The clinical, humanistic and economic burden of bronchiolitis obliterans syndrome in Europe

Noreen R. Henig, MD[1], Jennifer McGrain, MS RRT[1] , Clément François[2], Caroline Marre[2], Emilie Hofstetter[3], Peter Shadday[1]

[1]Breath Therapeutics, a Zambon company, Menlo Park, California, USA; [2]Creativ-Ceutical, 215 rue du Faubourg Saint Honoré, Paris, France; [3]HealthStrat Consulting, Munich, Germany.

Introduction

- 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] BOS results from an injury to the airways that precedes the development of BOS.[2]
- BOS occurs most frequently following lung transplantation (LTx) and allogenic Hematopoietic Stem Cell Transplant (alloHSCT), but can also occur as a result of environmental exposures, autoimmune disease and severe infections. Disease pathophysiology and progression are similar in adult and paediatrics patients regardless of etiology.[3]
- BOS is the leading cause of death 1-3 years after paediatric LTx, accounting for approximately 35% of the mortality.[4] BOS in paediatric alloHSCT patients shows a mortality rate between 11-67%.[5]
- Currently, there are no approved treatments for BOS.

Objectives

To begin to understand the disease burden of BOS patients in Europe, this study summarises the clinical, humanistic and economic burden of BOS in published sources.

Methods

A targeted literature review in Medline and Embase on the disease burden in Europe was performed in January 2019 and was supplemented with an Internet search. The studies were selected by one reviewer based on relevance to the topic but no systematic filter was applied. We were not able to identify any costing study with reported detailed information on Diagnosis Related Group for BOS.

Results

Prevalence

Post lung transplantation, the incidence of BOS is about 10% per year, with a prevalence of 30% and 50% at 3 and 5 years[6], respectively and a median survival of less than 6 years.[7]

The incidence of BOS in alloHSCT patients is 8.3%[8] with a prevalence from 3.4%-10.0%, and a 5 year overall survival of only 13%.[9]

The reported prevalence and incidence of BOS vary significantly across countries due to differences in study design and a lack of consensus regarding the clinical diagnostic criteria for BOS (Table 1).

Table 1. Prevalence of BOS in Europe

Country	Data on prevalence*
	In France, approximately 384 pulmonary transplants are performed each year, with a BOS prevalence of 45% at 5 years.[10]
	In the Swiss population observed for at least 2 years but less than 3 years, 22.17% of 1,263 LTx recipients developed BOS (2009 and 2014).[11]
	In Germany, the estimated prevalence of BOS reached 41.2% in 119 LTx recipients at a mean interval of 5.6 years.[12]
	In Italy, between 1991 and 2016, 22.5% of patients developed BOS after LTx at a mean follow-up of 11.6±7months; 60% of patients had BOS after 5 years.[13] Between 2000 and 2012, the prevalence of BOS after alloHSCT in an Italian cohort of paediatric patients was 7.8%.[14]
	71.4% of 998 LTx patients had BOS in a Spanish transplant unit (1990- 2017).[15]
	Between 1997 and 2007, out of 61 LTx recipients, 16.7% diagnosed with BOS post-transplant (10-86 months).[16]

*Data on BOS prevalence is limited.
Abbreviations: BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; LTx, lung transplantation.

Clinical burden of BOS

- BOS is a progressive life-threatening disease.
- 50% of LTx patients are dead after 5 years with BOS contributing to 35% of the mortality. The disease is irreversible and rapidly progressive.[17]
- The overview of clinical burden is presented in Table 2.

Table 2. Overview of clinical burden in Europe

Country	Clinical burden
	In a French cohort study, mortality rates 3 years after BOS following alloHSCT was 26.4%.[18] Another French study reviewed the data of all alloHSCT recipients. 27% patients with BOS died at 3 years.[19]
	In Sweden, the overall mortality rate of BOS following LTx was 24 ± 4% at 5 years, 36 ± 4% at 10 years, 40 ± 5% at 15 years, and 57 ± 6% at 20 years.[20]
	In Spain, patients who developed BOS after LTx had a mean survival of only 63.4 months (Spanish transplant unit).[15]
	In the UK, BOS was a common cause of death at the Freeman Hospital, 82% survival at 1 year, 62% at 5 years and 51% at 10 years post LTx.[21]

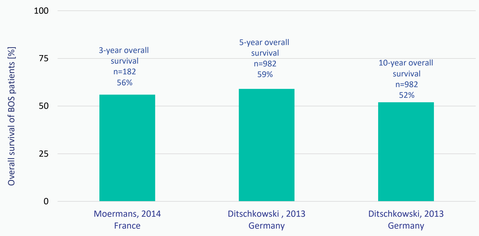
Abbreviations: BOS, bronchiolitis obliterans syndrome; HSCT, hematopoietic stem cell transplantation; LTx, lung transplantation.

Survival

- The mortality rate in patients with BOS following alloHSCT varies highly in historical series (Figure 1).[22]
- Diagnosis of BOS post alloHSCT confers a 1.6-fold increase in risk for mortality.[23]
- Median survival in LTx recipients following a BOS diagnosis is dependent on the grade of disease at the time of diagnosis: for initial diagnosis of BOS grade 1, median survival is 3.79 years; for BOS grade 2 or 3, 1.03 years.[24]
- A median overall survival in LTx recipients suffering from BOS is 5.8 years.[24]

Results (cont'd)

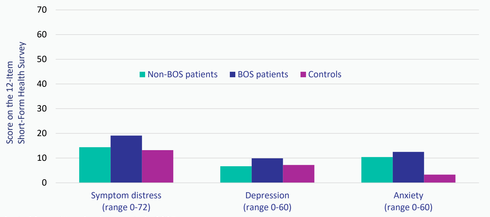
Figure 1. Overall BOS survival following alloHSCT [%][25,26]



Humanistic burden of BOS

- In patients following LTx, BOS significantly reduces patients' quality of life, especially physical functioning (the ability to perform daily living activities) and mental domains (symptom distress, anxiety and depression) – shown in Figure 2. It was also found to increase work absenteeism and caregiver burden.

Figure 2. Impact of BOS on health related quality of life[12]



Adapted from Künsebeck HW. et al., 2007.

Economic burden of BOS

- BOS is associated with the increased use of healthcare resources due to frequent hospitalisations, extensive immunosuppressive treatment and the use of diagnostic procedures. There is a 73% increase in cost related to lung transplant recipients developing BOS compared to BOS-free LTx recipients.[27]
- In the EU, the cost of hospitalisations due to BOS reaches up to €120 million per year.[28]

Conclusions

- **BOS is a common complication of LTx and alloHSCT and cause of mortality, but available data describing BOS is limited.**
- **BOS is associated with decreased QoL and a high economic and humanistic burden.**
- **There is no approved or effective treatment for BOS at this time.**
- **The available studies are mainly retrospective, single-centre, on heterogeneous groups and conducted on a small number of patients making it difficult to perform multivariate analyses.**
- **Further research on the disease burden and the development of effective treatments are warranted to alleviate the high unmet medical need in patients with BOS.**

Discussion

- A number of significant gaps in knowledge of BOS contributes to limited therapeutic options for patients with this debilitating disease.
- Differences in burden according to the aetiology of BOS (LTx vs alloHSCT) have not been investigated. Also, data for other causes of BOS are lacking.
- Gathering epidemiological data on patient populations and the prevalence of BOS as well as its economic and health outcomes impact is a key action for creating programs to treat the disease.

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