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REVIEW

Bronchiolitis obliterans following haematopoietic stem cell transplantation

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ABSTRACT: The aim of the present article is to review the available clinical data on bronchiolitis obliterans following haematopoietic stem cell transplantation (HSCT).

The data sources used were the Medline database and references from the identified articles related to bronchiolitis obliterans, noninfectious pulmonary complications and HSCT.

HSCT is an important treatment for a variety of malignant and nonmalignant conditions. However, the procedure is limited by significant complications that may involve every organ of the body. Pulmonary complications are seen in 40–60% of HSCT recipients. The recent advances in prophylaxis and treatment of infectious complications have increased the significance of late noninfectious pulmonary conditions.

Currently, bronchiolitis obliterans is one of the most challenging pulmonary complications facing clinicians who are taking care of haematopoietic stem cell transplantation recipients. This article reviews the clinical and pathological features of this condition, sheds some light on potential mechanisms of pathogenesis, and discusses the available management options.

KEYWORDS: Bone marrow transplantation, bronchiolitis

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Bronchiolitis obliterans (BO) is the most common late noninfectious pulmonary complication following allogeneic haematopoietic stem cell transplantation (HSCT). It is characterised by the onset of new air flow obstruction (AFO) following HSCT. It was first described following HSCT by BESCHORNER *et al.* [1] in 1978, who reported lymphocytic bronchitis in 10% of autopsies from patients who died following HSCT. In 1982, ROCA *et al.* [2] described fatal BO in a patient with a severe chronic graft *versus* host disease (GVHD) following HSCT. Since then, many reports have described this complication following HSCT (table 1), however, these reports are retrospective and are based on small case series. Furthermore, they lack uniform diagnostic criteria or management approach. The present review discusses the incidence, pathogenesis, clinical features and the management approaches of BO following HSCT.

INCIDENCE

The incidence of BO varies widely in different reports, in part due to the lack of a standardised definition. The reported incidence range is 0–48% (table 1). In a review of 2,152 allogeneic HSCT recipients reported in nine studies, the average incidence of BO was 8.3% [27]. In a recent report from Seattle (WA, USA), the incidence of BO in 1,131 allogeneic HSCT recipients was 26%; however, in patients with chronic GVHD, the incidence of BO was 32% [19]. The International Bone Marrow Transplantation Registry (IBMTR) reported that the incidence of BO was 1.7% 2 yrs after transplantation in 6,275 patients who received matched sibling HSCT [26]. One report specifically commented on the incidence of BO following peripheral blood stem cell transplantation and showed that there was three-fold increase in the risk of BO compared with bone marrow transplantation (BMT; hazard ratio 3.35; 95% confidence interval (CI) 1.79–6.27; $p=0.0002$) [26]. Regarding the incidence of BO in relation to the intensity of the conditioning regimen, one study reported that the incidence of BO following nonmyeloablative HSCT was 2.3% compared with 17% following conventional myeloablative HSCT [25]. The difference between these two groups was statistically significant, but the clinical course and outcome of BO was similar. In general, BO does not develop following autologous HSCT. There are only a few cases reported in the literature of BO developing following autologous HSCT with fatal outcome [28, 29]. Furthermore, there are very few reports of BO proven by lung biopsy developing in

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TABLE 1 The main studies on bronchiolitis obliterans (BO) following haematopoietic stem cell transplantation (HSCT)

First author [Ref.]	Year	Subjects n	Incidence %	Onset of BO	Risk factors	Treatment	Outcome	Comments
Wyatt [3]	1984	8	13	1.5–20 weeks	GVHD, TBI, infection	Corticosteroids	25% died after 20 months of diagnosis	Bronchodilators had no benefit
Urbanski [4]	1987	7	6	90–690 days	GVHD	NR	57% died	43% stabilised or improved
Clark [5]	1987	49	17	50–500 days	Age, HLA matching, GVHD, MTX, baseline PFT	NR	NR	Chronic GVHD and MTX were most important risk factors
Chan [6]	1987	11	11	1.5–23 months	GVHD	Prednisone, azathioprime, CsA	73% died within 2– 54 months post HSCT	All died of respiratory failure
Holland [7]	1988	7	2	40–400 days	Chronic GVHD, reduced Ig	NR	100% died 68–602 days post HSCT	86% died of respiratory failure
Clark [8]	1989	35	NR	80–500 days	Chronic GVHD, low Ig	Prednisone, CsA, azathioprime	65% died by 3 yrs	Higher risk of early death (within 150 days) and rapid drop in FEV_1 (>30%)
Schwarer [9]	1992	18	13	1–13 months	GVHD	Prednisone, azathioprime, thalidomide	21% died within 1–42 months of diagnosis	Respiratory infections were the main causes of death
Payne [10]	1993	19	18	NR	Chronic GVHD, not using CsA	Corticosteroids, CsA	NR	CsA protected against BO
Schultz [11]	1994	13	19	3–55.3 months	Chronic GVHD with liver involvement	NR	23% died within 13 months of diagnosis	23% had resolution of BO
Curtis [12]	1995	8	16	6–23 months	GVHD	Prednisone, CsA, thalidomide	No deaths related to BO during follow-up period	Reduction in FEV_1/FVC and $FEF_{25–75\%}$ may precede symptoms of BO
Philit [13]	1995	9	5	105–550 days	NR	Prednisone, azathioprime	56% died by an average of 397 days of diagnosis	All died of respiratory failure
Yokoi [14]	1997	8	10	110–430 days	GVHD	NR	All died	Study based on autopsies. Seven had concomitant CMV or aspergillosis
Sanchez [15]	1997	20	9	3.2–42 months	GVHD	Prednisone, CsA, azathioprime	40% no response to therapy on 65 months follow-up	Higher RV and lower MMFR had worse prognosis
Palmas [16]	1998	5	3	81–525 days	Chronic GVHD	Prednisone, CsA, azathioprime	39% died	20% responded to therapy. Lower FEV_1 was associated with a worse outcome. Respiratory failure is main cause of death.
Ringden [17]	1999	17	15		Busulfan			
Dudek [18]	2003	47	3	77–3212 days	Older donor or recipient, acute GVHD	Prednisone, CsA, azathioprime, pulse dose steroid, antithymocyte globulin	55% died within 5 yrs	Worse outcome if no response to first-line therapy; respiratory failure is main cause of death
Chien [19]	2003	299	26	NR	Older age, lower pre-HSCT FEV_1/FVC, chronic GVHD, respiratory viral infection	NR	Attributable mortality is 12% in 5 yrs	Worse outcome with older age, lower pre-HSCT FEV_1/FVC, chronic GVHD, recurrent malignancy, underlying disease, respiratory viral infection
Sakaida [20]	2003	7	9	94–540 days	Chronic GVHD, sicca syndrome	Prednisone, CsA, tacrolimus	43% died within 46 months follow-up	Respiratory failure was the primary cause of death
Marras [21]	2004	73	5	NR	Chronic GVHD, busulfan	NR	Mortality risk doubled with BO	
Chien [22]	2004	750	40	100 days	Age, pre-HSCT FEV_1/FVC, chronic GVHD	NR	Mortality is 15% at 5 yrs	AFO by 100 days is associated with increased risk of AFO by 1 yr, but not mortality
Ratjen [23]	2005	9	NR	NR	NR	Pulse steroid therapy	22% died at an average of 42 months follow-up	78% had stabilisation of lung function
Khalid [24]	2005	8	5	NR	GHVD	Prednisone, CsA, Azithromycim	NR	Average of 20% improvement in FEV_1
Yoshihara [25]	2005	14	10	102–350 days	Myeloablative regimen	NR	50% died within 618 days of diagnosis	Earlier onset (<200 days) associated with worse prognosis
Santo Tomas [26]	2005	76	2	65–2444 days	Peripheral blood stem cells, transplant to diagnosis >14 months, female donor to male recipient, acute GVHD	NR	NR	All patients had underlying leukaemia

The main studies that included five or more patients are displayed. GVHD: graft *versus* host disease; TBI: total body irradiation; NR: not reported; HLA: human leukocyte antigen; MTX: methotrexate; PFT: pulmonary function test; CsA: cyclosporine A; Ig: immunoglobulins; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $FEF_{25–75\%}$: mean forced expiratory flow between 25 and 75% of FVC; CMV: cytomegalovirus; RV: residual volume; MMFR: mid-maximum flow rate; AFO: air flow obstruction.

patients who received umbilical cord blood stem cell transplantation [30, 31].

RISK FACTORS

The main risk factors for BO following HSCT are summarised in table 2 [3–19, 20–22, 25, 32–34]. The most important association with BO is the presence of chronic GVHD. Earlier studies suggest that BO does not develop in patients without evidence of chronic GVHD [6, 11]. However, more recent studies from large HSCT centres report that BO may develop in a small percentage of patients who do not have manifestations of GVHD. In the IBMTR, 7% of patients with a diagnosis of BO did not have chronic GVHD [26]. In a study of 360 patients with AFO following allogeneic HSCT, 63 (18%) had no history of acute or chronic GVHD [19]. In this regard, the risk of BO appears to be higher in those with progressive chronic GVHD (which evolves without hiatus from active acute GVHD) as compared with those with quiescent chronic GVHD (that develops after an interval of response to treatment of acute GVHD) or *de novo* chronic GVHD (in patients who never had acute GVHD). In the study by CHIEN *et al.* [19], the adjusted relative risk for AFO obstruction was: 1.5 (95% CI 0.8–2.0) with *de novo* chronic GVHD; 1.6 (1.3–2.4) with quiescent chronic GVHD; and 1.9 (1.4–2.4) with progressive chronic GVHD. The difference between these different forms was statistically significant. In the majority of reports, acute GVHD alone does not appear to significantly increase the risk of BO. Other frequently observed risk factors for BO include: an older age of the recipient (>20 yrs); the presence of AFO (forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <70%) prior to HSCT; and respiratory viral infections, such as influenza, parainfluenza and respiratory syncytial virus, in the first 100 days following HSCT [19, 22]. There are other risk factors for BO that have been described by some studies, but not consistently so, and these include a busulfan-based conditioning regimen, mismatched or unrelated donor, hypogammaglobulinaemia (especially immunoglobulin (Ig)G and IgA), methotrexate prophylaxis against GVHD, older age of the donor, and HSCT for chronic myelogenous leukaemia [5, 7, 8, 17, 21]. In the report by the IBMTR [26], the risk factors for BO on multivariate analysis were blood-derived stem cells, a busulfan-based conditioning regimen, interval from diagnosis of leukaemia to transplantation >14 months, female donor to male recipient, prior interstitial pneumonitis, and an episode of moderate-to-severe acute GVHD.

CLINICAL PRESENTATION

BO is a late complication of allogeneic HSCT that usually presents after the first 100 days following transplantation [3, 5, 7, 8, 14, 18, 22]. Although there are reports of BO as early as 30 days following HSCT, ~80% of cases present between 6 and 12 months post-transplantation [7, 6, 13]. In the report by the IBMTR, the median interval from HSCT to diagnosis of BO was 431 days (range 65–2,444 days) post-transplantation [26]. The presentation of BO is usually insidious. In total, 23% of patients describe antecedent upper respiratory tract symptoms [8]. The main symptoms associated with BO are dry cough (60–100%) and dyspnoea (50–70%) [6, 8, 12, 35]. Wheezing and sinusitis are other frequent symptoms [8]. Fever is rare unless there is a concomitant infectious process. Approximately 20% of patients are asymptomatic and the diagnosis is suspected based on pulmonary function test (PFT) findings [8]. In the advanced stages of BO, the patients are physically limited due to severe obstructive airway disease and may require home oxygen therapy. Some patients may develop features of bronchiectasis with recurrent respiratory tract infections and colonisation of the airways by *Pseudomonas* spp., *Staphylococcus aureus* and, occasionally, *Aspergillus* spp.

On examination, the patients usually have signs of hyperinflation and decreased breath sounds. Wheezing and inspiratory squeaks may also be present. Basal crackles are rare. Conversely, the thoracic examination may be completely normal, especially in early stages [8, 36]. Almost all patients with BO have signs and symptoms of chronic GVHD, especially skin changes and sicca syndrome, with dryness in the eyes and mouth. In the data provided by the IBMTR on 6,275 patients, all except five had manifestations of GVHD [26].

The clinical course of BO is variable. The majority of patients have a slow progressive AFO, with episodes of acute exacerbation of AFO. In the minority of patients, the AFO progresses rapidly and patients develop respiratory failure within a few months. However, some patients may have stabilisation or even improvement in the AFO [11, 16].

RADIOLOGICAL EVALUATION

In the early stages of BO, the chest radiograph is normal. The presence of parenchymal changes suggests an infection or an unrelated process. As BO becomes more advanced, there are signs of hyperinflation on the chest radiograph and, later, there are changes consistent with bronchiectasis with dilated and thickened bronchi and areas of scarring. Pneumothorax, pneumomediastinum, and pneumopericardium may develop in advanced cases, and are usually associated with significant morbidity and mortality [5, 37–39].

High-resolution computed tomography (HRCT) of the chest is much more sensitive in detecting signs of BO and is the radiological procedure of choice in evaluating these patients [40–42]. While the study may still be normal in the early stages of BO, it usually shows signs of hyperinflation with areas of decreased attenuation. Bronchiectasis is seen in advanced cases. However, the most common radiological sign of BO on HRCT of the chest is the presence of air trapping during the expiratory phase of imaging. These views show areas of hypoattenuation that correspond to obstructed airways interspaced with areas of ground glass appearance corresponding to the pulmonary lobules with patent airways. This ''mosaic'' appearance is highly suggestive of BO, and has sensitivity and specificity in the diagnosis of BO with ranges between 74–91% and 67–94%, respectively [43–45]. Some studies demonstrated that the presence of expiratory air trapping preceded the PFT criteria for BO [44]. In a study of 11 patients with BO following HSCT who underwent HRCT of the chest, all were found to have abnormal findings, and all patients had progression of radiological findings over time [41]. The most common finding was decreased lung attention, especially in the lower lobes, and expiratory air trapping (n=11). Other common findings were subsegmental bronchial dilatation (n=6), diminishing of peripheral vascularity (n=6), centrilobular nodules, believed to be due to inspissated secretions in the distal airways, or plugging of the terminal bronchioles by granulation tissues

TABLE 2 The risk factors for bronchiolitis obliterans following haematopoietic stem cell transplantation (HSCT)

Consistent	Allogeneic HSCT
	Progressive chronic GVHD
Probable	*De novo* or quiescent chronic GVHD
	Older age of recipient
	AFO prior to HSCT
	Early respiratory viral infection
Possible	Acute GVHD
	Busulfan-based conditioning regimen
	Total body irradiation
	Methotrexate-based GVHD prophylaxis
	Hypogammaglobulinaemia
	CMV infection
	Older age of donor
	Underlying diseases (CML)
	Gastro-oesophageal reflux disease

GVHD: graft *versus* host disease; AFO: air flow obstruction; CMV: cytomegalovirus; CML: chronic myelogenous leukaemia.

(n=4). In addition, HRCT of the chest is very helpful in excluding co-existing conditions such as infections, bronchiolitis obliterans organising pneumonia (BOOP), or idiopathic pneumonia syndrome [16]. In summary, it is recommended that a HRCT of the chest with inspiratory and expiratory views be performed on all patients under evaluation for BO following HSCT.

BRONCHOSCOPY

Bronchoscopy has a limited role in the diagnosis of BO following HSCT. Bronchoalveolar lavage (BAL) is mainly carried out to rule out an infectious process in HSCT recipients who present with respiratory symptoms suggestive of BO. This is especially the case when there are infiltrates on chest radiograph or HRCT of the chest, or in the presence of fever. The main infections to be considered in this setting, and in which BAL may be useful, are viral infections such as cytomegalovirus (CMV), respiratory syncytial virus, influenza, parainfluenza, or herpes simplex virus. In addition, fungal infections and *Pseudomonas carinii* need to be considered if the patient is on systemic corticosteroids and/or immunosuppressive therapy [46].

BAL has also been studied to evaluate the cellular and chemical profile in patients with BO following HSCT. A few studies have demonstrated that there is neutrophil predominance in the BAL fluid in patients with BO following HSCT [47]. In a study of 12 patients with BO in whom BAL was carried out, five patients had predominance of neutrophils, while three had mainly lymphocytes in the lavage fluid [48]. In addition, BAL may be useful in the analysis of cytokines in patients with BO. A study compared HSCT recipients who had infectious pneumonia (n=14) to another group with idiopathic pneumonia syndrome or BO (n=6). The level of tumour necrosis factor (TNF)-α in the BAL fluid was significantly higher in the latter group [49]. Higher levels of TNF-α were associated with a worse outcome.

Bronchoscopy and BAL is generally well tolerated in patients with BO; however, caution should be exercised in patients with advanced disease, since the procedure may precipitate an acute AFO or pneumothorax [38, 50]. Another observation is that the BAL fluid return is usually scarce in patients with advanced BO due to the narrowing and collapsibility of the smaller airways [34].

Transbronchial biopsy has a limited role and is generally not recommended for the diagnosis of BO following HSCT. This is due to the fact that the disease is patchy and peripheral, and the biopsy sample obtained by this procedure is usually too small to show bronchiolar pathology. If histological confirmation of BO is necessary, then the best approach is a surgical lung biopsy obtained by video-assisted thoracoscopy. However, this procedure is rarely indicated for the diagnosis of BO following HSCT in clinical practice. YOUSEM [51] reviewed the histological findings of lung biopsies in 17 HSCT patients with GVHD-related pulmonary disease. Five patients had BO, and the biopsies showed cicatricial BO, in which the lumens of airways were obliterated by dense fibrous scar tissue. Some of these airways displayed eccentric subepithelial fibrous plagues. The epithelial cells were flattened at some locations, while other sites displayed metaplasia or hyperplasia. There was peribronchiolar mononuclear cellular inflammation, but no alveolar or interstitial involvement. The author's theory on the sequence of events leading to BO in these patients is that infiltration of the submucosa of the smaller airways by lymphocytes occurs. These cells migrate through the basement membrane of respiratory epithelium leading to epithelial cell necrosis and areas of ulceration. Myofibroblasts then grow through these denuded areas and deposit young collagen, creating intraluminal granulation tissue and scarring.

PULMONARY FUNCTION TESTS

Spirometry is the main study used to diagnose and follow-up patients with BO following HSCT. Spirometry usually shows evidence of AFO with reduction in FEV_1 and FEV_1/FVC. However, there has been a lack of consensus on the spirometric criteria for the diagnosis of BO following HSCT. Most of the studies define AFO as the new onset of drop in FEV_1, with an FEV_1/FVC ratio <0.7 [6–8, 13, 20]. Some specify the drop in FEV_1 to $>20\%$ from baseline, or $FEV_1<80\%$ of predicted with FEV_1/FVC <0.7 [8, 52]. Others focus on the reduction in the FEV_1/FVC ratio alone, and consider a drop in this ratio of $>20\%$ following HSCT to be suggestive of BO [21]. In a large study of 1,131 allogeneic HSCT recipients, the authors used the definition of AFO as an annualised decline in FEV_1 post-transplantation of $>5\%$ per year with the lowest documented FEV_1/FVC <0.8 [19]. Furthermore, there are some studies that suggest that a reduction in mean forced expiratory flow between 25 and 75% of FVC ($FEF_{25–75\%}$) may precede the decline in FEV_1, and is a sensitive but nonspecific indicator of subsequent development of BO [53–56]. Another study defined AFO as FEV_1 $<80\%$ and $FEF_{25–75\%}$ $<60\%$ of predicted [11]. It appears from the collective literature that the most clinically relevant spirometric criteria of BO following HSCT are FEV_1/FVC <0.7, and a reduction in FEV_1 $>20\%$ from the pre-transplantation value. A drop in FEV_1 $<20\%$ from baseline should alert clinicians to follow-up on those patients more carefully for signs of BO.

Other PFT findings consistent with BO include lack of significant improvement in FEV_1 post-bronchodilator treatment, increased residual volume and residual volume/total lung capacity ratio (consistent with air trapping), and increased airway resistance [6, 8]. Reduction in diffusion capacity is not a feature of BO, however, these patients commonly have a reduced diffusing capacity of the lung for carbon monoxide [57]. This finding is most likely to be related to other factors, such as high-dose chemotherapy, idiopathic pneumonia syndrome, or infections.

The spirometric findings of AFO are usually detected after the first 100 days following HSCT. The relation between detecting AFO prior to the first 100 days following HSCT and the development of long-term AFO and BO mortality was studied by CHIEN *et al.* [22]. The authors reviewed 1,892 myeloablative allogeneic HSCT who had PFT during the first 100 days following transplantation. Of these, 40% had AFO by day 100; however, only 26% had AFO 1 yr following transplantation. The presence of early AFO was associated with an increased risk of long-term AFO, but not with increased mortality. Moreover, patients who had the fastest decline in FEV_1 (>10% per year) between day 100 and 1 yr, had the highest mortality risk. This study suggests that it is useful to monitor PFT early (around 100 days) following HSCT, and closely monitor those with evidence of AFO, since these patients are at an increased risk for long-term AFO. Conversely, the study suggests that early AFO may be reversible in some patients. More studies are needed to identify the clinical characteristics of those patients who demonstrated reversible AFO.

As suggested above, one of the main problems facing the management of BO following HSCT is a lack of standardised criteria for its diagnosis. Recently, the National Institutes of Health (NIH) sponsored a consensus development project for clinical trials on chronic GVHD [58]. The workshop considered BO as the only diagnostic manifestation of chronic GVHD in the lung, and suggested that the diagnosis of BO is made when: 1) there is evidence of AFO with FEV_1/FVC <0.7 and FEV_1 <75% of predicted; 2) there is evidence of air trapping or small airway thickening or bronchiectasis on HRCT of the chest with inspiratory and expiratory cuts, residual volume on PFT >120% of predicted or pathological confirmation of constrictive bronchiolitis; and 3) absence of infection in the respiratory tract documented by clinical symptoms, radiological studies or microbiological cultures, obtained by sinus aspirate, upper respiratory tract viral screen, sputum culture or BAL. In addition, the statement mentioned that BOOP, not due to an infectious process, may represent a manifestation of either acute or chromic GVHD. Table 3 proposes diagnostic criteria of BO following HSCT that are based on clinical features, radiological and spirometric studies, and absence of infectious processes. Another significant decision by the NIH Consensus Development Project is to include BO in the scoring system for chronic GVHD following HSCT. Table 4 summarises the pulmonary scoring of chronic GVHD suggested by this workshop [58].

It is important in this context to differentiate between BO and BOOP [51, 59]. Although these two terms are commonly used interchangeably, they are two different entities with different clinical and pathological features and different outcomes. Table 5 shows the differences between these two diagnoses.

PATHOGENESIS

The pathogenesis of BO is not completely understood. Several theories have been suggested, although none satisfactorily explains the pathogenesis of BO. One of these theories is that BO is a lung injury precipitated by the conditioning regimen. This is based on the higher incidence of BO in busulfan-based conditioning regimen [17, 21], and the apparent lower incidence of BO in nonmyeloablative HSCT compared with conventional regimen [25].

Another proposed mechanism for the development of BO is that it is related to infectious processes. This mechanism is supported by different observations including the association of BO with low serum Igs [6, 7, 36]. This may lead to abnormal local defence mechanisms in the lungs, predisposing to unidentified infections that precipitate BO. This is also suggested by the observation that allogeneic HSCT recipients who develop respiratory viral infections early in the course following transplantation are at an increased risk of developing BO [19]. In addition, there is some evidence that chronic GVHD is associated with impaired mucociliary transport, which may lead to recurrent bronchial infections that may precipitate BO [60]. Also, CMV infection has been suggested as one causative agent of BO following lung transplantation, which is similar to BO following HSCT [61]. Furthermore, BO is known to develop following infection by respiratory syncytial virus, parainfluenza, influenza, adenovirus, measles, and mycoplasma in nontransplant patients [36, 62]. Thus, a subtle infection may still be an important mechanism in the pathogenesis of BO, although there is no exclusive evidence to prove this theory.

There are a few reports that suggest BO to be the end of the spectrum of acute lung injury following HSCT. In a case report of a patient who underwent allogeneic HSCT, and was thoroughly investigated for pulmonary problems by serial PFT, HRCT of the chest, bronchoscopies with BAL examination and transbronchial biopsies, and eventually by open lung biopsy, the authors argued that the patient developed interstitial pneumonitis, then BOOP, and eventually BO [47]. In discussing the histological findings of pulmonary disease associated with GVHD following HSCT, YOUSEM [51] suggested that BO seemed to represent the late stages of BMT-associated lymphocytic bronchiolitis and BOOP, and reflected irreversible pulmonary GVHD.

Another potential mechanism contributing to BO is recurrent aspiration due to oesophagitis associated with chronic GVHD. Microaspirations may promote chronic inflammation and recurrent infections in the lower airways that may lead to BO. Recurrent microaspiration has been suggested as one of the mechanisms of BO following lung transplantation [63–65]. Furthermore, gastro-oesophageal reflux disease (GERD) with recurrent microaspirations has been suggested as contributing to the pathogenesis of other pulmonary diseases [66].

The most important mechanism contributing to BO is probably an alloreactive immune process in which the donor T-lymphocytes target the epithelial cells of the bronchioles, leading to the inflammatory reaction seen in BO. This

TABLE 3 Suggested diagnostic criteria of broncholitis obliterans (BO) following haematopoietic stem cell transplantation (HSCT)

Allogeneic HSCT
Chronic GVHD[#]
Insidious onset of dyspnoea, cough and wheezing after 100 days following transplantation
Normal chest radiograph
HRCT of the chest (with inspiratory and expiratory views) showing areas of air trapping on expiratory views, hyperinflation or bronchial dilatation, with no parenchymal involvement
PFT showing new onset of airflow obstruction ($FEV_1/FVC < 0.7$ and $FEV_1 < 75\%$ of predicted), not responsive to bronchodilators
Exclusion of an infectious process by appropriate radiological, serological and microbiological studies (obtained by sinus aspirate, upper respiratory tract viral screen, sputum culture or BAL)

GVHD: graft *versus* host disease; HRCT: high-resolution computed tomography; PFT: pulmonary function test; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; BAL: bronchoalveolar lavage. [#]: The risk of BO is highest with progressive chronic GVHD, but it may develop in patients with quiescent or *de novo* GVHD, or without chronic GVHD.

mechanism is evident from the exclusive occurrence of BO following allogeneic HSCT, and the strong association between BO and chronic GVHD. Indeed, some authors suggest that BO is a manifestation of chronic GVHD [51]. Also, the reported stabilisation of BO in some HSCT recipients by systemic corticosteroids and intensification of immunosuppressive therapy supports the immune basis of BO following HSCT. In a well-characterised murine BMT model, significant non-infectious damage occurred in the animals with GVHD that was characterised by a decrease in dynamic lung compliance and airway conductance [67]. There was also expansion of reactive donor T-lymphocytes in the recipient lungs, with increased levels of inflammatory cytokines, such as TNF-α and interferon-γ, in the BAL fluid of the affected animals. Pathological examination of those animals that had GVHD with lung involvement revealed pneumonitis and mononuclear infiltration of the bronchi. Depletion of the donor T-lymphocytes prevented the development of systemic GVHD but did not eliminate the lung injury, indicating that the lungs are probably susceptible to smaller number of T-lymphocytes. The lungs may also represent a sanctuary site for the donor T-lymphocytes, even when systemic tolerance between the donor and host is established.

These immune mechanisms are thought to trigger inflammatory reactions that lead to BO. These inflammatory reactions are characterised by an increase in inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, IL-18 and TNF-α [68, 69]. In one study [49], 11 patients with pulmonary complications following allogeneic HSCT (six patients had idiopathic pneumonia syndrome and/or BO) who had BAL fluid analysis were compared with 11 healthy volunteers. The HSCT recipients with BO had significantly higher levels of lavage fluid TNF-α and IL-18 compared with the controls. It is also possible that the nitric oxide (NO) pathway plays a role in the inflammatory changes that lead to BO. In lung transplantation recipients with BO, there are increased levels of inducible NO synthase (iNOS) mRNA activity in the epithelial cells and other cells in a heterotropic rat tracheal allograft [70]. Inhibition of iNOS was associated with increased intensity of BO in these animals, while treatment with L-arginine, a precursor of NO, significantly reduced the bronchiolar obliteration. Furthermore, increased concentration of exhaled NO was demonstrated in lung transplantation recipients with BO [71], and one case report of a patient with BOOP following HSCT [72].

In summary, while the exact mechanisms leading to BO are not known, there are theories that chemotherapy, infection and alloreactive immune reaction play a role in the pathogenesis of this condition. It is also possible that combinations of the different mechanisms lead to the development of BO following HSCT.

MANAGEMENT

There are no controlled trials on the management of BO. The treatment approaches are based on small uncontrolled trials and expert opinions. However, in general, the management of BO is similar to that of chronic GVHD and consists of high-dose systemic corticosteroids and reinstitution or augmentation of immunosuppressive therapy. Systemic corticosteroids

TABLE 4 Scoring pulmonary chronic graft *versus* host disease based on symptoms and lung function score (LFS)[#,¶]

	Score 0	Score 1	Score 2	Score 3
Symptoms	No symptoms	Shortness of breath on climbing one flight of steps	Shortness of breath after walking on flat ground	Shortness of breath at rest, requiring oxygen
PFT	FEV_1 >80% or LFS 2	FEV_1 60–79% or LFS 3–5	FEV_1 40–59% or LFS 6–9	FEV_1 $\leqslant$39% or LFS 10–12

Data modified from [58]. PFT: pulmonary function test; FEV_1: forced expiratory volume in one second. [#]: LFS is the sum of FEV_1 % predicted and the % predicted diffusing capacity of the lung for carbon dioxide corrected for haemoglobin. The values are converted to numeric score as follows: >80%=1, 70–79%=2; 60–69%=3; 50–59%=4; 40–49%=5; <40%=6. The possible range of LFS is 2–12. [¶]: When there is discrepancy between the symptoms and PFT scores, the higher value is used.

TABLE 5 Comparison between broncholitis obliterans (BO) and broncholitis obliterans organising bacteria (BOOP) following haematopoietic stem cell transplantation (HSCT)

Features	BO	BOOP
Incidence %	0–48	<2
Onset following HSCT	Late (around 1 yr)	Usually in the first 100 days
Clinical presentation	Insidious; dyspnoea, cough, wheezing	Acute; dyspnoea, cough, fever
Radiological findings	Normal; hyperinflation, air trapping, bronchiectasis	Patchy consolidation (usually peripheral), ground glass attenuation, nodular opacities
PFT	Obstructive; normal $D_{L,CO}$	Restrictive; reduction in $D_{L,CO}$
BAL	Predominantly neutrophils	Predominantly lymphocytes
Diagnosis	Clinical criteria	Usually requires tissue, best by surgical lung biopsy
Histopathology	Granular plugs obliterating the bronchioles with inflammation and scarring; sparing of the alveoli and alveolar ducts	Granular plugs of bronchioles, extending to alveoli; interstitial inflammation and fibrosis
Treatment	Corticosteroids and immunosuppressive therapy	Corticosteroids
Outcome	Poor response to therapy; progressive disease with high mortality	Good response to therapy; potentially reversible

PFT: pulmonary function test; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; BAL: bronchoalveolar lavage.

are suggested in the form of prednisone at 1–1.5 $mg \cdot kg^{-1} \cdot day^{-1}$ (up to 100 $mg \cdot day^{-1}$) for 2–6 weeks. If there is clinical and physiological stabilisation, the dose is tapered every 2 weeks for 6–12 months. This regimen is based on expert opinions and small case series rather than controlled trials [3, 8, 10, 15, 18, 27, 34, 73, 74]. The immunosuppressive agents used are similar to those used in the treatment of chronic GVHD, namely cyclosporine A or tacrolimus [10, 15, 16, 18, 20, 75]. In addition, azathioprime has been added in several studies in doses up to 3 $mg \cdot kg^{-1} \cdot day^{-1}$ (maximum 200 $mg \cdot day^{-1}$) [8, 15, 16, 18]. The dose of cyclosporine A should be adjusted to serum level. It is possible that early treatment may prevent the progression of AFO [22]. Conversley, it was observed that the rapid taper of cyclosporine A (for prophylaxis against GVHD) was associated with increased late noninfectious pulmonary complications, including BO [76]. Treatment is recommended for 3–12 months; however, some studies suggest that further improvement is unlikely after 9 months of treatment [15]. Other treatment options include ''pulse'' dose corticosteroid therapy. In a study of nine children with BO, treatment with methylprednisolone at 10 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 days on monthly bases for 1–6 cycles led to stabilisation of FEV_1 after 2 months of treatment; this was maintained during an average of 42 ± 20 months of follow-up [23]. Thalidomide and antithymocyte globulins have been used in few studies with variable results [77–82]. Also, *i.v.* immunoglobulins have been given to patients with BO, with no proven benefit [83]. More recently, few reports suggest treating BO using anti-TNF-α (infliximab) [84]; however, there is no adequate data on the effectiveness of this therapy. Based on the experience using macrolides in the treatment of diffuse panbronchiolitis, cystic fibrosis and treatment of BO following lung transplantation, this class of medication is increasingly considered in the management of BO following HSCT [85–87]. Macrolides apparently down-regulate pro-inflammatory cytokines, such as TNF-α, so they may decrease the inflammatory reaction that leads to BO [87]. In a recent report of eight patients with BO, azithromycin was added at a dose of 250 mg three times a week for 12 weeks, and the authors reported an average of 281 mL (20.58%) improvement in FEV_1 [24]. However, the value of adding such agents to the treatment regimen of patients with BO following HSCT is still not known, and it appears that the response to this treatment is variable.

The role of inhaled corticosteroids in the prevention and management of BO following HSCT has not been studied. There are very few reports on the addition of inhaled corticosteroids to the standard immunosuppressive regimen in the management of BO following lung transplantation [88–92]. These reports do not show clinically significant benefit in the prevention or treatment of BO. One study reported that the addition of high-dose inhaled corticosteroids to the management of BO in 14 lung transplantation recipients resulted in reduction of exhaled NO concentration and improvement in FEV_1 in the majority of these patients after 1–2.5 months of treatment [90]. Until large, placebo-controlled, multicentre trials are conducted to examine the role of inhaled corticosteroids in the prevention and management of BO following HSCT, it is reasonable to consider a trial of inhaled corticosteroids for 3 months, especially if there is evidence of reversibility in AFO on spirometry. If there is no benefit, then they may be discontinued. Patients should be treated with bronchodilators if they are symptomatic and during acute exacerbations of respiratory symptoms; however, most of the studies show that the reversibility in AFO with these agents is generally negligible [3, 8, 13].

Extracorporeal photodynamic (ECP) therapy is another immunotherapeutic modality that has been used in the treatment of chronic GVHD and BO. This therapy is commonly used in the management of cutaneous T-cell lymphoma, scleroderma and other autoimmune disorders. It involves extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen, by exposure to ultraviolet A light, followed by re-infusion of the treated cells [93]. The treatment is repeated every 2–3 weeks and continued for several months [94, 95]. It is believed that the photoactivated

TABLE 6 Suggested approach to the management of broncholitis obliterans following haematopoietic stem cell transplantation

Excluding an acute pulmonary infection (by clinical, radiological, serological and microbiological studies; consider bronchoalveolar lavage in selected cases)
Systemic corticosteroids (prednisone 1–1.5 $mg \cdot kg^{-1} \cdot day^{-1}$); taper gradually over 6–12 months
Immunosuppressive therapy (cyclosporine A or tacrolimus with or without azathioprime)
Maintenance macrolide treatment
Inhaled bronchodilators
Prophylactic therapy against *Pseudomonas carinii*, fungi and CMV
Anti-reflux measures
Consider inhaled corticosteroids
Consider extracorporeal photodynamic therapy
Consider *i.v.* immunoglobulins
In advanced cases: 1) long-term oxygen therapy; 2) outpatient pulmonary rehabilitation; and 3) lung transplantation

CMV: cytomegalovirus.

8-methoxypsoralen binds to DNA, leading to initiation of apoptosis, and that it has a selective effect on autoreactive T-cells [93, 96, 97]. These observations led to the use of ECP in the management of refractory acute and chronic GVHD. Several studies reported improvement in skin, mucus membrane, liver and pulmonary GVHD, resulting in fewer symptoms and tapering or discontinuation of immunosuppressive therapy [94, 95, 98]. The studies show that the best results are when ECP was started in the first 10 months following HSCT [99, 100]. Furthermore, these studies showed that this therapy is well tolerated and that there is no increased risk of infectious complications [99, 100].

The role of ECP in the management of BO following HSCT has not been well studied. The benefits are limited to case reports or small numbers of cases in small trials [95, 101, 102]. In a prospective study of 25 patients with steroid-refractory chronic GHVD, two patients had pulmonary GVHD, and both had partial improvement in lung function following ECP [95]. In another study of 22 patients with chronic GVHD treated by ECP, the overall response rate was 70%, including two patients with BO who demonstrated improvement in lung function [101].

Supportive treatment is essential in the management of patients with BO following HSCT. Infectious processes should be excluded prior to starting immunosuppressive therapy. This is generally achieved by clinical and radiological evaluation, and routine serological and microbiological studies. Bronchoscopy with BAL is generally not necessary, except if there are pulmonary infiltrates or if the clinical presentation is atypical. Once immunosuppressive therapy is started, patients should be maintained on appropriate prophylactic measures against *P. carinii*. Prophylaxis against fungi and CMV should be considered in high-risk patients. In addition, appropriate vaccinations including influenza and pneumococcus are recommended. Prompt treatment of pulmonary infections is essential, since these tend to worsen the course and outcome of BO. Patients with advanced BO may require long-term oxygen therapy and may benefit from outpatient pulmonary rehabilitation.

Treatment of BO following HSCT is generally frustrating and response to the above approaches is marginal. Some patients may be considered for lung transplantation. There are a few reports of lung transplantation in patients with advanced BO with encouraging results [103–109]. In a review of nine patients who underwent such treatment, five patients had single lung transplantation, and four had double lung transplantation. The patients were followed up 9–72 months following lung transplantation. Three patients died of recurrent BO, chronic rejection or infection. The rest were doing well with no signs of BO [109]. The role of lung transplantation in the management of BO following HSCT remains limited by the availability of donor organs, the small number of centres that would consider HSCT recipients, the risks of intensive immunosuppressive therapy, and the potential for recurrence of BO. Table 6 summarises the management approaches to BO following HSCT.

PROGNOSIS

BO following HSCT is a progressive disease that leads, in the majority of patients, to irreversible AFO. Aggressive therapy results in improvement of lung function in only 8–20% of patients [4, 7, 11, 16, 110]. The best expectations in the management of patients with BO are to stabilise and prevent further drops in FEV_1. The mortality rate in patients with BO following HSCT varies 14–100%, with a median of 65% [3, 6–8, 13, 16, 27, 34]. In a large cohort study of patients with AFO following HSCT, the attributable mortality was 9% at 3 yrs, 12% at 5 yrs, and 18% at 10 yrs, while the attributable mortality in those with associated chronic GVHD was 22% at 3 yrs, 27% at 5 yrs, and 40% at 10 yrs [19]. Most patients with BO progress to respiratory failure, and some patients develop bronchiectasis with frequent bacterial exacerbations. Patients with advanced BO usually die from pneumonia [7, 13, 18, 20].

Factors that are associated with increased mortality related to BO following HSCT include rapid deterioration of FEV_1 (>10% per year), age >60 yrs, progressive chronic GVHD, underlying disease risk at transplantation, underlying disease relapse and history of respiratory viral infection [19, 22, 26]. Another study showed that the prognosis of BO following HSCT is worse in patients who develop AFO early (<150 days) following transplantation, and have rapid decline in FEV_1 (>30%) [8]. In addition, the prognosis of BO is worse if the patients do not respond to the primary treatment regimen [18]. The prognosis of BO appears not to be influenced by the presence of AFO prior to transplantation, the source of stem cells, degree of matching, CMV serological status or the type of GVHD prophylaxis [26].

BRONCHIOLITIS OBLITERANS SYNDROME FOLLOWING LUNG TRANSPLANTATION

The present review focuses on BO following HSCT; however, it is important to discuss the similarities and differences of this syndrome in lung transplantation and HSCT recipients. The diagnostic criteria for BO following lung transplantation are better defined and are universally adopted. The International Society for Heart and Lung Transplantation proposed the following classification of BO syndrome (BOS) following lung transplantation: BOS 0: FEV_1 >90% of baseline and $FEF_{25–75\%}$ >75% of baseline; BOS 0–p: FEV_1 81–90% of baseline and/or $FEF_{25–75\%}$ ⩽75% of baseline; BOS 1: FEV_1 66–80% of baseline; BOS 2: FEV_1 51–65% of baseline; and BOS 3: FEV_1 ⩽50% of baseline [52].

While chronic GVHD is the only established risk factor for BO following HSCT, there are several factors strongly implicated in the pathogenesis of BO following lung transplantation, and these include allograft rejection and that BO represents chronic rejection. In addition, there is evidence that the severity of BO following lung transplantation correlates well with the onset, number and severity of acute rejection episodes, and that early and aggressive treatment of acute rejection appears to prevent BO [52, 111–113]. Conversely, it is not clear that aggressive treatment of GVHD is protective against BO following HSCT. Alloimmune independent factors also play an important role in the pathogenesis of BO following lung transplantation, and are mainly related to airway ischaemia during the time interval between organ procurement and transplantation, and interruption of bronchial arterial supply after re-implantation of the graft [45, 114, 115]. This ischaemia leads to lymphocytic infiltration and the development of lymphocytic bronchitis and bronchiolitis which is a precursor of BO following lung transplantation [116]. Similar to BO following HSCT, CMV, other respiratory viral infections and GERD may play a role in the onset or exacerbation of BO following lung transplantation.

The clinical and radiological presentations of the BO in both patient populations appear to be similar; however, the incidence of BO following lung transplantation is higher and is reported to range 50–60% in patients who survive for 5 yrs after surgery (*versus* 0–48% following HSCT) [117, 118]. In addition, BO following lung transplantation is diagnosed later, with median time to diagnosis 16–20 months (*versus* 6–12 months following HSCT) [45]. Transbronchial biopsies play a more important role in the management of BO following lung transplantation than in HSCT recipients. The role of this procedure is not to confirm the diagnosis of BO, but rather to detect acute rejection. Some studies show that surveillance transbronchial biopsies have led to resolution or stabilisation of the condition in a large percentage of patients with early-stage BO following lung transplantation [113, 119]. In addition, the role of exhaled gases and condensates, such as exhaled NO and carbonyl sulphide, in detecting and monitoring BO has been better studied in lung transplantation recipients than for HSCT, but their role remains poorly established [71].

The management of BO following lung transplantation is generally similar to that outlined for HSCT. Intensification of immunosuppressive therapy is the mainstay of therapy. Minimising the graft ischaemia time, early treatment of respiratory infections, and treatment of GERD have been emphasised in the prevention and management of BO following lung transplantation [61, 63–65]. There are more reports on BO following lung transplantation describing the improvement of lung function using maintenance therapy with macrolides [86]. In addition, a recent report suggests that inhaled cyclosporine A may extend the periods of chronic rejection-free survival, and may have an impact on the development of BO following lung transplantation [120]. Mortality due to BO following lung transplantation is generally higher than that reported following HSCT [117].

FUTURE DIRECTIONS

Advances in haematopoietic stem cell transplantation techniques, and prophylaxis and treatment of infections, have significantly decreased the risks of infectious complications following transplantation. As a result, late complications, including broncholitis obliterans, are increasingly becoming a major cause of morbidity and mortality following haematopoietic stem cell transplantation. The management of broncholitis obliterans has been frustrating, with patients developing progressive air flow obstruction. Future efforts should focus on establishing uniform diagnostic criteria for broncholitis obliterans following haematopoietic stem cell transplantation that could guide clinical practice and research efforts. More animal models and clinical studies are needed to elucidate the inflammatory and immune mechanisms that lead to broncholitis obliterans following haematopoietic stem cell transplantation. At the same time, multicentre prospective trials are essential to define the risk factors, clinical course and the best management approach to this condition.

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