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Detection of Bronchiolitis Obliterans Syndrome after Pediatric Hematopoietic Stem Cell Transplantation

An Official American Thoracic Society Clinical Practice Guideline

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Abstract

Background: Many children undergo allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of malignant and nonmalignant conditions. Unfortunately, pulmonary complications occur frequently post-HSCT, with bronchiolitis obliterans syndrome (BOS) being the most common noninfectious pulmonary complication. Current international guidelines contain conflicting recommendations regarding post-HSCT surveillance for BOS, and a recent NIH workshop highlighted the need for a standardized approach to post-HSCT monitoring. As such, this guideline provides an evidence-based approach to detection of post-HSCT BOS in children.

Methods: A multinational, multidisciplinary panel of experts identified six questions regarding surveillance for, and evaluation of, post-HSCT BOS in children. A systematic review of the literature was undertaken to answer each question. The Grading of Recommendations, Assessment, Development, and Evaluation approach was used to rate the quality of evidence and the strength of recommendations.

Results: The panel members considered the strength of each recommendation and evaluated the benefits and risks of applying the intervention. In formulating the recommendations, the panel considered patient and caregiver values, the cost of care, and feasibility. Recommendations addressing the role of screening pulmonary function testing and diagnostic tests in children with suspected post-HSCT BOS were made. Following a Delphi process, new diagnostic criteria for pediatric post-HSCT BOS were also proposed.

Conclusions: This document provides an evidence-based approach to the detection of post-HSCT BOS in children while also highlighting considerations for the implementation of each recommendation. Further, the document describes important areas for future research.

Keywords: bronchiolitis obliterans syndrome; pediatrics; stem cell transplantation

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Summary of Recommendations

The American Thoracic Society recommendations, with regard to surveillance and detection of bronchiolitis obliterans syndrome (BOS) in children after allogeneic hematopoietic stem cell transplantation (HSCT), are summarized below and in Figure 1. A summary of implications of strength of recommendations for different stakeholders is shown in Table 1.

Recommendation 1. We recommend pre-HSCT spirometry, static lung volumes, and D_{LCO} for children who can perform them (strong recommendation, moderate certainty of evidence).

Recommendation 2a. We suggest active surveillance rather than testing only symptomatic patients using spirometry and, where feasible, static lung volumes and D_{LCO} beginning at 3 months post-HSCT (conditional recommendation, low certainty of evidence).

Recommendation 2b. We suggest that spirometry and, where feasible, static lung volumes and D_{LCO}, be performed every 3 months in the first year post-HSCT and every 3 to 6 months in the second year post-HSCT in patients who are not at high risk of BOS (conditional recommendation, low certainty of evidence).

Comment: More frequent testing may be indicated in those at high risk of pulmonary complications or with chronic graft versus host disease in other organs.

Recommendation 2c. For long-term follow-up in asymptomatic patients, we suggest surveillance using spirometry and, where feasible, static lung volumes and D_{LCO} every 6 months, between 2 and 3 years post-HSCT and yearly after 3 years, lasting until 10 years post-HSCT (conditional recommendation, low certainty of evidence).

Comment: In patients with ongoing symptoms, more frequent (every 3–6 mo) spirometry may be necessary until stability in lung function testing has been demonstrated.

Recommendation 3a. At centers with adequate technical expertise to perform multiple breath washout (MBW), we suggest including MBW and spirometry as part of a pre-HSCT assessment of pulmonary function, or MBW alone if spirometry is not feasible (conditional recommendation, low certainty of evidence).

Recommendation 3b. At centers with adequate technical expertise to perform MBW, we suggest the use of post-HSCT MBW as part of the diagnostic evaluation of suspected BOS, either as a complementary tool to spirometry or alone if spirometry is not feasible (conditional recommendation, very low certainty of evidence).

Recommendation 4a. We suggest performing a chest computed tomography (CT) scan, with inspiratory and expiratory views, in all children before allogeneic HSCT (conditional recommendation, low certainty of evidence).

Comment: In situations where the clinical team identifies a low risk of preexisting lung disease, it is reasonable to not perform a pre-HSCT CT scan. Additionally, a pre-HSCT CT scan does not need to be performed in patients with an ionizing radiation–sensitive condition (i.e., Fanconi anemia).

Recommendation 4b. We suggest performing a chest CT scan with inspiratory and expiratory views in all children post–allogeneic HSCT who develop obstructive lung function or in those children with clinical suspicion of BOS (conditional recommendation, low certainty of evidence).

Recommendation 5. We suggest that bronchoscopy with BAL be performed to assess for infection as part of the BOS evaluation (conditional recommendation, very low certainty of evidence).

Comment #1: If the pulmonary function testing result is unreliable because of technique, it is reasonable to repeat the test in 1–2 weeks and then only perform the bronchoscopy if the suspicion of BOS persists.

Comment #2: Where an infection has been diagnosed by means of a less invasive method (i.e., nasopharyngeal swab, sputum), it is reasonable to delay the bronchoscopy while treating the infection and/or waiting for the infection to resolve and then only perform the bronchoscopy if the clinical suspicion of BOS persists.

Recommendation 6. We suggest surgical lung biopsy in pediatric post-HSCT patients in cases where BOS is suspected but uncertainty regarding the diagnosis exists and the risks of biopsy are smaller than the risks of the uncertainty (conditional recommendation, low certainty of evidence).

Comment: Uncertainty regarding the diagnosis exists when 1) clinical evidence

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A data supplement for this document is available via the Supplements tab at the top of the online article.

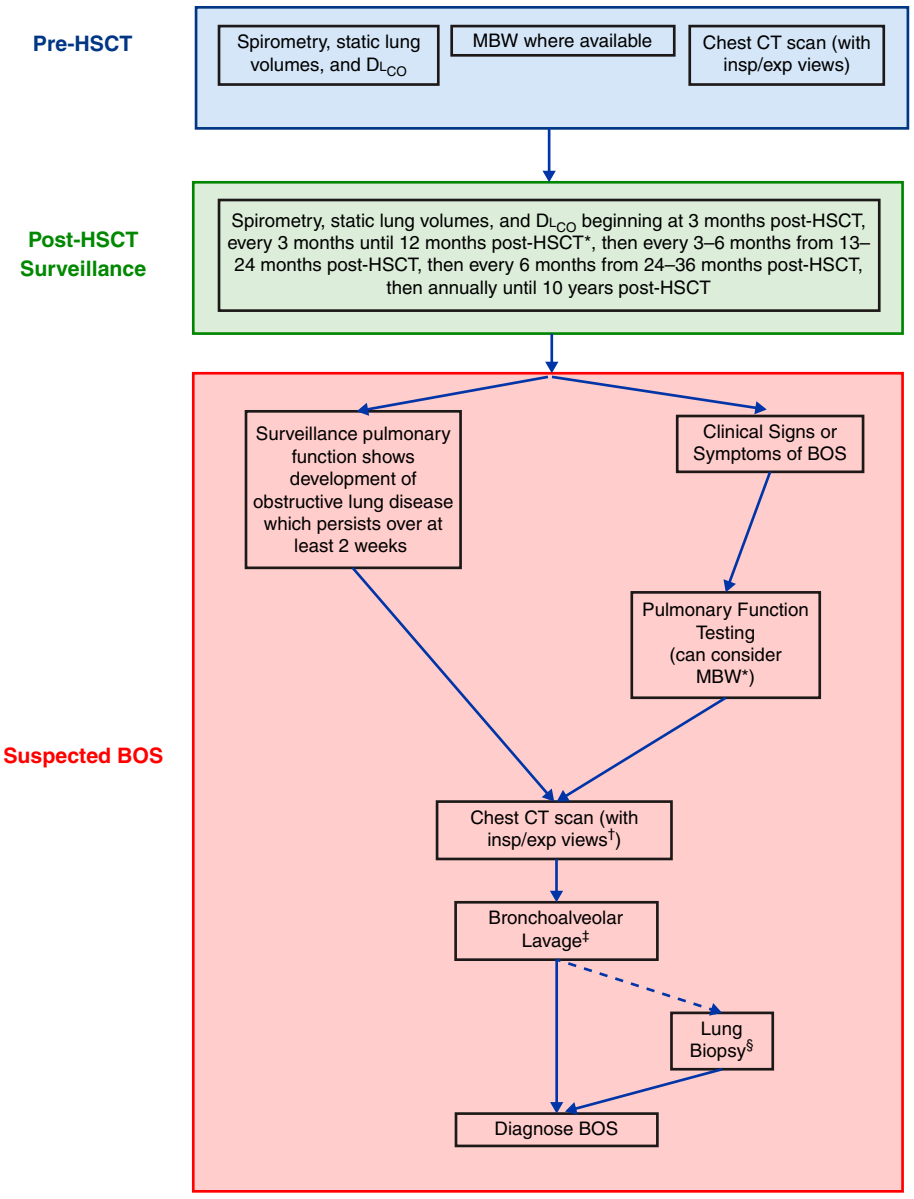

Figure 1. Surveillance and diagnosis of bronchiolitis obliterans syndrome (BOS). *Some children may be unable to complete pulmonary function testing (PFT), in which case they can be omitted. MBW can be assessed in addition to spirometry where available or as an alternate to spirometry if spirometry is not feasible (Recommendation 3B). †A computed tomography (CT) scan, with insp and exp views, is recommended for those with PFT results suggestive of BOS or if there are persistent clinical signs and symptoms of BOS with normal lung function (Recommendation 4b). ‡We suggest a BAL to assess for infection in all cases of suspected BOS, even if the CT scan is normal (Recommendation 5). If the CT scan is normal, it is reasonable to repeat PFTs 2 weeks after the CT; those with complete resolution of symptoms and lung function impairment can return to normal surveillance. If the BAL reveals infection, this should be treated, and clinical assessment should be repeated. Ongoing symptoms or signs of lung function impairment may signify BOS, and the pathway should be followed. §In cases where there is uncertainty about the BOS diagnosis or suspicion of an alternate or coexisting condition, which is based on the clinical presentation, a biopsy is suggested (Recommendation 6). HSCT = hematopoietic stem cell transplantation; insp/exp = inspiratory and expiratory; MBW = multiple breath washout.

(clinical background, CT scan, and pulmonary function testing) is discordant; 2) there is no alternate way to make the diagnosis; or 3) there is concern for an alternate and/or coexisting condition.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an established treatment for malignant as well as nonmalignant disease, the latter including hemoglobinopathies, inherited immune deficiencies, and metabolic disorders. Currently over 5,000 children undergo allogeneic HSCT each year globally, with rates increasing with time

Table 1. Implications of Strength of Recommendations to Stakeholders

Stakeholder	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the **recommended** course of action, and only a small proportion would not	The majority of individuals in this situation would want the **suggested** course of action, but many would not
Clinicians	Most individuals should receive the **recommended** course of action	Recognize that different choices will be appropriate for different patients and that you must help each patient arrive at a management decision consistent with her or his values and preferences
Policy makers	The recommendation can be adapted as policy in most situations, including for the use as performance indicators	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions

(1, 2). Although post-HSCT survival has improved, pulmonary complications are a significant contributor to morbidity and mortality, affecting 25–60% children after HSCT and causing 25–65% of nonrelapse mortality (3, 4). The current state of post-HSCT pulmonary complications in children was the focus of a recent NIH workshop, with several knowledge gaps identified, including the need for pediatric specific definitions of pulmonary complications and the need for a standardized approach to posttransplant monitoring (5). The most common noninfectious pulmonary complication after HSCT is bronchiolitis obliterans syndrome (BOS), a manifestation of lung chronic graft versus host disease (cGvHD) affecting 4.5–8.3% of children post-HSCT (6, 7). BOS can present as early as 3 months post-HSCT and is characterized by progressive obstructive lung disease, particularly affecting the peripheral airways. Given that the initial phases of BOS are often asymptomatic, surveillance with pulmonary function testing (PFT) is recommended (8–10).

The current approach for screening and diagnosis of BOS in children and adolescents poses several limitations. First, current international guidelines differ in terms of specific PFT maneuvers and frequency of testing recommended (8–10). This is reflected in clinical practice, with a recent multinational survey highlighting significant variation in care (11). Second, the current approach to screening is largely extrapolated from adult data and relies on spirometry, which risks failing to detect the early stages of BOS arising in peripheral airways. Moreover, many young children who undergo HSCT are unable to perform spirometry because of age and other factors (12). Finally, there is a lack of guidance for clinicians on how to respond to abnormal surveillance PFT results.

To address these limitations and to support both HSCT clinicians and pediatric pulmonologists, the American Thoracic Society (ATS) endorsed a multinational, multidisciplinary group of clinicians to review the current literature and make recommendations regarding surveillance and diagnosis of BOS in children post-HSCT.

Methods

This clinical practice guideline was developed in accordance with ATS policies and procedures. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (13, 14) to formulate clinical questions, identify and summarize relevant evidence, and develop recommendations for clinical practice. The co-chairs (S.S. and S.G.) submitted a proposal that was reviewed and approved by the ATS Assembly of Pediatrics, Program Review Subcommittee, and Board of Directors. A multidisciplinary panel of international specialists with expertise in pediatric HSCT, BOS, and guideline development methodology was formed. Represented disciplines included pediatric pulmonology, HSCT, oncology, immunology, radiology, surgery, pharmacy, and nursing, along with families of patients with BOS. Conflicts of interest were disclosed and managed appropriately. The committee identified six specific questions: Three addressed the role of screening PFT, and three focused on diagnostic tests in children with suspected post-HSCT BOS. The patient/intervention/comparator/outcome (PICO) format was used to formulate each question, and formal Medline searches were performed (*see* the online supplement). We included studies of infants, children, and adolescents who had undergone allogeneic HSCT. (For detailed methods, *see* the online supplement.)

Question 1: Should Pre-HSCT Screening Spirometry, Static Lung Volumes, and $D_{L_{CO}}$ Be Performed in Pediatric Patients Who Will Undergo Allogeneic HSCT?

Background. Among children who receive allogeneic HSCT, BOS is the primary lung manifestation of cGvHD and a significant source of morbidity and mortality (3, 4). Current clinical definitions of BOS are based on decline in FEV_1, requiring a baseline value to determine degree of change (15). In adult HSCT recipients, pre-HSCT impairments in FEV_1 and $D_{L_{CO}}$ are associated with post-HSCT all-cause mortality and respiratory failure (16).

Patients receiving HSCT may have a history of prior lung disease, which may be asymptomatic and undiagnosed, resulting in abnormal PFT results before transplant (17). This can range from mild asthma (the most common chronic respiratory disease of childhood) to sequelae of their primary disease process, which may include lung and/or airway injury from recurrent lower respiratory infections and/or iatrogenic injury from prior chemotherapy or radiation therapy. In adult HSCT recipients, preexisting airflow obstruction may also be a risk for post-HSCT BOS (18). For these reasons, accurate determination of lung function pre-HSCT is critical for prognosis and determining change.

Evidence Base. The systematic review that informed the committee's

recommendation is being published separately, so we summarize the salient findings here (19). The review included patients up to 25 years of age who underwent allogeneic HSCT and had pre-HSCT PFT results reported. The outcomes of interest were *1*) prevalence of pre-HSCT PFT abnormality; *2*) development of BOS; and *3*) other patient-centered outcomes, including post-HSCT pulmonary complications, ICU admissions, and mortality. A total of 30 articles were included. The definition of abnormal PFT results varied between studies, with most using a threshold of 80% of the predicted value.

Although few studies reported no pre-HSCT PFT abnormality, the majority reported a significant proportion of participants with pre-HSCT PFT impairment (see Evidence Table: PICO #1 in the online supplement). Spirometry based assessment of pulmonary function was performed in all studies. The prevalence of pre-HSCT abnormality detected was 4–41% for FEV_1 (0–13% reported severe abnormality), 10–31% for FVC, 5–20% for FEV_1/FVC, and 3–28% for forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$). Although fewer studies reported the results of pre-HSCT static lung volumes and tests of diffusion capacity, abnormalities were commonly reported with a prevalence of 9–29% for total lung capacity (TLC) and 3–100% for $D_{L_{CO}}$.

Some studies reported patterns of abnormalities, either from spirometry, static lung volumes, or both. The prevalence of a restrictive pattern ranged from 7 to 50%, that of an obstructive pattern ranged from 0 to 24%, and that of a mixed pattern ranged from 1 to 2%. In the studies that described respiratory symptoms, 90–100% of patients reported no symptoms before transplant.

Eight studies reported pretransplant PFT results in patients who later developed BOS (6, 7, 20–25). In seven studies, no association was reported between any pre-HSCT spirometry parameter (FEV_1, FEV_1/FVC, or $FEF_{25–75}$) and development of BOS (6, 7, 20–23, 25). Jung and colleagues reported that the extent of drop in FEV_1 from pre-HSCT baseline to that at the time of diagnosis of BOS was not associated with mortality (21). Three studies examined outcomes other than BOS. One found no association between pre-HSCT PFT results and subsequent development of any late-onset noninfectious pulmonary complication (23). Another found no association between pre-HSCT PFT results and post-HSCT obstructive lung disease with a poor prognosis (22). Finally, Srinivasan and colleagues reported that each unit decrease in pre-HSCT $FEF_{25–75}$ was associated with a threefold increased risk of developing post-HSCT pulmonary complications (26).

Five studies examined pre-HSCT PFT results in relationship to patient-centered outcomes. Pre-HSCT FEV_1 and FEV_1/FVC were associated with respiratory failure leading to mechanical ventilation (27). Several pre-HSCT PFT parameters are associated with poorer post-HSCT survival, specifically, FEV_1 (26, 28), FVC (26), TLC (26), residual volume (26), $D_{L_{CO}}$ (including after adjustment of alveolar volume) (29, 30), and restrictive lung disease (26).

Certainty of Evidence. The panel's confidence in the accuracy of the evidence regarding pre-HSCT PFT was moderate. The wide variation in the prevalence of abnormalities across studies reduced the panel's confidence.

Benefits. Pre-HSCT PFT provides a baseline for measuring the drop in lung function posttransplant. This is important because of the wide prevalence of pretransplant PFT abnormalities, most of which were among asymptomatic patients. Awareness of pretransplant PFT abnormalities may reduce unnecessary tests after transplant because, if pre-HSCT baseline values are unknown, then a clinician must assume that any post-HSCT abnormality is new and investigate further with tests such as a chest CT scan and BAL. In addition, pretransplant PFT abnormalities may be predictive of posttransplant mortality and pulmonary complications. The identification of previously undiagnosed conditions such as asthma permits therapeutic interventions, and the identification of PFT abnormalities may affect pre-HSCT preparation, including the selection of conditioning regimen agents and intensity.

Harms. PFT are noninvasive and generally painless tests. Compared with the aggregate time and monetary costs of HSCT, those of pretransplant PFT are negligible. Testing may require an additional clinic or hospital visit, but often these can be obtained on the same day as other evaluations. The potential for identifying unknown lung disease, inability to successfully complete testing, as well as falsely abnormal results could cause parental or patient anxiety. Families are prepared for multiple pre-HSCT evaluations, however, and are aware of the risk of post-HSCT pulmonary complications, so they generally are not opposed to completing testing.

Other Considerations. As HSCT is performed in highly resourced settings, access to PFT should not be an issue. In a recent multinational survey, all respondents had access to these tests (11).

Recommendation 1. We recommend pre-HSCT spirometry, static lung volumes, and $D_{L_{CO}}$ for children who can perform them (strong recommendation, moderate certainty of evidence).

Justification. The panel concluded that clear evidence exists showing high rates of pre-HSCT PFT abnormalities among children being scheduled for HSCT. History of respiratory symptoms alone is not a predictor of PFT abnormality and cannot be used to identify which children need pre-HSCT PFT. Pre-HSCT PFT data are essential to appropriately interpret post-HSCT PFT data. In the panel's opinion, most families would not see the pre-HSCT PFT as an added inconvenience and would value its role in the post HSCT screening for BOS.

Subgroup Considerations. Younger children or those with developmental delay may be unable to perform some or all the maneuvers required for PFT. Therefore, pre-HSCT results may be less robust or useful in this subset of patients. Children awaiting HSCT may be moderately to severely ill, and PFT results may be affected and not representative of the patient's true baseline when healthy. If the patient has a time-limited illness, such as a viral respiratory infection, testing should be delayed until recovered, if possible, but this must be balanced with the urgency of moving forward with HSCT. A small portion of patients requiring HSCT may have thoracic abnormalities, and normative data may not be available. For these patients, pretransplant PFT still have value to monitor for changes over time.

Implementation. Having a technologist who is experienced in pediatric PFT will help ensure the best results. As many as 20–30% of children may be unable to successfully complete spirometry on the first attempt (31). It is important to make sure that the results obtained are representative of the patient's best effort and are technically acceptable. If the baseline spirometry results are suggestive of obstruction,

postbronchodilator testing should be considered on a case-by-case basis.

It is important to use the most appropriate reference normative dataset for the interpretation of PFT, and for pediatrics, that is the Global Lung Initiative (GLI). Further, as per a recent ATS statement, race-specific normative equations should not be used (32). Because absolute and predicted PFT values change as children grow older, spirometry measurements must be evaluated using the percent predicted values at the time of measurement. It may be difficult for children to perform a battery of tests. If only one PFT maneuver can be performed before transplant, spirometry is the single test most supported by literature.

Where pre-HSCT pulmonary function impairment is identified, an evaluation to identify the cause should be undertaken, with treatment as appropriate. This may necessitate the involvement of pediatric pulmonology and further investigation; however, this should not be an issue, given previous work demonstrating that HSCT centers have access to these resources (11). The pre-HSCT PFT result should then serve as the baseline for interpretation of posttransplant change.

Areas for Future Research. Priority areas for future research include further characterization of the associations between pre-HSCT PFT impairment and outcomes, especially among different subgroups. Investigation of altering or customizing pre-transplant conditioning regimens based on pre-HSCT PFT results is another area where data are needed. Continued efforts to develop alternate PFT techniques that are easier to perform for younger children and/or those with developmental delay will allow these children to benefit from pre-HSCT assessment of respiratory function.

Question 2: Should Routine Surveillance Spirometry Be Performed Post–allogeneic HSCT in Pediatric Patients?

Background. The early phases of BOS and other pulmonary complications of HSCT are often asymptomatic. Therefore, surveillance PFT has been proposed to allow earlier detection and treatment. Although highly effective therapies are not yet available for post-HSCT BOS, it is hoped that early intervention may help arrest decline in lung function and lead to improved outcomes (33, 34). Although all current pediatric guidelines recommend PFT surveillance, the recommended frequency ranges from every 3 months to annually in the first year post-HSCT, and individual guidelines each recommend different combinations of tests (8–10). As a result, there is a need to determine the optimal frequency and which tests to use for post-HSCT surveillance in children.

Evidence Base. The systematic review that the committee used to inform their recommendation is being published separately (19), with only salient findings summarized here. The review identified 21 articles that addressed this question. Of these, 11 studies reported populations in which surveillance occurred, and 10 studies reported outcomes when no surveillance was performed.

The 11 articles that included routine surveillance PFT pre- and post-HSCT included institutions in the United States, Canada, Europe, and South Korea, spanning a timeframe from the mid-1980s to the present. PFT consisted of spirometry, measurement of static lung volumes, and D_{LCO} in 9 of the 11 studies, with the rest focusing solely on spirometry. All studies used pretransplant PFT results as the baseline. Frequency of testing posttransplant ranged from at least one test within Months 1–6 post-HSCT in the oldest study (35) to scheduled testing every 3 months (27, 36). Three studies followed pulmonary function through 24 months post-HSCT, and two reported annual PFT beyond the first year. Together, these 11 studies highlight several important insights into post-HSCT pulmonary complications. Most of the studies reported a median time to diagnosis of 6–12 months. Two studies reported that surveillance PFT identified asymptomatic children with BOS (7, 20). Mean percent predicted FEV_1 ranged from 37.8 to 84.4% (21, 22) at the time of diagnosis by surveillance PFT. PFT abnormalities were more common in children with cGvHD elsewhere.

Ten articles were published between 1994 and 2021 that involved participants who did not have surveillance PFT in the first 12 months post-HSCT and then were either tested at symptom onset or at some point thereafter. Most of the studies report a median time to BOS diagnosis of 6–24 months. The mean percent predicted FEV_1 at diagnosis was between 44 and 57% (24, 37), with one study reporting a mean FEV_1 z-score of -3.62 (38). Several studies also highlight that pulmonary function can continue to be impaired and decline for many years post-HSCT (39–41). For example, L'excellent and colleagues reported continued decline in lung function in 16 patients between 5 and 10 years post-HSCT, including in asymptomatic patients (41).

Certainty of Evidence. The panel's confidence in the accuracy of the evidence for this question was low, as all relevant studies were retrospective in nature, with a lack of data on critical outcomes such as hospitalization and mortality, and variation in the definition of BOS across studies.

Benefits. The primary benefit of surveillance lung function is earlier detection of pulmonary complications, including BOS. Surveillance was associated with a median time to detection of 6–12 months, whereas testing of symptomatic children resulted in a median time to detection of 6–24 months. Furthermore, in two studies, a small number of children with BOS who were asymptomatic were identified by means of surveillance PFT (7, 20). The benefits of using a comprehensive panel of PFT that includes spirometry, static lung volumes, and D_{LCO} are highlighted by Kaya and colleagues, demonstrating that TLC and D_{LCO} were the best predictors of BOS severity as measured by the development of respiratory failure (27).

Harms. Potential harms include anxiety for children and families regarding testing and test results and added burden to families generated by additional appointments for PFT. However, given the frequency of hospital visits and screening tests performed for other post-HSCT complications, these harms are viewed as being relatively small. Additional potential harms may result from subsequent testing and treatments that follow false-positive test results.

Other Considerations. The panel felt that, relative to the cost of HSCT and especially post-HSCT BOS, the cost of surveillance PFT was minimal.

Recommendation 2a. We suggest active surveillance rather than testing only symptomatic patients using spirometry and, where feasible, static lung volumes and D_{LCO} beginning at 3 months post-HSCT (conditional recommendation, low certainty of evidence).

Recommendation 2b. We suggest that spirometry and, where feasible, static lung volumes and D_{LCO}, be performed every 3 months in the first year post-HSCT and every 3 to 6 months in the second year post-HSCT in patients who are not at high risk of BOS (conditional recommendation, low certainty of evidence; Table 2).

Table 2. Recommended Frequency of PFT Testing in Children Post-HSCT

Months Post-HSCT	Recommended PFT Frequency
0–12 mo	Every 3 mo
13–24 mo	Every 3–6 mo
25–36 mo	Every 6 mo
⩾37 mo	Every 12 mo

Definition of abbreviations: HSCT = hematopoietic stem cell transplantation; PFT = pulmonary function testing.

Comment: More frequent testing may be indicated in those at high risk of pulmonary complications or with cGvHD in other organs.

Recommendation 2c. For long-term follow-up in asymptomatic patients, we suggest surveillance using spirometry and, where feasible, static lung volumes and $D_{L_{CO}}$ every 6 months between 2 and 3 years post-HSCT, and yearly after 3 years, lasting until 10 years post-HSCT (conditional recommendation, low certainty of evidence).

Comment: In patients with ongoing symptoms, more frequent (every 3–6 mo) spirometry may be necessary until stability in lung function testing has been demonstrated.

Justification. The panel concluded that the available literature supported the use of surveillance PFT, albeit with a low certainty of evidence. The recommendation to begin testing at 3 months post-HSCT and continue at tests that occur every 3 months for the first year is based on data showing that this is the most likely time when BOS is detected (22, 35, 36). As BOS can arise in the second year post-HSCT, testing at intervals of 3 to 6 months is recommended. It should be noted that the suggested testing frequency is based on the consensus expert opinion of the panel, as there is a lack of evidence to support an optimal frequency. Given BOS is more common in children with cGvHD in other organs, the panel concluded that it was reasonable to consider more frequent testing in these children but that the frequency of testing should be determined by the treating team on a case-by-case basis. Beyond 2 years post-HSCT the need for ongoing monitoring of PFT is supported by data showing that pulmonary complications and pulmonary function deficits still occur. Given that pulmonary function decline is more common in those with cGvHD or a history of pulmonary complications, increased frequency of testing can be considered in these cases (39, 41).

Subgroup Considerations. A major limitation of post-HSCT PFT surveillance is the inability of many children to complete the testing. This includes most children under 6 years of age (42), children with developmental delay, and those who are too unwell to perform the test. For this population, other modalities such as MBW (discussed in Question 3) may be an alternative. Some children may be able to perform spirometry with serial or repeated testing. Hence, an inability to perform PFT on first attempt should not preclude further attempts.

Implementation. The panel identified that implementation challenges may include creating appropriate working relationships between HSCT and pulmonology teams to ensure that PFT laboratories have the appropriate capacity to perform the tests and that the tests are appropriately reported and used to inform clinical management. As in Question 1, the panel supported the use of the non–race-based GLI reference dataset. Another challenge for implementation is when an abnormal result on surveillance testing should trigger further diagnostic evaluation (e.g., CT scan, bronchoscopy). The expert opinion of the panel was that any pulmonary function impairment should be persistent for at least 2 weeks before further testing should be pursued. In cases where there is significant acute decline and/or the clinical team decided that it would be unsafe to wait 2 weeks to undertake further evaluation, it is very reasonable to pursue further investigation earlier.

Areas for Future Research. Most studies identified for this question were single-center retrospective studies. There is a need for large, multicenter prospective studies that can assess the impact of different surveillance strategies on relevant outcomes. Within these studies, it would be ideal to identify high-risk patients who would benefit from higher frequency surveillance and low-risk patients who could have less frequent surveillance.

Question 3: In Pediatric Patients Who Have Had Allogeneic HSCT, Should the Routine Surveillance of Lung Function Be Conducted Using Spirometry or a Combination of MBW and Spirometry?

Background. MBW is a pulmonary function test with two main advantages compared with conventional PFT for the detection of BOS postpediatric HSCT. First, as an effort-independent test performed during tidal breathing, MBW is easier for the patient than spirometry, potentially extending down to infants (43–45). Second, when compared with spirometry, MBW is more sensitive to changes in the peripheral airways (46, 47), which is where BOS develops (48, 49). The lung clearance index (LCI) is the primary outcome measure generated using MBW (46), and normative reference equations have been published (50, 51). Theoretically, MBW may be able to provide superior feasibility and sensitivity compared with spirometry-based screening. However, it is unclear whether there are sufficient data to support its use in clinical practice.

Evidence Base. From the search that was performed for Questions 1–3, five studies were included for this question. Additional abstracts on this topic and one scoping review were acknowledged by the review team, but these were not formally used in the evidence synthesis (52–56). Of the five included studies, four were cross-sectional using nitrogen as a tracer gas (25, 57–59), and one was a longitudinal design using sulfur hexaflouride (12). One included study looked at adult survivors of pediatric cancer, of whom only a fraction had undergone HSCT (25).

Overall, the feasibility of MBW was very good. MBW and spirometry were compared in one study in which MBW was attempted and successful in all children ($n = 26$; 100%) in contrast to spirometry, which was attempted by 22 participants (not attempted in 4 children under 6 yr) and successful in 17 (77%) (59). Two additional studies (57, 58) reported 91% and 89% success in performing MBW studies, respectively, but spirometry success was not reported, and one study did not include preschoolers (58). Preschool-age children were included in the two remaining studies (12, 25), but feasibility was not reported.

Baseline (i.e., pre-HSCT) MBW data were described in only one small study, with almost half (48%; $n = 11/23$) of the participants showing an abnormal LCI at baseline (12). As a comparison, within this cohort, baseline FEV_1 and $D_{L_{CO}}$ were abnormal in 13% and 70%, respectively.

The prevalence of abnormal MBW indices post-HSCT varies between studies. In the two cross-sectional studies where this was reported, LCI was abnormal in 34% and 46% of post-HSCT patients (57, 59). Alternate MBW outcomes, including ventilation

inhomogeneity in the acinar lung zone and in the conductive airway zone, were only assessed in the study by Uhlving and colleagues (57) and were abnormal in 25% and 52% of participants, respectively. Additional data from adult studies (60, 61) and unpublished abstract data (52, 54) that were not formally included in this review also showed variable but significant proportions of people after HSCT with abnormal MBW indices.

Sensitivity and specificity were reported in two papers. In a cross-sectional study of 26 children assessed 90 days to 5 years after HSCT, Rayment and colleagues reported a significantly higher median LCI in those with a clinical history consistent with BOS compared with those without (59). The investigators also reported that an LCI threshold of ⩾9.0 provided the highest sensitivity (100%) and specificity (90%) for the correct categorization of BOS, with a threshold LCI of 7.1 (published upper limit of normal), resulting in a sensitivity of 100% and a specificity of 70%. In their longitudinal study of 28 children, Uhlving and colleagues reported similar results using the published upper limit of normal as a threshold, with sensitivity of 100% and specificity of 54% at the time of BOS diagnosis (12). Across other studies not formally included in this review, abnormal MBW indices among subjects with BOS was a consistent finding (52–55, 60, 61).

Longitudinal pediatric data have been described in only one included study by Uhlving and colleagues, which followed 28 children (6 of whom developed bronchiolitis obliterans [BO] or BOS) for 1 year after HSCT (12). When all participants were analyzed, there was no significant change in median LCI post-HSCT. There was no association between either the pre-HSCT LCI, or the 3 months post-HSCT LCI, and the development of BOS (odds ratio [OR], 5.1; 95% confidence interval [CI] = 0.5–56.9). All of the participants with BOS had elevated post-HSCT LCI, but of note in the 4 participants with pre-HSCT LCI results reported, two had baseline abnormality. The trajectory of LCI in the BOS population was not reported in this study. Data published in abstract form suggest that the longitudinal trajectory of MBW may be predictive of pulmonary cGvHD, but these data have not been confirmed in peer-reviewed articles (53, 54).

Certainty of Evidence. The panel concluded that the certainty of the evidence is low. The included studies were small, single-center studies with risk of selection bias. Additionally, different testing methods were used, and different thresholds for abnormal were applied.

Benefits. These data support the hypothesis that that the primary benefit of MBW is increased feasibility compared with spirometry, allowing a greater proportion of children to have pulmonary function surveillance. Although MBW may be believed to be more sensitive to detect early BOS, data to support this are less clear.

Harms. The panel identified three potential risks. First, clinicians should consider the additional time needed to perform the tests, especially in older children who can perform spirometry in whom the additional benefit of MBW is unclear. Second, there is a risk that centers naive to the technique may try to implement it without adequate expertise, which could result in incorrect or uninterpretable results. This is a particular risk if clinicians begin to base assessments on MBW results alone, which is not recommended in this guideline. Finally, because the specificity of LCI is unknown in this context, it is possible that false-positive results could induce more invasive testing, potentially resulting in patient discomfort or harm.

Other Considerations. The panel identified that that the availability of MBW, both in terms of equipment and expertise with regard to performing and interpreting the test, was a primary consideration. Technical ATS consensus recommendations have been published, which can aid centers in ensuring that testing is conducted with appropriate quality control (62, 63).

Recommendation 3a. At centers with adequate technical expertise to perform MBW, we suggest including MBW and spirometry as part of a pre-HSCT assessment of pulmonary function or using MBW alone if spirometry is not feasible (conditional recommendation, low certainty of evidence).

Recommendation 3b. At centers with adequate technical expertise to perform MBW, we suggest the use of post-HSCT MBW as part of the diagnostic evaluation of suspected BOS, either as a complementary tool to spirometry or alone if spirometry is not feasible (conditional recommendation, very low certainty of evidence).

Justification. The panel based their recommendations on the available evidence, risks, and benefits. The greatest potential benefit is in children in whom spirometry is not feasible. Further, the panel concluded that it was important to emphasize the recommendations that MBW should only be implemented at sites with adequate technical expertise to perform the test reliably. Finally, MBW should be regarded as an adjunct test, and we do not suggest making or excluding diagnoses exclusively on the basis of its results.

Implementation. As already discussed, the primary consideration is the availability of MBW equipment and expertise. The panel recommends centers seeking to develop this capacity to follow published guidelines on MBW in children (62, 63).

Areas for Future Research. Further research is needed to determine how MBW should be implemented into the clinical care of this vulnerable population. Specific questions should focus on the population in which MBW should be performed routinely, the frequency with which screening should be performed, and the role of MBW in monitoring disease progression or response to therapy.

Question 4: Should Pediatric Patients Post–allogeneic HSCT Who Have Abnormal Surveillance Lung Function Assessment Be Investigated with a Chest CT Scan?

Background. Further investigations are needed to confirm or rule out the diagnosis in children post-HSCT with a suspicion of BOS that is based on either surveillance PFT or clinical signs and symptoms. Criteria for the diagnosis of BOS in adults highlight the role of chest CT scans in looking for expiratory air trapping (a feature of BOS) as well as evaluating for alternate diagnoses (e.g., infection) (15). The role of CT scans in the evaluation of suspected post-HSCT BOS in children is less clear.

Evidence Base. We identified 14 relevant articles, 12 of which described findings in patients with known or suspected BOS and two evaluating the utility of chest CT scans before HSCT.

A study of 137 pediatric patients demonstrated that chest CT abnormalities were highly prevalent pre-HSCT (55%) and frequently considered clinically significant (13%) (64). A study of 390 predominantly adult patients who underwent both a chest CT scan and PFT before HSCT found that a normal chest CT was significantly associated with normal PFT (OR, 2.47; 95% CI = 1.22–4.97; $P = 0.012$) (65).

Most studies show that post-HSCT CT scans correlate with PFT results. Specifically, air trapping (66), low mean lung density

(67, 68), and the percentage of lung with low attenuation (38) all correlate with obstructive PFT results characteristic of BOS. Other chest CT abnormalities, such as bronchial dilatation and bronchial wall thickening, did not correlate with PFT results (25, 37, 38, 66, 69). One study of 34 children and adults compared CT and lung biopsy results and found no significant difference between the proportion of patients with air trapping or mosaic attenuation in the group with BOS compared with the group without BOS (55% vs. 78.6%; $P = 0.28$) (70). This paper did not describe CT technique, and the authors comment in the Discussion section that CT protocols had evolved over the study period, making systematic evaluation difficult. There were no studies evaluating CT results and morbidity or mortality.

Certainty of Evidence. The panel concluded that the certainty of evidence is very low because of the studies predominantly being small and in single centers, the lack of assessment of patient-related outcomes, and the variability in CT technique used.

Benefits. The panel felt that a chest CT scan is a noninvasive, accessible way to assess the entire lung parenchyma in patients in whom BOS is suspected. Moreover, chest CT can assess for other pathologies in addition to assessing for BOS. Evidence shows that chest CT measures of air trapping correlate well with other markers of BOS. It is important to note that chest CT may offer the only method to diagnose BOS in patients who cannot perform PFT.

Harms. CT results in radiation exposure to patients. Judicious use of diagnostic radiation is particularly important in pediatric patients and should always adhere to the "as low as reasonably achievable" principle (71). Some younger children may require general anesthesia (GA) for a chest CT scan. Patients frequently undergo other procedures that require GA, such as a bone marrow aspirate, central line placement, or BAL. Ideally, such procedures could occur under the same GA, minimizing additional risk.

Other Considerations. In general, parents, patients, and clinicians are accepting of the chest CT scan, as it can be reasonably expected to provide useful new information. Although CT is universally available at HSCT centers, expiratory CT images are necessary to fully evaluate air trapping, and this necessitates additional technical expertise in image acquisition as well as additional radiation exposure to children.

Recommendation 4a. We suggest performing a chest CT scan, with inspiratory and expiratory views, in all children before allogeneic HSCT (conditional recommendation, low certainty of evidence).

Comment: In situations where the clinical team identifies a low risk of preexisting lung disease, it is reasonable to not perform a pre-HSCT CT scan. Additionally, a pre-HSCT CT scan does not need to be performed in patients with an ionizing radiation–sensitive condition (i.e., Fanconi anemia).

Recommendation 4b. We suggest performing a chest CT scan with inspiratory and expiratory views, in all children post–allogeneic HSCT who develop obstructive lung function or in those children with clinical suspicion of BOS (conditional recommendation, low certainty of evidence).

Justification. The potential benefits of CT, including assessment of lung parenchyma with a relatively inexpensive, noninvasive test, outweigh the risks associated with radiation. Risks of chest CT are reduced with current protocols using lower radiation doses and, where necessary, coordinating chest CT with other procedures requiring GA. Before HSCT, a chest CT can lead to a change in management and provide a baseline that may be useful for comparison with subsequent CT scans. For those who cannot complete PFT, a normal pre-HSCT CT scan provides an assessment of baseline pulmonary status. Among the panel, there was debate regarding whether a pre-HSCT chest CT scan was required for all children or whether it could be omitted for those at low risk of premorbid lung disease. Some panel members concluded that low-risk patients could be identified, whereas others concluded that the signs and symptoms of pulmonary disease in children can be nonspecific and highly prevalent. As a result, the comment was added to Recommendation 4a to support clinical teams who assess their patient as low risk. In cases of suspected BOS post-HSCT, a chest CT provides additional information to PFT. Because findings on a chest CT scan can be nonspecific, results are best interpreted in conjunction with clinical findings and PFT data (when available). Additionally, there was debate regarding whether a CT scan should be performed after one abnormal PFT result or whether PFT abnormality should be present on repeated testing. Where there is a possible alternate explanation for the PFT abnormality (i.e., intercurrent viral infection, concern regarding patient technique), the panel thought it was reasonable to repeat PFT, at a time interval determined by the clinical team but at least 2 weeks, and only proceed with chest CT if the PFT impairment persists.

Subgroup Considerations. Young patients who are unable to comply with breath-holding instructions are likely to need GA for chest CT. In cases of suspected BOS after HSCT, CT with GA is indicated, given that alternatives include empiric treatment or more invasive tests, such as lung biopsy. However, scheduling a chest CT should ideally be coordinated with other procedures under GA. Further, patients with ionizing radiation–sensitive conditions (i.e., Fanconi anemia) may undergo HSCT; however, they are at risk of iatrogenic harm from CT scans. Clinicians must take this into account when caring for these patients and avoid ionizing radiation where possible.

Implementation. A primary concern of the panel was that CT scans are performed with the appropriate technique. The technique used in the included papers was variable between, and even within, studies (70). The optimal technique for CT scans to assess BOS is debatable. The panel concluded that the best technique was a volumetric acquisition of the entire chest in both inspiration and expiration (detailed in Table 3). Last, when scans need to be performed with GA, it is important to have close collaboration between radiology and anesthesia teams to minimize derecruitment artifact.

Areas for Future Research. Future research priorities include further studies of the role and optimal technique for quantitative CT in children. There are preliminary data regarding the use of quantitative assessment of CT images (38, 67, 68, 72); however, these techniques have not been validated. There may be a role for magnetic resonance imaging in BOS evaluation in the future (73), which would be especially beneficial for children with ionizing radiation–sensitive conditions, although current use is limited by several factors, including cost, availability, and the need for GA.

Question 5: Should Pediatric Patients Post–allogeneic HSCT Who Have Abnormal Surveillance Lung Function Assessment Be Investigated with a BAL/Bronchoscopy?

Background. The adult-focused NIH consensus criteria for BOS suggests that

Table 3. Recommendations for Chest CT in Children Undergoing HSCT

Recommendations for Optimal CT Technique
• Volumetric imaging of the entire chest on both inspiration and expiration is preferred
• Proactive patient preparation before the CT, ideally with experienced pediatric CT technologists and child life specialists (where available) to optimize results
• Lowest possible radiation dose that still results appropriate quality images
• Strategies to reduce the radiation dose include:
○ Suspending the automatic exposure control function on the CT scanner (which provides optimal imagine of the soft tissue, which is not needed in the evaluation of BOS, and increases radiation dose), instead applying a specific tube voltage (in kilovolts) and current (in milliamperes) according to patient size
○ A low radiation dose (approximately one third of that required for the inspiratory film) is needed to detect air trapping on the expiratory film.
○ Using this approach, the overall dose is approximately 0.5 mSv, which is equivalent to 2 mo of background radiation in the USA (NCRP 160), although it will vary depending on the CT scanner and patient size
• Decisions about CT technique at individual institutions need to factor in local resources, including the capabilities of available CT scanner(s), availability of pediatric anesthetic support, and experience of the CT technologists and interpreting radiologist(s)
Additional Considerations for Scans under General Anesthesia
• In many centers, general anesthesia is required for those younger than 5 yr old to achieve inspiratory and expiratory images, as well as those who are unable to comply with breath-holding instructions
• The addition of intravenous contrast may affect younger patients' ability to comply with breathing instructions) because of discomfort
• Communication between radiology and anesthesia technologists before the procedure is important
• Aim for optimal alveolar recruitment for inspiratory phase of scan
• Assess for significant atelectasis before the scan with scout film and two or three selected axial images obtained in the mid- to lower lung zones after recruitment maneuvers
• Atelectasis can be reduced with further recruitment maneuvers
• In a small number of cases, optimal recruitment may require the prone position

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CT = computed tomography; HSCT = hematopoietic stem cell transplantation; NCRP 160 = National Council on Radiation Protection and Measurements Report 160.

evaluation for BOS includes demonstrating an absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, including microbiologic cultures (15). Infectious complications in children post-HSCT have a high mortality, and diagnosis leads to changes in treatment, with effects on morbidity and overall survival. There is a lack of consensus on the best method to assess infection in the lower respiratory tract. Traditionally, flexible bronchoscopy with BAL is commonly used to investigate pulmonary infiltrates post–allogeneic HSCT, but its role in the evaluation of BOS is unclear.

Evidence Base. No studies describe a decline in lung function or evaluation of BOS as the indication for bronchoscopy with BAL post-HSCT. However, there are six pediatric studies (74–79) and seven studies with mixed pediatric and adult patient populations (80–86) that are relevant to the role of bronchoscopy with BAL in the pediatric HSCT population (summarized in Table 4). These are all retrospective single-center studies that report results of bronchoscopy with BAL performed to evaluate infiltrates on imaging or the presence of respiratory symptoms. Including only the pediatric studies, most data are from the 1990s or earlier. These six studies capture the full pediatric age range from infancy to 20 years of age. Bronchoscopy with BAL occurred from less than 1 month to 4 years after transplant. Therefore, some of the studies include data from bronchoscopy with BAL before the possible development of BOS. There is a wide range in yields (31–68%) of bronchoscopy with BAL reported in these studies, predominantly relating to pathogen infection; however, the identification of other pathologies such as diffuse alveolar hemorrhage is also described.

Among the additional studies of mixed pediatric and adult populations, the range in yield from bronchoscopy with BAL was 42–66%. These studies are also retrospective, single-center studies in which the indications for bronchoscopy with BAL were respiratory symptoms or imaging findings. Again, neither lung function decline nor evaluation for BOS was included as an indication for bronchoscopy with BAL.

An additional paper by Yanik and colleagues (87) is directly relevant to the role of bronchoscopy with BAL in the evaluation for BOS. The study involved 34 post-HSCT subjects, ages 8–65 years, with PFT impairment who were treated with etanercept. A total of 57 subjects were initially evaluated for study participation and underwent pretreatment bronchoscopy with BAL. Of these, 20 had positive BAL findings (12 with fungus, 5 with gram-negative bacteria, 2 with mycobacteria, and 1 with both fungus and mycobacteria). None had any signs or symptoms of infection. After antimicrobial therapy, 3 subjects died within 2 months, whereas 12 had further progression of their PFT abnormalities, and 5 subjects showed improvement in their PFT. This study demonstrates that asymptomatic infection, including fungal infection, can occur in this population. However, despite treatment of infection, the majority will continue to have PFT decline, demonstrating the coexistence of infection with BOS.

There are data from adult studies suggesting that the timing of bronchoscopy with BAL may be associated with yield. Shannon and colleagues reviewed adult patients who underwent bronchoscopy with BAL for new infiltrates within 100 days post-HSCT (88). The yield from bronchoscopy with BAL from 598 BALs in 501 patients was 55%. This yield was 2.5 times higher when bronchoscopy with BAL was performed in the first 4 days after the initial evaluation and 75% when performed within 24 hours. These data suggest that the timing of bronchoscopy with BAL will also be important in pediatric HSCT patients undergoing evaluation for BOS.

Table 4. Summary of Evidence regarding BAL in Post-HSCT Patients

Study	Study Period	Ages	Total No. of Subjects	# BAL	Timing of BAL	BAL Yield (%)
Pediatric-only studies						
Armenian *et al.*, 2007 (74)	1995–2003	7.9 yr (mean)	32	32	19 < 30 d; 50 < 100 d	**50**
Ben-Ari *et al.*, 2001 (75)	1995–1999	40 d–271 mo	63	86	89 d (1–1,460 d)	**31**
Eikenberry *et al.*, 2005 (78)	1995–1999	0.2–20.8 yr	90	>90	N/A	**43** post–100 d
Kasow *et al.*, 2007 (76)	1990–2002	0.8–23.5 yr	89	89	68 d (6–528 d for allo)	**67.9**
McCubbin *et al.*, 1992 (77)	1985–1990	1.7–17.6 yr	27	29	Median, 60 d (11–1,026 d)	**52**
Qualter *et al.*, 2014 (79)	?	2.3–14.9 yr	65	101	Median, 95 d	**40**
Mixed adult–pediatric studies						
Cordonnier *et al.*, 1985 (85)	1981–1983	8–45 yr	36	52	7 < 15 d; median, 67 d (9–713)	**50 or 52**
Feinstein *et al.*, 2001 (81)	1997–1999	18–59 yr	61	76	N/A	42.1
Glazer *et al.*, 1998 (84)	1991–1995	10 mo–56 yr	62	79	Median, 40 d (10 d–1.5 yr)	**67**
Hoffmeister *et al.*, 2006 (83)	1994–2004	14–67 yr	78	91	?	**49**
Kim *et al.*, 2015 (86)	2009–2012	17–78 yr	187 (80 for HSCT)	206	N/A	**65**
Stover *et al.*, 1984 (82)	1982–1984?	15–77 yr	97 (18 for HSCT)	97	N/A	**66**
Tang *et al.*, 2018 (80)	2013–2016	11–64 yr	130	149	176 d (17–1,480 d)	**58**

Definition of abbreviations: HSCT = hematopoietic stem cell transplantation; N/A = not applicable.
Bold value indicates the percentage of BAL that identified a pathogen.

There are few data on the sensitivity and specificity of findings from bronchoscopy with BAL in this population. This would require concordance between BAL findings and biopsy or autopsy results, and few studies include large enough groups of patients with pathology findings. One small pediatric study describes pathology and bronchoscopy with BAL results in 14 of 27 patients (77). In this study, the yield from bronchoscopy with BAL was 52%. The sensitivity of bronchoscopy with BAL was 75% (two false-negative BALs), and specificity was 100% (no false-positive BALs).

Certainty of Evidence. The certainty of evidence to support the role of bronchoscopy with BAL in the evaluation of BOS is very low. All studies offer indirect evidence that bronchoscopy with BAL can be useful in identifying infection in pediatric HSCT patients with symptoms or infiltrates. In this population, the yield from bronchoscopy with BAL can be high with a wide range. Additionally, reported yields from bronchoscopy with BAL may be limited because of the timing of the procedure post-HSCT, the use of empiric antimicrobials, and limitations of microbiologic testing. Many of the included studies predate the use of PCR testing to identify microbial pathogens. Moreover, a common pathogen reported in several studies is cytomegalovirus, for which HSCT patients now receive antiviral prophylaxis. There are no studies that describe bronchoscopy with BAL as part of the evaluation of BOS in children, and none of the reviewed studies describe BOS outcomes in their study populations other than 3 patients in two studies.

Benefits. Most diagnoses made by bronchoscopy with BAL are infection related, frequently leading to a change in clinical management. In addition, occult infection can occur in asymptomatic patients with PFT changes being evaluated for BOS, supporting the use of bronchoscopy with BAL to identify infection in this population (87).

Harms. Potential harm associated with a recommendation to perform bronchoscopy with BAL in this population is the potential for increased anxiety among patients and their family members who are confronting an additional invasive procedure and need for sedation. There is also the potential harm from a possible delay in diagnosing and treating BOS caused by organizing and performing a bronchoscopy with BAL and then awaiting results and possibly initiating antimicrobial therapy, although there are no data to support this possibility. In addition, there is the risk of complications associated with bronchoscopy with BAL. Most of the studies included in this review describe only minor or transient complications. A single pediatric study describes an instance of pulmonary hemorrhage after bronchoscopy with BAL with resultant respiratory failure (74), and additional studies describe very small numbers of patients who experience respiratory distress, failure, or arrest (a total of 7 patients) (76, 77). In these cases, the complications were not felt to be directly attributable to bronchoscopy, and similar complications may have occurred after more invasive procedures such as lung biopsy. A study of 42 pediatric and adult patients with thrombocytopenia after HSCT reported a 12% complication rate with bronchoscopy with BAL (89). All complications were minor and self-limited, except one (severe life-threatening epistaxis). An additional pediatric study evaluated the safety of bronchoscopy with BAL in HSCT patients compared with patients with pneumonia (90). The HSCT group experienced a complication rate of 66.7%, compared with 22.5% in the pneumonia group. Complications in the HSCT group included mucosal bleeding (12) and transient fever (6), hypoxemia (5), tracheospasm (4), epistaxis (3), and respiratory depression (3). There were no cases of pneumothorax, intubation, mechanical ventilation, or death after bronchoscopy with BAL.

Other Considerations. Resources and cost of bronchoscopy with BAL were not evaluated. A recommendation to perform bronchoscopy with BAL is equitable, as most centers that perform HSCT have access to specialists who can perform the test (11).

Recommendation 5. We suggest that bronchoscopy with BAL be performed to assess for infection as part of the BOS

evaluation (conditional recommendation, very low certainty of evidence).

Comment #1: If the PFT result is unreliable because of the technique, it is reasonable to repeat the test in 1–2 weeks and then only perform the bronchoscopy if the suspicion of BOS persists.

Comment #2: Where an infection has been diagnosed by means of a less invasive method (i.e., nasopharyngeal swab, sputum), it is reasonable to delay the bronchoscopy while treating the infection and/or waiting for the infection to resolve and then only perform the bronchoscopy if the clinical suspicion of BOS persists.

Justification. The justification for the recommendation is summarized in Table 5. Several studies in both children and mixed populations of children and adults show a relatively high yield of BAL, mainly in diagnosing infection. In addition, several studies suggest that the risk of bronchoscopy with BAL is limited with mainly minor and transient complications. The study by Yanik and colleagues reveals that occult infection can occur post-HSCT in patients with PFT impairment and that infection and BOS can coexist (87). Therefore, this paper supports the evaluation of infection in a population undergoing evaluation for BOS regardless of symptoms.

Implementation. Existing data suggest that bronchoscopy with BAL is readily available at HSCT centers (11). The panel was concerned about the ability to organize bronchoscopy with BAL in a timely manner, especially given the association of higher yield with earlier BAL in studies in adults (88).

Research Priorities. Because of the paucity of direct evidence, we also recommend that investigators report data that will expand our knowledge in this area. An area of research priority is the number of patients who fail to meet NIH criteria for BOS due to infection on the basis of results of bronchoscopy with BAL. In addition, patient outcomes after antimicrobial therapy is of high importance.

Question 6: In Allogeneic HSCT Pediatric Patients with Suspected BO, Should Lung Biopsy Be Used to Diagnose BO?

Background. The 2014 NIH Consensus Conference provided an update for histopathologic diagnostic criteria for organs affected by cGvHD (91). The document stated specific pathologic criteria for cGvHD, with constrictive bronchiolitis obliterans (CBO) as the pulmonary correlate in the lung. CBO is defined by dense eosinophilic scarring beneath the respiratory epithelium, resulting in luminal narrowing or complete fibrous obliteration. This may be preceded by lymphocytic bronchiolitis (LB). The pathology causes pulmonary dysfunction in the form of irreversible obstructive airway disease, air trapping, and decreased diffusion capacity, along with symptoms such as progressive shortness of breath and cough. The document further states that open lung biopsy may be considered if the characteristic PFT and CT findings of BOS are not accompanied by a distinctive clinical manifestation or if alternative diagnoses are being evaluated (including infection). However, biopsy can be problematic. There are risks associated with a surgical procedure in this vulnerable population. A lung biopsy captures only one moment and can miss findings that become clearer with disease progression. Additionally, lung biopsy results may be unclear if prior immunosuppression has been used or if multiple processes co-occur. The location, quality, and processing of the sample may complicate findings as well.

Evidence Base. We screened 1,846 abstracts. Of these, 26 full-text articles were selected for final analysis for the current question. A review of the published literature yielded six articles that described biopsy in pediatric patients after allogeneic HSCT. Seven other studies were reviewed for supportive evidence, one was reviewed for safety, and one was reviewed for cost. No studies directly address PICO Question 6; most of the studies included were evaluations of the select few who had lung biopsies performed and had clinical data collected retrospectively. We considered studies that had mixed populations (adult and pediatric patients) as well as those that included biopsies performed for other indications besides BOS.

The six studies that described biopsy in pediatric patients post–allogeneic HSCT were descriptive studies of cohorts of patients who had lung biopsy or lung pathology available, with a retrospective collection of patient characteristics that could be associated with the occurrence of BO. All six studies were published in the past 15 years. Some of the studies attempted to correlate the NIH clinical criteria for BOS with the pathologic diagnosis of BO. One study

Table 5. Role of Bronchoscopy with BAL in the Evaluation of Suspected Post-HSCT BOS in Children

Clinical Scenario	Recommendation	Justification
Asymptomatic, PFT decline, CT with infiltrate	Bronchoscopy with BAL	Yield and safety of BAL in investigating infection
Asymptomatic, PFT decline, CT suggests BOS	Bronchoscopy with BAL	Patients presenting with features of BOS can have occult infection and may improve with treatment of infection
Asymptomatic, PFT decline, unrevealing CT	Repeat PFT (1–2 wk) Bronchoscopy with BAL if PFT decline persists	Patients presenting with features of BOS can have occult infection and may improve with treatment of infection
Symptomatic, persistent PFT decline	Bronchoscopy with BAL	Yield and safety of BAL in investigating infection
Unable to complete PFT AND symptoms OR CT suggestive of infection or BOS	Bronchoscopy with BAL	Yield and safety of BAL in investigating infection

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CT = computed tomography; PFT = pulmonary function testing.

correlating PFT and biopsy data evaluated the fulfillment of the modified NIH criteria for BOS at time of biopsy and found that only 11 out of 21 (52%) patients with BO had fulfilled the modified NIH criteria (70). Additionally, Holbro and colleagues reported that 6 out of 25 (24%) cases of biopsy-proven BO had simultaneous evidence of infection on biopsy (92). This suggests that if BO is suspected but clinical criteria are not met, a biopsy could be useful to confirm BO or obtain an alternative and/or coexisting diagnosis. Holbro and colleagues also evaluated histology patterns and the outcome of patients with BOS and found that 7 out of 10 patients with CBO met NIH criteria, whereas 3 out of 9 patients with LB met the criteria (92). Pulmonary function was better over the follow-up period in the LB group compared with the CBO cohort. Considering that LB could be a precursor to CBO, the results suggest that early detection and treatment might be beneficial. A third study from Denmark looked at 13 pediatric patients with confirmed BO, 9 of whom completed pulmonary function testing (93). None of the 9 patients met the complete NIH clinical criteria for BOS.

Certainty of Evidence. The studies included provide an indirect answer to the PICO question. Most of the studies included were studies of select patients who underwent lung biopsies (for suspected BOS or other pulmonary complications) and had clinical data evaluated and correlated retrospectively. This may contribute to only capturing patients with more severe BOS, as more mild cases may not have led to biopsy. In addition, the included studies used differing definitions of BOS. This contributes to a very low certainty of evidence.

Benefits. All of the studies were retrospective, reviewing patients who underwent lung biopsy and were found to have BO or an alternative diagnosis. One study showed a better prognosis with LB (92). Moreover, earlier diagnosis of BO permits earlier initiation of therapy. Biopsy can also help determine alternative or coexisting diagnoses in patients in whom BO is suspected because of declining lung function. In discussion, panel members also highlighted that biopsy results—in particular, the presence of active inflammation versus fibrosis without inflammation—may inform the use of immune suppression. Although data to support this approach leading to improved patient outcomes are not available, panel members still felt that it was relevant, given the potential harms of immune suppression.

Harms. There is a higher risk of complications from biopsy compared with diagnosis by means of clinical, CT, and PFT. In a systematic review that included adults, a biopsy demonstrated a fourfold increased risk of death as compared with bronchoscopy with BAL (94). In addition, there is increased morbidity and length of hospitalization (including need for chest tube, recovery, and pain control) postoperatively immediately after surgical lung biopsy (95). The consideration for surgery naturally leads to anxiety among the patient and family members, especially in an individual whose lung function might already be compromised. Last, as noted in one study, there is a much higher cost burden for patients who undergo lung biopsy (96). It should be noted these data are confounded by current clinical practice where only the most unwell patients tend to have a lung biopsy.

Other Considerations. Patients and families may value having a firm diagnosis (and resultant ability to tailor treatment with potentially improved outcomes), and this must be weighed against the risks of the procedure, especially if other NIH consensus criteria are met. Most pediatric centers have access to a pediatric surgeon with expertise in surgical lung biopsy (11). The panel also discussed the different methods for performing lung biopsy, including open surgical biopsy, video-assisted thoracopic biopsy, and transbronchial biopsy by means of bronchoscopy. The panel strongly felt transbronchial biopsy was inappropriate. The decision regarding video-assisted thoracopic biopsy versus open surgical biopsy is more dependent on specific characteristics of each case, and a decision should be based on multidisciplinary input. In general, the approach that maximizes the chance of obtaining appropriate tissue for diagnostic evaluation, although minimizing morbidity, should be chosen.

Recommendation 6. We suggest surgical lung biopsy in pediatric post-HSCT patients where BOS is suspected, but uncertainty regarding the diagnosis exists and the risks of biopsy are smaller than the risks of the uncertainty (conditional recommendation, low certainty of evidence).

Comment: Uncertainty regarding the diagnosis exists when: 1) clinical evidence (clinical background, CT scan, and pulmonary function testing) is discordant, 2) there is no alternate way to make the diagnosis, and 3) there is concern for an alternate/coexisting condition.

Justification. A diagnosis of BOS can be made without a lung biopsy in some cases, but retrospective case series highlight cases of biopsy-proven BO that do not meet the criteria for BOS on the basis of other tests (6, 70, 92, 93, 97, 98). As such, there are situations in which clinicians may suspect BOS or an alternate pathology, and a biopsy is the only way to make a firm diagnosis. In this situation, clinicians must weigh the harms and benefits of biopsy, as opposed to managing the patient empirically without a biopsy. The benefits and harms of biopsy are detailed earlier. The potential harms of empiric management include not using a potentially beneficial treatment, iatrogenic harm from unhelpful treatments, and lack of clarity regarding prognosis.

Implementation. Access to a surgical lung biopsy should not be an issue, on the basis of previous reports (11). There is a need for expertise in processing of surgical lung biopsy specimens and pathologist expertise in biopsy interpretation. This may not be as widely available and may need centers to collaborate with centers of expertise (as is done in other areas, such as childhood interstitial lung disease).

Research Priorities. Data to date are limited to a small number of patients. There are ethical and size challenges when considering evaluation of the benefits of biopsy in a randomized prospective trial. A multicenter or even international prospective registry of lung biopsy post–childhood HSCT with standardized metadata collection may represent the most pragmatic way to generate data regarding the utility of biopsy in this setting. Further, novel imaging techniques or diagnostic biomarkers may obviate the need for lung biopsy in the future.

Proposed Criteria for Diagnosis of BOS Post–pediatric HSCT

During review of the available evidence, the panel identified that the current criteria for diagnosis of post-HSCT BOS in children have several limitations, which include a reliance on spirometry, use of outdated PFT reference equations, use of a fixed FEV_1 threshold, requirement for the absence of infection, and omission of tests such as MBW. Further, as described in PICO 6, many children with biopsy-proven BO do not fulfill the current criteria for diagnosis. The panel has described these limitations in detail in a separate publication (99).

Table 6. New Proposed Criteria for the Diagnosis of Pediatric Post-HSCT BOS

In children who can perform spirometry (GLI to be used at the reference equation for spirometry and plethysmography)
- Relative decline of FEV_1 percent predicted, compared to pre-HSCT baseline, by 15% which persists on two tests at least 2 wk apart

AND
- Supporting features (two or more of the following)
  - FEV_1/VC below lower limit of normal
  - Evidence of air trapping on expiratory CT
  - Evidence of air trapping on plethysmography (residual volume or residual volume/total lung capacity elevated above the upper limit of normal)
  - Lung clearance index >8.0
  - cGvHD (active or past history) in another organ

AND
- Persistence of suspicion of BOS after directed treatment or expected resolution of any identified infection. Assessment of infection should include investigations directed by clinical symptoms, such as chest radiographs, CT scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral testing, sputum culture, BAL)

In children who cannot perform spirometry
- Clinical symptoms (e.g., wheeze, shortness of breath with activity)

AND
- Two or more of the following
  - Evidence of air trapping on expiratory CT
  - Lung clearance index >8.0
  - cGvHD (active or past history) in another organ

AND
- Persistence of suspicion of BOS after directed treatment or expected resolution of any identified infection. Assessment of infection should include investigations directed by clinical symptoms, such as chest radiographs, computed tomography (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral testing, sputum culture, BAL)

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CT = computed tomographic; cGvHD = chronic graft versus host disease; CT = computed tomography; GLI = Global Lung Initiative; HSCT = hematopoietic stem cell transplantation.

As a result, the panel utilized a modified Delphi process to develop new criteria for diagnosis of post-HSCT BOS in children. (For further detail, *see* the online supplement.) *A priori*, consensus was defined as >70% participation in voting and >70% agreement. Two sets of criteria were developed: one for children who can perform spirometry and one for those who cannot. Initially, a small working group developed a first draft of criteria; then the entire panel provided feedback on the draft criteria. The criteria were then iteratively revised until consensus was achieved. The final criteria are shown in Table 6, with 100% consensus regarding the criteria for children who can perform spirometry and 94.7% of panel members agreeing with the criteria for children who cannot perform spirometry.

Limitations and Future Directions

Despite the large number of children undergoing allogeneic HSCT each year, we were only able to make one strong recommendation, and most recommendations were weak or conditional using the GRADE methodology to assess available evidence. This reflects the published evidence in this field, which consists predominantly of retrospective, single-center studies. Given the prevalence and significant morbidity and mortality associated with post-HSCT BOS, there is a need for better evidence to inform clinical practice. Multicenter prospective, and. possibly. international clinical trials that assess different surveillance techniques and their ability to detect BOS earlier would be the ideal. These prospective studies should use GLI race-neutral reference datasets for PFT interpretation, which would overcome another limitation of the current evidence—the use of variable reference datasets. These prospective studies can also assess the performance of the newly proposed criteria for BOS and likely lead to improvements in these criteria.

The published literature highlight that even when "gold-standard" screening with traditional PFT and/or MBW is used, significant pulmonary function impairment will have occurred at the time BOS is detected. To diagnose BOS at earlier stages, one option would be to use the current tests with much more regular frequency (i.e., weekly). This approach has been used in adult patients performing home spirometry (100, 101), but data suggest that this is less feasible in children (59). Another approach is to identify pathobiology-based biomarkers of BOS, which detect BOS before pulmonary function impairment. Such studies could utilize excess BAL fluid, collected at the time of clinically indicated procedures, to study soluble and cellular inflammatory mediators of BOS as both potential diagnostic biomarkers and therapeutic targets.

Another limitation of the current evidence and the recommendations in this guideline is that they take a "one-size-fits-all" approach to surveillance for BOS. In reality, children undergoing HSCT represent a heterogenous group in terms of indication for HSCT, pre-HSCT respiratory morbidity, age, developmental stage, and post-HSCT

course, all of which alter individual risk of BOS and ability to complete screening and diagnostic assessments. Ideally, children would have a personalized surveillance plan, on the basis of their risk profile, which optimizes the ability to detect BOS while minimizing burden and risk.

This guideline has not addressed optimal treatment and support for children with BOS. Additional pulmonary complications associated with significant morbidity and mortality are also not addressed. This limitation stems from the rigor of the GRADE methodology that requires, per ATS policies, a focus limited to six key questions.

Conclusion

BOS is the most common noninfectious pulmonary complication post-HSCT and can have devastating impact on children and families including prolonged hospital admissions, reduced quality of life, need for supplemental oxygen, and death. This clinical practice guideline, developed by an international and multidisciplinary committee will aid HSCT and pulmonology teams in the surveillance and diagnosis of BOS in the post-HSCT pediatric population. This is a crucial first step in addressing the current poor outcomes associated with post-HSCT BOS. Future work should aim to define BOS incidence using the surveillance strategy outlined, and improve BOS surveillance focusing on multicenter studies to develop strategies for earlier detection and a personalized approach to screening.

Editor's Note: The ATS Quality Improvement and Implementation Committee reviewed the guideline and determined that Recommendation 1 is potentially suitable for performance measure development. ■

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