HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2018 April 23.

Published in final edited form as:

Bone Marrow Transplant. 2018 February ; 53(2): 193–198. doi:10.1038/bmt.2017.238.

Transbronchial biopsy in the management of pulmonary complications of hematopoietic stem cell transplantation

David N. O'Dwyer, MB, BCh, PhD[1], **Adam S. Duvall, MD, MPH**[2], **Meng Xia**[3], **Timothy C. Hoffman**[2], **Kiernan S. Bloye**[2], **Camille A. Bulte**[2], **Xiaofeng Zhou, PhD**[1], **Susan Murray, Sc.D**[3], **Bethany B. Moore, PhD**[1,4], and **Gregory A. Yanik, MD**[2]

[1]Division of Pulmonary and Critical Care Medicine, Dept. of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

[2]Dept. of Pediatrics, University of Michigan, Ann Arbor, MI, USA

[3]Dept. of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA

[4]Dept. of Microbiology and Immunology, University of Michigan, Ann Arbor, MI, USA

Abstract

The utility of transbronchial biopsy in the management of pulmonary complications following hematopoietic stem cell transplantation has shown variable results. Herein, we examine the largest case series of patients undergoing transbronchial biopsy following hematopoietic stem cell transplantation. We performed a retrospective analysis of 130 transbronchial biopsy cases performed in patients with pulmonary complications post-hematopoietic stem cell transplantation. Logistic regression models were applied to examine diagnostic yield, odds of therapy change and complications. The most common histologic finding on transbronchial biopsy was a non-specific interstitial pneumonitis (n= 24 cases, 18%). Pathogens identified by transbronchial biopsy were rare, occurring in < 5% of cases. A positive transbronchial biopsy significantly increased the odds of a subsequent change in corticosteroid therapy (OR=3.12, 95% CI 1.18–8.23; p=0.02) but was not associated with a change in antibiotic therapy (OR=1.01, 95% CI 0.40–2.54; p=0.98) or changes in overall therapy (OR=1.92, 95% CI 0.79–4.70; p=0.15). Patients who underwent a transbronchial biopsy had increased odds of complications related to the bronchoscopy (OR=3.33, 95% CI 1.63–6.79; p=0.001). In conclusion, transbronchial biopsy may contribute to the diagnostic management of non-infectious lung injury post-hematopoietic stem cell transplantation, while its utility in the management of infectious pulmonary complications of HSCT remains low.

Corresponding Author: David N. O'Dwyer MB BCh PhD, 4448 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI 48109., dodwyer@med.umich.edu.

Author Contributions: D.O.D, G.A.Y and B.B.M conceived the study, contributed to analysis and interpretation, and wrote the manuscript. A.D, T.H, K.B, C.B. and X.Z collected. M.X and S.M carried out statistical analysis and contributed to the manuscript.

Conflicts of Interests:
The authors have no conflicts of interest to declare.

Keywords

hematopoietic stem cell transplantation; pulmonary; bronchoscopy; biopsy

INTRODUCTION

Approximately 50% of hematopoietic stem cell transplantation (HSCT) recipients will develop pulmonary complications with an associated mortality of 32–61% [1–7]. The onset of respiratory symptoms and chest radiographic opacities in HSCT recipients can provide clinicians with a diagnostic and management dilemma.

Flexible bronchoscopy has been employed in the examination of pulmonary radiographic opacities in HSCT patients, with a role for early bronchoalveolar lavage (BAL) identified in infectious pneumonitis [8]. However, the role of transbronchial biopsy (TBBx) as an adjunct to bronchoscopy remains unclear in HSCT recipients, with only a small number of retrospective studies having examined TBBx in this patient population [9]. These studies were limited by sample size, the largest study comprising 71 TBBx cases (Table 1) [10]. The studies have noted variable diagnostic yield, therapy modifications and overall survival following the use of TBBx [10–16]. Furthermore, a recent survey of clinicians in both academic and non-academic settings reports varying approaches towards the use of bronchoscopy in the management of pulmonary complications [17]. We now report our experience with 130 TBBx cases at a single center, with diagnostic yield and therapy modifications examined in this clinical setting. Establishing guidelines for the optimal bronchoscopic approach in HSCT recipients would enhance our ability to care for patients with pulmonary complications.

METHODS

Study Subject Demographics

Medical records from all patients who underwent HSCT and flexible bronchoscopy at the University of Michigan Medical Center between the 2000 and 2015 were reviewed. All participants enrolled in the study gave written informed consent, and the study was approved by the Institutional Review Board (IRB) at the University of Michigan. Indications for bronchoscopy included cough, dyspnea, fever and/or the presence of new opacities on chest radiograph or computed tomography (CT) of the chest. All patients received antimicrobial prophylaxis according to institutional guidelines (see online Supplement).

Bronchoscopy Procedure and Sample Processing

Flexible bronchoscopy was performed according to established guidelines [18, 19]. For further details see online supplement. There are no standardized algorithms to guide clinicians in the diagnostic approach to employing bronchoscopy at our institution. The histopathological results were obtained from the final pathology report and tissue culture results were obtained from the final microbiological report. The identification of potential pathogens was recorded from final microbiological reports, including special stains (gram, fungal, acid fast), cultures (viral, fungal, and bacterial) and PCR based assays for cytomegalovirus (CMV) and other viral pathogens performed after 2005. Potential complications of bronchoscopy included

hemorrhage, arrhythmia, refractory hypoxia (lasting > 24 hours), respiratory failure with need for mechanical ventilation, pneumothorax, and/or hypotension. Prior to 2006, the number of TBBx biopsies performed per TBBx procedure was not recorded. Therefore, analysis of the association between the number of TBBx performed per bronchoscopy and other variables is limited (n=67).

Clinical Outcomes

Our primary endpoint was the change in medical management after bronchoscopy. Medical records were reviewed for 7 days post bronchoscopy to determine if bronchoscopy results contributed to a change in patient therapy. Changes included a) escalation or de-escalation of antimicrobial therapy, b) escalation or de-escalation of systemic corticosteroid therapy, c) addition or removal of cytokine directed therapy [tumor necrosis factor (TNF) inhibitors]. Therapy escalation included increases in dosing by > 50% of a previous dose, or addition of another therapeutic agent. Multiple therapy changes within each category were recorded. This approach is consistent with previous studies [10, 11, 13]. A TBBx was defined as positive based upon the presence of a histopathological abnormality and/or an infectious pathogen on histopathology or tissue culture. A TBBx was defined as negative or non-diagnostic if histopathology findings did not demonstrate an abnormality and tissue culture was negative. A positive BAL was indicated by culture of an infectious pathogen.

Statistical Analysis

Associations with change in therapy (overall, antibiotic, corticosteroid and anti-TNF/etanercept) were assessed using univariate logistic regression followed by multivariate logistic regression modeling. For each separate change outcome, a forward selection procedure determined statistically significant associations. Model fitting was then repeated to include all identified predictors (and potential confounders) in a consistent manner across therapy modification models. Similar logistic regression methods with forward selection procedure were used to evaluate associations with positive TBBx results and, separately, whether the patient experienced complications. No statistically significant interactions were identified in any of the regression models. Area under curve (AUC) receiver operating characteristic (ROC) curves were used to assess the predictive value of various models. Models including PFT measurements of Forced Vital Capacity (FVC) excluded 11 patients due to missing FVC values. Parametric descriptive data was analyzed using a student's t-test. Non-parametric descriptive data was analyzed using a Chi-squared test or Fischer's exact test for data in supplementary Table S1. A p value of <0.05 was employed as the level of statistical significance. Kaplan Meier curves were generated with hazard ratios and 95% confidence intervals to examine all-cause mortality outcomes. All statistical analysis for this paper was generated using SAS software (© version 9.4, SAS Institute, Cary, NC, USA).

RESULTS

Clinical characteristics of the study cohort

The study population consisted of 600 HSCT recipients who underwent bronchoscopy at the University of Michigan Medical Center between 2000 and 2015 (Supplementary Table S1). We identified 130 patients who underwent TBBx and BAL as a combined intervention from

this cohort (Table 2). The mean age of patients undergoing TBBx was 50 (+/− 12 S.D) years at the time of bronchoscopy. There were 102 (78%) allogeneic and 28 (22%) autologous HSCT recipients within the TBBx cohort. CT results (chest) are reported in Supplementary Table S1. When compared to patients that underwent BAL alone (n=470), the TBBx cohort (n=130) were significantly older at time of HSCT ($p<0.0001$) and bronchoscopy ($p<0.0001$), displayed higher pre-bronchoscopy platelet levels ($p<0.0001$) and neutrophil counts ($p<0.01$). The TBBx cohort demonstrated lower pre-morbid pulmonary function testing with significantly lower percentage predicted measures of FVC ($p=0.01$), forced expiratory volume (FEV1)($p=0.01$) and diffusion coefficient for carbon monoxide transfer (DLCO) ($p<0.0001$) compared to those undergoing BAL alone (Supplementary Table S1).

Investigating the yield of TBBx in HSCT

Abnormal histologic findings were noted in 61 (47%) of the 130 TBBx cases. Rates of positive and negative TBBx and BAL results are depicted in Supplementary Table S2. The most common histopathological finding on TBBx was a non-specific interstitial pneumonitis (n=24, 18%) (Table 3). Bronchiolitis obliterans was identified in 12 cases (9%), in which 7 cases had pre-bronchoscopy evidence of obstructive physiology on pulmonary function testing and 5 cases had normal pulmonary physiology (data not shown). There were only 5 cases (4%) of infectious pathology identified on TBBx, including nocardia (n=1), aspergillus sp (n=1), non-specified fungal disease (n-=2) and one mycetoma. Cultures of BAL fluid likewise identified aspergillus sp. in the same case in which aspergillus was identified on TBBx, and also identified aspergillus in the mycetoma. In two other cases, nocardia sp. and rhinovirus were detected on BAL, when a non-specific fungus was noted on TBBx. There was a significant association between a positive TBBx and the number of TBBx performed on univariate logistic regression analysis (odds ratio (OR)=1.66, 95% CI 1.16–2.39; $p<0.01$) which was maintained on multivariate analysis (OR=1.58, 95% CI 1.11–2.26; $p=0.01$). There was no association between a positive TBBx and time from HSCT to bronchoscopy ($p=0.17$). Univariate and multivariate model results for a positive TBBx are reported in Supplementary Table S3.

Therapy modifications based upon TBBx

We did not find that that TBBx results impacted therapy modifications post-HSCT in our case series of 130 HSCT recipients receiving TBBx. Modifications of antibiotic therapy after TBBx occurred in 60 (47%) cases, with modifications in systemic corticosteroids in 36 (28%) (Supplementary Table S4). A positive TBBx was not significantly associated with an increased odds of a therapy modification ($p=0.15$), when compared with cases whereby TBBx was either negative or non-diagnostic in multivariate analysis. Variables that increase the odds of a change in therapy after multivariate logistic regression analysis included a positive BAL result ($p<0.001$) and the number of antibiotic agents administered prior to bronchoscopy ($p<0.01$). A higher pre-bronchoscopy FVC was associated with a reduced odds of change in therapy ($p=0.01$). Logistic regression analysis is reported in Table 4. In cases whereby the BAL result was also positive, the increased odds ratio of therapy change associated with a positive BAL was of similar magnitude, direction and significance whether a TBBx was positive ($p=0.03$) or negative ($p=0.02$). The interaction between BAL and TBBx test results in affecting therapy changes was not statistically significant ($p=0.85$) (Table 4).

Modifications in corticosteroid therapy post TBBx

We subsequently examined variables associated with a change in systemic corticosteroid therapy post TBBx in our series of 130 patients. There were 19 cases where systemic corticosteroids were escalated following a positive TBBx and 12 cases of systemic corticosteroid escalation following a negative TBBx (Supplementary Table S4). Whereby a positive TBBx was associated with an increased odds of a change in systemic corticosteroid therapy (p=0.05), a positive BAL was not significantly associated with changes in corticosteroid therapy (p=0.23) (Table 5). After multivariate analysis, only a positive TBBx (p=0.02) and the number of antibiotics prior to bronchoscopy (p<0.01) were associated with an increased odds of corticosteroid therapy change, while a higher FVC (p<0.001) and longer time from HSCT to bronchoscopy (p=0.08) were associated with reduced odds of therapy change or were deemed to be of marginal significance (Table 5). Neither a positive TBBx (p=0.25) or a positive BAL (p=0.62) were significantly associated with a change in anti-TNF therapy (etanercept, Amgen Inc), although numbers of events were relatively small (n=5) (Supplementary Table S5).

Changes in antibiotic therapy post TBBx

The impact of TBBx on modifications of antibiotic therapy was examined in our case series of 130 HSCT. There were 60 (47%) cases in which changes in antibiotics occurred post TBBx (Supplementary Table S4). No significant association was found between a positive TBBx result and subsequent changes in antibiotic therapy (p=0.96). In multivariate analysis, variables significantly associated with a change in antibiotic therapy included a positive BAL result (p<0.0001), the number of antibiotics administered prior to bronchoscopy (p=0.01) and the time from HSCT to bronchoscopy (p=0.01). The interaction between a positive BAL and a positive TBBx result was not significant (p=0.87). Univariate and multivariate analysis are reported in Table 6.

Complications associated with bronchoscopy in HSCT patients

Procedural related complications (Supplementary Table S6) were more common in the 130 HSCT recipients that underwent TBBx when compared to the 470 that underwent BAL alone, without TBBx (14% vs 5%, p< 0.001). Univariate and multivariate analysis for all bronchoscopy related complications are reported in Table 7. We report an increased odds of a bronchoscopy related complication if TBBx were performed (p=0.001), with a lower pre-bronchoscopy FVC (p=0.05) and with a clinical history of myeloablative conditioning (p=0.04). There was no significant association between the number of TBBx performed and a complication (p=0.16) (Supplementary Table S7). Given that studies reported inferior outcomes in patients experiencing procedure related adverse events [4], we examined 30 day mortality in the TBBx cohort (Supplementary Fig. S1). We report no statistically significant difference in all-cause mortality between HSCT patients with procedure related complications (HR=1.24, 95%CI=0.57–2.69; p=0.58).

DISCUSSION

The role of TBBx post-HSCT has been described by small case series to date, with diagnostic yields of 5% to 82% reported [10–16](Table 1). Given the limitations of the current

literature, we now describe the largest case series of patients undergoing TBBx following HSCT, with a diagnostic yield < 50%. The most frequent histologic finding in our study was a non-specific interstitial pneumonitis (18%). A diagnosis of non-specific interstitial pneumonitis is frequently reported in the literature and in many cases the histopathological data have not been representative of the patient's clinical condition[8, 10, 13].

The perceived value of TBBx is its ability to provide histopathological data to guide decision making, particularly in the setting of non-infectious lung pathology. Non-infectious lung complications are common post-HSCT, and are classically defined by both clinical and radiographic criteria [20]. Recent work has highlighted the potential for under-recognized ante-mortem non-infectious pathology on post mortem examination, given further consideration to the importance of tissue acquisition for an accurate diagnosis in HSCT patients[21]. In the current report, BOS was identified in 12 (9%) cases. In 7 of these 12 cases, spirometric data (pre-TBBx) revealed air trapping or airflow obstruction, supporting a diagnosis of BOS. In five of the 12 cases, however, BOS was only identified by TBBx, without signs of airflow obstruction present.

Our reported association between a positive TBBx and a change in corticosteroid therapy would give plausibility to the benefit of TBBx in cases where a non-infectious pathology was suspected. However, further studies in larger numbers of patients will be required to confirm this finding. It is also possible that the absence of infectious pathogens on TBBx and BAL will guide decisions regarding the management of non-infectious pathology in the lung. In two cases, negative microbial assays on BAL and TBBx resulted in the initiation of cytokine directed therapy with TNF inhibitors. Anti-TNF receptor treatment with etanercept was previously been shown to be potentially beneficial in the management of idiopathic pneumonia syndrome (IPS), a proposed non-infectious post-transplant lung injury syndrome [22].

The utility of BAL in the diagnosis of infectious pathogens has been previously reported in several retrospective studies and one meta-analysis which included both HSCT and oncology patients [9, 10]. Transbronchial biopsies though had low diagnostic yields for identifying pathogens, with rates < 5% reported [10]. In our current study, histologic confirmation of pathogens was likewise rare, with less than 5% of TBBx demonstrating a potential infectious process. In general, the most common pulmonary complication in both autologous and allogenic HSCT is the development of infectious lobar and/or bronchopneumonia [23]. Early recognition and appropriate anti-microbial treatment may improve mortality in such patients [4, 24]. A positive BAL result in patients who underwent TBBx was the variable most likely to lead to a change in all therapy and specifically antibiotic therapy in our data, re-emphasizing the important utility of this modality in HSCT recipients with evolving pulmonary complications. Evolving tools include the availability of next generation sequencing such as unbiased next generation sequencing of RNA (UMERS) in clinical samples to improve diagnostic yields of infectious pathogens [25]. Future developments may obviate the use of TBBx in HSCT cases.

In our current study, procedural complications occurred with 14% of TBBx procedures, with no association between the number of TBBx and complication rates. Lower pre-

bronchoscopy FVC and myeloablative conditioning are associated with an increased risk of complication in our data. Complication rates of bronchoscopy in the HSCT population are historically higher than the general population with a rate of 9–15% reported [4, 10, 11, 26]. Though TBBx related complications are (in general) poorly defined in the literature, complication rates of 30% have been reported in one study, with a 2nd report noting a 6-fold increased risk of complications compared to performing a BAL alone [26, 27]. Selected studies have noted inferior outcomes in patients who experience complications associated with bronchoscopy or TBBx [4]. Our data does not support an association between increased all-cause mortality and bronchoscopy related complications.

There are several limitations to our study. The retrospective nature of our study may introduce bias and we cannot attest to causality. As a single center study with treatment specific protocols and clinical care guidelines, our results may not be broadly applicable to other centers. The decision to proceed to TBBx was determined by the consulting pulmonologist, and thus confounding variables that cannot be controlled for exist, with the potential for sampling bias in subject selection for TBBx. There are significant differences in several important parameters in patients undergoing BAL alone versus TBBx and BAL which must be noted and would support selection bias. Importantly, we do not make comparisons between these two groups and this study only analyses the 130 patients who underwent TBBx. Despite the large study size, there is still limited power for subgroup analysis. A detailed review of medical records was carried out to reconcile bronchoscopy results with management and therapy changes; by a team of investigators. A comparison between outcomes in HSCT patients with pulmonary complications who did not undergo bronchoscopy was not possible. BAL and TBBx are not mutually exclusive, however our goal was to report and better understand the implications of TBBx in this cohort of patients. The impact of BAL diagnostics on clinical decision making in HSCT recipients is well-studied. Lastly, decision making is subject to an assessment of the pre-test probability of any given diagnosis and not solely determined by the results of bronchoscopy alone.

In conclusion, the addition of a TBBx during bronchoscopy was not associated with modifications in antibiotic therapy, or improved diagnostic yield for infectious pathogens in HSCT recipients. TBBx has no additive value over BAL in the diagnosis and management of infectious pneumonitis. The TBBx intervention may be associated with increased odds of a procedure related complication. There may be a role for TBBx in the diagnostic evaluation of non-infectious pulmonary complications; further prospective study with appropriate design and "a priori" questions is required to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support: NIH grants AI117229 and HL127805 (BBM)

The authors thank the patients who participated and our study coordinator, Connie Varner.

References

1. Krowka MJ, Rosenow EC 3rd, Hoagland HC. Pulmonary complications of bone marrow transplantation. Chest. 1985; 87(2):237–46. [PubMed: 2981658]
2. Soubani AO, Miller KB, Hassoun PM. Pulmonary complications of bone marrow transplantation. Chest. 1996; 109(4):1066–77. [PubMed: 8635332]
3. Harris B, Lowy FD, Stover DE, Arcasoy SM. Diagnostic bronchoscopy in solid-organ and hematopoietic stem cell transplantation. Ann Am Thorac Soc. 2013; 10(1):39–49. [PubMed: 23509331]
4. Dunagan DP, Baker AM, Hurd DD, Haponik EF. Bronchoscopic evaluation of pulmonary infiltrates following bone marrow transplantation. Chest. 1997; 111(1):135–41. [PubMed: 8996007]
5. Lucena CM, Torres A, Rovira M, Marcos MA, de la Bellacasa JP, Sanchez M, et al. Pulmonary complications in hematopoietic SCT: a prospective study. Bone Marrow Transplant. 2014; 49(10): 1293–9. [PubMed: 25046219]
6. Allareddy V, Roy A, Rampa S, Lee MK, Nalliah RP, Allareddy V, et al. Outcomes of stem cell transplant patients with acute respiratory failure requiring mechanical ventilation in the United States. Bone Marrow Transplant. 2014; 49(10):1278–86. [PubMed: 25111514]
7. Yadav H, Nolan ME, Bohman JK, Cartin-Ceba R, Peters SG, Hogan WJ, et al. Epidemiology of Acute Respiratory Distress Syndrome Following Hematopoietic Stem Cell Transplantation. Crit Care Med. 2016; 44(6):1082–90. [PubMed: 26807683]
8. Shannon VR, Andersson BS, Lei X, Champlin RE, Kontoyiannis DP. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2010; 45(4):647–55. [PubMed: 19684637]
9. Chellapandian D, Lehrnbecher T, Phillips B, Fisher BT, Zaoutis TE, Steinbach WJ, et al. Bronchoalveolar lavage and lung biopsy in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review and meta-analysis. J Clin Oncol. 2015; 33(5):501–9. [PubMed: 25559816]
10. Patel NR, Lee PS, Kim JH, Weinhouse GL, Koziel H. The influence of diagnostic bronchoscopy on clinical outcomes comparing adult autologous and allogeneic bone marrow transplant patients. Chest. 2005; 127(4):1388–96. [PubMed: 15821221]
11. White P, Bonacum JT, Miller CB. Utility of fiberoptic bronchoscopy in bone marrow transplant patients. Bone Marrow Transplant. 1997; 20(8):681–7. [PubMed: 9383232]
12. Soubani AO, Qureshi MA, Baynes RD. Stem Cell Transplantation S. Flexible bronchoscopy in the diagnosis of pulmonary infiltrates following autologous peripheral stem cell transplantation for advanced breast cancer. Bone Marrow Transplant. 2001; 28(10):981–5. [PubMed: 11753555]
13. Gilbert CR, Lerner A, Baram M, Awsare BK. Utility of flexible bronchoscopy in the evaluation of pulmonary infiltrates in the hematopoietic stem cell transplant population -- a single center fourteen year experience. Arch Bronconeumol. 2013; 49(5):189–95. [PubMed: 23455477]
14. Qualter E, Satwani P, Ricci A, Jin Z, Geyer MB, Alobeid B, et al. A comparison of bronchoalveolar lavage versus lung biopsy in pediatric recipients after stem cell transplantation. Biol Blood Marrow Transplant. 2014; 20(8):1229–37. [PubMed: 24769329]
15. Springmeyer SC, Silvestri RC, Sale GE, Peterson DL, Weems CE, Huseby JS, et al. The role of transbronchial biopsy for the diagnosis of diffuse pneumonias in immunocompromised marrow transplant recipients. Am Rev Respir Dis. 1982; 126(5):763–5. [PubMed: 6293351]
16. Campbell JH, Blessing N, Burnett AK, Stevenson RD. Investigation and management of pulmonary infiltrates following bone marrow transplantation: an eight year review. Thorax. 1993; 48(12):1248–51. [PubMed: 8303632]
17. Wahla AS, Chatterjee A, Khan II, Conforti JF, Haponik E. Survey of academic pulmonologists, oncologists, and infectious disease physicians on the role of bronchoscopy in managing hematopoietic stem cell transplantation patients with pulmonary infiltrates. J Bronchology Interv Pulmonol. 2014; 21(1):32–9. [PubMed: 24419184]
18. Committee BTSBG. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax. 2001; 56(Suppl 1):i1–21. [PubMed: 11158709]

19. Du Rand IA, Blaikley J, Booton R, Chaudhuri N, Gupta V, Khalid S, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax. 2013; 68(Suppl 1):i1–i44. [PubMed: 23860341]
20. Pena E, Souza CA, Escuissato DL, Gomes MM, Allan D, Tay J, et al. Noninfectious pulmonary complications after hematopoietic stem cell transplantation: practical approach to imaging diagnosis. Radiographics. 2014; 34(3):663–83. [PubMed: 24819788]
21. Gazourian L, Spring L, Meserve E, Hwang D, Diaz AA, Ash SY, et al. Pulmonary Clinicopathological Correlation after Allogeneic Hematopoietic Stem Cell Transplantation: An Autopsy Series. Biol Blood Marrow Transplant. 2017
22. Yanik GA, Ho VT, Levine JE, White ES, Braun T, Antin JH, et al. The impact of soluble tumor necrosis factor receptor etanercept on the treatment of idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. Blood. 2008; 112(8):3073–81. [PubMed: 18664626]
23. Afessa B, Abdulai RM, Kremers WK, Hogan WJ, Litzow MR, Peters SG. Risk factors and outcome of pulmonary complications after autologous hematopoietic stem cell transplant. Chest. 2012; 141(2):442–50. [PubMed: 21778261]
24. Rano A, Agusti C, Benito N, Rovira M, Angrill J, Pumarola T, et al. Prognostic factors of non-HIV immunocompromised patients with pulmonary infiltrates. Chest. 2002; 122(1):253–61. [PubMed: 12114367]
25. Fischer N, Indenbirken D, Meyer T, Lutgehetmann M, Lellek H, Spohn M, et al. Evaluation of Unbiased Next-Generation Sequencing of RNA (RNA-seq) as a Diagnostic Method in Influenza Virus-Positive Respiratory Samples. J Clin Microbiol. 2015; 53(7):2238–50. [PubMed: 25972420]
26. Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, et al. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. Monaldi Arch Chest Dis. 2009; 71(1):8–14. [PubMed: 19522159]
27. Burgher LW. Complications and results of transbronchoscopic lung biopsy. Nebr Med J. 1979; 64(8):247–8.
28. Glazer M, Breuer R, Berkman N, Lossos IS, Kapelushnik J, Nagler A, et al. Use of fiberoptic bronchoscopy in bone marrow transplant recipients. Acta Haematol. 1998; 99(1):22–6. [PubMed: 9490561]
29. Huaringa AJ, Leyva FJ, Signes-Costa J, Morice RC, Raad I, Darwish AA, et al. Bronchoalveolar lavage in the diagnosis of pulmonary complications of bone marrow transplant patients. Bone Marrow Transplant. 2000; 25(9):975–9. [PubMed: 10800066]
30. Feinstein MB, Mokhtari M, Ferreiro R, Stover DE, Jakubowski A. Fiberoptic bronchoscopy in allogeneic bone marrow transplantation: findings in the era of serum cytomegalovirus antigen surveillance. Chest. 2001; 120(4):1094–100. [PubMed: 11591544]
31. Hofmeister CC, Czerlanis C, Forsythe S, Stiff PJ. Retrospective utility of bronchoscopy after hematopoietic stem cell transplant. Bone Marrow Transplant. 2006; 38(10):693–8. [PubMed: 16980989]

Table 1

Summary of studies evaluating yield and utility of TBBx in HSCT

Reference	Time Period	Bronchoscopy, No.	TBBx, (/Total No.)	Yield (%)[a]
Spingmeyer *et al*[15]	1975–1978	24	14	58
Cambpell *et al*[16]	1982–1990	27	4	50
Dunagan *et al*[4]	1990–1994	71	2	NR[b]
White *et al*[11]	1993–1995	68	42	12
Glazer *et al*[28]	1991–1995	79	7	43
Huaringa *et al*[29]	NR	124	NR	-
Soubani *et al*[12]	NR	27	14	71
Feinstein *et al*[30]	1997–1999	76	7	14
Patel *et al*[10]	1997–2001	169	8	-[c]
Hoffmeister *et al*[31]	1994–2004	91	21	5
Shannon *et al*[8]	1994–1999	598	65	68
Gilbert *et al*[13]	1996–2009	162	22	82
Current study	2000–2015	600	130	47

Adapted from references [11] and [31] and with literature review and Medline search terms "Transbronchial biopsy" "HSCT"

[a] % of biopsies with abnormal/diagnostic histopathological findings

[b] not reported

[c] study reported 82% of biopsies were non-specific, 10% showed malignancy

Table 2

Clinical Characteristics and Demographics of the TBBx study cohort

	TBBx Cohort
No.	130
Age yrs (+/− S.D)	
at HSCT,	49.0 (12)
at Bronchoscopy,	50.0 (12)
Male, No. (%)	76 (58)
GVHD[a], No. (%)	
Yes	67 (51)
No	63 (49)
Platelet count, K/uL (+/− S.D)	184.0 (97.0)
Neutrophil count, K/uL (+/− S.D)	5.6 (3.9)
Conditioning, No. (%)	
Reduced Intensity	35 (27)
Myeloablative	95 (73)
Type, No. (%)	
Autologous	28 (22)
Allogenic	102 (78)
MUD	42 (41)
RB	59 (58)
UCB	1 (1)
Source, No. (%)	
BM	5 (4)
DBLUCD	1 (0.5)
PB	123 (95)
UCB	1 (0.5)
Diagnosis, No. (%)	
NHL/Hodgkin's	46 (35)
AML/MDS/MF	43 (33)
ALL	10 (8)
Myeloma	4 (3)
Others	27 (21)
Pulmonary Function, (+/− S.D)	
FVC, % predicted	82 (19)
FEV1, %	82 (25)
DLCO, %	59 (19)
Pulmonary Imaging, No. (%)	
CT present	113 (93)
HRCT	81 (68)
Bronchoscopy	
Time from HSCT to TBBx[b]	364 (346)

	TBBx Cohort
Time from CT to TBBx[c]	9.4 (1.0)
No. of TBBx per procedure[b]	5.2 (1.9)
Time from PFT to TBBx[c]	55 (8)
Time from Abx to TBBx[c]	6.0 (1.3)

MUD=matched unrelated donor

RB=Related blood

UCB=Umbilical cord blood

BM=Bone marrow

DBLUCD=Double umbilical cord blood

PB=Peripheral blood

NHL=Non-Hodgkin's lymphoma

AML=acute myeloid leukemia/

MDS=myelodysplastic syndrome

MF=marrow failure

ALL=acute lymphoblastic leukemia

FVC=forced vital capacity, % predicted

Fev1=forced expiratory volume in 1 second

DLCO=diffusion capacity for carbon monoxide

HRCT=high resolution computed tomography

[a] acute and/or chronic

[b] mean days or number +/− S.D

[c] mean days +/− S.E.M, Abx=antimicrobials, n=113 for days from CT to TBBx, n=120 for days from PFT to TBBx

Table 3

Histopathological diagnosis by Transbronchial biopsy

	(N=130)
TBBx Positive (%)	61 (47)
Bronchiolitis Obliterans (%)[a]	12 (20)
Organizing Pneumonia (%)	4 (7)
BO-OP[b] (%)	7 (11)
Malignancy (%)	1 (2)
Infection (%)	5 (8)
Pneumonitis (%)	24 (39)
Fibrosis (%)	6 (10)
Other (%)	2 (3)

[a] % of positive biopsy

[b] Bronchiolitis obliterans-organizing pneumonia

Table 4

Logistic regression model of change of therapy post TBBx

Variables	OR	95% CI		P value
Univariate Model				
TBBx +	1.30	0.64	2.66	0.47
BAL +	4.93	1.88	12.90	**0.001**
Interaction[a]				0.85
BAL + in patients of TBBx +	4.43	1.12	17.51	**0.03**
BAL + in patients of TBBx −	5.33	1.38	20.61	**0.02**
Clinical:				
Male	1.87	0.91	3.84	0.09
Age	1.00	0.97	1.03	0.78
Allogenic[b]	1.91	0.82	4.46	0.13
Reduced intensity conditioning[c]	0.88	0.40	1.94	0.74
GVHD[d]	1.34	0.66	2.74	0.41
Platelet count	1.00	0.99	1.00	0.95
Neutrophil count	1.03	0.94	1.14	0.53
Pulmonary physiology:				
FVC[e]	0.84	0.68	1.02	0.08
FEV1[e]	0.90	0.78	1.05	0.20
DLCO[e]	0.96	0.77	1.19	0.69
Radiology:				
Diffuse Nodules	0.47	0.22	1.04	0.06
Bronchoscopy:				
Antibiotic therapy prior to TBBx[f]	2.01	0.96	4.21	**0.06**
Antibiotics prior in days[g]	1.01	0.95	1.06	0.81
No. of antibiotics prior to TBBx	1.48	1.06	2.07	**0.02**
No. of TBBx per procedure[h]	0.92	0.70	1.22	0.57
Time from HSCT to TBBx[i]	1.03	0.93	1.15	0.55
Multivariate Model (AUC=0.775)				
TBBx +	1.92	0.79	4.70	0.15
BAL +	6.14	2.19	17.22	**<0.001**
No. of antibiotics prior to TBBx	1.90	1.22	2.95	**<0.01**
FVC[e]	0.73	0.57	0.93	**0.01**
Time from HSCT to TBBx[i]	1.09	0.95	1.24	0.21

[a] Interaction btw BAL+ and TBBx+ OR=odds ratio

[b] vs autologous

[c] vs myeloablative conditioning

[d] acute and/or chronic

[e] per 10% increase in % predicted measure

[f] antibiotics prior to procedure, yes vs no

[g] per increase by 1

[h] per increase by 1

[i] per 100 days

Certain CT radiological features are not depicted with p>0.1

Table 5

Logistic regression model of corticosteroid therapy change

Variables	OR	95% CI		P value
Univariate Model				
TBBx +	2.22	1.01	4.86	**0.05**
BAL +	0.58	0.24	1.42	0.23
Interaction[a]				0.71
Clinical:				
Male	1.62	0.72	3.61	0.24
Age	1.00	0.97	1.03	0.86
Allogenic[b]	1.19	0.46	3.11	0.72
Reduced intensity conditioning[c]	0.71	0.29	1.75	0.46
GVHD[d]	1.25	0.58	2.70	0.57
Platelet count	1.0	0.99	1.00	0.95
Neutrophil count	0.99	0.89	1.09	0.81
Pulmonary Physiology:				
FVC[e]	0.74	0.59	0.94	**0.01**
FEV1[e]	0.91	0.77	1.07	0.25
DLCO[e]	0.79	0.62	1.01	0.06
Radiology:				
Diffuse air space disease	2.70	1.11	6.55	**0.03**
Diffuse Nodules	0.32	0.13	0.83	**0.02**
Bronchoscopy:				
Antibiotic therapy prior to TBBx[f]	2.77	1.26	6.12	**0.01**
Antibiotic prior in days[g]	1.01	0.96	1.06	0.73
No. of antibiotic prior to TBBx[h]	1.55	1.15	2.10	**<0.01**
No. of TBBx per procedure	1.10	0.79	1.52	0.57
Time from HSCT to TBBx[i]	0.83	0.71	0.97	**0.02**
Multivariate Model (AUC=0.81)	**OR**	**95% CI**		**P value**
TBBx +	3.12	1.18	8.23	**0.02**
BAL+	0.76	0.26	2.19	0.61
No. of antibiotic prior to TBBx	1.83	1.21	2.75	**<0.01**
FVC[e]	0.62	0.47	0.82	**<0.001**
Time from HSCT to TBBx[i]	0.85	0.71	1.02	0.08

[a] Interaction btw BAL+ and TBBx+ OR=odds ratio

[b] vs autologous

[c] vs myeloablative conditioning

[d] acute and/or chronic

[e] per 10% increase in % predicted measure

[f] antibiotics prior to procedure, yes vs no

[g] per increase by 1

[h] per increase by 1

[i] per 100 days

Certain CT radiological features are not depicted with p>0.1

Table 6

Logistic regression model of specific antibiotic therapy change

Variables	OR	95% CI		P value
Univariate Model				
BAL +	10.29	4.05	26.10	**<0.0001**
TBBx +	0.98	0.49	1.96	0.96
Interaction[a]				0.87
Clinical:				
Male	1.89	0.93	3.85	0.08
Age	1.01	0.98	1.03	0.75
Allogenic[b]	2.60	1.05	6.44	**0.04**
Reduced intensity conditioning[c]	1.14	0.53	2.48	0.74
GVHD[d]	1.01	0.51	2.01	0.98
Platelet count	1.00	1.00	1.00	0.75
Neutrophil count	1.05	0.95	1.15	0.34
Pulmonary physiology:				
FVC[e]	1.04	0.86	1.26	0.71
FEV1[e]	1.03	0.89	1.19	0.70
DLCO[e]	1.10	0.89	1.36	0.38
Radiology:				
Bronchoscopy:				
Antibiotic therapy prior to TBBx[f]	2.19	1.08	4.46	**0.03**
Antibiotics prior in daysg	1.01	0.96	1.07	0.64
No. of antibiotic prior to TBBx	1.35	1.01	1.81	**0.04**
No. of TBBx per procedure[h]	0.82	0.62	1.09	0.17
Time from HSCT to TBBx[i]	1.13	1.02	1.27	**0.02**
Multivariate Model (AUC=0.84)	**OR**	**95% CI**		**P value**
TBBx	1.01	0.40	2.54	0.98
BAL +	13.81	4.93	38.69	**<0.0001**
No. of antibiotics prior to TBBx	1.67	1.13	2.47	**0.01**
FVC[e]	1.01	0.79	1.30	0.92
Time from HSCT to TBBx[i]	1.19	1.04	1.36	**0.01**

[a] Interaction btw BAL+ and TBBx+ OR=odds ratio

[b] vs autologous

[c] vs myeloablative conditioning

[d] acute and/or chronic

[e] per 10% increase in % predicted measure

[f] antibiotics prior to procedure, yes vs no

[g] per increase by 1

[h] per increase by 1

[i] per 100 days

Certain CT radiological features are not depicted with p>0.1

Table 7

Logistic regression model of bronchoscopy related complications (n=600)

Variable	OR	95% CI		P value
Univariate Model	N=600			
With TBBx	3.27	1.70	6.31	**<0.001**
BAL negative	1.03	0.51	2.07	0.94
Clinical:				
Female	2.07	1.09	3.94	**0.03**
Age	1.00	0.99	1.02	0.61
Autologous[a]	1.35	0.64	2.84	0.43
Myeloablative conditioning[b]	1.65	0.68	4.01	0.27
GVHD[c]	1.12	0.57	2.19	0.74
Platelet count	1.00	1.00	1.01	0.11
Neutrophil count	1.06	0.99	1.12	0.10
Pulmonary physiology:				
FVC[d]	1.23	1.02	1.48	**0.03**
FEV1[d]	1.16	1.00	1.34	**0.05**
DLCO[d]	1.29	1.05	1.59	**0.01**
Bronchoscopy:				
Antibiotics, no[e]	2.10	1.10	4.00	**0.02**
No of antibiotics prior to bronchoscopy	1.30	1.01	1.67	**0.04**
Antibiotics prior in days[f]	1.08	1.01	1.15	**0.03**
Multivariate Model (AUC=0.688)	**OR**	**95% CI**		**P value**
With TBBx	3.33	1.63	6.79	**0.001**
Myeloablative[b]	3.08	1.04	9.11	**0.04**
FVC[d]	1.02	1.00	1.04	**0.05**

[a] vs allogenic

[b] vs reduced intensity

[c] acute and/or chronic

[d] per 10% decrease in % predicted value

[e] antibiotics prior to bronchoscopy, no vs yes

[f] per 1 day decrease

Certain CT radiological features are not depicted with p>0.2