Prevalence of Bronchiolitis Obliterans Syndrome Following Allogeneic Haematopoietic Stem Cell Transplant in the United States, Europe, and Japan

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Background

- Bronchiolitis obliterans syndrome (BOS) is a progressive obstructive airway disease characterised by inflammation and fibrosis that reduces the internal diameter of the bronchioles and results in respiratory failure and death[1,2]
- Regardless of preceding injury, BOS is characterised by T cell–mediated inflammation and fibrosis of bronchiolar walls that reduce the diameter of the bronchioles, resulting in progressive and irreversible airflow obstruction[3]
- BOS occurs most frequently following lung transplantation and allogeneic haematopoietic stem cell transplant (alloHSCT), but it can also occur as a result of environmental exposures, autoimmune disease, and severe infections[1,4]
- BOS is a well-described complication following lung transplant, with a 5-year prevalence rate of 50%.[5] However, BOS is less well described following alloHSCT
- The aims of this study were to describe the prevalence and assess potential geographic differences of BOS following alloHSCT in the United States (US), Europe, and Japan

Methods

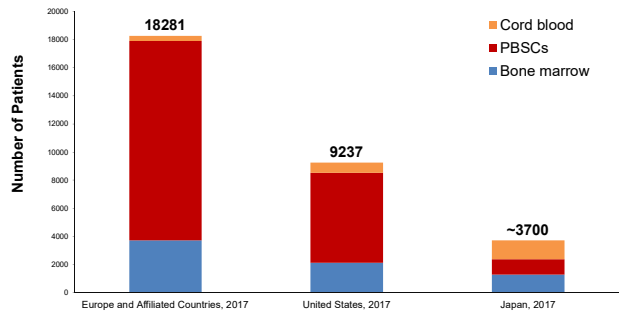
- To evaluate the total number of alloHSCTs performed, a review and analysis of the following data sources were performed
  - AlloHSCT activity reports from the European Society for Blood and Marrow Transplantation 2017[6,7]
  - The Center for International Blood and Marrow Transplant Research 2017[8-10]
  - Health Resources and Services Administration Report 2017[11,12]
  - The Japanese Data Center Hematopoietic Cell Transplantation 2017[13]
- To evaluate the prevalence of BOS in alloHSCT, a PubMed literature search was conducted to identify publications using the following criteria
  - Published from 2011 to 2017
  - Including >100 patients
  - Key terms "bronchiolitis obliterans and haematopoietic stem cell," "bronchiolitis obliterans after stem cell transplant," and "prevalence"
  - A potential limitation of this analysis is that data on the prevalence and potential risk factors for BOS were obtained from retrospective studies with the absence of a specific ICD-10 code for BOS
- Case reports, reviews, and redundant publications were excluded

Results

Total number of alloHSCTs performed

- Approximately 31,200 alloHSCTs were performed in 2017 in the US, Europe, and Japan, according to published regional reports (**Figure 1**)[6-13]
- In Europe and the US, peripheral blood stem cells are the major source of alloHSCTs, followed by bone marrow. Cord blood represents less than 10% of total alloHSCTs
- In Japan, each cell source accounts for approximately one-third of total alloHSCTs

Figure 1. The Number of AlloHSCTs Performed in 2017[6-13]

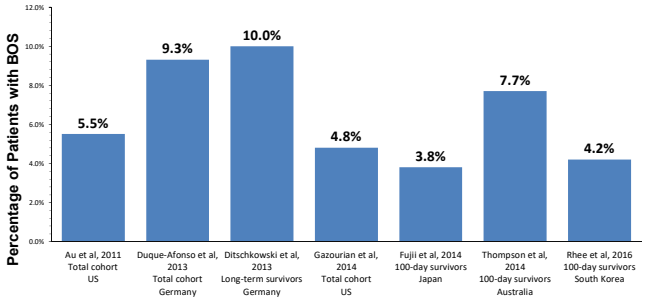


Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplant; PBSCs, peripheral blood stem cells.

Prevalence of BOS following alloHSCT

- Based on eligible studies identified by the literature search, the reported prevalence of BOS in patients who underwent alloHSCT ranged from 3.8% to 10% (**Figure 2**)[14-20]

Figure 2. Prevalence of BOS in Patients Treated With AlloHSCT[14-20]



Note 1: For Duque-Afonso et al (2013), only patients with reduced-intensity conditioning were included in the study
Note 2: For Ditschkowski et al (2013), "long-term survivor" was not defined in the publication
Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplant; BOS, bronchiolitis obliterans syndrome.

Results (cont'd)

- Median time to diagnosis of BOS following alloHSCT was 273 to 547 days post-transplant
- Attempts have been made to identify the most important risk factors for developing BOS, but the results have not been consistent across studies (**Table 1**)[14-20]
- Many studies have identified myeloablative protocols as a risk factor for BOS
- All studies identified chronic graft-versus-host disease (cGVHD) and peripheral blood stem cell transplant (PBSCT) as risk factors, and some studies found them to be among the most important
- The presence of busulfan-based conditioning, which is associated with acute lung injury and pulmonary fibrosis[21], was also identified as an important risk factor for BOS by some studies

Table 1. Risk Factors/Predictors for the Development of BOS in Patients Treated With AlloHSCT[14-20]

Study	Method	Type of AlloHSCT	Main Risk Factors		
			1st	2nd	3rd
Au et al, 2011; n=946	Multivariate Cox regression for risk of BOS	All	cGVHD (*P*<0.001)	Low IgG (*P*=0.024)	
Duque-Afonso et al, 2013; n=259	Multivariate Cox regression for risk of BOS	FBM preparative regimen	Patients <55 years at alloHSCT (*P*=0.03)	Lung disease after alloHSCT (*P*=0.04)	
Ditschkowski et al, 2013; n=952	Patient characteristics BOS vs. no BOS	Myelo-ablative alloHSCT	PBSCT (NS)	Presence of cGVHD (*P*<0.001)	ABO blood group incompatibility (*P*=0.028)
Gazourian et al, 2014; n=1845	Multivariate analysis[1]	All	Busulfan-based conditioning (*P*<0.001)	Unrelated donor (*P*<0.01)	Female donor (*P*=0.03)
Fujii et al, 2014; n=465	Multivariate Cox regression for risk of BOS	All	Female gender (*P*=0.006)	cGVHD (*P*=0.011)	
Thompson et al, 2014; n=265	Multivariate Cox regression for risk of BOS	All	Busulfan-based conditioning (*P*<0.001)	Trend age (*P*=0.054)	
Rhee et al, 2016; n=976	Logistic regression for risk factors of BOS	All	PBSCT (*P*=0.008)		

[1]cGVHD was not included in the model
Note: The number of identified predictors varied between studies
Abbreviations: alloHSCT, allogeneic haematopoietic stem cell transplant; BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; FBM, fludarabine, carmustine, and melphalan; IgG, immunoglobulin G; NS, not statistically significant; PBSCT, peripheral blood stem cell transplant.

Conclusions

- **Approximately 31,200 alloHSCTs were performed in 2017, mostly using PBSCs as the source**
- **With an estimated prevalence of BOS (based on publications) of approximately 6%, and a prevalence range of 3.8% to 10.0%, up to ~3000 new cases of BOS following alloHSCT could be diagnosed annually**
- **The time to diagnosis of BOS varies from several months to 2 years post-alloHSCT and is not likely associated with the potential risk factors. Further research is needed to determine the predictors of BOS in alloHSCT to improve awareness and diagnosis of BOS**
- **A potential limitation of this analysis is that data on the prevalence and potential risk factors for BOS were obtained from retrospective studies. The absence of an ICD-10 code for BOS makes the estimation of BOS prevalence more challenging. An ICD-10 code is much needed for this devastating condition**

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Author Disclosures

- Emilie Hofstetter and Dominik Kappeler are consultants to Breath Therapeutics, a Zambon company and received consultancy fees. Noreen Roth Henig is a former employee of Breath Therapeutics, a Zambon company. Anne Bergeron has no disclosures.

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