AMERICAN THORACIC SOCIETY DOCUMENTS

Detection of Bronchiolitis Obliterans Syndrome Following Pediatric Hematopoietic Stem Cell Transplantation

An Official American Thoracic Society Clinical Practice Guideline

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

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ABSTRACT

Background: Many children undergo allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of malignant and non-malignant conditions. Unfortunately, pulmonary complications occur frequently post-HSCT, with bronchiolitis obliterans syndrome (BOS) being the most common non-infectious pulmonary complication. Current international guidelines contain conflicting recommendations regarding post-HSCT surveillance for BOS, and a recent National Institutes of Health 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. 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.

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

Keywords: bronchiolitis obliterans syndrome; pediatrics; stem cell transplantation

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

CONTENTS

SUMMARY OF RECOMMENDATIONS

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

The ATS recommendations, with regards to surveillance and detection of bronchiolitis obliterans syndrome (BOS) in children following 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 diffusing capacity of the lungs for carbon monoxide (DL_{CO}) 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 DL_{CO} beginning at 3 months post-HSCT (conditional recommendation, low certainty of evidence).

Recommendation 2b. We suggest spirometry and where feasible static lung volumes and DL_{CO}, 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 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 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 DL_{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).

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Comment: In patients with ongoing symptoms, more frequent (3-6 monthly) 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 prior to allogeneic HSCT (conditional recommendation, low certainty of evidence).

Comment: In situations where the clinical team identifies a low risk of pre-existing 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).

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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

Comment #1: If PFT result is unreliable due to 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 via a less invasive method (i.e., nasopharyngeal swab, sputum), it is reasonable to delay the bronchoscopy while treating the infection/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 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: A) clinical evidence (clinical background/CT scan/pulmonary function testing) is discordant; B) there is no alternate way to make the diagnosis; C) there is concern for an alternate/co-existing condition.

INTRODUCTION

HSCT is an established treatment for malignant as well as non-malignant disease, the latter including hemoglobinopathies, inherited immune deficiencies, and metabolic disorders. Currently over 5000 children undergo allogeneic HSCT each year globally, with rates increasing with time (1, 2). While post-HSCT survival has improved, pulmonary complications are a significant contributor to morbidity and mortality, affecting 25% to 60% children following HSCT and causing 25% to 65% of non-relapse mortality (3, 4). The

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current state of post-HSCT pulmonary complications in children was the focus of a recent National Institutes of Health (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 post transplant monitoring (5). The most common non-infectious pulmonary complication following HSCT is BOS, a manifestation of lung chronic graft vs. host disease (cGvHD) affecting 4.5-8.3% of children post-HSCT (6, 7). BOS can present as early as three months post-HSCT and is characterized by progressive obstructive lung disease, particularly affecting the peripheral airways. Given the initial phases of BOS are often asymptomatic, surveillance with pulmonary function testing (PFT) is recommended (8, 9, 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, 9, 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 undergoing HSCT are unable to perform spirometry due to 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.

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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, hematopoietic stem cell transplantation, 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 addressing the role of screening PFT and three focusing 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. Detailed methods are included in the online supplement.

Question 1: Should pre-HSCT screening spirometry, static lung volumes, and DL_{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 forced expiratory volume in one second (FEV_1), requiring a baseline value to determine degree of change (15). In adult HSCT

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recipients, pre-HSCT impairments in FEV_1 and DL_{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 prior to 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/airway injury from recurrent lower respiratory infections and/or iatrogenic injury from prior chemo- or radiation therapy. In adult HSCT recipients, pre-existing 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 which informed the committee's recommendation is being published separately and so we summarize the salient findings (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, intensive care 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.

While few studies reported no pre-HSCT PFT abnormality, the majority reported a significant proportion of participants with pre-HSCT PFT impairment (Supplement, Evidence Table, PICO 1). 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%

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reported severe abnormality), 10-31% for forced vital capacity (FVC), 5-20% for FEV_1/FVC, and 3-28% for forced expiratory flow at 25–75% of FVC (FEF25-75%). While 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 DL_{CO}.

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

Eight studies reported pre-transplant PFT results in those who later developed BOS (6, 7, 20, 21, 22, 23, 24, 25). In seven studies, no association was reported between any pre-HSCT spirometry parameter (FEV_1, FEV_1/FVC, or FEF25-75%) and development of BOS (6, 7, 20, 21, 22, 23, 25). Jung et al., 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 non-infectious 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 et al., reported that each unit decrease in pre-HSCT FEF25–75% 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

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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), DL_{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 post-transplant. This is important because of the wide prevalence of pre-transplant PFT abnormalities, most of which were among asymptomatic patients. Awareness of pre-transplant PFT abnormalities may reduce unnecessary tests after transplant since, if pre-HSCT baseline values are unknown, then a clinician must assume any post-HSCT abnormality is new and investigate further with tests such as chest CT scan and BAL. In addition, pre-transplant PFT abnormalities may be predictive of post-transplant mortality and pulmonary complications. 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 non-invasive and generally painless tests. Compared to the aggregate time and monetary costs of HSCT, those of pre-transplant 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.

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Families are prepared for multiple pre-HSCT evaluations, however, and are aware of the risk of post-HSCT pulmonary complications, so 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 DL_{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

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requiring HSCT may have thoracic abnormalities and normative data may not be available. For these patients, pre-transplant 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 results obtained are representative of the patient's best effort and are technically acceptable. If the baseline spirometry results are suggestive of obstruction, post-bronchodilator testing should be considered on a case-by-case basis.

It is important to use the most appropriate reference normative dataset for 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 of 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 done prior to 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 HSCT centers have access to these resources (11). The pre-HSCT PFT result should then serve as the baseline for interpretation of post-transplant change.

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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). While 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, 9, 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.

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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 diffusing capacity in 9 of the 11 studies, with the rest focusing solely on spirometry. All studies used pre-transplant PFT results as the baseline. Frequency of testing post-transplant ranged from at least one test within months 1 to 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 2 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 37.8-84.4% (21, 22) at time of diagnosis by surveillance PFT. PFT abnormalities were more common in children with cGvHD elsewhere.

Ten articles were published between 1994 and 2021, involving 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 – 57% (24, 37), with one study reporting a mean FEV_1 z score of -3.62 (38). Several studies also highlight pulmonary function can continue to be impaired and decline for many years post-HSCT (39, 40, 41). For example, L'Excellent et al., reported continued decline in lung function in 16 patients between 5 and 10 years post-HSCT, including in asymptomatic patients (41).

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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, a lack of data on critical outcomes including 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 there were a small number of children with BOS identified via surveillance PFT who were asymptomatic (7, 20). The benefits of using a comprehensive panel of PFT including spirometry, static lung volumes, and DL_{CO} are highlighted by Kaya et al., demonstrating that TLC and DL_{CO} 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.

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

Recommendation 2b: We suggest spirometry and where feasible static lung volumes and DL_{CO}, 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 not at high risk of BOS (conditional recommendation, low certainty of evidence; Table 2).
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 DL_{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 (3-6 monthly) 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 three months post-HSCT and continue at three monthly intervals for the first year is based on data showing this is the most likely time that BOS is detected (22, 35, 36). As BOS can arise in the second year post-HSCT, testing at 3- to6-monthly intervals 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

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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 like MBW (discussed in question 3) may be an alternative. Some children may be able to perform spirometry with serial/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 appropriate capacity to perform the tests, 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 (such as CT scan, bronchoscopy etc). 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 it

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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, multi-center 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 done using spirometry or a combination of MBW and spirometry?

Background: MBW is a pulmonary function test with two main advantages compared to conventional PFT for the detection of BOS post pediatric-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, 44, 45). Second, when compared to 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 than spirometry-based screening. However, it is unclear if 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. There are additional abstracts on this topic and one scoping review that were acknowledged by the review team, but these were not formally used in the evidence synthesis (52, 53, 54, 55, 56). Of the five included studies, four were cross-sectional using N_2

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as a tracer gas (25, 57, 58, 59) and one was a longitudinal design using SF_6 (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 where 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 years) 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 aged 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 DL_{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 S_{acin} and S_{cond} were only assessed in the study by Uhlving et al., (57) and were abnormal in 25% and 52% of participants respectively. Additional data from adult studies (60, 61) and unpublished abstract data (52, 54) not formally included in this review also showed variable, but significant proportions of people after HSCT with abnormal MBW indices.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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 et al., reported a significantly higher median LCI in those with a clinical history consistent with BOS compared to 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 specificity of 70%. In their longitudinal study of 28 children, Uhlving et al., 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 BOS subjects was a consistent finding (52, 53, 54, 55, 60, 61).

Longitudinal pediatric data have been described in only one included study by Uhlving et al., which followed 28 children (6 of whom developed BO or BOS) for one 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 (OR 5.1; 95% CI 0.5-56.9). All of the participants with BOS had elevated post-HSCT LCI, but of note in the four 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).

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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 to spirometry, allowing a greater proportion of children to have pulmonary function surveillance. While 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 naïve 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, since 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 in terms of performing and interpreting the test, was a primary consideration. Technical ATS consensus recommendations have been published, which can aid centers in ensuring testing is done with appropriate quality control (62, 63).

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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 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 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 based on 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

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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 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 to look for expiratory air trapping (a feature of BOS) as well as evaluating for alternate diagnoses (such as infection) (15). The role of CT scans in 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 prior to 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 prior to HSCT found that a normal chest CT was significantly associated with normal PFT (OR 2.46, p 0.012) (65).

Most studies show that post-HSCT CT scans correlate with pulmonary function test 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

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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 to 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 the certainty of evidence is very low due to the studies predominantly being small and single center, the lack of assessment of patient related outcomes, and variability in CT technique used.

Benefits: The panel felt that a chest CT scan is a non-invasive, 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. Importantly, 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 bronchoalveolar lavage. Ideally, such procedures could occur under the same GA, minimizing additional risk.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

Other Considerations: In general, parents, patients and clinicians are accepting of chest CT scan as it can be reasonably expected to provide useful new information. While 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 prior to allogeneic HSCT (conditional recommendation, low certainty of evidence).

Comment: In situations where the clinical team identifies a low risk of pre-existing 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 bronchiolitis obliterans syndrome (conditional recommendation, low certainty of evidence).

Justification: The potential benefits of CT, including assessment of lung parenchyma with a relatively inexpensive, non-invasive test outweighs 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. Prior to HSCT, chest CT can lead to 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-

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

HSCT CT scan provides an assessment of baseline pulmonary status. Amongst 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 pre-morbid 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 non-specific 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, chest CT provides additional information to PFT. Since findings on a chest CT scan can be non-specific, 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 following HSCT, CT with GA is indicated given that alternatives include empiric treatment or more invasive tests such as lung biopsy. However, scheduling of 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 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.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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). Lastly, when scans need to be performed with GA, it is important to have close collaboration between radiology and anesthesia to minimize derecruitment artefact.

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 are not 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 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 after 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 following allogeneic HSCT, but its role in the evaluation of BOS is unclear.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

Evidence Base: No studies describe a decline in lung function or evaluation of BOS as the indication for bronchoscopy with BAL following HSCT. However, there are six pediatric studies (74, 75, 76, 77, 78, 79) and seven studies with mixed pediatric and adult patient populations (80, 81, 82, 83, 84, 85, 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 is from the 1990s or earlier. These six studies capture the full pediatric age range from infancy to age 20 years. Bronchoscopy with BAL occurred from <1 month to 4 years after transplant. Therefore, some of the studies include data from bronchoscopy with BAL prior to 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 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 are included as indications for bronchoscopy with BAL.

An additional paper by Yanik et al., (87) is directly relevant to the role of bronchoscopy with BAL in the evaluation for BOS. The study involved 34 post-HSCT subjects, aged 8-65 years, with PFT impairment who were treated with etanercept. A total of 57 subjects were initially

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

evaluated for study participation and underwent pre-treatment bronchoscopy with BAL. Of these, 20 had positive BAL findings (13 with fungus, 5 with gram negative bacteria, 3 with mycobacteria). None had any signs or symptoms of infection. Following antimicrobial therapy, three subjects died within two months, while 12 had further progression of their PFT abnormalities, and five subjects had 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 et al., 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 if bronchoscopy with BAL was performed in the first 4 days following initial evaluation and 75% if within 24 hours. These data suggest the timing of bronchoscopy with BAL will also be important in pediatric HSCT patents undergoing evaluation for BOS.

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).

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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 due to the timing of the procedure post-HSCT, the use of empiric antimicrobials, and limitations of microbiologic testing. Many of the included studies pre-date the use of polymerase chain reaction 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 three patients in two studies.

Benefit: Most diagnoses made by bronchoscopy with BAL are infection-related, frequently leading to 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, though there are no data to support this possibility. In addition, there is the risk of complications associated with bronchoscopy with BAL. Most of

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

the studies included in this review describe only minor or transient complications. A single pediatric study describes an instance of pulmonary hemorrhage following bronchoscopy with BAL with resultant respiratory failure (74), and additional studies describe very small numbers of patients who experience respiratory distress, failure, or arrest (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 following more invasive procedures such as lung biopsy. A study of 42 pediatric and adult patients with thrombocytopenia following 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 to patients with pneumonia (90). The HSCT group experienced a complication rate of 66.7% compared to 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 following 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 bronchoscopy with BAL be performed to assess for infection as part of the BOS evaluation (conditional recommendation, very low certainty of evidence).

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

Comment #1: If PFT result is unreliable due to 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 via a less invasive method (i.e., nasopharyngeal swab, sputum), it is reasonable to delay the bronchoscopy while treating the infection/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 et al., reveals that occult infection can occur following 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 suggests that bronchoscopy with BAL is readily available at HSCT centers (11). The panel were 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: Due to 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

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

based on results of bronchoscopy with BAL. In addition, patient outcomes following 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 GvHD (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 airways 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 1846 abstracts. Of these, 26 full text articles were selected for final analysis for the current question. Review of the published literature yielded 6 articles that described biopsy in pediatric patients following allogeneic HSCT. Seven other studies were reviewed for supportive evidence, 1 for safety, 1 for cost. No studies directly address

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

PICO question 6; most of the studies included were evaluation 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 6 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 6 studies were published in the last 15 years. Some of the studies attempted to correlate the NIH clinical criteria for BOS with the pathologic diagnosis of BO. One study 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 et al., reported that 6/25 (24%) of 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/co-existing diagnosis. Holbro et al., also evaluated histology patterns and the outcome of patients with BOS and found that 7 out of 10 patients with CBO met NIH criteria, while 3 out of 9 patients with LB met criteria (92). Pulmonary function was better over the follow-up period in the LB group compared to the CBO cohort. Considering that LB could be a precursor to CBO, the results may 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.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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/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, included studies use 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 co-existing diagnoses, in patients in whom BO is suspected due to declining lung function. In discussion panel members also highlighted that biopsy results, and in particular the presence of active inflammation vs. fibrosis without inflammation, may inform the use of immune suppression. While data to support this approach leading to improved patient outcomes is not available, panel members still felt it was relevant given the potential harms of immune suppression.

Harms: There is a higher risk of complications from biopsy compared with diagnosis via clinical/CT scan/pulmonary function testing. In a systematic review that included adults, biopsy demonstrated a four-fold increased risk of death as compared to bronchoscopy with BAL (94). In addition, there is increased morbidity and length of hospitalization (including need for chest tube, recovery, and pain control) post-operatively immediately following surgical lung biopsy (95). The consideration for surgery naturally leads to anxiety amongst the patient and family members, especially in an individual whose lung function might already be compromised. Lastly, as noted in one study, there is a much higher cost burden for

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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 thorascopic (VATS) biopsy, and transbronchial biopsy via bronchoscopy. The panel strongly felt transbronchial biopsy was inappropriate. The decision regarding VATS vs. 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, while 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: A) clinical evidence (clinical background/CT scan/pulmonary function testing) is discordant; B) there is no alternate way to make the diagnosis; C) there is concern for an alternate/co-existing 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 which do not meet criteria for

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BOS based on other tests (6, 70, 92, 93, 97, 98). As such, there are situations where 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 above. 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 surgical lung biopsy should not be an issue based on 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 evaluating the benefits of biopsy in a randomized prospective trial. A multi-center 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,

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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).

As a result, the panel utilized a modified Delphi process to develop new criteria for diagnosis of post-HSCT BOS in children. Further detail is provided in the supplement. A priori, consensus was defined as greater than 70% participation in voting, and greater than 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. Multi-center 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 which is the use of variable reference

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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 employed, significant pulmonary function impairment will have occurred at the time BOS is detected. In order to diagnose BOS at earlier stages, one option would be to employ 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 suggests is less feasible in children (59). Another approach is to identify pathobiology-based biomarkers of BOS, which detect BOS prior to pulmonary function impairment. Such studies could utilize excess bronchoalveolar lavage 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, based on 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

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

also not addressed. This limitation stems from the rigor of the GRADE methodology that requires, per ATS policies, a focus to 6 key questions.

CONCLUSION

BOS is the most common non-infectious 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, 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.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

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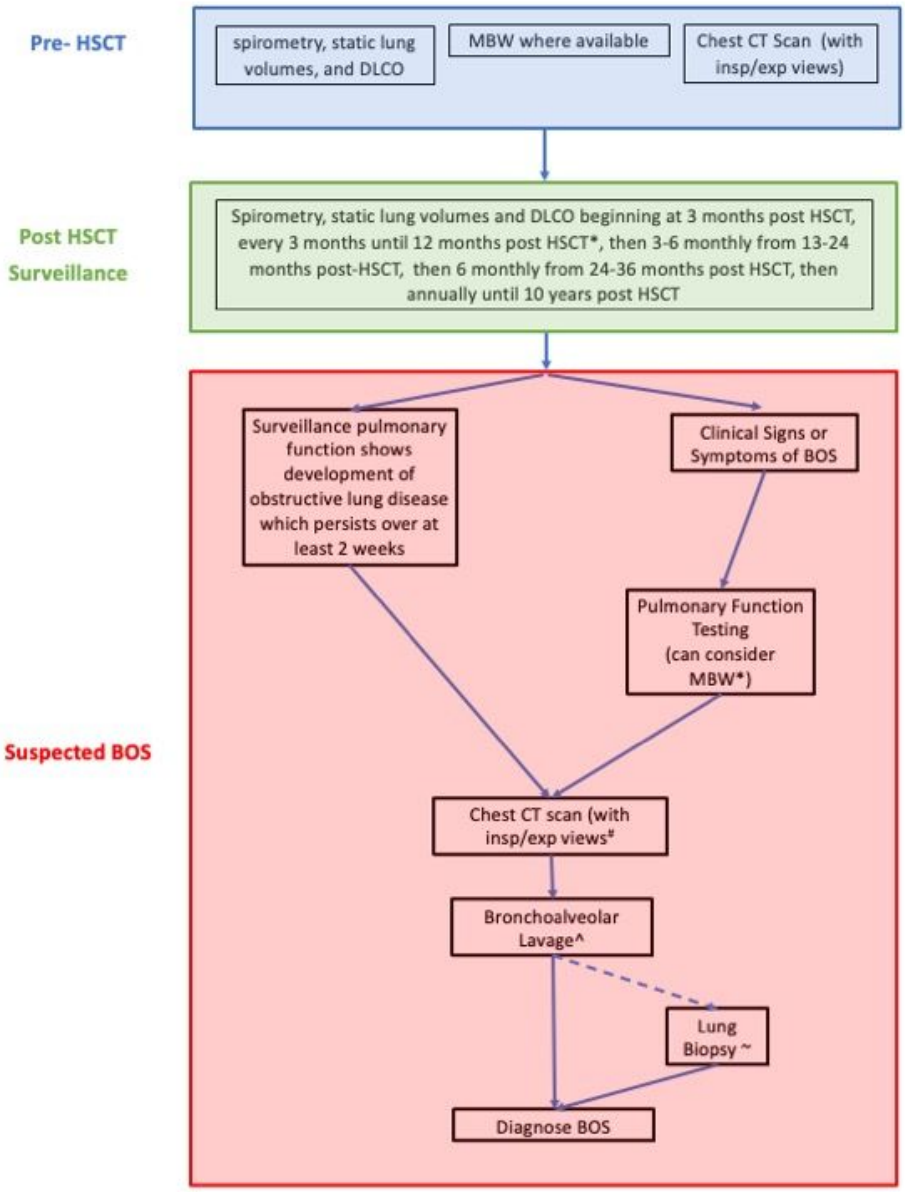
AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

Figure 1. Surveillance and diagnosis of BOS. *Some children may be unable to complete 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 CT scan, with inspiratory and expiratory views, is recommended in those with PFTs suggestive of BOS OR if there are persistent clinical signs and symptoms of BOS with normal lung function(recommendation 4b). ^We suggest a bronchoalveolar lavage 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/lung function impairment can return to normal surveillance. If the bronchoalveolar lavage reveals infection, this should be treated and clinical assessment should be repeated. Ongoing symptoms/signs or 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/co-existing condition, based on the clinical presentation, a biopsy is suggested (recommendation 6).

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST



AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

TABLES

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.

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

Table 2. Recommended frequency of PFT testing in children post-HSCT

Months post-HSCT	**Recommended PFT Frequency**
0 -12 months	Every 3 months
13-24 months	Every 3-6 months
25-36 months	Every 6 months
37 months on	Every 12 months

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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 prior to 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:
  o Suspending the automatic exposure control function on the CT scanner (which provides optimal imagine of the soft tissue which is not needed in evaluation of BOS, and increases radiation dose), instead applying a specific tube voltage (kV) and current (mAs) according to patient size.
  o A low radiation dose (approximately one third of that required for the inspiratory film) is needed to detect air trapping on the expiratory film.
  o Using this approach, the overall dose is approximately 0.5 mSv which is equivalent to 2 months of background radiation in the USA (NCRP160), although it will vary depending on the CT scanner and patient size.
- Decisions about CT technique at individual institutions needs 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 less than 5 years to achieve inspiratory/expiratory images, as well as those who are unable to comply with breath holding instructions

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- The addition of intravenous contrast may affect younger patients' ability to comply with breathing instructions) due to discomfort.
- Communication between radiology and anesthesia prior to procedure is important.
- Aim for optimal alveolar recruitment for inspiratory phase of scan
- Assess for significant atelectasis prior to scan with scout film and 2-3 selected axial images obtained in the mid to lower lung zones following recruitment maneuvers
- Atelectasis can be reduced with further recruitment maneuvers.
- In a small number of cases, optimal recruitment may require the prone position.

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Table 4. Summary of evidence regarding BAL in post-HSCT patients

Study	Study period	Age range	Total subjects	# BAL	Timing of BAL	BAL Yield
Pediatric only studies						
Armenian 2007	1995-2003	7.9y (mean)	32	32	19 < 30d 50 <100d	**50%**
Ben-Ari 2001	1995-1999	40d - 271m	63	86	89d (1-1460d)	**31%**
Eikenberry 2005	1995-1999	0.2 - 20.8y	90	>90	n/a	**43%** post 100d
Kasow 2007	1990-2002	0.8 - 23.5y	89	89	68d (6-528d for allo)	**67.9%**
McCubbin 1992	1985-1990	1.7 - 17.6y	27	29	Median 60d (11-1026d)	**52%**
Qualter 2014	?	2.3 - 14.9y	65	101	Median 95d (for allo)	**40%**
Mixed adult pediatric studies						
Cardonnier 1985	1981-1983	8-45y	36	52	7 <15d; Median 67d (9-713)	**50 or 52%**

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

Feinstein 2001	1997-1999	18-59y	61	76	n/a	42.1%
Glazer 1998	1991-1995	10m-56y	62	79	Median 40d (10d-1.5y)	**67%**
Hoffmeister 2006	1994-2004	14-67y	78	91	?	**49%**
Kim 2015	2009-2012	17-78y	187 (80 HSCT)	206	n/a	**65%**
Stover 1984	1982-1984?	15-77y	97 (18 HSCT)	97	n/a	**66%**
Tang 2018	2013-2016	11-64y	130	149	176d (17-1480d)	**58%**

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Table 5. Role of bronchoscopy with BAL in 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 weeks) Bronchoscopy with BAL if PFT decline persistent	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

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Table 6. New proposed criteria for 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 weeks 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, computed tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral testing, sputum culture, bronchoalveolar lavage).

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In children who cannot perform spirometry:

- Clinical symptoms (i.e. 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 tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral testing, sputum culture, bronchoalveolar lavage).

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Detection of Bronchiolitis Obliterans Syndrome Following Pediatric Hematopoietic Stem Cell Transplantation: An Official American Thoracic Society Clinical Practice Guideline – Online Supplement

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Contents

AJRCCM Articles in Press. Published June 18, 2024 as 10.1164/rccm.202406-1117ST

List of Abbreviations

ATS - American Thoracic Society

BAL - Bronchoalveolar Lavage

BOS - Bronchiolitis Obliterans Syndrome

BO - Bronchiolitis Obliterans

CBO - Constrictive Bronchiolitis Obliterans

CT - Computed Tomography

DLCO - Diffusing Capacity of the Lungs for Carbon Monoxide

FEV1 - Forced Expiratory Volume in One Second

FEF25-75% - Forced Expiratory Flow at 25–75% of FVC

FVC - Forced Vital Capacity

GA - General Anesthesia

GLI - Global Lung Initiative

GvHD - Graft vs. Host Disease

cGvHD - Chronic Graft vs. Host Disease

GRADE - Grading of Recommendations, Assessment, Development, and Evaluation

HSCT - Hematopoietic Stem Cell Transplantation

LCI - Lung Clearance Index

LB - Lymphocytic Bronchiolitis

MBW - Multiple Breath Washout

NIH - National Institutes of Health

PFT – Pulmonary Function Testing

PICO - Patient/ Intervention/ Comparator/ Outcome

TLC - Total Lung Capacity

VATS - Video-Assisted Thorascopic Surgery

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Methods

We used the GRADE approach (1, 2) to formulate clinical questions, identify and summarize relevant evidence, and develop recommendations for clinical practice. We used a modified Delphi process to develop a consensus based criteria for diagnosing pediatric bronchiolitis obliterans (BOS). Methods are summarized below.

Committee composition

The guidelines panel included specialists from multiple disciplines with expertise in the management of pediatric bronchiolitis obliterans (BOS) and four experts in guideline development methodology. The panel included 13 pediatric pulmonologists, 6 pediatric stem cell transplant clinicians, and 1 of each of the following: adult pulmonologist, radiologist, nurse, pharmacist, pediatric surgeon, and medical imaging scientist. During the guideline development process, 3 patients with BOS, and their primary caregivers, provided insight about the outcomes that were important to patients and the priorities for children with BOS. The panel had two Co-Chairs (SG and SS) and was divided into six sub-groups; one each for the six PICO questions.

Conflict of Interest management and sponsorship

Committee members disclosed all potential conflicts of interest, as per the policy of American Thoracic Society (ATS). Individuals with manageable conflicts took part in discussions about the evidence but did not participate in formulating or grading recommendations.

ATS staff provided logistical support and funding.

Formulating clinical questions

The committee used expert opinion to identify 6 specific questions of importance to patients with BOS, their caregivers, and clinicians who treat patients with BOS. The questions for this guideline were finalized using a survey in which the panel members were asked to propose questions that are of importance to patients with BOS. The proposed questions were ranked by the panel members based on their priority to patients and providers. Based on ATS clinical practice guideline policy, we chose the top six questions to be included in the guideline.

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A list of outcomes of interest for each of the clinical questions was created. Outcomes were then rated as “critical”, “important”, or “less important.” As suggested by the GRADE method, only outcomes that were considered ‘critical’ or ‘important’ were considered while formulating the recommendations. Patient/Intervention/Comparator/Outcome (PICO) format was used to formulate the questions for the guideline.

Literature search

We searched Medline using the search strategy described in the online supplement. The search was performed between June 2022 and September 2022. For each PICO question, two methodologists conducted a title and abstract review. Full texts of potentially relevant studies were reviewed by PICO leads to determine eligibility. Using a standardized data collection instrument, we abstracted relevant data on study characteristics, types of participants, interventions and outcomes of interest.

Evidence review and development of clinical recommendations

We used GRADEpro Guideline Development Tool online software (McMaster University, Hamilton, ON, Canada) to develop evidence profiles for each PICO question (1, 3, 4). The evidence profiles summarized the quality of evidence and results for each outcome of importance. When randomized controlled trials (RCT) were available, only these were used to create the evidence profiles. Observational studies were used only when relevant outcome data was not available from RCTs.

The certainty of evidence (quality of evidence) for each outcome was defined as the degree of confidence that an estimate of the effect is correct. The evidence quality therefore depends on overall risk of bias, precision, consistency, directness of the evidence, risk of publication bias, presence of dose-effect, magnitude of effect and the effect of plausible residual confounding. The certainty of evidence was categorized as high, moderate, low or very low. The overall certainty of evidence was determined across all outcomes considered critical for decision making.

Recommendations were described as ‘strong’ or ‘conditional’ (also referred to as ‘weak’) and the categorization was based on the evidence to decision (EtD) framework, which includes the following items: priority of the clinical problem, magnitude of the desirable effects, magnitude of the undesirable effects, overall certainty of the evidence, variability in patient values, the balance of desirable and undesirable effects of the intervention, acceptability of the intervention and

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feasibility of implementing the recommendation (5). Recommendations were decided by consensus. A strong recommendation implies that the balance of benefits, harms and other consideration in the (EtD) framework is such that most patients and providers would want the recommended course of action. A weak/conditional recommendation, on the other hand, implies that the balance of various considerations in the EtD framework still favors the recommended course of action in the majority of patients. However, with a conditional recommendation, individual patient values or considerations of cost and feasibility may lead to a course of action other than that recommended in the guideline.

We offered 'no recommendation' when our confidence in estimates of benefits and harms was so low that the panel believed that any recommendation would be speculative and / or the management options had very different consequences that would be sensitive to patient preferences.

Modified Delphi process methodology

We planned a two round, modified-Delphi process to achieve consensus on a new diagnostic criterion for pediatric bronchiolitis obliterans (BOS). Delphi technique was chosen because it allows rapid and systematic development of expert consensus. We followed the Conducting and REporting of DElphi Studies (CREDES) for the conduct and reporting of the Delphi process (6). The process was conducted online and we used the Redcap survey tool for the surveys included in the process (7). This process involved a panel of 23 participants. Of the 23, 18 were members of the panel who developed the guideline, including 12 pediatric pulmonologists and 6 pediatric HSCT clinicians. Five members were added to this group including 3 pediatric pulmonologists, 1 pediatric HSCT clinician, and 1 adult pulmonologist. The process was overseen by an expert in guideline development methodology. All panelists completed the conflict of interest forms provided by the ATS and any conflicts identified during this process were managed per the established ATS conflict of interest policies. The first version of the new criteria was developed by a five-person executive committee who reviewed the existing evidence on different aspects of the current 2014 NIH BOS criteria and the pitfalls of using the criteria in children. This first version of the new pediatric BOS criteria and the associated summary of evidence was shared with the full expert panel. The full expert panel was then anonymously (to reduce the social pressure for conformity) surveyed (survey#1) for agreement with the proposed criteria. A 70% threshold to establish agreement was chosen a priori. Next, an online meeting was held among all panel members to discuss the results of the first survey. Any item not reaching 70% threshold was modified or removed based on the feedback received in the meeting. During the

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meeting, several panel members sought more information and evidence on the PRISm criteria. A second survey (survey#2) was conducted after a summary of existing literature on PRISm in pediatrics was shared with the panel. This second survey showed a lack of agreement to include the PRISm. Therefore, PRISm was removed from the final version of the criteria. The final version of the BOS criteria was presented to the full panel (survey#3) to survey the panels agreement on the criteria as a whole rather than agreement on individual items.

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PICO 1. Pre- HSCT Lung function

Search strategy. PICO 1-3: Pre- HSCT Lung function, Post-HSCT Lung function Surveillance and Spirometry vs MBW

1	exp Pediatrics/ or exp Infant/ or exp Child/ or exp Adolescent/	3896875
2	(pediatric* or infant* or baby or babies or child or children or adolescent* or teen*).ti,ab,kw,kf.	2118118
3	1 or 2	4377917
4	exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/	135602
5	((bone marrow or stem cell) adj3 (transplant* or graft*)).ti,ab,kw,kf.	95124
6	4 or 5	164354
7	exp Lung Diseases/ or exp Respiratory Function Tests/	1309370
8	((bronchiolit* adj2 (obliteran* or obliterative* or constrictive* or exudative* or proliferative*)) or (pulmonary adj2 (graft versus host or graft vs host)) or (lung adj2 disease*) or ((lung or pulmonar* or respirator*) adj2 function test*) or airway resistan* or blood gas analysis or oximetry or bronichial provocation or capnography or lung compliance or lung volume measure* or total lung capacit* or maximal respiratory pressure* or plethysmography or pulomonary gas exchange or pulmonary diffusing capacit* or ventilation-perfusion ratio* or forced expiratory flow rate* or forced expiratory volume* or maximal voluntary ventilat* or spirometr* or bronchospirometr* or valsalva maneuver or ventilation-perfusion scan* or work of breathing or DLCO or diffusion capacit* or diffusing capacit* or transfer factor* or residual volume* or multiple breath washout or lung clearance index or inert gas washout or ((peripheral airway* or small airway*) adj2 (disease* or function*))).ti,ab,kw,kf.	180549
9	7 or 8	1364529
10	3 and 6 and 9	2003

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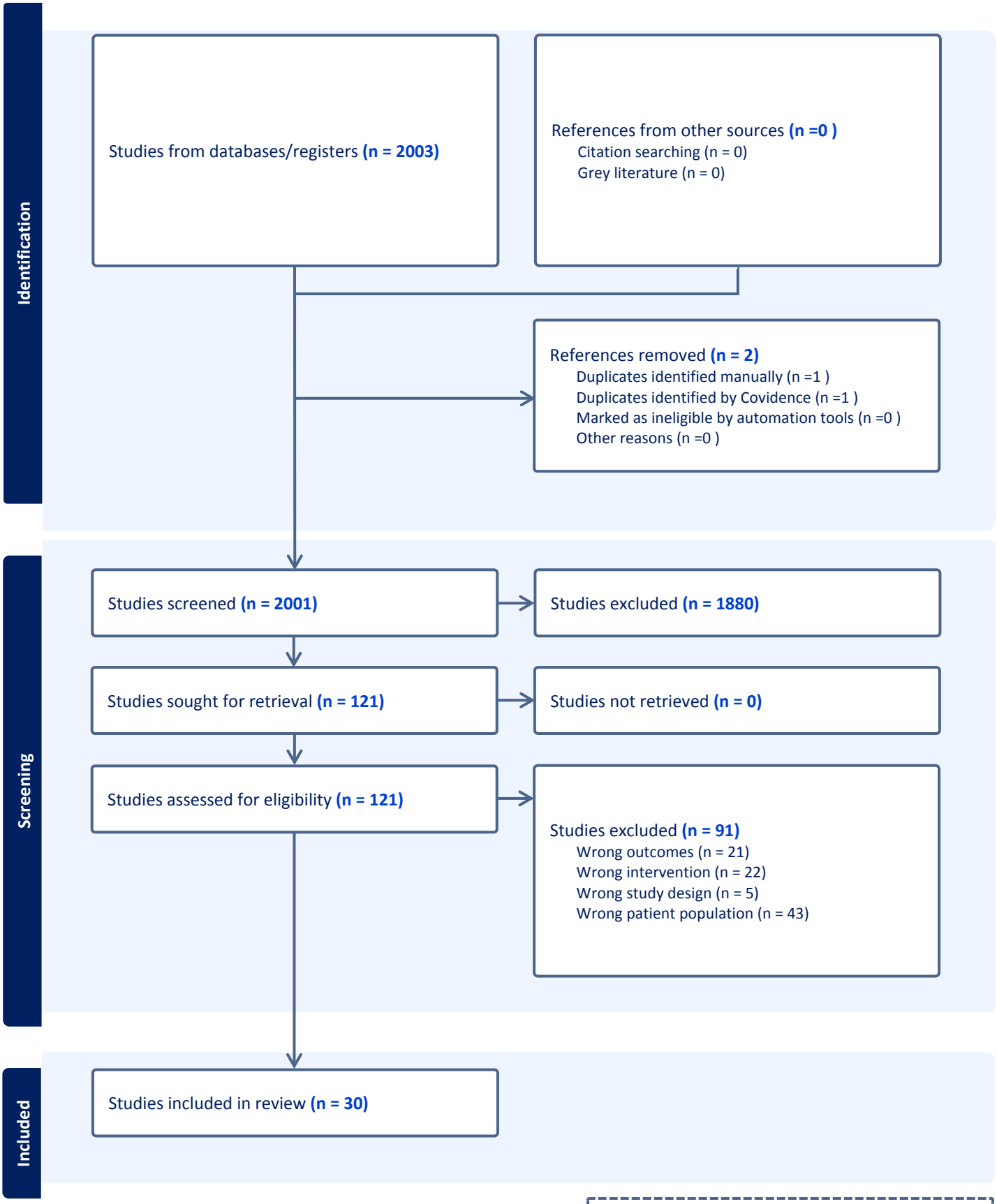
PRISMA Flow diagram. PICO 1: Pre-HSCT screening spirometry



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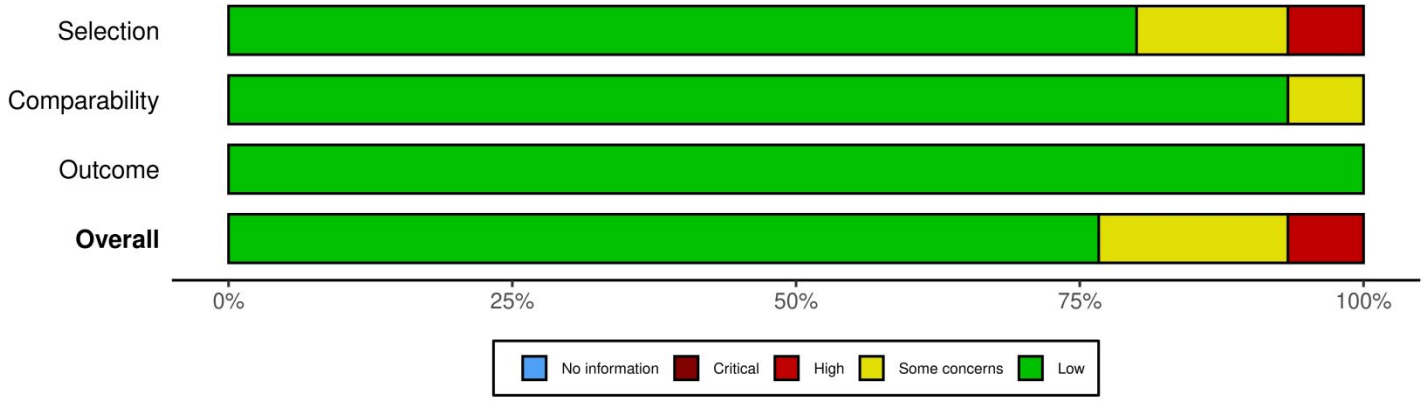
Risk of Bias assessment (Newcastle-Ottawa Scale). PICO 1: Pre-HSCT Lung function.



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Evidence table: PICO#1

Question: Should pre-HSCT screening spirometry, plethysmography and test of diffusion capacity be performed in pediatric patients who will undergo allogenic HSCT?

Intervention: Pre-HSCT lung function

Comparator: No Pre-HSCT lung function

Setting: Outpatient

Quality assessment							No. of patients	Result	Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**				
Diagnostic yield: FEV1										
16	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	2200	Normal FEV1 in 3 studies Range of prevalence of abnormal: 4- 41%. Severe abnormalities: 0- 13%	Moderate	Important
Diagnostic yield: FEV1/FVC										
13	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	909	Normal FEV1/FVC in 2 studies. Range of abnormalities: 5-20%.	Moderate	Important
Diagnostic yield: FEF25-75										
4	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	655	Range of abnormalities: 3-28%	Moderate	Important
Diagnostic yield: FVC										
10	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	1543	Range of abnormalities: 10-31%.	Moderate	Important
Diagnostic yield: DLCO										
10	Observational	No serious risk of bias	Serious*	None	None	Possibility of very large percentage of abnormal tests	914	Normal DLCO in 1 study. Range of abnormalities: 3-100%	Moderate	Important

*Wide range of pre-transplant PFT abnormalities among studies.

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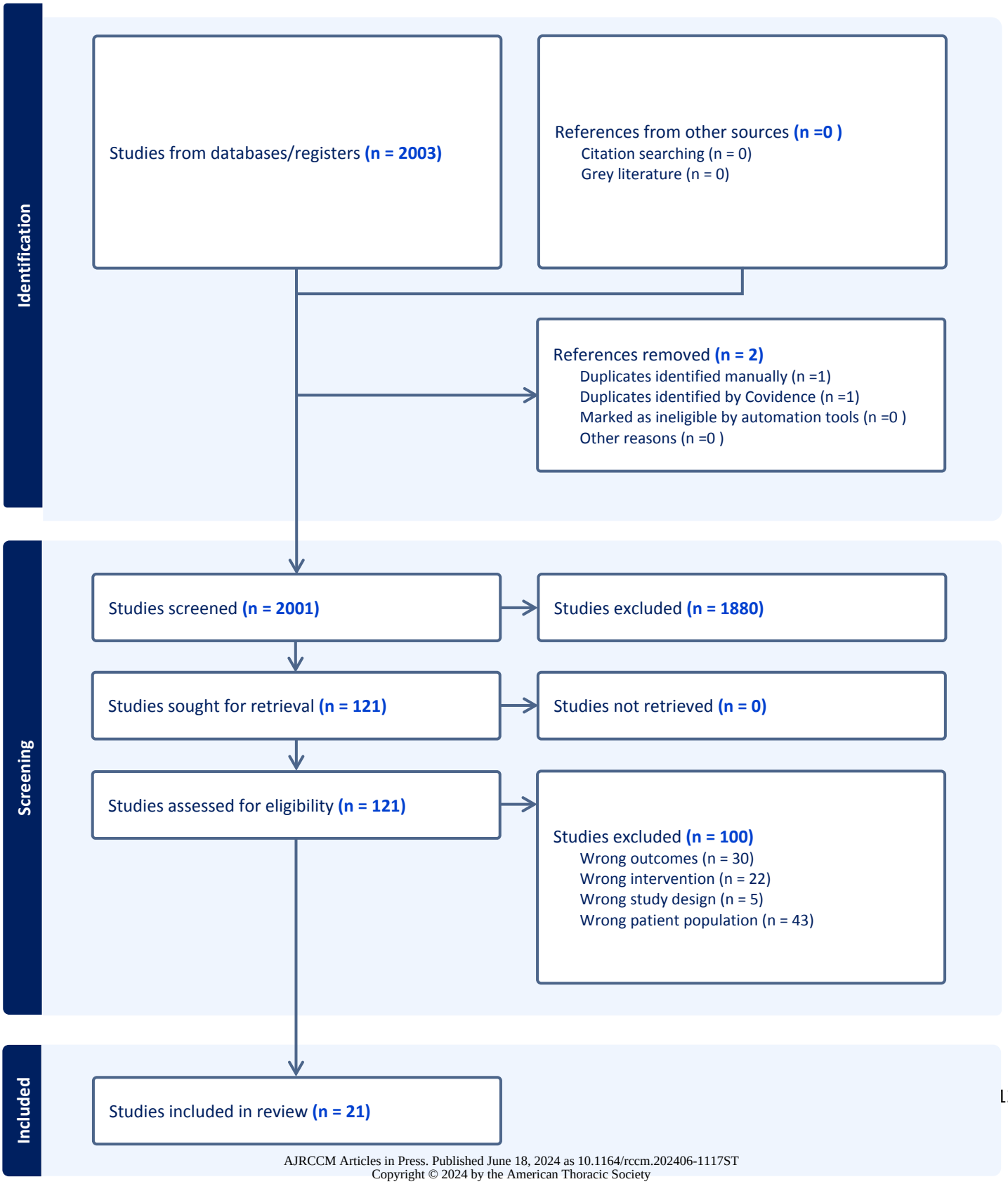
PICO2. Post-HSCT screening lung function

PRISMA Flow diagram. PICO 2: Post-HSCT screening lung function



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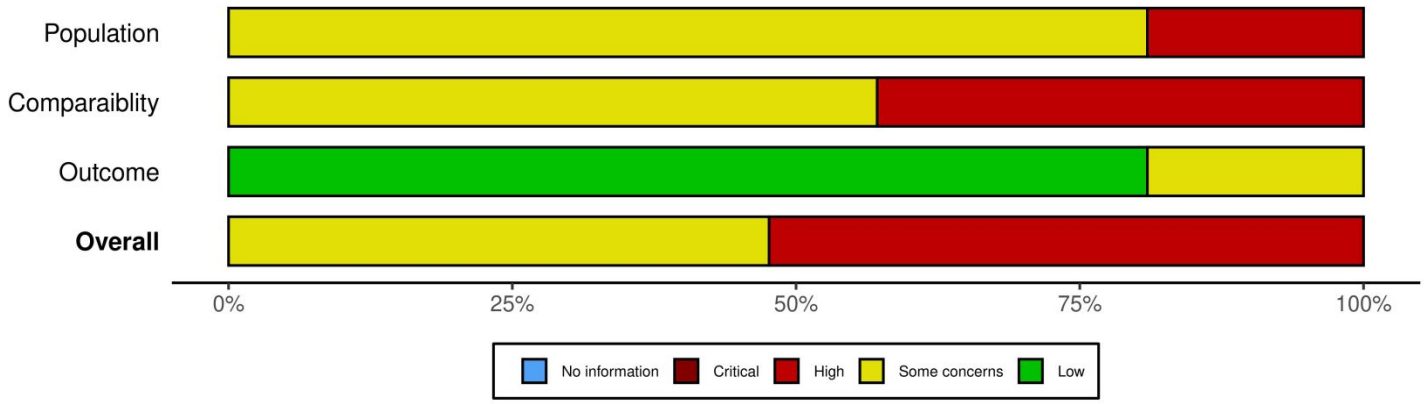
Risk of Bias assessment (Newcastle-Ottawa Scale). PICO 2: Post-HSCT Lung function.



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Evidence table: PICO#2

Question: At what frequency should pediatric patients who have had allogenic HSCT undergo surveillance spirometry, plethysmography and tests of diffusion capacity?

Intervention: Regular post-transplant surveillance

Quality assessment							No. of patients	Result	Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**				
Timing of BOS diagnosis										
21	Cohort studies	Serious*	None	None	None	None	1895	Surveillance: Most of the studies report a median time of 6-12 months No surveillance: Median time 6-24 months 12 months.	Low	Critical
FEV1 decline at the time of diagnosis										
21	Cohort studies	Serious*	Serious†	None	None	None	1895	Surveillance: 37-58% predicted; 2 studies reported 4 patients being asymptomatic at BOS diagnosis No surveillance: 51-57% predicted and in one study FEV1 Z score time of diagnosis -3.62 (-4.77, -2.48)	Very Low	Critical

Comparator : Testing only if clinically indicated

Setting: Outpatient

*Wide range of BOS severity among studies; some studies only included patients with BOS. Some studies only described obstructive airway disease without sub-classifying them into BOS. Confounding variables such as conditioning regimens and pre-existing abnormal lung function tests were not controlled in most studies.

†Wide range of FEV1 scores at diagnosis between studies.

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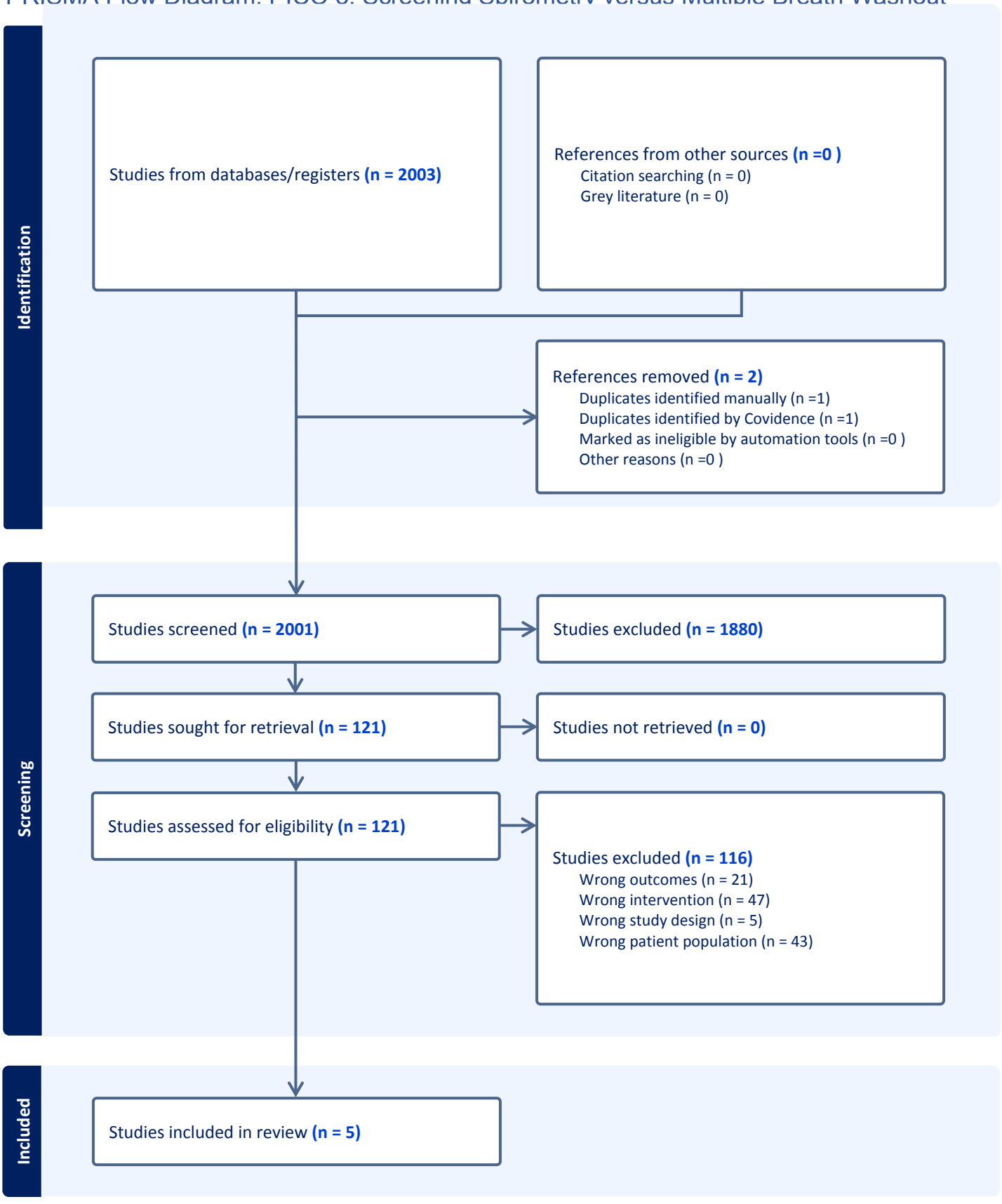
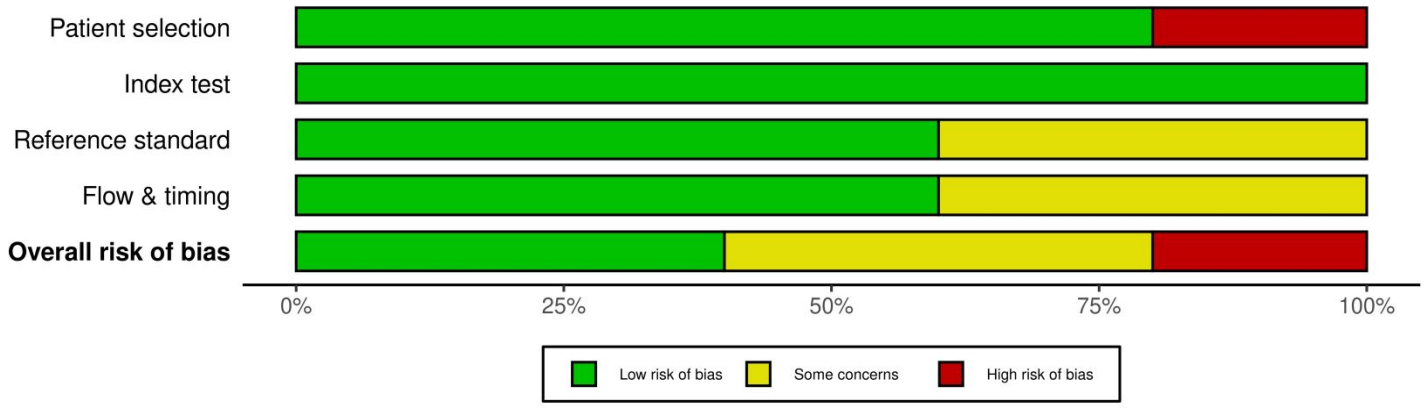
PICO 3. Screening Spirometry versus Multiple Breath Washout

PRISMA Flow Diagram, PICO 3: Screening Spirometry versus Multiple Breath Washout



Risk of Bias assessment (QUADAS-2). PICO 3: Screening Spirometry versus Multiple Breath Washout.



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Evidence table: PICO#3

Question: In pediatric patients who have had allogenic HSCT, should the routine surveillance of lung function be done using spirometry or a combination of MBW and spirometry?

Intervention: Multiple Breath Washout (using Nitrogen or Sulfur Hexaflouride. Measure: Lung Clearence Index [LCI])

Comparator: Spirometry (Measure: FEV1)

Setting: Outpatient

Quality assessment							No. of patients	Result	Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**				
Test accuracy (LCI versus FEV1 as reference)										
2	Cohort	Serious*	None	None	Serious†	None	54	Pooled sensitivity 1.00 (0.99,1.00); pooled specificity 0.75 (0.42, 0.92).	Very low	Critical
Test feasibility in young children										
1	Cohort	No risk of bias	None	None	None	None	26	Spirometry was successfully performed in 17/26 (65%) patients. MBW was successfully performed in 26/26 (100%) patients.	Low	Important

*No longitudinal follow up. Pre-transplant values are not known and not adjusted for. Different thresholds for diagnosing BOS.

†Wide confidence intervals for sensitivity.

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PICO 4. CT scan in BOS evaluation

Search strategy. PICO 4, CT Scan:

1	exp Pediatrics/ or exp Infant/ or exp Child/ or exp Adolescent/	3915586
2	(pediatric* or infant* or baby or babies or child or children or adolescent* or teen*).ti,ab,kw,kf.	2133642
3	1 or 2	4403380
4	exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/	136406
5	((bone marrow or stem cell) adj3 (transplant* or graft*)).ti,ab,kw,kf.	96108
6	4 or 5	165657
7	exp Lung Diseases/ or exp "Tomography, X-Ray Computed"/	1588592
8	((bronchiolit* adj2 (obliteran* or obliterative* or constrictive* or exudative* or proliferative*)) or (pulmonary adj2 (graft versus host or graft vs host)) or (comput* adj2 tomograph*) or (CT adj2 scan*)).ti,ab,kw,kf.	440690
9	7 or 8	1787560
10	3 and 6 and 9	2331

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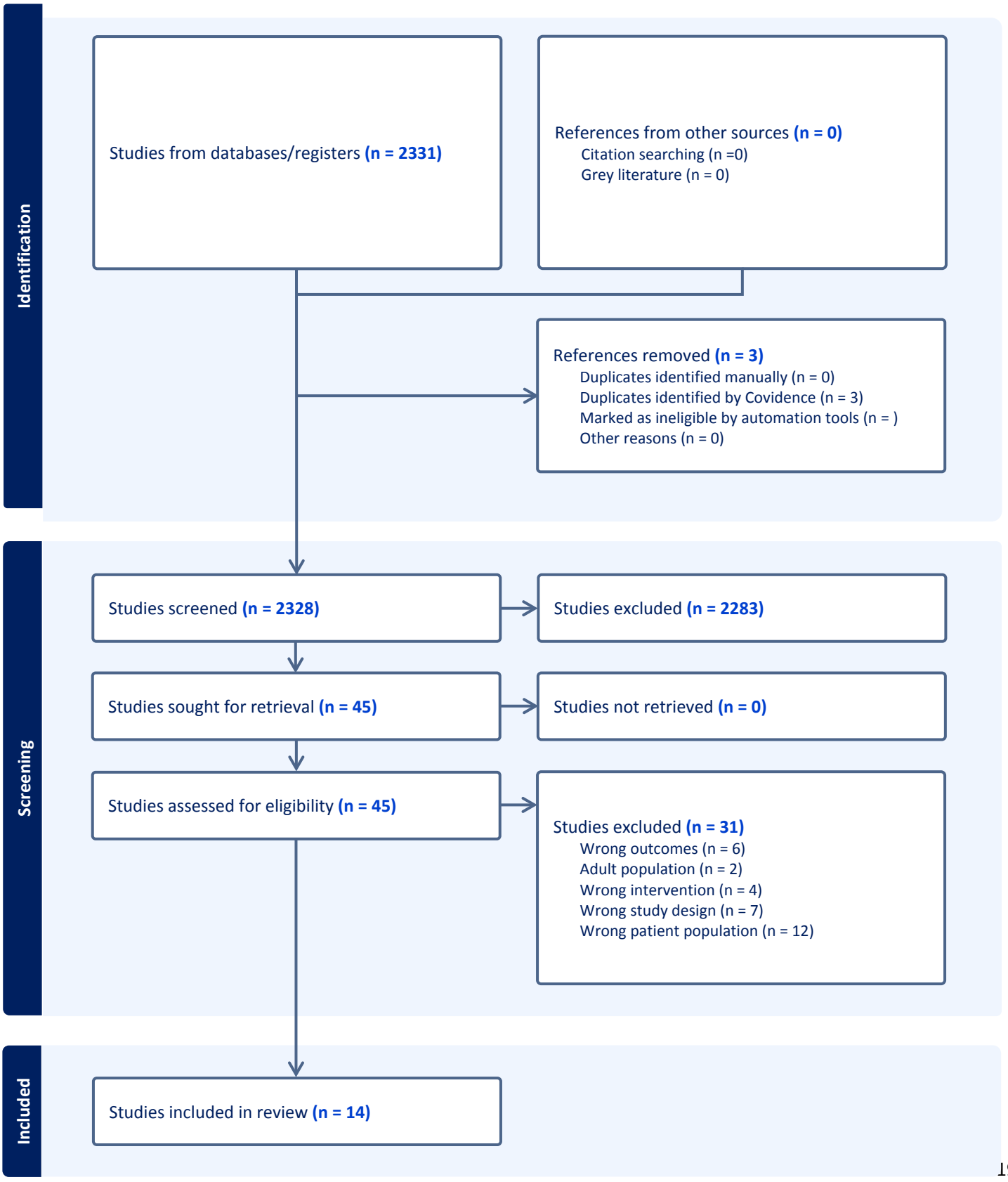
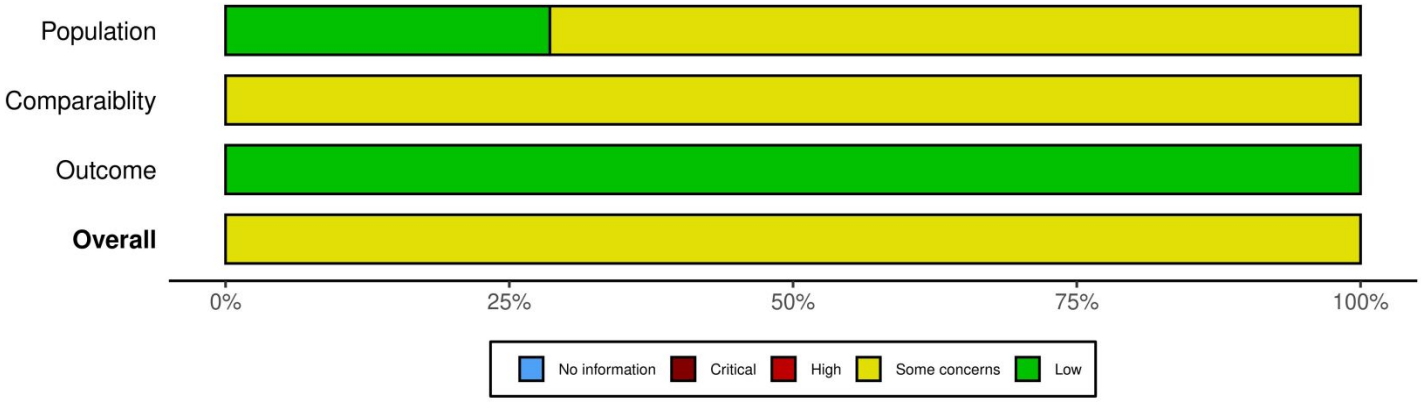
PRISMA Flow diagram. PICO 4: CT Scan



Risk of Bias assessment (Newcastle-Ottawa Scale). PICO 4: CT scan in BOS.



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Evidence table: PICO#4

Question: Should pediatric patients post allogenic HSCT who have abnormal surveillance lung function assessment be investigated with a CT chest scan?

Intervention: CT scan

Quality assessment							No. of patients	Result	Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other				
Diagnostic yield (pre-HSCT)										
2	Cohort	No risk of bias	None	Serious*	None	None	532	Normal CT findings and the absence of emphysema were significantly associated with normal PFT. Abnormal findings were noted in 50-55% of patients. Clinically significant findings noted in 13% patients.	Low	Critical
Diagnostic yield (post HSCT)										
12	Cohort	Serious risk of bias†	None	Serious‡	None	None	297	CT alone unable to differentiate BO from non-BO in 2 studies (Merlini 2008 and Uhlving 2015). Air trapping: regional or diffuse hypoattenuation-100% (2 studies). Areas of parenchymal hypoattenuation noted in 48-100% scans. % lung volume with low attenuation significantly different in BOS (16.4%) versus patients without BOS (0.61%) (Moutafidis 2021).	Very low	Critical
Comparison of CT findings with Spirometry										
3	Cohort	Serious risk of bias†	None	Serious‡	None	None	59	% lung volume with low attenuation correlated with FEV1: 0.62- 0.77 (moderate to high correlation) and FEV1/FVC: 0.65- 0.79 (moderate to high correlation). Mean lung density and relative area of lung below -800 on expiration was correlated with FEV1 (Oh 2013).	Very low	Important

Comparator: No CT scan

Setting: Outpatient

*Impact of CT scan not prospectively collected; impact reported in one study.

†No pre-HSCT-CT, no controlling for confounding variables, different CT techniques that were spread over several decades.

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‡Some studies with mixed-adult and pediatric populations.

PICO 5. Bronchoscopy in BOS evaluation

Search strategy. PICO5, Bronchoscopy

1	exp Pediatrics/ or exp Infant/ or exp Child/ or exp Adolescent/	3915586
2	(pediatric* or infant* or baby or babies or child or children or adolescent* or teen*).ti,ab,kw,kf.	2138642
3	1 or 2	4403380
4	exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/	136406
5	((bone marrow or stem cell) adj3 (transplant* or graft*)).ti,ab,kw,kf.	96108
6	4 or 5	165657
7	exp Lung Diseases/ or exp Bronchoscopy/ or exp Bronchoalveolar Lavage/	1184410
8	((bronchiolit* adj2 (obliteran* or obliterative* or constrictive* or exudative* or proliferative*)) or (pulmonary adj2 (graft versus host or graft vs host)) or bronchoscop* or ((bronchoalveolar or bronchopulmonary or bronchial or lung) adj2 lavage*)).ti,ab,kw,kf.	69332
9	7 or 8	1201937
10	3 and 6 and 9	1904

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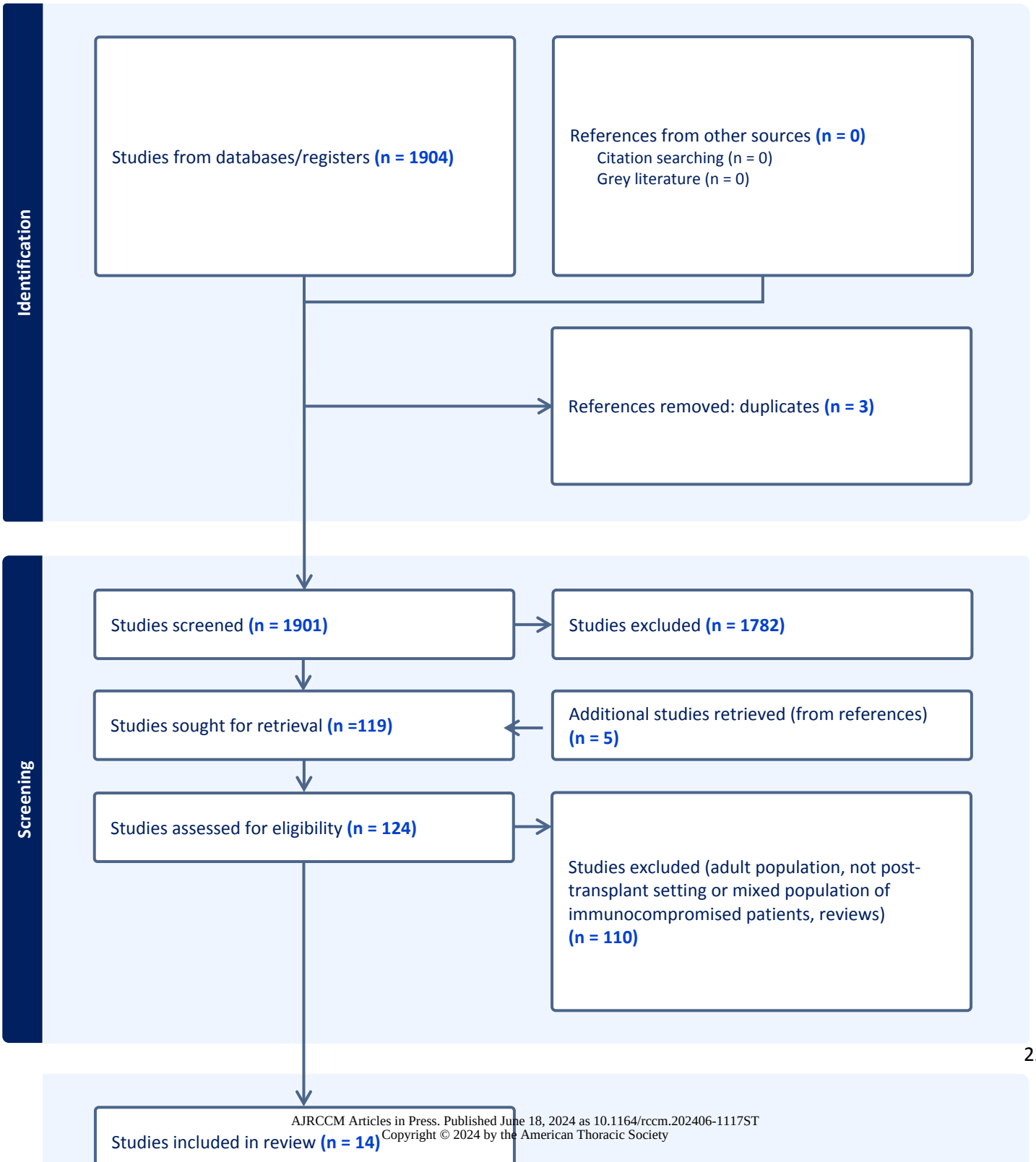
PRISMA Flow diagram. PICO 5: Bronchoscopy



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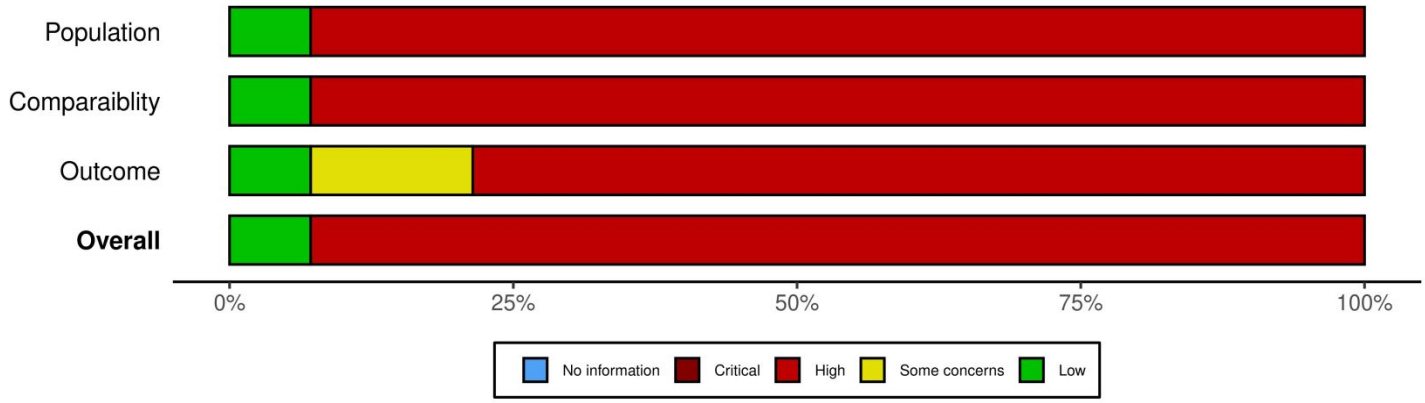
Included

Risk of Bias assessment(Newcastle-Ottawa Scale). PICO 5: Bronchoscopy in BOS.



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Evidence table: PICO#5

Question: Should pediatric patients post-allogenic HCT who have abnormal surveillance lung function assessment be investigated with a BAL/bronchoscopy?

Intervention: Bronchoscopy with bronchoalveolar lavage

Comparator: No bronchoscopy / Non-invasive or other tests for microbiologic or pathologic diagnosis

Setting: Outpatient/In-patient

Quality assessment							No. of patients/BAL procedures	Result	Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness** †	**Imprecision**	**Other**				
BAL Yield										
14	Cohort studies without any controls	Very serious*	Very serious	Very serious	None‡	None	790/1144	BAL yield varied widely from 31-68%	Very low	Critical
Complications										
11	Cohort studies without any controls	Very serious*	Very serious	Very serious	None‡	None	383/701	Complications from BAL were few, and very rarely serious	Very low	Critical

*Study designs were suboptimal, most being retrospective cohorts of patients who underwent BAL for clinical reasons. No studies had an appropriate control group to allow assessment of the utility of bronchoscopy in BOS diagnosis. Additionally, confounders such as antibiotic usage were inconsistently (or not) reported. Microbiologic techniques used for testing also varied greatly over time.

† Overall, zero or very few cases of BOS are described in these studies (except Yanik et al); although the population studied was mainly s/p HCT, bronchoscopy and BAL was not performed as part of the evaluation of BOS.

‡Given the heterogeneity of studies (with regards to study populations, study time period, microbiologic testing, described complications, etc), imprecision was not quantifiable and is reported as “none” although likely to be very serious.

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PICO6. Lung biopsy in BO diagnosis

Search strategy. PICO6, Lung Biopsy

1	exp Pediatrics/ or exp Infant/ or exp Child/ or exp Adolescent/	3915586
2	(pediatric* or infant* or baby or babies or child or children or adolescent* or teen*).ti,ab,kw,kf.	2138642
3	1 or 2	4403380
4	exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation/	136406
5	((bone marrow or stem cell) adj3 (transplant* or graft*)).ti,ab,kw,kf.	96108
6	4 or 5	165657
7	exp Lung Diseases/ or (exp Biopsy/ and exp Lung/)	1164912
8	((bronchiolit* adj2 (obliteran* or obliterative* or constrictive* or exudative* or proliferative*)) or (pulmonary adj2 (graft versus host or graft vs host)) or (lung* adj4 biops*)).ti,ab,kw,kf.	18325
9	7 or 8	1169000
10	3 and 6 and 9	1846

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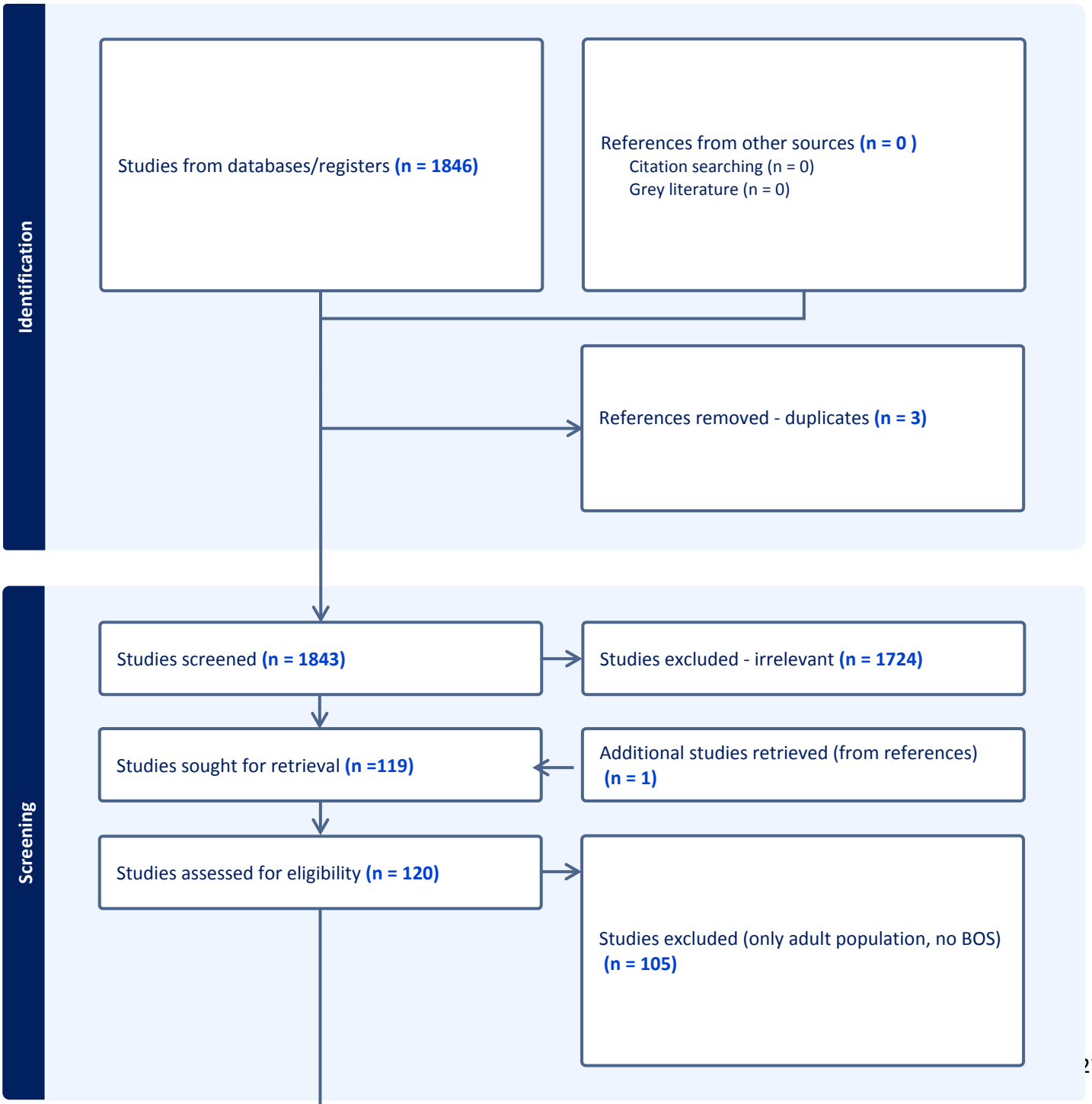
PRISMA Flow diagram. PICO 6: Lung biopsy



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Included

Included studies ongoing **(n = 0)**
Studies awaiting classification **(n = 0)**

Pediatric BOS Criteria process

New Proposed Criteria (Version_1)

In children who can perform spirometry: *(GLI to be used at the reference equation for spirometry and plethysmography)*

- Decline of FEV_1 relative to pre-HSCT baseline by 15%

AND

- Supporting Features (two of these)
  - FEV1/VC below lower limit of normal
  - PRISm pattern (FEV1 <LLN, FEV1/VC >LLN)
  - Evidence of expiratory 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 >9.0
  - 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 tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).

In children who can not perform spirometry:

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- Clinical symptoms (i.e. wheeze, shortness of breath with activity)

AND

- One of the following
  - Evidence of expiratory air trapping on expiratory CT
  - Lung clearance index >9.0
  - 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 tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).

Pediatric BOS Criteria process: Results of sequential surveys

Survey#1 results

1. Do you agree with '% decline from baseline' rather than an absolute FEV1 level?
   a. Responses = 21
   b. Yes= 21

2. If a criteria using relative change in FEV1 is to be used, what amount of decrease from baseline should be part of the criteria?
   a. Responses = 19
   b. 10%= 4 (21%)
   c. 15%= 10 (53%)
   d. 20%= 5 (26%)

3. How many supporting features should be required?
   a. Responses = 21
   b. 1 = 3 (14%)
   c. 2 = 16 (76%)
   d. Other= 2 (10%). Comment: None. CT without airtrapping should also essentially rule BOS out

4. What should be the threshold for lung clearance index: >9.0 (based on Rayment et al, Transplant Cell Ther 2022;28(6):328) or >8.0 (conventional upper limit of normal)?
   a. Responses = 19
   b. >9.0 = 12 (63%)
   c. >8.0 = 7 (37%)

5. Do you want to add mid-expiratory flow (MEF25%-75%)
   a. Responses = 20
   b. Yes= 12 (60%)

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c. No= 8 (40%)

6. For the cGVHD criteria, do you prefer active GVHD or past history of cGVHD in another organ vs Grade 2 or more cGVHD
    a. Responses = 21
    b. Active/ past cGVHD= 19/21 (90.5%)
    c. Grade 2 or more cGVHD= 2 (9.5%)

7. For the spirometry based supporting features - is using the LLN as the threshold appropriate or should we use relative decline?
    a. Responses = 21
    b. Lower limit of normal = 12 (57%)
    c. Relative threshold = 9 (43%)

8. If you prefer relative criteria, describe what % decline should be used.
    a. Responses = 9
    b. 10%: 2
    c. 12% or higher: 1
    d. 15%: 3
    e. 10% or 15%: 1
    f. > 20% decline in FEV1 or > 25% decline in FEF25-75, from baseline: 1
    g. If referring to FEV1 then 20% as we don't have the evidence as yet to state 15% is more appropriate (may be wrong). If referring to FEV1/FVC then keep as lower limit of normal (ideally defined as z score). Above aims to align with adult approach

9. Do you want to remove any of the supporting feature criteria?
    a. Responses = 20
    b. Yes= 4 (20%)
    c. No= 16 (80%)

10. Which supportive criteria do you want to remove?
    a. Responses = 4
    b. PRISm pattern - I'm not sure what that is, but it is describing restrictive physiology, not BOS
    c. The absence of infection
    d. All except GVHD in other organ, IF volumes completed, having air trapping and NOT normal. IF completed a CT, with air trapping and NOT normal.
    e. GVHD in any other organ

11. Do you suggest adding any criteria to the supporting features?
    a. Responses = 19
    b. Yes= 3 (12%)
    c. No= 16 (88%)

12. What measure do you want to add to the supportive criteria?
    a. I wonder if additional weight should be given to CT findings; also should symptoms be included?
    b. Cough as a symptom
    c. MBW

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13. For children who can not perform spirometry, what should be the threshold for lung clearance index: >9.0 (based on Rayment et al, Transplant Cell Ther 2022;28(6):328) or >8.0 (conventional upper limit of normal)?
    a. Responses = 18
    b. >9.0 = 11 (61%)
    c. >8.0 = 7 (39%)

14. For children who can not perform spirometry, for the cGVHD criteria, do you prefer: active GVHD or past history of cGVHD in another organ versus Grade 2 or more cGVHD?
    a. Responses = 20
    b. Active/past cGVHD= 18 (90%)
    c. Grade or more cGVHD= 2 (10%)

15. For children who can not perform spirometry, how many supporting features should be required?
    a. Responses= 21
    b. One= 10 (48%)
    c. Two= 11 (52%)

16. Do you want to remove any of the supporting feature criteria?
    a. Responses = 21
    b. Yes= 0%
    c. No= 21 (100%)
17. Do you suggest adding any additional criteria?
    a. Responses = 21
    b. Yes= 2 (9.5%)
    c. No= 19 (90.5%)

18. What measure(s) do you want to add to the supportive criteria?
    a. iOS when available? consider adding 3D recon with air trapping?
    b. MBW

19. Additional comments:
    a. I think we need to address, or at least acknowledge, the possibility of restrictive physiology in chronic GVHD. We keep referencing lung transplant criteria, and they have completely gone away from BOS as the only form of CLAD. They make clear distinctions between the BOS and RAS phenotype of CLAD, and a similar distinction should be acknowledge in chronic lung GVHD.
    b. I think as simple as possible would be best...
    c. Perhaps radiographic findings should hold more weight?
    d. LCI thresholds were established using the old Spiroware software version (3.2). I am in the process of re-processing the dataset to see if this changes the threshold -- I expect it will, as it dropped the healthy ULN from 7.9 to 7.1. So the LCI thresholding question is complicated and likely changing...
    e. In the future we should be incorporating oscillometry as another available test in the preschool age range which may be more broadly accessible - but we have not incorporated that into our working group outputs as yet, so save it for the next update of the document

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20. *Points needing further discussion:* The panel was keen to receive more information regarding the PRISm before making a judgement on whether it should be included as a supporting feature. The evidence was summarised and sent to the panel as a separate document.

Survey#2 results

1. Do you think we should include PRISm (defined as FEV1 <LLN, FVC <LLN, normal FEV1/FVC, normal TLC if available) as a supporting feature?
    a. Responses: 16
    b. Yes= 9 (56%)
    c. No= 7 (44%)
    d. Comments:
        i. Not enough paediatric specific data & variability in spirometry in kids
        ii. The evidence supporting PRISm as equivalent to BOS in adults post-BMT is very weak (a single paper with questionable methodology), and there is no evidence in children post-BMT. There is more evidence supporting the use of MBW in children post-BMT, but that was dropped because we all agreed it lacked enough evidence to be included in a guideline statement. Further, there is too much overlap with the restrictive/PPFE phenotype (what is called RAS in lung transplant) and with respiratory muscle weakness / deconditioning for this to be included in a proposed definition for BOS.
        iii. I think with patients that are not great at baseline with PFT's this will over diagnose BOS.
        iv. Worried about specificity of this measure in pediatrics - inadequate care exhalation could really meet this criterion (false positive). Probably less of an issue in adults, but a grumpy 8 year old will do this all the time.

Survey#3 results

1. Do you agree with the proposed criteria to diagnose BOS in children who can perform spirometry?
    a. Responses: 19
    b. Yes= 19 (100%)
    c. No= 0 (0%)

2. Do you agree with the proposed criteria to diagnose BOS in children who CAN NOT perform spirometry?
    a. Responses: 19
    b. Yes= 18 (95%)
    c. No= 1 (5%)

3. Additional comments:
    a. For those who can't do spirometry, I think it needs to be made more clear that the clinical symptoms are persistent for a prolonged period of time and we need to specify that time frame in the definition like we do for the group who can do spirometry; at least 2 but preferably 4

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weeks. Persistence is implied in the paragraph at the bottom, but it needs to be stated more explicitly to avoid over diagnosis of BOS in patients with pre-school wheezing.

b. "Respiratory tract viral screen" is a funny term - it's not a screen, it's a diagnostic test. It's just semantic though. Otherwise looks great!
c. Agree with the decision to not include PRISm criteria at this stage - part of my delay in answering that question was because it was not a straightforward answer. Good plan to include as a discussion point.

References

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