

GUIDELINE

Taiwan consensus on pulmonary chronic graft-versus-host disease: A joint statement from the Taiwan Society of Blood and Marrow Transplantation (TBMT) and Taiwan Society of Pulmonary and Critical Care Medicine (TSPCCM)

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Summary

Pulmonary chronic graft-versus-host disease (cGVHD), particularly bronchiolitis obliterans syndrome (BOS), is a severe complication of allogeneic haematopoietic stem cell transplantation (allo-HSCT) with significant morbidity and mortality. This report, developed collaboratively by experts from the Taiwan Society of Blood and Marrow Transplantation (TBMT) and the Taiwan Society of Pulmonary and Critical Care Medicine (TSPCCM), provides consensus statements for the diagnosis, surveillance and management of pulmonary cGVHD. Early detection through pulmonary function tests (PFTs) is critical, with serial monitoring recommended after allo-HSCT. High-resolution computed tomography (HRCT) serves as a valuable diagnostic tool, whereas bronchoalveolar lavage along with multiplex polymerase chain reaction (PCR) helps rule out infectious aetiologies. The first-line treatment approach includes inhaled and systemic corticosteroids, bronchodilators and azithromycin. The fluticasone–azithromycin–montelukast (FAM) regimen has demonstrated notable efficacy in stabilizing lung function. Emerging therapies such as ruxolitinib, belumosudil, abatacept and axatilimab offer promising benefits for refractory cases, whereas lung transplantation is a viable last resort for advanced

Abbreviations: 6MWT, 6-minute walk distance test; Allo-HSCT, allogeneic haematopoietic stem cell transplantation; BAL, bronchoalveolar lavage; BO, bronchiolitis obliterans; BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; CSF1R, colony-stimulating factor 1 receptor; DLCO, diffusing capacity of the lungs for carbon monoxide; ECP, extra-corporeal photopheresis; EBMT, European Society for Blood and Marrow Transplantation; FAM, fluticasone–azithromycin–montelukast; FEF, forced mid-expiratory flow; FEV1, forced expiratory volume in 1 s; FVC, functional vital capacity; GERD, gastro-oesophageal reflux disease; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LLN, lower limit of normal; MEF, maximal expiratory flow; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; NCCN, National Comprehensive Cancer Network; NIH, National Institutes of Health; NTM, non-tuberculosis mycobacterium; ORR, overall response rate; PEEP, positive end-expiratory pressure; PFT, pulmonary function test; PR, pulmonary rehabilitation; ROCK2, rho-associated coiled-coil-containing protein kinase 2; RV, residual volume; TBMT, Taiwan Society of Blood and Marrow Transplantation; TLC, total lung capacity; TSPCCM, Taiwan Society of Pulmonary and Critical Care Medicine; VC, vital capacity.

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disease. Comprehensive supportive care, encompassing pulmonary rehabilitation and infection prophylaxis, is an essential component of management. This consensus report highlights the importance of standardized PFT surveillance, early intervention and individualized immunosuppressive strategies. Future research should focus on refining diagnostic biomarkers and optimizing therapeutic approaches to improve patient outcomes.

KEY WORDS

allogeneic haematopoietic stem cell transplantation, bronchiolitis obliterans syndrome, consensus, graft-versus-host disease, pulmonary complication

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a common complication of allogeneic haematopoietic stem cell transplantation (allo-HSCT), occurring in 30%–70% of recipients and serving as a significant cause of both late morbidity and mortality.^{1,2} Among its manifestations, pulmonary cGVHD, particularly bronchiolitis obliterans syndrome (BOS), is a well defined but severe presentation that affects 3%–10% of allo-HSCT recipients. The incidence increases to over 14% when associated with concomitant confirmed cGVHD.^{2–6} BOS is characterized by progressive airflow obstruction resulting from immune-mediated damage and fibrosis of the terminal bronchioles and is associated with significant declines in lung function and poor prognosis.⁶

The diagnosis and management of pulmonary cGVHD remain complex and challenging. The National Institutes of Health (NIH) consensus guidelines have established diagnostic criteria based on pulmonary function tests (PFTs),¹ emphasizing early recognition to prevent irreversible lung damage. However, routine PFTs are often not performed in clinical practice,⁷ which may lead to an underestimation of the incidence and a delay in diagnosis.¹ Regarding treatment, there is currently no standard of care. Various strategies, including the use of corticosteroids, azithromycin, montelukast, calcineurin inhibitors or other novel agents, are hindered by inconsistent efficacy and the absence of standardized treatment protocols.^{8,9} These limitations highlight the difficulty of balancing therapeutic benefits against risks when managing pulmonary cGVHD.

This consensus document, developed by the Joint Lung GVHD Working Group of the Taiwan Society of Blood and Marrow Transplantation (TBMT) and the Taiwan Society of Pulmonary and Critical Care Medicine (TSPCCM), provides comprehensive consensus statements regarding the diagnosis, surveillance and management of pulmonary cGVHD. By integrating evidence-based guidance with clinical expertise, this report aims to standardize care practices and improve outcomes for allo-HSCT recipients.

METHODS

We established a steering committee consisting of eight physician members, including two project leaders, two executive

secretaries and four subject matter experts in haematology and respiratory medicine. The primary responsibilities of the steering committee included formulating the study protocol, drafting preliminary consensus statements and organizing the expert panel. The intent was to assemble an expert panel with diverse backgrounds in transplantation and pulmonology to ensure comprehensive expertise and a broad spectrum of perspectives while maintaining manageable administrative efforts.

The final consensus panel comprised 17 physicians, including the eight steering committee members. Panellists were nominated by the TBMT and the TSPCCM based on their recognized clinical and academic expertise in HSCT and pulmonary medicine. To ensure national representativeness, experts were selected from major transplantation and medical centres across Taiwan. The selection criteria included institutional leadership roles, extensive clinical experience, academic contributions and active participation in GVHD-related initiatives.

Following the formation of the panel, the steering committee first conducted a teleconference to identify the scope of the project and invite potential panel members. An in-person meeting was held in February 2023, during which 17 haematologists and pulmonologists convened to define the study scope and key issues based on their clinical practice experience. Members of the steering committee also presented targeted literature reviews on relevant topics to provide a shared foundation for subsequent discussion.

After the meeting, the steering committee drafted 26 preliminary consensus statements informed by literature evidence and expert input. These statements were circulated electronically to the consensus panel for review. In July 2023, an in-person voting session was convened. During this session, subject matter experts within the steering committee presented each statement along with supporting evidence, followed by an anonymous electronic rating by panel members using a Likert scale.

The RAND/UCLA-modified Delphi panel method was used. Of the initial 26 statements, two were removed due to redundancy, resulting in 24 final statements (Table 1). Consensus was defined as $\geq 75\%$ agreement among panel members. Statements that did not reach this threshold were revised using feedback from the panel and re-evaluated in a second round of voting. The finalized consensus statements were graded according to the strength and level of evidence,

TABLE 1 Consensus statements on the diagnosis, surveillance and treatment of post-HSCT pulmonary GVHD.

Consensus statements		Agreement percentage (round of votes)
<i>Diagnosis</i>		
1.	BOS is a form of pulmonary cGVHD and is commonly accompanied by cGVHD in other organs (Level of evidence: 1)	100% (vote 1)
2.	The characteristic feature of BOS is a newly developed, irreversible process of respiratory airflow obstruction (Level of evidence: 1)	94% (vote 1)
3.	The current standard diagnosis of BOS relies on the recommendations of the 2014 National Institutes of Health Chronic GVHD Consensus Guidelines* (Level of evidence: 1) *For patients already diagnosed with cGVHD in other organs, the criteria for diagnosis include all of the following criteria ¹ : 1. FEV1/VC < 0.7 or the lower limit of normal 2. FEV1 < 75% of predicted with ≥ 10% decline over < 2 years and does not correct to > 75% with bronchodilator	100% (vote 1)
4.	The use of FEV1/VC < 0.7 as a diagnostic criterion for airflow obstruction is not applicable to all patients. Specific patient populations (either too young or too old) could use FEV1/VC < the lower limit of normal values for the diagnosis of airflow obstruction (Level of evidence: 2B)	100% (vote 2)
5.	If a patient lacks other cGVHD organ involvement, high-resolution computed tomography (inspiratory and expiratory phase) or residual volume measures (> 120% of predicted) can aid in diagnosing airflow obstruction (Level of evidence: 2A)	100% (vote 2)
6.	Lung biopsy should not be routinely performed for the diagnosis of BO (Level of evidence: 2B)	100% (vote 2)
<i>Surveillance</i>		
7.	A complete PFTs should be performed before allogeneic haematopoietic stem cell transplantation (Level of evidence: 2A)	100% (vote 1)
8.	Regular PFT monitoring for asymptomatic allo-HSCT patients, including spirometry, lung volumes and DLCO, should be performed every 3 months for the first year and every 6 months for the second year, followed by yearly monitoring until 5 years, as clinically indicated (Level of evidence: 2A)	100% (vote 1)
9.	At the time of diagnosis of extra-pulmonary cGVHD, a complete set of PFTs should be performed (Level of evidence: 2A)	100% (vote 1)
10.	For patients newly diagnosed with extra-pulmonary cGVHD, PFTs should be performed every 3 months for the first year and then every 6 months for 1 year, followed by at least yearly as clinically indicated (Level of evidence: 2A)	100% (vote 1)
11.	Serial PFT or spirometry at short intervals is suggested for patients with respiratory viral infection and concomitant FEV1 decline or asymptomatic decline in FEV1 (Level of evidence: 2A)	100% (vote 1)
<i>Topic treatment and supportive treatment</i>		
12.	Combining inhaled corticosteroids and bronchodilators is effective in patients with BOS after HSCT (Level of evidence: 2A)	100% (vote 1)
13.	Adding inhalation therapy (corticosteroids and bronchodilators) to systemic treatment is beneficial for patients with BOS after HSCT (Level of evidence: 2A)	100% (vote 1)
14.	Pulmonary infection should be evaluated when treating patients with BOS (Level of evidence: 2A)	100% (vote 2)
15.	Gastro-oesophageal reflux disease (GERD) should be evaluated in patients with BOS (Level of evidence: 2B)	100% (vote 1)
16.	Pulmonary rehabilitation is beneficial for patients with BOS (Level of evidence: 2B)	100% (vote 1)
17.	Special considerations (particularly minimized PEEP) for ventilator support is suggested for patients with respiratory failure (Level of evidence: 2B)	100% (vote 1)
<i>Systemic treatment and lung transplantation</i>		
18.	The fluticasone/azithromycin/montelukast (FAM) regimen should be started at the time of BOS diagnosis (Level of evidence: 2A)	100% (vote 1)
19.	Systemic corticosteroids should be combined with FAM regimen once BOS is diagnosed. Other systemic immunosuppressive agents that are used before BOS is diagnosed should be continued (Level of evidence: 2A)	100% (vote 1)
20.	Steroid pulse therapy is an option in addition to the FAM regimen with systemic corticosteroids for moderate or severe BOS (Level of evidence: 2B)	100% (vote 1)
21.	PFTs should be performed 4 weeks after treatment is initiated to guide further treatment decisions (Level of evidence: 2A)	100% (vote 1)
22.	If PFT further declined after treatment with FAM and systemic corticosteroids, ruxolitinib can be added (Level of evidence: 1)	100% (vote 1)

(Continues)

TABLE 1 (Continued)

Consensus statements		Agreement percentage (round of votes)
23	Prolonged use of azithromycin is not suggested if BOS has resolved, due to an increased risk of underlying disease relapse (Level of evidence: 2A)	100% (vote 1)
24	Lung transplantation should be considered for patients with progressive lung function decline despite pharmacological management or in cases of progression to respiratory failure (Level of evidence: 2B)	100% (vote 1)

Abbreviations: Allo-HSCT, allogeneic haematopoietic stem cell transplantation; BO, bronchiolitis obliterans; BOS, bronchiolitis obliterans syndrome; cGVHD, chronic graft-versus-host disease; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 s; PEEP, positive end-expiratory pressure; PFT, pulmonary function test; VC, vital capacity.

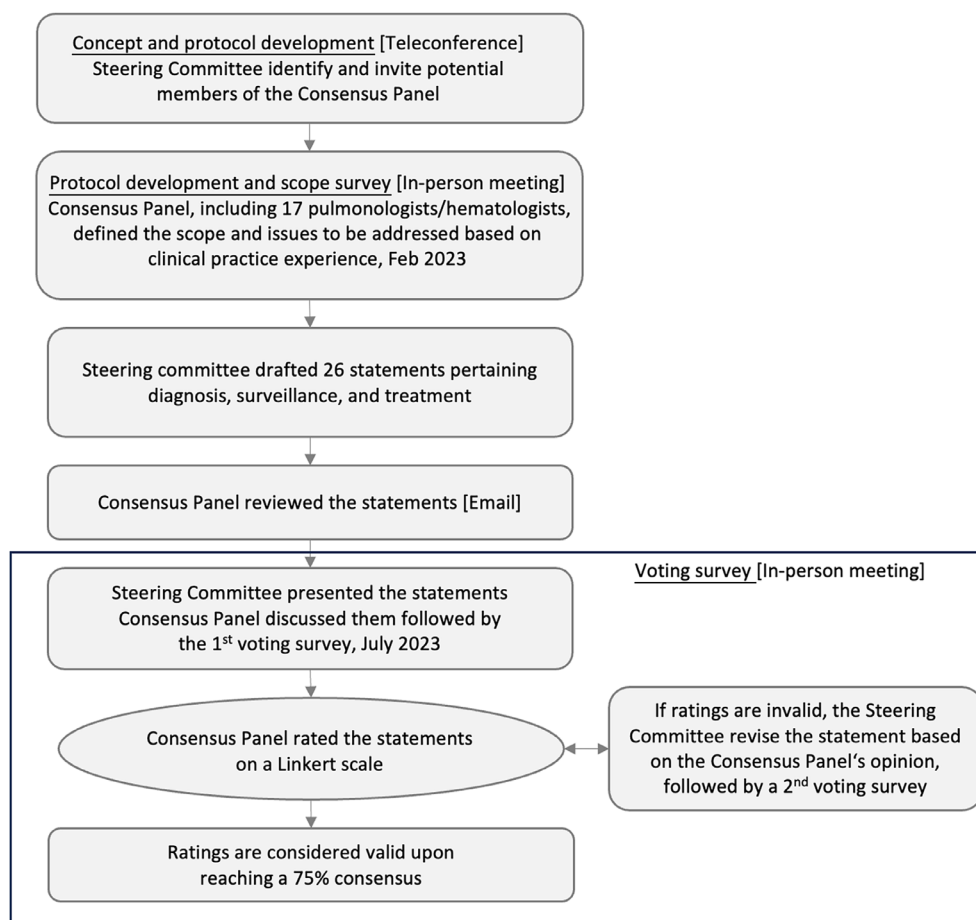


FIGURE 1 Flow chart for developing the consensus.

following the National Comprehensive Cancer Network (NCCN) clinical practice guidelines.¹⁰ Further details regarding the systematic step-by-step approach used in this project are outlined in Figure 1.

RESULTS

Diagnosis

Statement 1. BOS is a form of pulmonary cGVHD and is commonly accompanied by cGVHD in other organs (Level of evidence: 1).

Statement 2. The characteristic feature of BOS is a newly developed, irreversible process of respiratory airflow obstruction (Level of evidence: 1).

BOS can develop at any time after allo-HSCT, including as late as several decades post-transplant, although it most commonly occurs within the first 2 years, with a median time to diagnosis between 9 and 18 months.^{4,11–13} Symptoms arise due to progressive airway obstruction, and by the time symptoms are noticeable, the forced expiratory volume in 1 s (FEV1) is often less than 50% of the predicted value. However, when new respiratory symptoms occur after transplantation, infection should be considered first, with

bronchoalveolar lavage recommended to rule out microbial infection before the diagnosis of BOS.¹⁴

Statement 3. The current standard diagnosis of BOS relies on the recommendations of the 2014 National Institutes of Health Chronic GVHD Consensus Guidelines (Level of evidence: 1).

The diagnosis of bronchiolitis obliterans (BO) typically hinges on pathological findings, characterized by bronchial wall thickening, lumen narrowing and fibrosis. However, due to the high risk associated with biopsies in patients with suspected BO, the diagnosis often shifts towards BOS, which is based on clinical criteria, including lung function assessments and radiologic findings. The current diagnostic standards for BOS still adhere to the NIH consensus established in 2014 and 2020^{1,15} and are summarized in Figure 2.

For patients already diagnosed with cGVHD in other organs, the criteria for diagnosis are based on an obstructive lung function pattern and a persistent decrease in FEV₁ within 2 years. The specific criteria are as follows:

1. FEV₁/vital capacity (VC) <0.7 or the lower limit of normal.
2. FEV₁ <75% of the predicted value with a ≥10% decline over <2 years and does not correct to >75% with a bronchodilator.

In addition to the obstructive pattern observed in BOS, restrictive^{16,17} or mixed¹⁸ ventilatory defects are also frequently encountered after allo-HSCT. These may arise from interstitial lung disease or extra-pulmonary causes, such as chest wall abnormalities or neuromuscular dysfunction.^{19,20} Due to the diagnostic complexity, especially in mixed patterns, referral for multidisciplinary discussion is recommended.

Statement 4. The use of an FEV₁/VC <0.7 as a diagnostic criterion for airflow obstruction is not applicable to all patients. Specific patient populations (either too young or too old) could use FEV₁/VC < the lower limit of normal values for the diagnosis of airflow obstruction (Level of evidence: 2B).

An individual's lung function generally peaks between the ages of 20 and 30 and then gradually decreases annually, with FEV₁ declining faster than VC. Consequently, using an FEV₁/VC less than 70% as the standard criterion for diagnosing airflow obstruction in young patients could result in false-negative results, potentially leading to underdiagnosis of this condition.²¹ The use of a measure of FEV₁/VC less than the lower limit of the normal range (defined as the lower boundary of the predicted 90% confidence interval) can aid in minimizing the occurrence of false-negative results in the diagnosis of airflow obstruction. In contrast, for older patients, especially

those over 80 years of age, even if their FEV₁/VC ratio is less than 70%, they may still be within the normal range if their values are at or above the 5th percentile of the predicted value. Consequently, using an FEV₁/VC less than 70% as a criterion for diagnosing obstructive airway disease in this age group could lead to false-positive results. A study from the Health Management Center of Taipei Veterans General Hospital provided reference data for lung function for the Taiwanese population.²² Despite potential biases due to the generally older age of the participants and the presence of pre-existing health conditions, the study offers valuable insights. One significant finding is the estimated LLN for the FEV₁/FVC ratio, identified as 70%, which is applicable to both male and female individuals aged over 60 years.

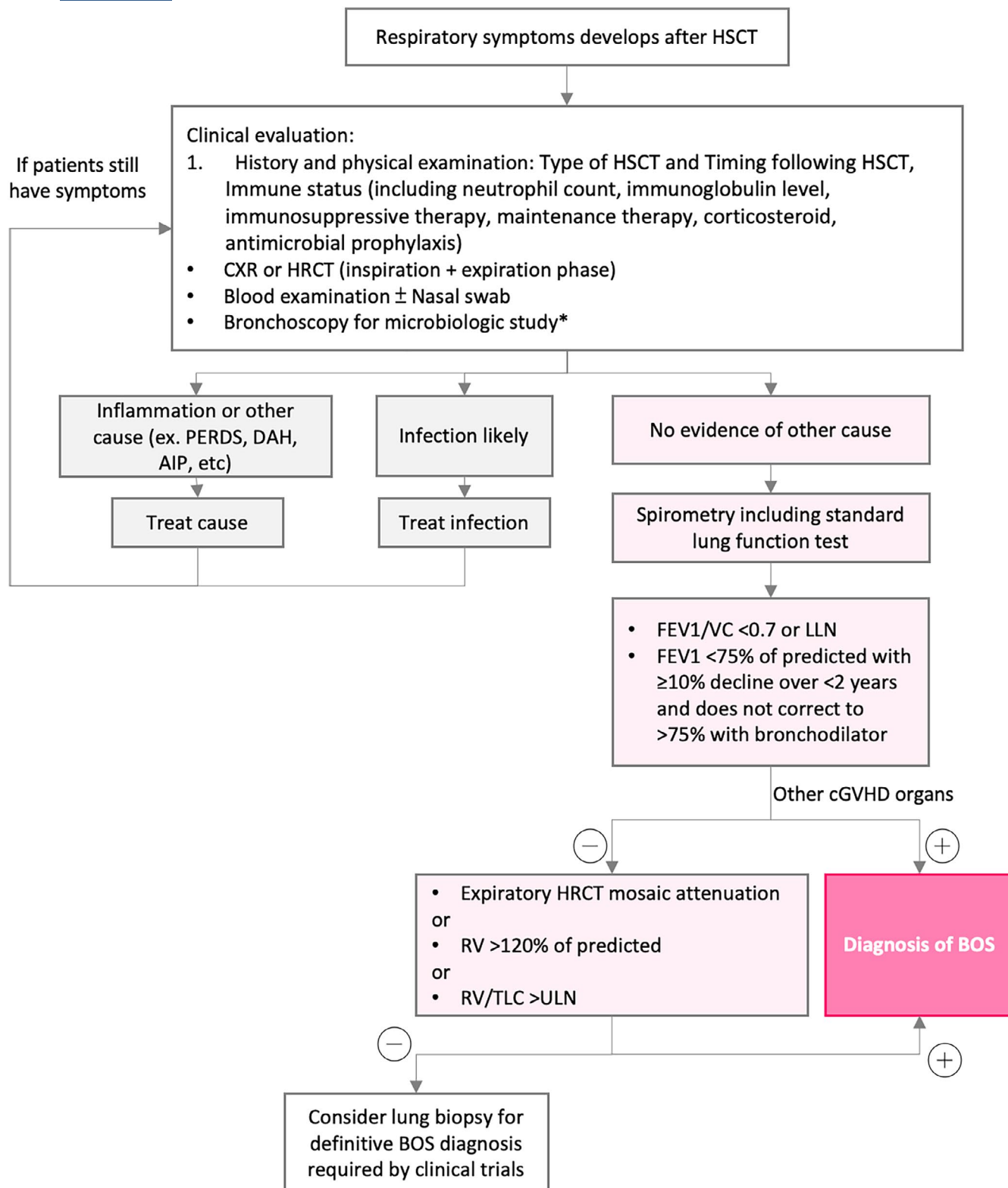
As BOS primarily affects the small airways, forced expiratory flow between 25% and 75% of the maximum (FEF_{25%-75%}) serves as an early marker of obstruction in the distal airways and is valuable for the early identification of BOS, especially in lung transplant populations.^{3,23,24} In the setting of HSCT, reductions in FEF_{25%-75%} have been closely linked to the future onset of BOS²⁵ and may offer greater sensitivity than FEV₁ in early detection.²⁶ Accordingly, it is advisable to monitor both FEF_{25%-75%} and FEV₁ routinely following HSCT.

Statement 5. If a patient lacks other cGVHD organ involvement, high-resolution computed tomography (inspiratory and expiratory phase) or residual volume measures (>120% of predicted) can aid in diagnosing airflow obstruction (Level of evidence: 2A).

For patients who lack other cGVHD organ involvement but are under suspicion for BOS, high-resolution computed tomography (HRCT) scans during both inspiration and expiration are recommended. Typical findings include geographic mosaic attenuation, air trapping on expiratory imaging and lobular hypoattenuation, which are consistent with small airway obstruction.^{18,27-29} Regions exhibiting ground glass opacity are indicative of normal lung tissue, whereas hyperlucency indicates air trapping. Hyperinflation and bronchial wall thickening may also be observed in more advanced cases.^{18,30} These features, especially when infectious aetiologies are excluded, support a diagnosis of BOS and help differentiate it from interstitial lung disease or infectious pneumonia. However, a normal HRCT does not exclude BOS, particularly in early or mild stages.^{18,28} In such cases, diagnosis relies on integrating pulmonary function data, clinical symptoms and the exclusion of alternative causes.

Air trapping in the lungs may also be identified by standard pulmonary function tests showing a residual volume (RV) >120% of the predicted value or an RV/total lung capacity (TLC) ratio exceeding the upper predicted limit of the 90% confidence interval.¹⁵

Statement 6. Lung biopsy should not be routinely performed for the diagnosis of BO (Level of evidence: 2B).



*Suggest bronchoalveolar lavage for patients with abnormal findings on HRCT. May consider to do viral multiplex PCR or next-generation sequence study

FIGURE 2 Management of patients experiencing post-HSCT respiratory symptoms. AIP, acute interstitial pneumonitis; ARDS, acute respiratory distress syndrome; DAH, diffuse alveolar haemorrhage; HRCT, high-resolution computed tomography; PERDS, peri-engraftment respiratory distress syndrome; PFT, pulmonary function test.

At present, the application of lung biopsy for the diagnosis of BO is discouraged, not only due to the procedural risks such as pneumothorax and pneumomediastinum but also due to its limited diagnostic yield³¹ resulting from the patchy distribution of airway involvement and the small size of transbronchial or CT-guided biopsy samples. However, for the purposes of clinical trial enrolment, if BOS is the sole manifestation of cGVHD, a lung biopsy may be necessary to confirm the diagnosis of cGVHD.^{32,33}

Surveillance

Statement 7. A complete set of PFTs should be performed before allogeneic haematopoietic stem cell transplantation (Level of evidence: 2A).

The pre-allo-HSCT PFTs play a crucial role as a baseline reference for interpreting post-allo-HSCT PFTs results.^{34,35} Specific pre-allo-HSCT parameters, including the FEV1/FVC ratio, have been demonstrated to be effective in identifying patients at high risk of developing pulmonary complications or mortality after allo-HSCT.^{36–43} The predictive value may be potentially enhanced by integrating PFTs and pulmonary metatranscriptomes and airway epithelial gene expression signatures.^{44–46} All patients receiving allo-HSCT are recommended to undergo a complete set of PFTs before transplantation. Comprehensive PFTs include spirometry, lung volume assessment and measurement of the diffusing capacity of the lungs for carbon monoxide (DLCO). The spirometry components cover the forced vital capacity (FVC), the FEV1 of the FVC manoeuvre, FEF_{25%–75%} and the FEV1/FVC ratio. The lung volume should encompass the TLC, RV and VC. The algorithm used to evaluate patients experiencing post-allo-HSCT lung function impairment is summarized in Figure 3. Ongoing research is exploring the potential use of CT scans,⁴⁷ or MRI⁴⁸ in cases where patients are unable to undergo PFTs.

Statement 8. Regular PFT monitoring for asymptomatic allo-HSCT patients, including spirometry, lung volumes and DLCO, should be performed every 3 months for the first year and every 6 months for the second year, followed by yearly monitoring until 5 years, as clinically indicated (Level of evidence: 2A).

FEV1 rapidly decreases during the 6 months before the diagnosis of lung cGVHD,⁴⁹ even before the onset of symptoms. Therefore, regular PFTs are critical for the early identification of lung cGVHD. This proactive approach enables the possibility of earlier intervention, offering a valuable opportunity for timely and effective management.²⁶ Regular PFT monitoring for asymptomatic allo-HSCT recipients at 3-month intervals during their first post-allo-HSCT year^{1,26,50} and at 6-month

intervals during the second year and yearly thereafter for at least 5 years, as clinically indicated, is recommended.⁵¹ After 5 years, continued annual screening remains appropriate according to the National Institutes of Health (NIH) guidance.¹ However, we suggest that the continuation of frequent PFTs beyond that point could be guided by clinical judgement, considering individual patient circumstances and institutional considerations. Notably, alternative modalities, such as home handheld spirometry, have demonstrated feasibility for the early detection of airway obstruction.^{5,52}

Statement 9. At the time of diagnosis of extra-pulmonary cGVHD, a complete set of PFTs should be performed (Level of evidence: 2A).

Statement 10. For patients newly diagnosed with extra-pulmonary cGVHD, PFTs should be performed every 3 months for the first year and then every 6 months for 1 year, followed by at least yearly as clinically indicated (Level of evidence: 2A).

Regular PFT surveillance is particularly crucial for high-risk patients, such as those with cGVHD, which may confer a doubled incidence.^{4,53,54} Once a patient is diagnosed with extra-pulmonary cGVHD, the committee recommends a complete set of PFTs at the time of cGVHD diagnosis. Then, the committee suggests a regular follow-up of spirometry, with a frequency of every 3 months during the first year and every 6 months during the second year. This monitoring schedule aims to track pulmonary function changes over time and facilitate timely intervention if needed. Data regarding the optimal frequency of PFT monitoring after BOS diagnosis remain limited. The monitoring interval may depend on disease severity and the rate of decrease in FEV₁.

Statement 11. Serial PFT or spirometry at short intervals is suggested for patients with respiratory viral infection and concomitant FEV1 decline or asymptomatic decline in FEV1 (Level of evidence: 2A).

Airway infections are common complications following allo-HSCT,^{55,56} with viral pathogens playing a particularly significant role in subsequent airflow decline.^{57,58} The severity and timing of this decline may depend on the specific viral species and the location of the infection.⁵⁹ Additionally, prolonged viral shedding is not uncommon among patients undergoing allo-HSCT.⁶⁰ Several studies have shown that respiratory viral infections may coexist with or even contribute to the development of pulmonary chronic GVHD.^{57–59,61} The 2020 National Institutes of Health (NIH) Chronic GVHD Consensus update¹ recognizes limitations in the 2014 diagnostic criteria BOS,¹⁵ particularly the requirement for the absence of infection in the respiratory tract.

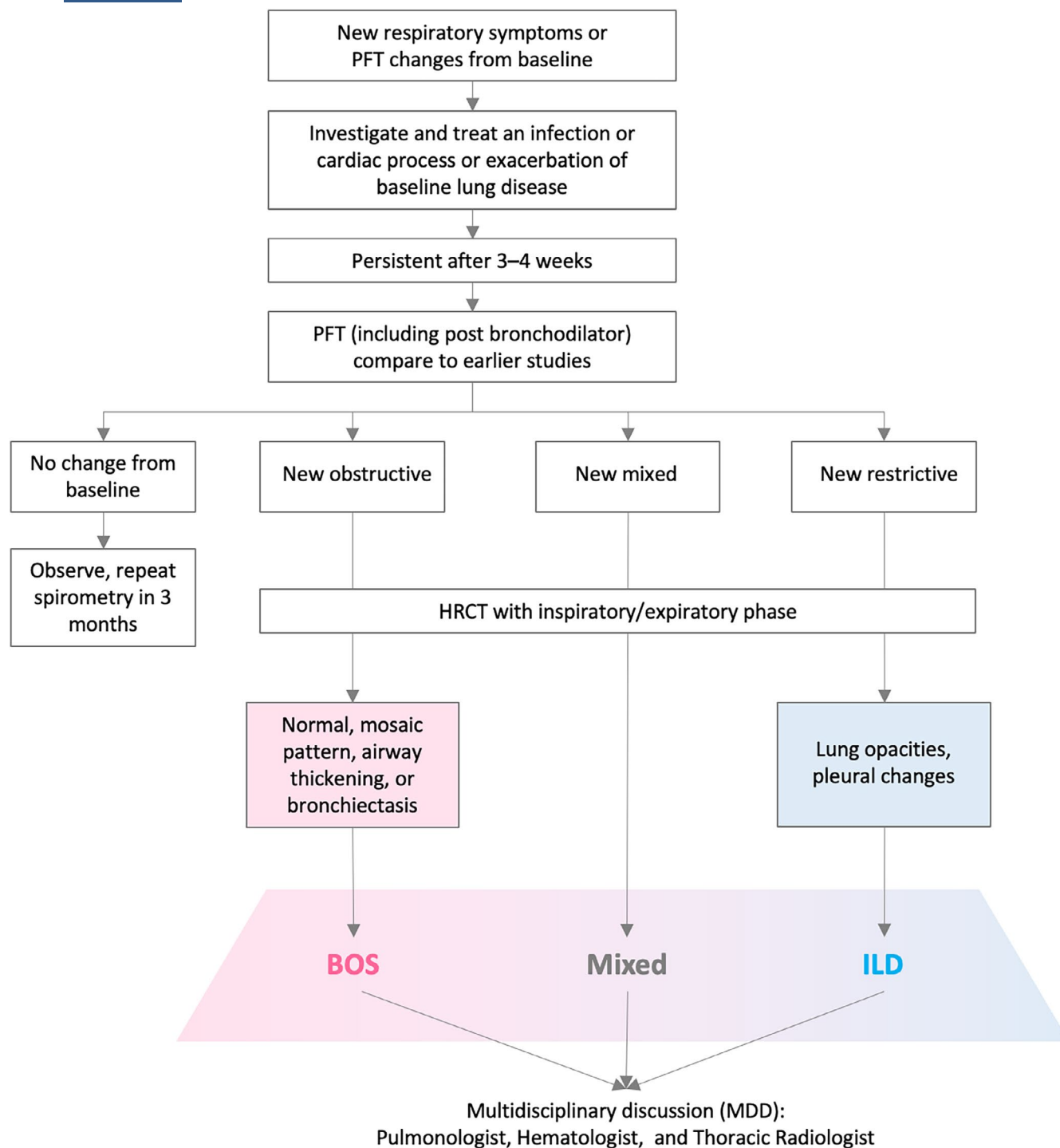


FIGURE 3 Management of patients experiencing post-haematopoietic stem cell transplantation (HSCT) lung function impairment.

Therefore, the presence of infection should not preclude a BOS diagnosis, especially when there is persistent lung function decline. This shift reflects growing awareness that reliance on infection status may delay diagnosis and appropriate intervention. The committee recommends PFT or spirometry at short intervals for patients with respiratory viral infection, especially those exhibiting a concomitant decline in FEV1 or experiencing asymptomatic decreases in FEV1.

Topical treatment and supportive treatment

Statement 12. Combining inhaled corticosteroids and bronchodilators is effective in patients with BOS after HSCT (Level of evidence: 2A).

Statement 13. Adding inhalation therapy (corticosteroids and bronchodilators) to systemic

treatment is beneficial for patients with BOS after HSCT (Level of evidence: 2A).

The pathophysiology of cGVHD involves an immune-mediated response leading to chronic airway inflammation and fibrosis.¹⁵ The hallmark presentation of BOS is bronchiolar inflammation with airway obstruction, and consequently, inhalation therapy with anti-inflammatory drugs and bronchodilators is warranted.

Bergeron et al. reported that the respiratory symptoms of patients with clinically suspected mild to moderately severe BO post-allo-HSCT improved after treatment with inhaled budesonide/formoterol (800/24 µg) in combination with other regular medicines, with a statistically significant increase in FEV1 and mean expiratory flow between 25% and 75% of FVC (MEF_{25%-75%}).⁶² The median follow-up time was 12.8 months (range: 5–29 months). Although this was a retrospective study with only 13 patients enrolled, the results provide new insight regarding the management of these patients. Bergeron et al. subsequently conducted a randomized, double-blind, crossover trial in which 32 allo-HSCT patients diagnosed with mild to severe BOS were divided into two groups to receive budesonide/formoterol (800/24 µg) or placebo for 6 months.⁶³ The results revealed that the median FEV1 increased by 260 mL in the budesonide/formoterol arm compared with 5 mL in the placebo arm ($p=0.012$) at the first month. Thirteen patients who completed 6 months of treatment maintained the effect. Although 37% of patients in the budesonide/formoterol arm were unblinded early due to a lack of response, the treatment was well tolerated overall. Additional retrospective data have suggested that escalating budesonide/formoterol from a low dose (160/4.5 µg bid) to a high dose (320/9 µg bid) may provide clinical benefit in a subset of patients without increasing the risk of infection.⁶⁴

In addition, a prospective study of 17 patients demonstrated that the combination of albuterol and tiotropium resulted in significant improvements in FEV₁ (mean increase of 8%), partial forced expiratory flow (40% increase) and markers of lung hyperinflation.⁶⁵ While 41% of patients met conventional reversibility criteria based on FEV₁ and FVC improvements, an additional subset demonstrated clinical improvement in small-airway function.

Furthermore, in a retrospective study, adding fluticasone propionate to systemic immunosuppressive therapies helped stabilize previously declining lung function and improved respiratory symptoms, with clinical benefit observed in 94% of patients,⁶⁶ outperforming traditional systemic immunosuppression, which had a reported 60% response rate.^{66,67}

While BOS is characterized by fixed airflow obstruction due to bronchiolar fibrosis,^{9,12} ICS/LABA may provide symptomatic relief and modest improvements in pulmonary function for select patients. These benefits likely reflect partial reversibility in early-stage disease, relief of dynamic airway collapse or enhancement of small airway tone. Therefore, bronchodilators can be considered adjunctive therapies aimed at symptom management and airflow

improvement. However, they are not considered disease-modifying treatments.

Collectively, these findings reinforce the role of inhaled corticosteroids and bronchodilators, particularly ICS/LABA combinations, as part of adjunctive therapy in BOS after HSCT, which is consistent with international guideline recommendations.⁹

Statement 14. Pulmonary infection should be evaluated when treating patients with BOS (Level of evidence: 2A).

Infections are a leading cause of death in patients with BOS after HSCT. In a prospective study, only 4% of patients were free of infection after extensive evaluation. The pathogens identified in these patients were as follows: 36% bacterial (most commonly Gram-negative), 47% viral (most commonly influenza), 16% fungal (mostly *Aspergillus*) and 2% mycobacterial infections. The high rate of coinfections highlights the importance of careful and thorough evaluation of these patients.^{14,54,68,69} *Non-tuberculosis mycobacterial (NTM)* infections and Gram-negative bacteria, both associated with BOS, frequently colonize patients with bronchiectasis.⁷⁰ NTM has also been noted in lung transplant recipients and is linked to BOS progression.⁷¹

Although this consensus does not issue a specific recommendation regarding prophylactic antimicrobial regimens, we acknowledge that prophylaxis against *Pneumocystis jirovecii* and encapsulated organisms may be considered for all patients receiving immunosuppressive therapy, in line with current guidelines, regardless of cGVHD status.^{9,72} As part of comprehensive infection prevention, vaccinations including annual influenza immunization, a four-dose pneumococcal conjugate vaccine series, and COVID-19 boosters should be administered according to standard post-HSCT protocols.⁷⁰ Respiratory syncytial virus (RSV) vaccination is suggested to be considered in recipients older than 60 years of age⁷¹; however, because of the lack of clinical trials in the HSCT population, its efficacy and optimal vaccination schedule remain uncertain. Despite these preventive strategies, preventing and managing infectious complications remain major clinical challenges in BOS to optimize long-term outcomes.

Statement 15. Gastro-oesophageal reflux disease (GERD) should be evaluated in patients with BOS (Level of evidence: 2B).

The pathophysiology of BO involves injury to and inflammation of epithelial cells and subepithelial structures of the small airways, which leads to excessive fibroproliferation and aberrant tissue repair. Recent data suggest an association with GERD in lung transplant patients.^{73,74} Khalid et al.⁷⁴ conducted a study enrolling seven patients with BOS post-allo-HSCT. Five patients were diagnosed with GERD by 24-hour pH monitoring and treated with omeprazole, and the patients' PFTs results were stable at the third month

of follow-up. These findings suggest that GERD may be a potential risk factor for the development of BOS in these patients; therefore, proper evaluation and management are essential.

Statement 16. Pulmonary rehabilitation is beneficial for patients with BOS (Level of evidence: 2B).

Pulmonary rehabilitation (PR) has been shown to improve exercise tolerance, reduce dyspnoea and enhance quality of life, making it a standard therapy for chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease.⁷⁵ The characteristics of BOS post-allo-HSCT, including the clinical symptoms of cough and dyspnoea, are similar to those of chronic lung disease. However, the role of PR in BOS remains underexplored. Tran et al. evaluated the benefit of a PR in patients with BOS. Ten patients completed the programme, all of whom demonstrated improvements in the 6-minute walk distance test (6MWT), with an average increase of 307 feet in walking distance. The physical functioning score also significantly improved.⁷⁶ Further supporting evidence comes from a recent case series by Choi et al., although only four patients were enrolled.⁷⁷ After more than 2 months of PR, three patients showed improvements in FVC, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak oxygen uptake. Although current studies are limited by small sample sizes, early findings suggest that PR may serve as a valuable adjunctive therapy for patients with BOS, especially in the early stages of the disease. Larger, well-designed studies are needed to provide more robust evidence and confirm the long-term benefits of PR for this patient population.

In addition to pulmonary rehabilitation, long-term oxygen therapy can be considered in patients with persistent resting hypoxaemia, following the same principles used in chronic lung diseases such as COPD or interstitial lung disease. Current guidelines recommend that oxygen supplementation for at least 15 h per day in patients with severe hypoxaemia at rest and up to 24 h per day may be of additional benefit.⁷⁸ In addition, ambulatory oxygen may be considered in patients who experience oxygen desaturation during physical exertion to improve activity tolerance and quality of life.

Statement 17. Special consideration (particularly minimized PEEP) for ventilator support is suggested for patients with respiratory failure (Level of evidence: 2B).

Acute hypoxaemia is rare in patients with BOS and is often linked to acute infection; therefore, the most important management strategy is to treat the underlying disease. When ventilatory support becomes necessary, clinicians must consider fixed small airway obstruction and significant air trapping characteristics in BOS.

In these patients, positive pressure ventilation should be minimized to reduce the risk of barotrauma and exacerbate air trapping. Unlike the dynamic airway collapse observed in diseases such as COPD, where moderate PEEP may help overcome intrinsic PEEP (auto-PEEP) and stent open the airways, BOS is defined as concentric, irreversible, fibrotic narrowing of the small airways. As a result, PEEP generally does not reopen narrowed airways and may instead increase the degree of risk. Other strategies, such as low tidal volume, prolonged expiratory time and permissive hypercapnia, follow standard approaches used in obstructive airway disease and remain appropriate.⁷⁹ Furthermore, the exhalation time should be prolonged to meet patients' requirements. In addition, close blood gas monitoring is essential to avoid severe hypercapnia, which can lead to life-threatening apnoea, especially during oxygen administration.⁸⁰

Systemic treatment and lung transplantation

Statement 18. The fluticasone/azithromycin/montelukast (FAM) regimen should be started at the time of BOS diagnosis (Level of evidence: 2A).

The most promising literature regarding BOS treatment comes from a phase 2 study reported by Williams et al.,¹¹ which evaluated the efficacy of a combination regimen consisting of FAM (Table 2) for newly diagnosed BOS within 6 months after allo-HSCT. In this single-arm, open-label trial, all patients received the FAM regimen along with a short course of systemic corticosteroids at 1 mg/kg/day for 2 weeks. The biological rationale for this regimen is grounded in BOS pathophysiology: Inhaled corticosteroids reduce bronchiolar inflammation,⁶⁶ azithromycin exerts immunomodulatory effects by reducing neutrophilia and interleukin-8 levels⁸¹ and montelukast, a leukotriene receptor antagonist, helps decrease airway inflammation.⁶⁹ The regimen was well tolerated and yielded encouraging outcomes. Treatment failure, defined as a $\geq 10\%$ decline in FEV1 at 3 months, occurred in only 6% of patients, which was significantly lower than the historical rate of 40%. Although the failure rate increased to 36% by 6 months, nearly half of the patients (48%) were able to reduce their systemic steroid

TABLE 2 Suggested dosage of fluticasone, azithromycin and montelukast.

Drug	Fluticasone	Azithromycin	Montelukast
Dosage	440 µg BID (≥ 12 y/o) 220 µg BID (6–11 y/o)	250 mg PO QW 1,3,5 (≥ 19 y/o) 5 mg/kg, max 250 mg, PO QW 1,3,5 (6–18 y/o)	10 mg PO QD (≥ 14 y/o) 5 mg PO QD (6–13 y/o)

Abbreviations: BID, twice daily; PO, oral administration; QD, once daily; QW, every week; y/o, years old.

dose by more than 50%. The 6-month overall survival rate was 97%. Due to the encouraging data, this FAM regimen is the recommended treatment for BOS in the consensus recommendation of GVHD management from EBMT.⁸²

In Taiwan, most of the available fluticasone products are combined with long-acting beta-agonists (LABAs), such as fluticasone/formoterol (Flutiform® MDI), fluticasone/vilanterol (Relvar® Ellipta) and fluticasone/salmeterol (Seretide® Accuhaler). Physicians may select their own preference provided the dose of fluticasone is appropriate.

Statement 19. Systemic corticosteroids should be combined with the FAM regimen once BOS is diagnosed. Other systemic immunosuppressive agents that are used before BOS is diagnosed should be continued (Level of evidence: 2A).

Systemic corticosteroids remain the drug of choice when cGVHD develops. For BOS, systemic corticosteroids have been recommended as first-line treatments in several guidelines, with a dosage of 1 mg/kg/day.^{83,84} In the FAM trial mentioned above, systemic corticosteroids (1 mg/kg/day) were administered concomitantly with the FAM regimen.¹¹ Therefore, 1 mg/kg/day is the suggested systemic corticosteroid dose.

The duration of systemic corticosteroid use is not specified in most studies, with the exception of the FAM trial, which specified a 2-week course followed by tapering. However, prolonged systemic corticosteroid treatment is associated with increased mortality from infectious complications.¹⁴ Therefore, the duration of systemic corticosteroid should be carefully individualized by the treating physicians according to the patient's condition.

Statement 20. Steroid pulse therapy is an option in addition to the FAM regimen with systemic corticosteroids for moderate or severe BOS (Level of evidence: 2B).

Although systemic corticosteroids have been recommended as the first-line treatment option for BOS, the long-term outcome is not satisfactory.⁵⁴ Steroid pulse therapy has been tested for BOS, but the evidence is mainly based on paediatric patients.^{85,86} In a 12-patient cohort, five patients (42%) had a good response to treatment, four patients (33%) stabilized with moderate lung disease and three patients (25%) progressed to end-stage disease.⁸⁶ Additionally, in a survey of 31 centres in Germany, Austria and Switzerland, 16 of 31 centres administer a pulse of steroids during the course of BOS, with six centres administering steroids at the time of diagnosis of pulmonary cGVHD and four centres administering it as a second-line therapy.⁸⁴ Based on this evidence, steroid pulse therapy at a dosage of 10 mg/kg/day for 3 days has been listed as a 2C recommendation in two guidelines.^{83,84} Due to the relatively low evidence level, we reserve steroid pulse therapy as an option for more advanced BOS, as an adjunct to the FAM regimen and regular systemic corticosteroids.

Statement 21. PFTs should be performed 4 weeks after treatment is initiated to guide further treatment decisions (Level of evidence: 2A).

After initiating treatments, PFTs should be performed to guide ongoing treatments. The timing of the first PFT follow-up is approximately 4 weeks among the different guidelines.^{84,87} This timing aligns with the EBMT consensus recommendation for preliminary assessment of first-line cGVHD treatment.⁸² Therefore, 4 weeks is considered appropriate to first evaluate the efficacy of the initial treatment of BOS and could provide further guidance regarding the duration of corticosteroid and possibly second-line medications. The timing of second and further PFT follow-up is seldom mentioned. In the Fred-Hutchinson long-term follow-up guidelines, PFT should be performed every 4–6 weeks in the first 6 months while the patient is on a corticosteroid taper. If the FEV1 stabilizes after 3 months, the frequency of PFT follow-up may be spaced out every 2–3 months for at least 1 year.⁸⁷ The ERS/EBMT guidelines recommend performing spirometry every 3 months in patients with BOS. In addition, a full PFT is advised at the time of BOS diagnosis, annually during follow-up, and whenever there is evidence or concern for disease progression. More frequent monitoring should be considered in clinically unstable patients, following the onset of new respiratory symptoms or GVHD in other organs, after a respiratory infection, or after a change in therapy. If the patient remains clinically stable after treatment initiation, the frequency of spirometry may be gradually reduced to every 6–12 months. If lung function declines or new respiratory symptoms develop, a follow-up chest CT is warranted.⁹

Statement 22. If PFT further declined after treatment with FAM and systemic corticosteroids, ruxolitinib can be added (Level of evidence: 1).

There is no consensus regarding second-line treatments if BOS progresses after first-line treatment. Several agents, including calcineurin inhibitors, mammalian target of rapamycin inhibitors, mycophenolate mofetil, extra-corporeal photopheresis (ECP),^{14,84} etanercept⁸⁴ and imatinib,^{83,84} have been evaluated. Rituximab has been used to treat BOS after lung transplantation, though it is rarely used to treat BOS after allo-HSCT.^{6,88}

In recent years, ruxolitinib has become the drug of choice for treating corticosteroid-refractory cGVHD, as supported by findings from the REACH3 study.⁸⁹ Compared with the best available treatment, ruxolitinib demonstrated superior efficacy, with a higher overall response rate (ORR) at week 24 (49.7% vs. 25.6%), an improved best ORR (76.4% vs. 60.4%), a longer median duration of response (not reached vs. 6.24 months) and a prolonged median failure-free survival (> 18.6 months vs. 5.7 months). The specific pulmonary response rate at week 24 was 8.6% (6 of 70 patients) in the ruxolitinib arm and 6.1% (3 of 49 patients) in the control

arm, although the time to diagnosis of lung cGVHD was not available. In addition to three retrospective studies showing that ruxolitinib can stabilize or improve PFT and serve as a potential steroid-sparing agent,^{90–92} a multicentre prospective phase 2 study further revealed that 27.8% of patients with newly diagnosed BOS achieved an improvement in FEV1 $\geq 10\%$.⁹³ Among patients with established BOS (diagnosed for ≥ 6 months), 92.3% had stable FEV1. The best lung-specific ORR was 34.7% in the total population, and the ORR was closely correlated with the baseline NIH lung score. Notably, infections are generally infrequently associated with ruxolitinib treatment^{92,93}; however, when infections occur, respiratory tract infections are the most common. Therefore, ruxolitinib may be a reasonable option for treating BOS progression, though the infection risk and patient history should be considered.

Although it remains unavailable in Taiwan, ECP has a good response rate of 65%–70% as a second-line treatment for cGVHD.⁹⁴ ECP also showed good efficacy for BOS specifically. In two retrospective studies of ECP for BOS, the response rates were 40% (2 of 5 patients) and 67% (6 of 9 patients).^{95,96} In addition, ECP is administered for the treatment of BOS by 15 of 31 centres in Germany, Austria and Switzerland, mainly as third- and fourth-line treatment options.⁸⁴ However, in a recent retrospective matched cohort study, ECP improved survival in allo-HSCT patients with BOS but had no significant impact on pulmonary function.⁹⁷ ECP is recommended in the ERS/EBMT joint guidelines⁹ as a second-line option to be added to systemic immunosuppression. However, its application is often constrained by high resource demands and the need for central venous access.

There are three promising agents for the treatment of pulmonary cGVHD: belumosudil, abatacept and axatilimab. Belumosudil, an oral selective inhibitor of rho-associated coiled-coil-containing protein kinase 2 (ROCK2), has demonstrated significant efficacy in treating steroid-refractory cGVHD. In the phase 2 ROCKstar study, patients were randomized to receive belumosudil 200 mg daily or 200 mg twice daily.⁹⁸ The best ORRs for belumosudil at 200 mg daily and 200 mg twice daily were 74% and 77% respectively. The median duration of response was 54 weeks, and 44% of the patients remained on therapy for more than 1 year. Among 59 patients with BOS who were enrolled and treated in two prospective belumosudil trials, the best overall response rate for BOS was 32%, with 17% achieving partial response and 15% achieving complete response.⁹⁹ Abatacept, a selective T-cell co-stimulation modulator, inhibits T-cell activation by binding to CD80 and CD86 on antigen-presenting cells, thereby blocking the CD28-mediated costimulatory signal. A retrospective study demonstrated that abatacept has an excellent ORR of 89% based on lung severity score and/or PFTs.¹⁰⁰ In the phase 2 trial evaluating its efficacy in steroid-refractory cGVHD, abatacept achieved an ORR of 58%. Among patients with pulmonary cGVHD at baseline ($n=22$), an ORR of 57% was observed, with a CR rate of 35%.¹⁰¹ Similarly, axatilimab, a colony-stimulating factor 1 receptor (CSF1R)-blocking humanized IgG4 antibody that

inhibits monocyte and macrophage function, has demonstrated promising outcomes in the phase 2 AGAVE-201 study.¹⁰² At a dose of 0.3 mg, an ORR of 74% was achieved, including a lung-specific ORR of 47%, with a CR rate of 16%. These findings are consistent with the ORR of 31% reported in the earlier phase I/II study.¹⁰³ Although these novel agents have demonstrated encouraging potential, the optimal dose, schedule and duration of treatment for patients with lung cGVHD remain to be determined and have therefore not been included in this consensus document.

Statement 23. Prolonged use of azithromycin is not suggested if BOS has resolved, due to an increased risk of underlying disease relapse (Level of evidence: 2A).

In the ALLOZITHRO randomized trial, patients received either 250 mg of azithromycin or placebo three times per week for 2 years, starting at the time of the conditioning regimen. However, the trial was terminated early due to a higher incidence of haematological relapse in the azithromycin arm (2-year cumulative incidence, 33.5% vs. 22.3%).¹⁰⁴ Although azithromycin was used for BOS prophylaxis in this trial, safety concerns remain for its therapeutic use. In addition, a multicentre retrospective study evaluated the impact of azithromycin in 316 patients with BOS after HCT.¹⁰⁵ While the study did not find a significant association with relapse, azithromycin use was independently associated with a twofold increased risk of developing secondary neoplasms (adjusted HR 2.00; 95% CI 1.01–3.99). Notably, the majority of these neoplasms were cutaneous, with squamous cell carcinoma being the most frequent histological type (60% of secondary neoplasms in the azithromycin group), raising additional concerns about its long-term safety. Reflecting these data, prolonged use of azithromycin after resolution of BOS is not recommended by the EBMT consensus due to the possibility of increased risk of relapse.⁸² Azithromycin is also the first agent to be discontinued if PFT remains stable or improves after 6 months of FAM treatment according to the Fred Hutchinson guidelines.¹⁰⁶ Therefore, treating physicians should weigh the risks and benefits of BOS control and the risks of underlying disease relapse and avoid prolonged use of azithromycin if BOS is resolved.

Statement 24. Lung transplantation should be considered for patients with progressive lung function decline despite pharmacological management or in cases of progression to respiratory failure (Level of evidence: 2B).

Lung transplantation remains the ultimate option for the treatment of progressive BOS, especially for patients with oxygen dependence or severe limitations in quality of life.^{6,14,83,84,88} In a systematic review, the 3-year survival probability of 84 patients who received lung transplantation after allo-HSCT was 79%. Twenty-five patients developed recurrent BOS, and only two patients experienced underlying

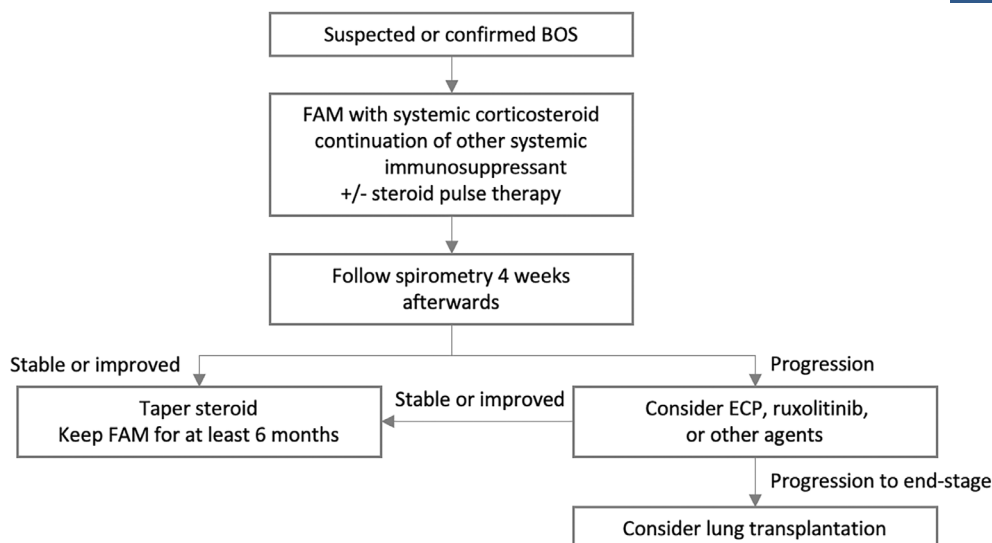


FIGURE 4 Treatment algorithm for patients with lung graft-versus-host disease (GVHD).

disease relapse during follow-up.¹⁰⁷ Although the outcome of lung transplantation has improved, patients should still be carefully selected, counterbalanced with the risk of underlying disease relapse, infection and progression of prior end-organ damage.^{14,84} Physicians should have a detailed discussion with the lung transplant team to evaluate the risks and benefits for each patient. A summary of the BOS treatment algorithm is shown in Figure 4.

CONCLUSION

Pulmonary cGVHD, particularly BOS, is a severe complication of allo-HSCT. Although less common than other cGVHD manifestations, BOS is associated with high morbidity and mortality due to its progressive nature and limited therapeutic options. These consensus statements address diagnostic challenges, optimize treatment strategies and improve outcomes in adult patients with pulmonary cGVHD.

Early diagnosis is crucial, with routine PFT and HRCT recommended to detect airflow obstruction and differentiate BOS from other conditions. Serial PFTs following transplant are essential for early detection, enabling timely therapeutic intervention before irreversible damage occurs. Treatment approaches for BOS include inhaled and systemic corticosteroids, as well as combination regimens such as FAM, which have demonstrated efficacy in stabilizing or improving lung function. Emerging therapies, such as ruxolitinib, belumosudil, abatacept and axatilimab, have shown promising efficacy in reducing disease progression and improving lung function, although their effectiveness requires further validation through large-scale, BOS-specific randomized clinical trials. ECP may offer therapeutic benefit in select patients; however, its broader implementation is often constrained by its resource-intensive nature, the need for central venous access and the requirement for frequent visits to specialized health care facilities. For patients with advanced disease

unresponsive to medical therapy, lung transplantation remains a viable option, emphasizing the need for timely referral to transplant centres. Supportive interventions are also a cornerstone of management, including pulmonary rehabilitation to improve exercise capacity and quality of life; infection prophylaxis to mitigate the risks associated with immunosuppression; and vaccination against influenza, pneumococcus, COVID-19 and RSV. Long-term oxygen therapy may benefit patients with chronic hypoxaemia. This consensus report emphasizes the importance of a multidisciplinary approach to pulmonary cGVHD, integrating rigorous monitoring, treatments and supportive care. Future research should focus on identifying reliable biomarkers for early diagnosis, evaluating the long-term efficacy and safety of novel agents and developing targeted therapies to address refractory cases and improve patient outcomes.

AUTHOR CONTRIBUTIONS

BSK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. XCHT was responsible for conceptualization, investigation, project administration, formal analysis and writing (original draft, review & editing). ZHY, SWC and HCW were responsible for investigation, project administration, formal analysis and writing (original draft). YCL, CHC, SPY, WCH, TLL, TMY, CHL, HKK, HHH and SLC were responsible for formal analysis. YWK was responsible for the conceptualization, project administration and formal analysis. CCL was responsible for conceptualization, formal analysis, supervision and funding acquisition. BSK and HCW were responsible for conceptualization, formal analysis, supervision, writing (review and editing) and funding acquisition.

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CONFLICT OF INTEREST STATEMENT

XCHT: Astellas (honorarium and advisory board), AstraZeneca (honorarium), Beigene (honorarium), BMS (honorarium), DiethelmKellerSiberHegner (honorarium and advisory board), GSK plc (honorarium), Johnson & Johnson (honorarium), Meiji Seika Pharma (advisory board), Novartis (honorarium and advisory board), Pfizer (honorarium). ZHY: AstraZeneca (honorarium), Boehringer Ingelheim (honorarium), Novartis (honorarium), Pfizer (honorarium). SWC: Amgen (honorarium), Novartis (honorarium). YWK: AstraZeneca (honorarium), Novartis (honorarium), Pfizer (honorarium). HCH, YCL, CHC, SPY, WCH, TLL, TMY, CHL, HKK, HHH, SLC, CCL, HCW: No conflicts of interest declared. BSK: Astellas (honorarium), AstraZeneca (honorarium), Beigene (honorarium), BMS (honorarium), GSK plc (honorarium), Johnson & Johnson (honorarium), Meiji Seika Pharma (advisory board), Novartis (honorarium and advisory board), Ono Pharmaceutical (honorarium), Pfizer (honorarium).

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