to detect early small airway impairment, as considerable peripheral lung damage can occur in airways less than 2 mm in diameter before this is sufficient to have an impact on airflow and to be detected by spirometry.[21,22] Clinical studies have shown that the lung clearance index (LCI), a global measure of ventilation heterogeneity obtained by multiple breath washout (MBW) testing, is a feasible and sensitive tool to detect early small airway impairment in chronic lung diseases in children.[23,24] Previous studies have used MBW measurements in pediatric patients with BOS and have revealed that LCI increased progressively according to the cGvHD score and was more sensitive compared with FEV1/forced vital capacity (FVC).[25,26] Therefore, LCI can be considered as a potential early biomarker for the development of BOS.

The objective of this study is to assess the incidence of BOS in pediatric patients after aHSCT and to describe the long-term follow-up of PFTs and LCI in children with BOS after aHSCT.

2 | MATERIALS AND METHODS

2.1 | Patient setting

This is a retrospective cohort study of 526 children who underwent aHSCT between 2000 and 2017 at the Division for Stem Cell Transplantation, Immunology, and Intensive Care Medicine in Frankfurt/Main, Germany. The study was approved by the Ethics Committee of the Goethe University Frankfurt (number 116/19) and patient's consent was waived.

BOS was defined as follows: clinical deterioration with respiratory symptoms such as tachypnea, cough, wheezing, exercise intolerance, and hypoxemia, impaired lung function pattern according to the NIH-CC, new onset of changes on CT including mosaic patterns, hyperinflation, bronchial wall thickening.

Medical data were collected from the patients' charts and included routine clinical visits as well as additional consultations, for example, upon sudden deterioration. Patients that died within the first 4 weeks after aHSCT were excluded from the subsequent evaluation.

TABLE 1 Characteristics of patients with aGvHD after aHSCT

Number of patients	Sex	Race	Diagnosis	Donor	Organ manifestation
n = 236 (45%)	Female: 38.41%	Caucasian: 100%	ALL: 42.37%	MUD: 46.19%	Skin: 87%
	Male: 61.86%		AML: 15.25%	Haplo: 31.36%	GIT: 28%
			MDS: 11.44%	MSD: 19.07%	Liver: 10%
				MMUD: 2.54%	

Abbreviations: ALL, acute lymphoblastic leukemia; aGvHD, acute graft vs host disease; aHSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myloid leukemia; GIT, gastrointestinal tract; MDS, myelodysplastic syndrome; MMUD, mis-matched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor.

All patients with BOS were thoroughly investigated which included the analysis of 271 PFTs, 46 HRCT scans, and eight results of bronchoalveolar lavage (BAL).

2.2 | Pulmonary function tests

PFTs were performed using a body plethysmograph (CareFusion, Germany) according to the recommendations of the American Thoracic Society (ATS)[27] and the European Respiratory Society (ERS).[28] The following measurements were obtained: FVC, FEV1, FEV1/FVC, RV, and RV/total lung capacity (TLC).

The LCI was measured using the MBW method by EasyOne Pro Lab (ndd Medical Technologies, Zurich, Switzerland) as described by Uhlving et al[29] and Belachew et al.[30] The LCI was defined according to the ERS/ATS consensus statement, as the number of lung volume turnovers (the cumulative expired volume divided by the functional residual capacity [FRC]) needed to lower the end-tidal tracer gas concentration to less than 1/40th (2.5%) of the starting concentration.[31] The mean LCI result from three (minimum two) MBW measurements in each patient was used for the analysis.

PFT and LCI results and curves from each BOS patient were assessed by a pediatric pulmonologist. Suspicious PFTs and LCIs were reassessed and confirmed by a second pediatric pulmonologist.

2.3 | High-resolution computed tomography

High-resolution computed tomography (HRCT) were acquired on a 128 slice CT scanner system (Somatom Definition AS+, Siemens). Results of 46 HRCT were reassessed by a pediatric radiologist, looking for high and low-density areas, bronchiectasis, mosaic patterns, and bronchial wall thickening in particular.

TABLE 2 Number of organ systems involved with GvHD and mortality

Organ systems with GvHD	Number of patients	Died (n)	Mortality (%)
1	n = 172	n = 50	29.07
2	n = 46	n = 16	34.78
3	n = 18	n = 11	61.11

Abbreviation: GvHD, graft vs host disease.

2.4 | BAL

General inhalation anesthesia was performed and BAL was carried out using the internal pediatric standardized protocol.

2.5 | Statistical analysis

The data were analyzed using the statistical program GraphPad Prism and Microsoft Excel. Group differences between patients with BOS were analyzed using a Student two-tailed *t* test or two-tailed Wilcoxon-Mann-Whitney test depending on normality assumptions and homogeneity of variances. A probability of $P < .05$ was regarded as significant. Figures of PFT parameters were created with GraphPad Prism 5.

3 | RESULTS

From a total of 526 patients aged 0.2 to 27.2 years (median 9.8 years) diagnosed with aHSCT, 236 (45%) developed an acute GvHD and are characterized in Table 1. Interestingly, the number of organ systems that were involved at the time of acute GvHD was directly related to mortality, as shown in Table 2.

The exact number of acute GvHD of the lung was difficult to determine, since systemic involvement and early death of patients hindered regular PFTs. Of 526 patients, 14 (2.7%) were identified with BOS. The diagnosis was based on a combination of respiratory symptoms (14/14), impaired lung function pattern (8/14), low FEV1 (8/14), and abnormalities on HRCT (13/14). In addition, BAL was obtained in seven (7/14) patients and investigated for noticeable differential cell counting. Table 3 shows the clinical characteristics and risk factor profile of these 14 patients with BOS.

In addition, acute pulmonary infections were excluded in patients by laboratory results (14/14) and by bronchoscopy and BAL (7/14).

3.1 | Pulmonary function tests

PFTs of children with BOS that were able to perform spirometry and body plethysmography according to current ATS/ERS guidelines[27,28] were analyzed over a period of median 4.67 (1.00-13.58) years. In total, 271 available lung function tests were evaluated and

TABLE 3 Profile of risk factors in BOS

Patient number	Gender	Diagnosis	Donor	Age at HSCT	Busulfan conditioning	GvHD prophylaxis	Radiation	CMV (donor/patient)	Infections after HSCT	cGvHD	aGvHD
1	Male	ALL	Haplo	6.50	No	None	None	+/+	CMV blood, adeno blood + stool		Skin
2	Female	Fanconi anemia	MSD	6.33	No	Unknown[a]	Unknown[a]	Unknown	Unknown[a]		GIT
3	Male	ALL	Haplo	3.42	No	None	Full body (12,6 Gy)	+/+			Skin
4	Female	MDS	MSD	6.75	Yes	CSA, sirolimus, and MMF	None	−/−	Polyoma blood + urine	Gastrointestinal tract	Gastrointestinal tract and eyes
5	Male	AML	MUD	4.50	Yes	CSA and MTX	None	−/−			Gastrointestinal tract and skin
6	Male	AML	MUD	5.81	No	CSA and ATG	Full body (12 Gy)	+/−			Gastrointestinal tract and skin
7	Female	ALL	MUD	9.80	Yes	CSA and MTX	None	+/−	Sepsis		Skin
8	Male	MDS	MSD	0.84	No	None	None	−/+		Skin and eyes	Gastrointestinal tract and skin
9	Female	ALL	Haplo	1.28	No	CSA and MTX	None	−/−	Adeno blood + stool		Skin
10	Female	MDS	MSD	16.67	No	CSA and MTX	None	−/+		Skin and eyes	Liver
11	Male	MDS	MSD	5.17	Yes	CSA	None	−/−		Skin and eyes	Skin
12	Male	ALL	Haplo	10.25	No	MMF	Craniospinal (18 Gy)	+/−	BK		Gastrointestinal tract and skin
13	Male	ALL	MSD	12.25	No	CSA	Full body (12 Gy)	−/+	CMV blood, BK urine		Skin
14	Male	ALL	MUD	5.17	No	CSA and MTX	Full body (12 Gy)	−/+	CMV, adeno, and BK		

Abbreviations: ALL, acute lymphoblastic leukemia; aGvHD, acute graft vs host disease; AML, acute myloid leukemia; ATG, anitthymocyte globin; BK, human polyomavirus 1; BOS, bronchiolitis obliterans syndrome; cGvHD, chronic graft vs host disease; CSA, ciclosporin; CMV, cytomegalovirus; Gy, gray; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MSD, matched sibling donor; MTX, methotrexate; MUD, matched unrelated donor.

[a]Patient was transplanted outside our department for Stem Cell Transplantation.

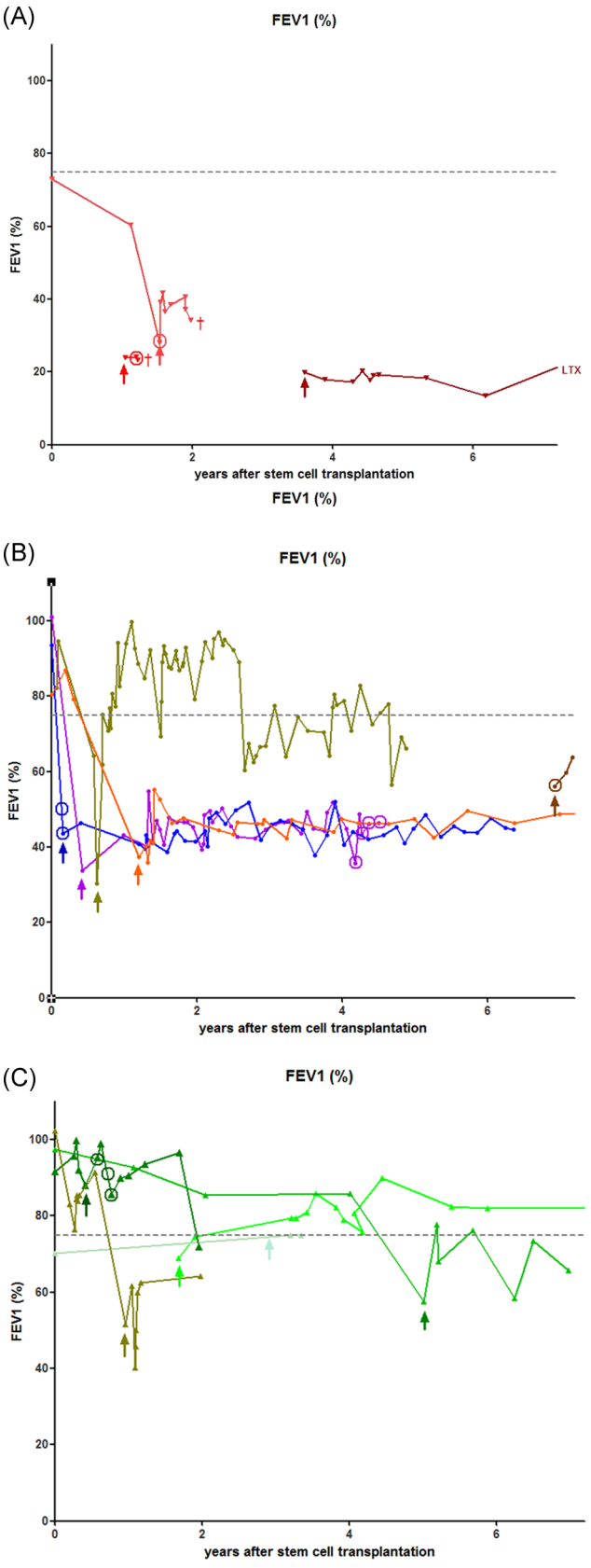


FIGURE 1 A, Long-term FEV1 in patients with respiratory failure. B, Long-term FEV1 in patients with chronic BOS. C, Long-term FEV1 in patients with transient BOS. BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 second [Color figure can be viewed at wileyonlinelibrary.com]

longitudinal changes in lung function parameters were analyzed (Figures 1–4). None of the patients showed abnormalities of PFT before aHSCT.

Three patterns of lung function decline were noted. Three out of 14 patients developed a significant progressive deterioration of their BOS despite intravenous steroid pulses (15-20 mg/kg high-dose systemic corticosteroid pulse on 3 consecutive days for 3 consecutive months) and maximal oral therapy with FAM (fluticasone, montelukast, and azithromycin). Two patients died, one patient received a lung transplant.

Five out of 14 patients developed persistent BOS with severe but almost compromised lung function, showing a combined restrictive and obstructive pattern with hyperinflation (FVC < 70%, FEV1 < 60%, FEV1/FVC < 70%, and RV/TLC > 150%). In addition, LCI revealed a significant inhomogeneity of lung ventilation with significantly elevated LCI measurements (median 14.90; range 12.59-20.90) (Table 4). Interestingly, one of the persistent patients with BOS (patient 6; Table 5), who had high levels of lymphocytes (23%) in the BAL, responded well to oral corticosteroids (OS). However, when OS were stopped due to severe side effects including adrenocortical insufficiency, bone fractures, and Cushing's syndrome, lung function rapidly deteriorated showing that GvHD was still active and only masked by OS (Figures 1, 2, and 4).

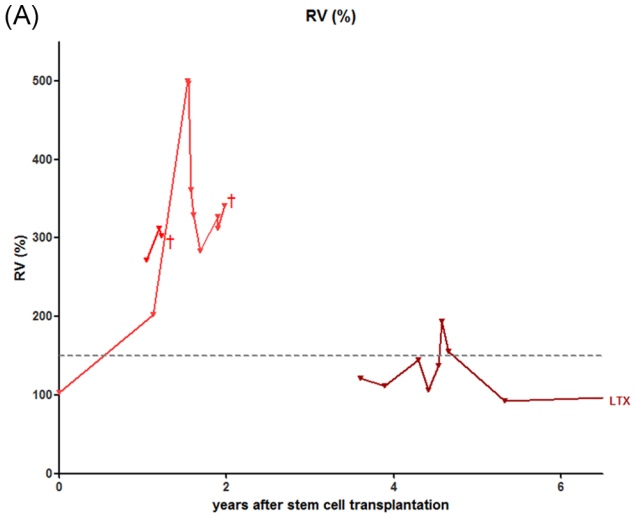
Lung function of patients with persistent BOS remained almost stable when expressed at the predicted level of normal during follow-up (Figures 1, 2, and 4). But there was a significant increase in lung volume growth (FVC: mean increase 13.08% per year and FEV1: mean increase of 9.40%, respectively) (Figure 3). Six out of 14 patients recovered completely after mild to moderate lung function impairment, clinical symptoms and signs of BOS on HRCT such as bronchial wall thickening and mosaic pattern of perfusion. Their PFT improved to normal values during the course of the disease (Table 4).

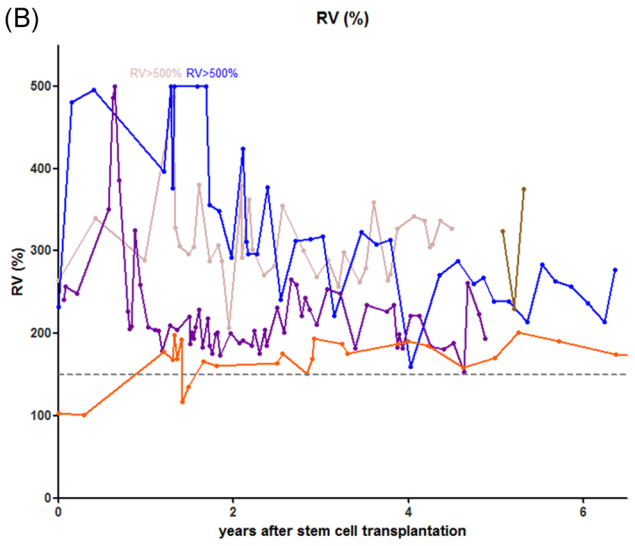
3.2 | HRCT and BAL findings

All 14 patients (14/14) diagnosed with BOS received a HRCT and seven patients (7/14) received a bronchoscopy with BAL: the results are listed in Table 5. Interestingly, BAL revealed a predominantly neutrophilic inflammation. These findings were in line with previous findings.[32]

4 | DISCUSSION

The diagnosis and treatment of BOS continues to be a challenge for the clinician. BOS is a severe, chronic inflammation of the airways, leading to obstruction of the bronchioles. However, at the beginning, BOS is often asymptomatic, and may be overlooked by clinicians, patients, and caregivers.[16] As transplanted patients do not regularly exercise, it is difficult to assess their breathlessness early in the disease, as it was the case in our cohort, patients 4 and 8 were diagnosed with BOS in less than 2 years after the aHSCT. The true





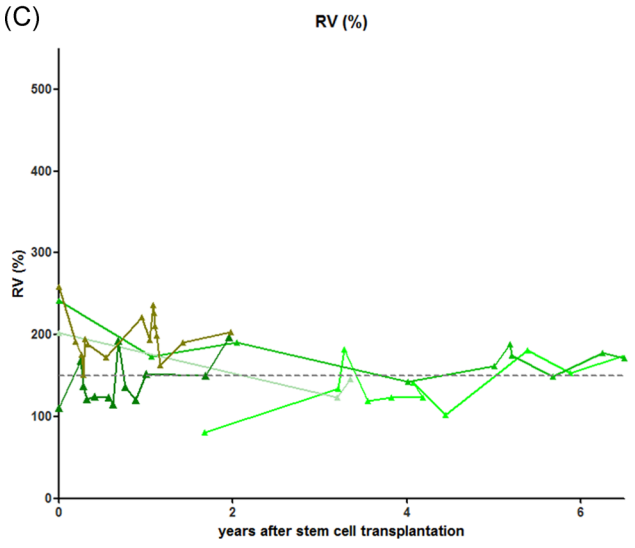
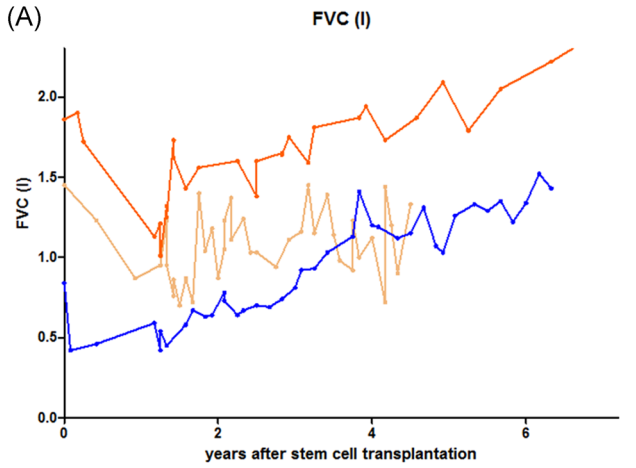


FIGURE 2 A, Long-term RV in BOS patients with respiratory failure. B, Long-term RV in patients with chronic BOS. C, Long-term RV in patients with transient BOS. BOS, bronchiolitis obliterans syndrome; RV, residual volume [Color figure can be viewed at wileyonlinelibrary.com]



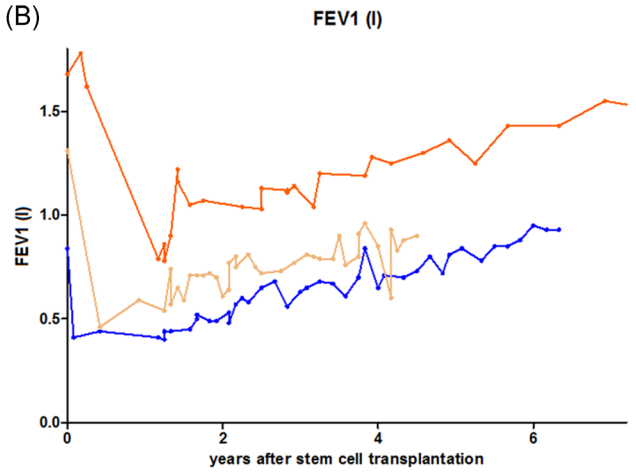


FIGURE 3 A, Long-term FVC in absolute values (l) in chronic BOS. B, Long-term FEV1 in absolute values (l) in chronic BOS. BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity [Color figure can be viewed at wileyonlinelibrary.com]

incidence of BOS is difficult to determine in view of several difficulties such as the inability to perform PFTs in very sick post-transplanted patients, the lack of regular PFTs, and CT scans, the focus on infections or the absence of potential early biomarkers such as LCI. The prevalence for BOS in our patient population was 2.7%, which was significantly lower than it has been described in adults, showing a prevalence of 4.8% to 6.5%, respectively.[9-11] Older age of both, recipient and donor, increases the probability of GVHD.[33] This is most likely the main reason why the incidence of BOS is higher in adults compared with children.

Multiple factors are known to increase the risk of BOS after aHSCT.[34] The presence of GvHD at another organ site is closely associated with the development of BOS and also decreases survival in patients with BOS.[18,35] In our cohort, all patients with BOS suffered from an acute or chronic GvHD of at least one organ site. Furthermore, we revealed that the mortality was significantly higher when three organ sites were affected by GvHD (Table 2). Known important risk factors, which may contribute to BOS such as myeloablative

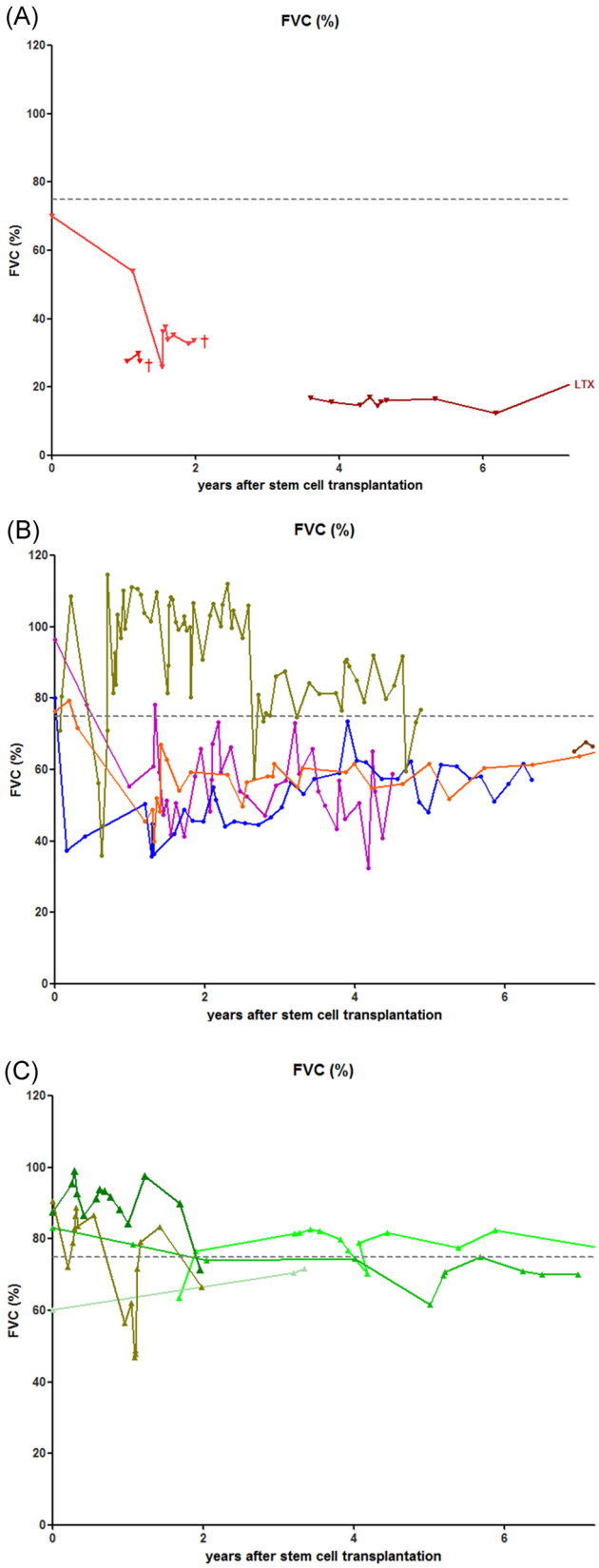


FIGURE 4 A, Long-term FVC in patients with respiratory failure. B, Long-term FVC in patients with chronic BOS. C, Long-term FVC in patients with transient BOS. BOS, bronchiolitis obliterans syndrome; FVC, forced vital capacity [Color figure can be viewed at wileyonlinelibrary.com]

busulfan-based conditioning regimen, unrelated donor, gastroesophageal reflux disease, acute or chronic viral, and bacterial infections,[13,34,36] were investigated and displayed in Table 3. Seven patients suffered from infections after aHSCT, four patients received a busulfan-based conditioning regime, and four patients had an unrelated donor. The pulmonary toxicity of busulfan has been described in the past and interestingly, 30% of our patients diagnosed with BOS post aHSCT received busulfan-based conditioning while there were only 11% of our patient aHSCT cohort who received busulfan-based conditioning and were not diagnosed with BOS. Although all patients received regular antibiotic prophylaxis (co-trimoxazol 5 mg/kg 3 d/wk until day +200, aciclovir 15 mg/kg per day until day +200, penicillin 25.0000 IE/kg until 2 years post aHSCT, voriconazol or AmBisome/Mykamine until T-cells stable >200/µL, IgG if IgG levels < 600, and immunization with Infanrix Hexa and Prevenar 13 from day 200 onwards), 50% of our patient group had underlying infections which may have influenced the influx of neutrophils and triggered the chronic inflammatory response.[32]

The decline of FEV1 in BOS has been shown to be variable, from rapid progression to chronic BOS and from transient decline to full recovery.[37] Lung function testing of our patients with BOS revealed three distinctive patterns: In patients with persisting BOS, the spirometry showed a restrictive and obstructive flow volume curve (FVC < 60%, FEV1 < 50%, and FEV1/FVC < 70). The body plethysmography showed a significantly increased residual volume (RV) and functional residual capacity (RV/TLC).

During follow-up, four out of five patients with a persistent disease presented with constantly low FEV1 < 50%, and showed no or little response to treatment with FAM or OS whereas one patient responded to OS. It is well known that steroid resistance is often associated with a very poor prognosis.[38] Importantly, although predicted levels of lung function in patients with persistently stable BOS were constantly below the 50%, total lung function volume increased during their regular follow-ups. These findings indicate that lung growth is present in children with BOS. This positive effect on lung growth was also described in patients with postinfectious bronchiolitis.[32] The steady growth of lung volume went along with a better performance during exercise and less symptoms during viral infection.

Taking the strict criteria of the NIH-CC into account, most patients fulfilled these criteria. However, several investigators already discussed that the NIH-CC criteria for BOS have some limitations in children.[39]

Previous longitudinal studies in lung transplanted adults revealed, that a concurrent FEV1 and FVC decline from the baseline is associated with a poor prognosis,[40] which accords with our study cohort where patients with mild BOS presented with a mild decline in FEV1 and FVC and had a much better clinical prognosis, despite similar clinical symptoms. In addition, in a recent study of 1461 adults undergoing HSCT 95 (6.5%) patients were diagnosed with BOS.[11] Interestingly, a 25% decline in FEV1 within the first 3 months after BOS separated the patients' group into a subgroup with an initially rapid decline and another subgroup with an initially gradual decline in lung function.[11] The overall survival was significantly worse in the group with the rapid decline. Although our pediatric group was small,

TABLE 4 Lung function parameters correlated with lung clearance index in BOS

Patient number	Follow-up- time	LCI	FVC (%)	FEV1 (%)	FEV1/FVC	RV (%)	RV/TLC (%)	Outcome
1	1.98		33.7	36.5	95.87	329.7	288.1	Death due to respiratory failure
2	1.23		27.6	23.9	78.70	272.2	285.2	Death due to respiratory failure
3	13.58		54.8	53.4	81.13	133.60	171.0	Successful LTX
4	4.50	12.59	58.7	46.5	67.96	327.3	262.0	Chronic BO
5	6.33	19.30	59.0	43.1	61.47	312.8	236.8	Chronic BO
6	4.83	14.90	73.4	69.2	79.43	223.3	185.8	Chronic BO
7	9.75	14.69	67.6	55.2	69.10	154.9	180.1	Chronic BO
8	6.37	20.90	54.1	56.1	77.41	323.8	244.5	Chronic BO
9[a]	3.18							Recovered
10	11.08	8.02	83.3	89.5	93.49	148.9	140.3	Recovered
11	6.92	7.79	70.7	68.0	82.12	175.1	179.6	Recovered
12	3.33		70.4	74.8	88.57	123.4	143.1	Recovered
13	1.92	6.51	71.5	71.9	86.92	197.0	175.4	Recovered
14	1.92		79.1	62.4	66.76	163.1	167.0	Recovered

Abbreviations: BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LCI, lung clearance index; LTX, lung transplant; RV, residual volume; TLC, total lung capacity.
[a]Patient was too young to perform spirometry.

we showed that patients with an early rapid decline had a very poor outcome.

It is well known that current guidelines recommend the need to find new sensitive lung function indices to detect early small airway impairment in BOS.[41] With regard to the literature, data are scant of studies using MBW methods for patients post aHSCT.[26] In a longitudinal study of 33 adults post aHSCT, Lahzami et al[25] showed elevated LCI and Sacin values. These findings are in line with a study which included 225 patients post aHSCT, describing highly pathological LCI values in 96% of cases whereas FEV1/FVC was decreased only in 57% of cases.[26] This is in accordance with our study, which showed that all patients with chronic BOS had significantly elevated LCI values. In view of this, LCI is not only a valuable tool to improve early diagnosis of BOS, but would be specifically useful to diagnose early BOS in younger patients as it is independent from active breathing maneuvers compared with spirometry. In addition, in patients without reproducible pulmonary lung function testing, HRCT can reveal changes of BOS such as vascular attenuation, mosaic perfusion, central bronchiectasis, and air trapping in time.[42]

At present, there is no accepted treatment protocol for BOS and there are only few randomized placebo-controlled trials in children with BOS. Most published reports on treatment options suffer from a small number of patients, absence of controls, and a diversity of patients at the start of therapy. The overall consensus is, that in addition to optimal supportive therapy, anti-inflammatory drugs like corticosteroids pulses, which impair lymphocyte proliferation, should be used as a first line treatment. Although steroids are effective during an acute deterioration and by improving lung function and exercise capacity, the long-term benefit is largely unknown.

There are several limitations of our retrospective cohort study. There was a lack of standardized follow-up protocol for lung function to detect BOS. We suggest that this may have resulted in an underestimation of the true prevalence of BOS in our population. However, the diagnosis of BOS is specifically difficult to establish in those children, who recover completely after a transient loss of lung function post aHSCT.

5 | CONCLUSION

Our results indicate that BOS presents with three distinctive patterns of pulmonary function: a rapid decline, a transient decline with full recovery, and a chronic but stable course. Long-term follow-up of patients with chronic BOS showed severely impaired PFTs, displaying an obstructive and secondarily restrictive pattern with air trapping. Risk factors such as busulfan induction, nonrelated donors, and especially silent infections have to be looked at carefully. In addition to PFTs, LCI can be a helpful tool to assess ventilation inhomogeneity

TABLE 5 HRCT, BAL, treatment, and outcome in BOS

Patient number	CT findings	BAL	FAM	IV Steroids	Outcome
1	Mosaic pattern with low density areas		Yes	Yes	Death due to respiratory failure
2	Mosaic pattern with high density areas		Yes	Yes	Death due to respiratory failure
3	Bronchial wall thickening, bronchiectasis, and mosaic pattern high density areas		No	No	Successful LTX
4	Bronchiectasis and mosaic pattern with high density areas	88% Alveolar macrophages, 6% neutrophils, and 6% lymphocytes	Yes	Yes	Chronic BO
5	Mosaic pattern with high density areas and bronchial wall thickening	4% Alveolar macrophages, 94% neutrophils, and 0% lymphocytes	Yes	Yes	Chronic BO
6	Bronchiectasis	66% Alveolar macrophages, 11% neutrophils, and 23% lymphocytes	Yes	No	Chronic BO
7	Mosaic pattern with high density areas, bronchial wall thickening, bronchiectasis, and lymphadenopathy	15% Alveolar macrophages, 79% neutrophils, and 4% lymphocytes	Yes	No	Chronic BO
8	Mosaic pattern with low density areas		Yes	Yes	Chronic BO
9	Mosaic pattern with high density areas		No	No	Recovered
10	Mosaic pattern with low density areas, bronchial wall thickening, and bronchiectasis		No	Yes	Recovered
11	Mosaic pattern with high density areas	9% Alveolar macrophages, 91% neutrophils, and 0% lymphocytes	No	No	Recovered
12	Bronchial wall thickening, bronchiectasis, and mosaic pattern with low density areas		No	No	Recovered
13	Normal	95% Alveolar macrophages, 0% neutrophils, and 5% lymphocytes	No	Yes	Recovered
14	Mosaic pattern with low density areas and lymphadenopathy	4% Alveolar macrophages, 95% neutrophils, and 1% lymphocytes	Yes	No	Recovered

Abbreviations: BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; CT, computed tomography; FAM, fluticasone, montelukast, and azithromycin; HRCT, high-resolution computed tomography; IV, intravenous; LTX, lung transplant.

and to detect BOS early and accurately. Although BOS is a severe, chronic disease, pediatric patients with BOS still have lung growth.

CONFLICT OF INTERESTS

All the authors declared that there are no conflict of interests.

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REFERENCES

1. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1863-1869.
2. Duarte RF, Labopin M, Bader P, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant*. 2019;54:1525-1552.
3. Bakhtiar S, Woelke S, Huenecke S, et al. Pre-emptive allogeneic hematopoietic stem cell transplantation in ataxia telangiectasia. *Front Immunol*. 2018;9:2495.
4. D'Souza A, Lee S, Zhu X, Pasquini M. Current use and trends in hematopoietic cell transplantation in the United States. *Biol Blood Marrow Transplant*. 2017;23:1417-1421.
5. Hildebrandt GC, Fazekas T, Lawitschka A, et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone Marrow Transplant*. 2011;46:1283-1295.
6. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40000 transplants annually. *Bone Marrow Transplant*. 2016;51:786-792.
7. Choi SW, Levine JE, Ferrara JL. Pathogenesis and management of graft-versus-host disease. *Immunol Allergy Clin North Am*. 2010;30:75-101.
8. Chien JW, Duncan S, Williams KM, Pavletic SZ. Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation-an increasingly recognized manifestation of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2010;16:106-114.
9. Au BK, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2011;17:1072-1078.
10. Gazourian L, Rogers AJ, Ibanga R, et al. Factors associated with bronchiolitis obliterans syndrome and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Am J Hematol*. 2014;89:404-409.
11. Kwok WC, Liang BM, Lui MMS, et al. Rapid versus gradual lung function decline in bronchiolitis obliterans syndrome after haematopoietic stem cell transplantation is associated with survival outcome. *Respirology*. 2019;24:459-466.
12. Afessa B, Litzow MR, Tefferi A. Bronchiolitis obliterans and other late onset non-infectious pulmonary complications in hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;28:425-434.
13. Dudek AZ, Mahaseth H, DeFor TE, Weisdorf DJ. Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. *Biol Blood Marrow Transplant*. 2003;9:657-666.
14. Bergeron A, Godet C, Chevret S, et al. Bronchiolitis obliterans syndrome after allogeneic hematopoietic SCT: phenotypes and prognosis. *Bone Marrow Transplant*. 2013;48:819-824.
15. Jagasia MH, Greinix HT, Arora M, et al. 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*. 2015;21:389-401.
16. Thompson PA, Lim A, Panek-Hudson Y, et al. Screening with spirometry is a useful predictor of later development of noninfectious pulmonary syndromes in patients undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:781-786.
17. Uhlving HH, Buchvald F, Heilmann CJ, Nielsen KG, Gormsen M, Müller KG. Bronchiolitis obliterans after allo-SCT: clinical criteria and treatment options. *Bone Marrow Transplant*. 2012;47:1020-1029.
18. Even-Or E, Ghandourah H, Ali M, Krueger J, Sweezey NB, Schechter T. Efficacy of high-dose steroids for bronchiolitis obliterans syndrome post pediatric hematopoietic stem cell transplantation. *Pediatr Transplant*. 2018;22:22.
19. Bergeron A, Chevret S, Granata A, et al. Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant: the ALLOZITHRO randomized clinical trial. *JAMA*. 2017;318:557-566.
20. Bergeron A, Chevret S, Chagnon K, et al. Budesonide/formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation. *Am J Respir Crit Care Med*. 2015;191:1242-1249.
21. Horsley A, Siddiqui S. Putting lung function and physiology into perspective: cystic fibrosis in adults. *Respirology*. 2015;20:20-45.
22. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr*. 2004;144:145-146.
23. Aurora P, Bush A, Gustafsson P, et al. London cystic fibrosis collaboration. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. *Am J Respir Crit Care Med*, 2004;171:249-256.
24. Rayment JH, Stanojevic S, Davis SD, Retsch-Bogart G, Ratjen F. Lung clearance index to monitor treatment response in pulmonary exacerbations in preschool children with cystic fibrosis. *Thorax*. 2018;73:73-458.
25. Lahzami S, Schoeffel RE, Pechey V, et al. Small airways function declines after allogeneic haematopoietic stem cell transplantation. *Eur Respir J*. 2011;38:1180-1188.
26. Nyilas S, Baumeler L, Tamm M, et al. Inert gas washout in bronchiolitis obliterans following hematopoietic cell transplantation. *Chest*. 2018;154:157-168.
27. Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society echnical statement. *Am J Respir Crit Care Med*. 2017;196:1463-1472.
28. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26:153-161.
29. Uhlving HH, Skov L, Buchvald F, et al. Lung clearance index for early detection of pulmonary complications after allo-HSCT in children. *Pediatr Pulmonol*. 2019;54:1029-1038.
30. Belachew N, Jerkic S, Michel F, Schubert R, Zielen S, Rosewich M. Lung function, lung clearance index und bronchial inflammation in children and adolescents with bronchiolitis obliterans. *Pneumologie*. 2019;73:399-406.
31. Schulzke SM, Frey U. Consensus statement on inert gas washout measurement: at the threshold of clinical use. *Eur Respir J*. 2013;41:500-502.
32. Rosewich M, Eckrich J, Zielen S. Long-term lung function in post-infectious bronchiolitis obliterans. *Thorax*. 2015;70:792.
33. Jacobsohn DA. Acute graft-versus-host disease in children. *Bone Marrow Transplant*. 2008;41:215-221.
34. Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med*. 2014;370:1820-1828.
35. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood*. 2002;100:406-414.

36. Yomota M, Yanagawa N, Sakai F, et al. Association between chronic bacterial airway infection and prognosis of bronchiolitis obliterans syndrome after hematopoietic cell transplantation. *Medicine*. 2019;98: e13951.
37. Clark JG, Crawford SW, Madtes DK, Sullivan KM. Obstructive lung disease after allogeneic marrow transplantation. Clinical presentation and course. *Ann Intern Med*. 1989;111:368-376.
38. Elgaz S, Kuçi Z, Kuçi S, Bönig H, Bader P. Clinical use of mesenchymal stromal cells in the treatment of acute graft-versus-host disease. *Transfus Med Hemother*. 2019;46:27-34.
39. Cuvelier GDE, Nemecek ER, Wahlstrom JT, et al. Benefits and challenges with diagnosing chronic and late acute GvHD in children using the NIH consensus criteria. *Blood*. 2019;134: 304-316.
40. Belloli EA, Wang X, Murray S, et al. Longitudinal forced vital capacity monitoring as a prognostic adjunct after lung transplantation. *Am J Respir Crit Care Med*. 2015;192:209-218.
41. Uhlving HH, Mathiesen S, Buchvald F, et al. Small airways dysfunction in long-term survivors of pediatric stem cell transplantation. *Pediatr Pulmonol*. 2015;50:704-712.
42. Liptzin DR, DeBoer EM, Giller RH, Kroehl ME, Weinman JP. Evaluating for bronchiolitis obliterans with low-attenuation computed tomography three-dimensional reconstructions. *Am J Respir Crit Care Med*. 2018;197(6):814-815.

How to cite this article: Walther S, Rettinger E, Maurer HM, et al. Long-term pulmonary function testing in pediatric bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Pediatric Pulmonology*. 2020;55: 1725–1735. https://doi.org/10.1002/ppul.24801