How I treat bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation

Running title: How I treat BOS after HSCT

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Abstract:

In past years, a diagnosis of bronchiolitis obliterans syndrome (BOS) after allogeneic hematopoietic cell transplant (HCT) conferred nearly universal mortality secondary to lack of consensus for diagnostic criteria, poorly understood disease pathogenesis, and very few studies of therapeutic or supportive care interventions. Recently, however, progress has been made in these areas: revised consensus diagnostic guidelines are now available; supportive care has improved; there is greater understanding of potential mechanisms of disease and prospective trials are being conducted. This article describes these advances and provides suggestions to optimize therapy for patients with BOS after HCT.

Introduction:

Despite advances in the treatment of graft-versus-host disease (GVHD) and supportive care after HCT, lung manifestations of chronic GVHD (cGVHD) continue to confer poor prognosis.1-3 Lung cGVHD or bronchiolitis obliterans syndrome (BOS), results from immune attack of the small airways, leading to fibrotic occlusion and subsequent obliteration. BOS is often an asymptomatic, insidious disease occurring within the first 2 years of HCT with other manifestations of cGVHD. The diagnosis relies upon obstructive decline in pulmonary function in the absence of other etiologies. Diagnosis, supportive care, and treatments for this disease have improved in recent years. Here, I describe my approach to BOS diagnosis and treatment via discussion of illustrative cases.
Case reports:

Case 1: Diagnostic criteria

Patient 1 is a child who underwent matched sibling peripheral blood stem cell transplantation (PBSCT) for acute leukemia. Her course was complicated by cGVHD of multiple organs and declining forced expiratory volume at 1 second (FEV1) to less than 50% predicted, though ratio of FEV1/FVC (forced vital capacity) remained greater than 0.7. Inspiratory CT showed reticulonodular disease. The patient underwent right upper lobe biopsy, which was complicated by pneumothorax, pneumomediastinum, pneumatoses, and subcutaneous emphysema. Biopsy showed bronchiolitis obliterans and infectious tests were negative.

Discussion of Case 1:

As the current case highlights, lung biopsy in these patients can be associated with high morbidity. While historically, this was the preferred method of diagnosis, now pulmonary function test (PFTs) criteria are sufficient for most patients after HCT. In the thirty-five years since the first accounts of lung cGVHD, noninvasive diagnostic criteria for BOS have been developed and refined by international consensus. The current definition of BOS includes: 1) FEV1<75% predicted and an irreversible >or = to10% decline in <2 years, 2) FEV1/VC ratio <0.7 or the lower limit of the 90% confidence
interval of the ratio, 3) absence of infection, and 4) either: a) pre-existing diagnosis of cGVHD, or b) air trapping by expiratory CT, or c) air trapping on PFTs by residual volume RV > 120% or RV/TLC exceeding the 90% confidence interval (Figure 1a). These new diagnostic criteria incorporated several important updates. Firstly, air trapping was no longer a required criteria for patients who had obstructive disease and cGVHD, as this finding is often absent early in the disease course. Secondly, a standard threshold for the FEV1/FVC ratio (of 0.7) was supplemented by consideration of the normal age-adjusted confidence interval. Because the ratio of young children is 1 and declines with age, both children and the elderly may be misdiagnosed using the 0.7 ratio cutoff. Patient 1 would have met criteria for BOS by PFTs alone using current definitions, using National Health and Nutrition Examination Survey equations. Similarly, elderly individuals may have appropriate age-related decline in FEV1 to less than 0.7, and not de facto meet criteria for obstruction. Finally, the slow vital capacity may now be used rather than FVC, as some BOS patients require slow exhalation to reveal full VC due to early airway collapse with the forced expiratory maneuver. Patients with more severe disease may have evidence of air trapping by PFTs (elevated RV) or on expiratory CT scan (mosaic pattern); however, as suggested by the NIH 2014 guidelines, these features are not required to diagnose BOS. One final population that is particularly challenging to diagnose are those with extra-pulmonary restriction, which may be due to sclerotic GVHD of the pulmonary girdle, GVHD myositis (with elevated creatine kinase or aldolase), steroid myopathy, or polyneuritis affecting respiratory muscles. The maximum inspiratory and expiratory pressures (MIP/EP) may be a marker of muscle weakness. The extra-pulmonary restriction will also diminish total lung capacity and VC,
thus yielding a misleading picture of restriction, in contrast to intrapulmonary restriction (Figure 1a). For these patients, PFTs need to be repeated after the extra-pulmonary process improves to determine if lung cGVHD is also present.

It is very important to exclude other diagnoses, including idiopathic pneumonia syndrome, cryptogenic organizing pneumonia, pulmonary fibrosis and late radiation effects, infection, asthma, or chronic obstructive pulmonary disease (COPD), and rare disorders such as tracheomegaly, tracheobronchomalacia, alpha-1 antitrypsin deficiency. Infection must be excluded to diagnose BOS and requires a thorough investigation. The FEV1 decline in asthma is reversible with albuterol in contrast to BOS. Idiopathic pneumonia syndrome typically presents earlier after transplant, and, in addition to pulmonary fibrosis, late radiation effects, should be excluded by the absence of obstruction. Tracheomegaly occurs in adulthood and is diagnosed by an enlarged trachea on CT as well as a characteristic notch in the expiratory flow volume loop (Figure 1b). This can also be seen in tracheobronchomalacia, which can mimic BOS, and may be diagnosed by bronchoalveolar lavage (BAL). Cryptogenic organizing pneumonia (COP) usually presents with restriction but a mixed picture with obstruction may be present. COP, previously termed “bronchiolitis obliterans organizing pneumonia (BOOP)” should include a new consolidation on CT and respond rapidly to steroids in contrast to BOS. Alpha-1-anti-trypsin deficiency also presents with obstructive disease, and while there is often some obstruction present pre-HCT, this may be much more pronounced after HCT. I typically test for this if there is family history or obstruction pre-HCT, or if other cGVHD manifestations are absent. Smokers or those with COPD present a unique challenge, since airflow obstruction may progress without BOS.
Although FEV1 in patients with COPD declines at twice the expected age-related loss in lung function, this should not exceed the BOS-defined 10% decline within 2 years.\textsuperscript{15} One final rare complication deserves mention, that of broncho-obliterans (obliteration of large airways), which likely represents similar allo-immunity but may be visualized by bronchoscopy and potentially treated through lysis of the webs, and may be co-incident with BOS.\textsuperscript{16} Notably, BOS can occur outside the setting of allogeneic HCT and rarely reported after autologous HCT.\textsuperscript{17}

While I view the complete PFTs, most patients may be diagnosed by FEV1\% predicted below 75\%, with greater than 10\% decline from pre-transplant, with FEV1/SVC below the confidence interval. For any patients with new obstruction, I perform an intensive work-up for infections, which may either cause the FEV1 decline, or often, be a co-factor. Finally, I recommend BAL, which may be critical to diagnose and help guide therapy for co-infections or colonization or resistant bacteria that may lead to subsequent infectious episodes and guide therapy, and to rule out bronchomalacia or broncho-obliterans (\textbf{Figure 4}). In the rare circumstance a diagnosis is not achieved through these methods, and the index of suspicion for infection remains high, I will pursue lung biopsy. Severity of disease may be classified by: mild FEV1 > 60\%, moderate FEV1 40-59\%, and severe FEV1 < 39\%.\textsuperscript{9}

\textbf{Case 2: Importance of frequent monitoring}
Patient 2 is an adult female who underwent PBSCT with busulfan and cyclophosphamide for leukemia, complicated by CMV reactivation and acute GHVD early after HCT, prompting resumption of cyclosporine and protracted taper. Approximately 3 years after HCT and soon after completion of taper, she developed lichenoid skin changes, hepatitis, and vaginal symptoms. She was diagnosed with cGVHD and mycophenylate mofetil administered. Despite immunosuppressive therapy, GVHD progressed to include oral and ophthalmic GVHD and a non-productive cough. Despite pulmonary symptoms, the first PFTs were administered greater than 2 years after initial cGVHD diagnosis, showed new obstruction, and were consistent with BOS with considerable FEV1 decline to 50% predicted with ratio of FEV1/VC of 0.5.

Discussion of Case 2:

This case highlights the potential benefit of frequent screening PFTs, permitting the earliest diagnosis of disease, prior to the onset of symptoms. Symptoms of BOS may include chronic non-productive cough, dyspnea on exertion, decrease in exercise tolerance, wheezing, or pneumomediastinum. Clinical symptoms of disease are often associated with moderate/severe FEV1 decline, suggesting that a window of time has already passed in which more mild obstruction might have been identified. However, this case is not unusual. A recent study of 82 patients diagnosed with BOS by current criteria showed that the median FEV1 was 53% at diagnosis and risk factors for poorer prognosis included diagnosis within one year and decreased FVC. Further, as described in this manuscript, the modern trajectory of BOS is characterized by a rapid decline in
FEV1 followed by a period of relative stabilization, likely due to recognition and interventions. Thus, theoretically, earlier detection could lead to a plateau at a higher, and less morbid FEV1. A good way to monitor lung function is to follow the regression slope of FEV1 volume versus time (Figure 2). The slope also removes any influence of different PFT equations, which can significantly alter FEV1 % predicted (up to 27%).13 In addition to quickly revealing FEV1 changes, the rate of decline can be compared inter-patient to compare disease severity and intra-patient to evaluate the success of therapies. Notably, for pediatric patients, the necessity of growth is important to include, thus it is best to evaluate the % predicted slope for prognosis (showing sufficient recruitment of lung for growth).19 For children with pneumothorax limiting PFTs, 6-minute walk assessment can be a good surrogate for progression in the absence of other cGVHD manifestations that impair mobility. Another important means to monitor these patients include the NIH cGVHD organ grading and patient reported outcome measures such as the Lee symptom scale.9,20

PFT monitoring is especially important for patients at highest risk of BOS, including those with chronic GVHD, which doubles the incidence from 5-6% to 13%.10,21-24 Other risk factors for BOS after HCT include: preparative regimens containing busulfan, peripheral blood stem cell source, viral infections early after HCT, history of significant acute GVHD, as seen in our patient, as well as ABO incompatibility prior lung disease, and post-transplant lung disease.25-32 Published guidelines for PFT monitoring have promoted every 3 months monitoring for a year after transplant.33 However, given that the median diagnosis of new-onset BOS was 1.5 years from HCT, in a recent prospective
study, I prescribe PFTs at least every 3 months for at least the first 1-2 years, which was also recently endorsed by the NIH consensus and European expert groups.\textsuperscript{34,35} I also include PFTs at the time of chronic GVHD flare or signs of other organ progression, especially for those with risk factors for BOS present. Practitioners have reported that there are challenges to frequent PFT monitoring such as accessibility of PFT laboratories, requirements for the test, and the cross discipline collaboration required. Hand held spirometers may address these concerns, offering facile and economical means to frequently assess of FEV1. While not yet used in general practice, these devices may be used in the practitioner’s office, or even distributed for home use. These have shown sensitivity to detect FEV1 decline, which may then prompt full PFTs to potentially yield earlier, more efficient diagnosis of BOS.\textsuperscript{36}

A novel imaging modality termed parametric response mapping (PRM) may aid in the diagnosis of BOS. PRM permits spatial assessment and quantification of heterogeneity of lung parenchyma. Clinical high-resolution helical chest CTs obtained upon inspiration and expiration can be manipulated to overlay an expanded exhalation scan ‘over’ the inspiratory scan. Small voxels segment lung parenchyma informing the spatial position of airflow pathology, permitting differentiation of normal airflow, from airflow obstruction (normal inhalation and impaired exhalation), and restrictive disease (impaired inhalation and exhalation. This technique been applied to BOS patients to show impaired exhalation and differentiate areas of infection from obliterative disease.\textsuperscript{37,38} PRM may useful to monitor individuals unable to perform PFTs (e.g. young children), to potentially
diagnose patients earlier, and provide a quantitative measure of airspace disease over time.

Another important consideration is whether we could identify patients who have begun the pathological process of obliterative bronchiolitis prior to the severe decline of FEV1 below 75% predicted. An early stage has been defined in lung transplant BOS (host versus graft disease) and labeled BOS-0p, which identifies patients at higher risk to progress to BOS. In lung transplantation, 30% of these patients will progress to BOS. A similar definition has recently been evaluated in HSCT patients. BOS-0p was defined as: decline in FEV1 of >10% or midflow rate (FEF25-75) of >25% decline and not meeting BOS criteria. In HCT recipients, BOS-0p was sensitive for the development of BOS. These data suggest that not only could more frequent PFTs better identify patients at highest risk for BOS progression, but also permit early interventions in a population already suffering from allo-immune bronchiole damage. Prospective studies should test whether interventions at this point can prevent BOS altogether, potentially providing the best opportunity for averting disease.

**Case 3: Infectious disease and supportive care approaches**

Patient 3 developed BOS in the first year following haplo-identical HCT. She was referred for an intervention trial (NCT00656058) and underwent BAL as part of this work-up. Chest x-ray was normal while chest CT showed large nodules concerning for
fungus. BAL revealed: Parainfluenza III, Aspergillus, and CMV, precluding initiation of study drug. During the course of her treatment, the patient was also diagnosed with nocardia, ESBL Klebsiella, Scopulariopsis and Geosmithia/Paecilomyces—all obtained from BAL or fine needle lung aspirations. Treatment included multiple antimicrobials including posaconazole, caspofungin, miltefosine (compassionate use), imipenem, moxifloxacin, valgancyclovir, tobramycin nebulizers, and tigecycline. Unfortunately, respiratory status worsened, resulting in tracheostomy and chronic ventilation, then death. At the time of autopsy, in addition to obliterative bronchiolitis, aspergillus and CMV were evident in the lungs, despite negative BAL and blood tests.

Discussion of Case 3:

This case highlights several key supportive care issues in BOS. In our prospective study NCT00656058, patients underwent extensive evaluation for infection, including bronchoalveolar lavage (n=19). All but one patient (4%) presented without evidence of infection. Despite this, 25% of patients had infections identified through BAL, including: pseudomonas infection (n=1), mycobacteria infection (n=2), aspergillus infection (n=2), CMV pneumonitis (n=1), and nocardia (n=1). Excluding these baseline infections, a total of 45 infections were experienced in 24 patients on study, 36% bacterial (most commonly gram negative), 47% viral (most commonly influenza), 16% fungal (mostly aspergillus), and mycobacterial infection (2%). This high rate of co-infections requires vigilance on the part of the provider, as infections are a leading cause of death in these patients. 16,22,41
Investigation for fungal disease including beta-D-glucan and galactomannan in the BAL are helpful, the newer blood PCR tests for Aspergillus may have a role in these patients, and strong consideration should be given to voriconazole or posaconazole for prophylaxis with frequent assay of blood levels, especially in patients on protracted systemic steroids. The high rate of mycobacterial and nocardia infections in this patient population (21% total) deserves further consideration, and suggest that BAL should be strongly considered in patients with acute decline. This relative increase in non-tuberculous mycobacteria has been noted in lung transplant recipients and linked to BOS progression. Interestingly, other bacterial infections identified were exclusively gram-negative (pseudomonas, morexella, klebsiella, E. coli, stenotrophomonas). Both these non-tuberculosis mycobacterial infections and gram-negative bacteria may be related to colonized bronchiectasis, which is often associated with BOS. Treatment is likely critical not just to avoid progression of infection, but these infections may incite chemokines and accelerate BOS progression and death. Further, similar to patients with bronchiectasis from other causes, patients with BOS can be colonized with gram-negative organisms, and experience exacerbations similar to cystic fibrosis. I have seen benefit from inhaled aminoglycosides to constrain these organisms (typically employing a one month on and one month off approach), using spontaneous or induced sputum to follow the organism burden. In addition, early treatment with fluoroquinolones (or other sensitive anti-microbials) in the setting of sputum production and increased cough has clinically seemed beneficial for these patients. However, recommended anti-microbials for BOS patients should include prophylaxis against: pneumocystis jiroveci pneumonia (with Trimethoprim/sulfamethoxazole preferentially), Streptococcus with penicillin, and fungi
as described above. I administer IVIG for patients with IGG less than 500mg/dL, though studies have not evaluated its benefit in BOS patients. Finally, influenza can be life-threatening in BOS patients, and prompt treatment with neuraminidase inhibitors is critical at the earliest sign of disease. Immunizations may be important to protect against these lung infections when patients are sufficiently immunocompetent. Further study of the best ways to diagnose, treat, and prevent these infectious complications will be important to improve outcomes in BOS.

It is important to note that chest x-rays may not reliably show infections in BOS patients, as the trapped air can effectively conceal even larger infiltrates, as in patient 3. Furthermore, for infections such as mycobacteria and fungal disease, evaluation by CT is necessary to identify the minute nodules of mild disease. CTs can also show bronchiectasis, suspicious for gram-negative bacterial colonization.

Other supportive care considerations include opportunities to minimize further infectious exposures and inflammatory sources while optimizing remaining pulmonary function. Studies have suggested that gastroesophageal reflux disease (GERD) may be associated with BOS genesis and progression, and maximizing GERD therapies may diminish progression of BOS. Further, data in lung transplantation even support Nissen fundoplication procedures, though this has not been studied in BOS after HCT. Optimization of nutrition is important and may require supplemental nutrition while treating severe BOS. Supplemental nutrition is especially important in patients with continued weight loss. For patients who have some mild benefit by increased FEV1% by more than 12% with beta-agonists, these agents may modestly increase endurance. For these patients, I initiate a trial with albuterol and may prescribe a long-acting beta-agonist
additionally. However, albuterol can also lead to bronchomalacia if over-used (due to reduced smooth muscle tone), and I have seen this occur following misdiagnosis and days of continuous albuterol. Pulmonary rehabilitation improves exercise tolerance and quality of life.\textsuperscript{34,50} Similarly, if patients require anti-hypertensive treatment, agents other than beta-blockers or ACE-inhibitors may be better from a pulmonary perspective. Anemia should be corrected and patients with good hematopoiesis will often compensate with mildly elevated hemoglobin. Acute hypoxemia is a rare presentation of BOS, most often linked either to acute infection or methemoglobinemia (often associated with dapsone). Finally, should patients require ventilatory support, the pathophysiology of BOS is important to consider. Because these patients have significant air trapping and fixed small airway obstruction, additional positive pressure should be minimized as this will increase the risk of barotrauma and exacerbate air-trapping. Further, the settings should reflect that patients require added time for exhalation. Tracheostomy will increase the impedance to airflow. Finally, they should be carefully monitored for hypercapnea, which can lead to life-threatening apnea in the setting of oxygen administration.\textsuperscript{51}

\textbf{Case 4: Therapeutic options}

Patient 4 had received tacrolimus, mycophenylate mofetil, methotrexate, steroids, etanercept, oral budesonide, and extracorporeal photopheresis prior to onset of BOS for the treatment of acute GVHD after haploidentical BMT. PFTs performed 1 year after HCT, in the setting of weaning immunosuppression showed mild BOS with FEV\textsubscript{1} of
70% predicted and long-acting beta-agonist was started. Two months later a GVHD flare led to resumption of systemic steroids and tacrolimus and sirolimus was soon added. Six months after BOS presentation and 1.5 years after HCT, FEV1 was 45% predicted, prompting initiation of Tiotropium bromide in addition to steroids, sirolimus, tacrolimus, followed by rituximab, then soon after by radiation therapy with 1 Gy total body irradiation. At 3 years post-HCT, FEV1 had declined to 36%, with FEV1 slope of -3, despite a treatment regimen that now included mycophenylate mofetil, azithromycin, advair, tacrolimus, and he was referred for a trial of montelukast at NIH.

Discussion Case 4:

A rapid persistent decline in FEV1 despite interventions continues to be associated with high mortality.\textsuperscript{52} However, recent data suggest that survival is improving in BOS. In 2008, review of the literature suggested that survival was dismal, just 40% at 2 years and 20% at 5 years, and had been unchanged in the prior 20 years.\textsuperscript{10,21-23} However, recent survival estimates show that 2-3 year survival is 60-75% and 5 year survival of 40-50%, likely reflecting enhanced recognition and incorporation of newer therapies and better supportive care, and supported by a recent survey study of cGVHD practitioners.\textsuperscript{29,30,52,53}

Historically, protracted systemic steroids and agents that impair lymphocyte proliferation and activation (calcineurin inhibitors, azathioprine) have formed the backbone of BOS therapy. Extended systemic steroid courses are no longer recommended for BOS therapy, as this is associated with high mortality from infectious complications. In the
past 10 years, several novel options for therapy have emerged, many from studies of lung transplant BOS (*host vs. graft disease*). For the treatment of new-onset BOS after HCT, a study of inhaled fluticasone, azithromycin, and montelukast (*FAM*) with brief steroid burst (1mg/kg/day prednisone) and rapid taper has been reported (0.25mg/kg/week) Figure 4. This prospective, multi-institutional study of 36 patients showed stabilization or improvement in 94% of patients at 3 months and overall survival of 97% at 6 months. Based on these results, I initiate FAM therapy for all newly diagnosed patients in addition to continuation or resumption of classical cGVHD therapy with calcinuerin inhibitor or sirolimus. The mechanistic rationale for these agents are: inhaled steroids provide local anti-inflammatory effects, azithromycin impairs interleukin-8 production and neutrophilia, and montelukast blocks leukotriene activity, impairing cellular homing and activation and possibly blocking fibroblast proliferation and collagen deposition (figure 3). Prior studies had showed safety and some (though not all) had suggested benefit for these agents in BOS. Since this trial was initiated, a prospective randomized placebo-controlled study showed efficacy for inhaled budesonide/formoterol as well, supporting the use of inhaled steroids early in BOS therapy. In addition, there is a recent retrospective study on the use of budesonide/formoterol, montelukast and n-acetylcysteine for BOS after HCT, which showed stabilization of FEV1, though the eligibility criteria for BOS was not the consensus definition. I continue *FAM* components indefinitely as these have been nontoxic and, in many patients, permitted slow withdrawal of all other immunosuppression without decline in FEV1, and in some patients, even increases in FEV1. To date, the longest duration of FAM treatment for
BOS patients in my experience exceeds 10 years, supporting tolerability. However, the optimal length of treatment is unknown and will hopefully be addressed in future trials.

For progressive disease, extracorporeal photopheresis (ECP) has benefited patients with BOS (published cGVHD schedule), with 60% of HCT patients achieving stable disease, mirroring lung transplant data. Data suggest that ECP facilitates a milieu of transplantation tolerance, decreasing effector lymphocyte populations, enriching for regulatory lymphocytes and suppressor antigen presenting cells. One study showed benefit for BOS patients with etanercept, which inhibits the tumor necrosis factor receptor, and diminishes ensuing inflammation. While there are exciting translational data emerging for the role of B cells in BOS, to date, data has not shown efficacy for treatment with rituximab, nor have I witnessed benefit with this agent. For young patients with refractory severe BOS despite all interventions and best supportive care, who have no other active GVHD on minimal or no immunosuppression, without other end organ damage, greater than one year post-HCT without relapse, I will recommend lung transplantation.

Because of the rarity and severity of BOS after HCT, it is critically important to consider clinical trials to both better understand disease pathogenesis and identify the best therapeutic options. Currently, 13 interventional studies are listed on Clinicaltrials.gov specifically for BOS after HCT, though many have been completed (and discussed above). Studies are in development for the prevention and treatment of this disease. In addition, translational studies to identify biomarkers to predict who will develop BOS or
to identify those at high risk for progression will be invaluable. Few biomarkers have been suggested to date specifically for BOS such as serum krebs von den lungen-6 or surfactant protein D, but with the increase in trials and translational efforts, hopefully more will be forthcoming.88,89

Conclusions

While the pathogenesis of BOS remains poorly understood, progress has been made in the diagnosis and treatment of these patients. Consensus of diagnostic criteria has enabled interpretation of the risk factors, prognosis, supportive care, and comparison of treatment strategies. Prospective trials have shown efficacy and offered new therapies. Incorporation of all of these advances has improved survival. However, much remains to be done in this field to better elucidate the biology underlying BOS, identify biomarkers to predict disease, develop more effective targeted therapies, monitoring for disease progression, and perhaps, in the future, allow prevention or pre-emption of BOS after HCT entirely.

Acknowledgements

Drs. Greg Yanik, Jennifer Holter-Chakrabarty, Ronald Gress, Stephanie Lee, and Guang-Shing Cheng reviewed the manuscript. Dr. Ronald E. Gress supported the prospective trial efforts of KMW in the field of cGVHD.

This work was supported in part by the intramural research program of the National Cancer Institute.

Authorship

Contribution: KMW wrote the manuscript.
Conflict-of-interest disclosure: The author does not have any conflicts of interest.
Figure Legends:

**Figure 1a:** Representative flow volume loop of a patient with BOS (red) compared to a patient with normal exhalation (grey) (left). Spirogram representation of BOS (red) as compared to normal lung volumes (grey) and those of a patient with sclerotic GVHD (blue) or extrapulmonary restriction (right). Within the spriogram, the forced expiratory volume at 1 second (FEV1) is shown first, then the forced vital capacity (FVC) and residual volume (RV), and then the total lung capacity (TLC = RV+VC). Below the spirogram are representative PFT parameters for each of the three groups of patients: normal in grey, BOS in red, and sclerotic GVHD in blue. Reprinted with permission from Journal of American Medical Association.10

**Figure 1b:** Representative flow volume showing the notch characteristic of tracheomegaly or tracheobronchomalacia.

**Figure 2:** Graph of FEV1 (mL) versus time (days) of Patient 2 with the time of cGVHD diagnosis (dx) and clinical symptoms (cough) as well as the time of BOS diagnosis (dx) noted by arrows.

**Figure 3:** Diagram of the proposed immune mechanisms linked to BOS pathogenesis, the current treatments in BOS, and the pathways blocked by these treatments. ECP = extracorporeal photopheresis. IL-8= interleukin 8. Cytokine/chemokine = TNF alpha for etanercept and multiple activating chemokines and cytokines for ECP.
Figure 4: Summary algorithm for diagnosis, work-up, supportive care considerations, and treatment of BOS.

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**Figure 4: Algorithm for Diagnosis, work-up, and treatment of BOS**

- **Evaluate PFTs:**
  - FEV1 < 75%
  - FEV1/VC < 90% CI
  - Absent infection
  - cGVHD or
    - air trapping RV >120% or RV/TLC >90% CI
    - air trapping by expiratory CT

- **Rule out:**
  - Tracheomegaly
  - Alpha-1 antitrypsin
  - Cryptogenic organizing pneumonia

- **Work-up**
  - Inspiratory/ expiratory CT
  - Consider bronchoalveolar lavage
  - Blood cx, CMV PCR

- **Treatment**
  - FAM + Steroid pulse/rapid taper

- **Progression:**
  - ECP
  - Etanercept
  - Clinical Trials

- **Supportive care**
  - PCP ppx
  - Fungal ppx (vori or posa if systemic steroid)
  - Penicillin ppx
  - Pulmonary rehabilitation
  - Consider IVIG
  - Nutritional support
  - GERD therapy
  - for Methemoglobinemia if hypoxic
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