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The Influence of Diagnostic Bronchoscopy on Clinical Outcomes Comparing Adult Autologous and Allogeneic Bone Marrow Transplant Patients*

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Study objectives: **To review our experience with diagnostic bronchoscopy in the evaluation of pulmonary infiltrates in adult hematopoietic stem cell transplantation (HSCT) recipients in the era of Pneumocystis prophylaxis and cytomegalovirus antigen testing. The study focused on diagnostic yields and the influence of bronchoscopic findings on pharmacologic therapy and mortality, comparing allogeneic (allo) HSCT patients to autologous (auto) HSCT patients.**
Design: **Case series review.**
Setting: **Tertiary care academic urban medical centers.**
Patients: **All adult allo-HSCT and auto-HSCT patients undergoing bronchoscopy for the evaluation of pulmonary infiltrates from January 1997 to September 2001.**
Measurements and results: **The review identified 169 bronchoscopies that had been performed on HSCT patients, representing 12.5% of all HSCT patients (allo-HSCT patients, 125 bronchoscopies; auto-HSCT patients, 44 bronchoscopies). Bronchoscopy was requested more often in allo-HSCT patients (18.7%) compared to auto-HSCT patients (6.6%). Findings at bronchoscopy provided a specific diagnosis more frequently in allo-HSCT patients (50%) compared to auto-HSCT patients (34%). For both allo-HSCT and auto-HSCT patients, most diagnoses were obtained by BAL alone, whereas transbronchial biopsy (TBBx) provided additional specific information in < 10% of cases. For select patients (n = 27), surgical lung biopsy following bronchoscopy provided unique diagnoses in 47 to 50% of cases. Information from bronchoscopy influenced clinical decisions more often in allo-HSCT patients (50%) than in auto-HSCT patients (36%), and allowed for the discontinuation or addition of antimicrobial, corticosteroid, or antineoplastic agents to treatment. Complications from bronchoscopy occurred in 9% of all HSCT patients (n = 15), and were associated with higher in-hospital mortality rates in allo-HSCT patients (82%; n = 9) compared to auto-HSCT patients (50%; n = 2). The overall in-hospital mortality rates for allo-HSCT and auto-HSCT patients having bronchoscopy was similar (38% vs 27%, respectively; p = 0.25), and establishing a specific diagnosis by bronchoscopy did not improve the in-hospital mortality rate for allo-HSCT or auto-HSCT patients.**
Conclusions: **Bronchoscopy may provide clinically useful information in the evaluation of adult allo-HSCT and auto-HSCT recipients with pulmonary infiltrates. The results of testing BAL fluid samples alone suggested an etiology in most cases, whereas the findings of TBBx provided unique diagnoses infrequently. Further studies are warranted to improve the utility of diagnostic bronchoscopy in the evaluation of HSCT patients.** ***(CHEST 2005; 127:1388–1396)***

Key words: bone marrow transplantation; bronchoscopy; immunocompromised host

Abbreviations: allo = allogeneic; auto = autologous; CMV = cytomegalovirus; DAD = diffuse alveolar damage; DAH = diffuse alveolar hemorrhage; FIO_2 = fraction of inspired oxygen; HSCT = hematopoietic stem cell transplantation; PT = prothrombin time; SaO_2 = arterial oxygen saturation; SLB = surgical lung biopsy; TBBx = transbronchial biopsy

Hematopoietic stem cell transplantation (HSCT) has been used increasingly for a variety of medical indications since its inception in 1968.[1] The International Bone Marrow Transplant Registries[2] have estimated that 50,000 HSCTs are performed annually, including approximately 30,000 autologous (auto) HSCTs and approximately 17,000 allogeneic (allo) HSCTs. Pulmonary complications develop in 40 to 60% of HSCT recipients,[3–5] with an associated mortality rate of 32 to 61%.[4–6]

Bronchoscopy is often requested to evaluate HSCT patients with respiratory symptoms and chest

radiographic abnormalities. Bronchoscopy is generally considered a safe and minimally invasive procedure with which to establish the diagnosis in these patients. However, the reported diagnostic yield is highly variable, with prior studies[6–10] reporting diagnostic yields of 31 to 80% of patients. Diagnoses provided by bronchoscopy often influence decisions that are related to pharmacologic therapy, although the identification of a pathogen by bronchoscopy in these studies did not influence mortality, and the reported complication rates were reported as 0 to 27%.

The wide disparity in reported diagnostic yields, their influence on therapeutic decisions, and bronchoscopy-related complications may be multifactorial, and may in part reflect changes in the management of HSCT patients and the specific characteristics of the populations of HSCT recipients who were examined. Most prior studies were performed prior to the routine use of cytomegalovirus (CMV) antigen testing and Pneumocystis prophylaxis, and the clinical utility of bronchoscopy in this context has not been fully examined. With the routine use of prophylaxis, the spectrum of pulmonary complications may be evolving, and whether bronchoscopy remains helpful in the evaluation remains uncertain. Finally, prior studies have reported the experience of bronchoscopy in combined populations of allo-HSCT and auto-HSCT patients[6,8] or have focused on allo-HSCT patients only.[9,10] Recognizing differences in the spectrum of pulmonary complications for these two populations, prior studies did not directly compare allo-HSCT patients to auto-HSCT patients. The purpose of this study was to review our experience with diagnostic bronchoscopy in the evaluation of pulmonary infiltrates in adult HSCT recipients at urban tertiary care medical centers in the era of Pneumocystis prophylaxis and CMV antigen testing. Particular emphasis focused on diagnostic yields and the influence of bronchoscopic findings on clinical pharmacologic therapy and mortality, comparing allo-HSCT patients to auto-HSCT patients.

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Materials and Methods

Identification of Study Subjects

HSCT patients who underwent bronchoscopy during the period January 1997 to September 2001 were identified by a review of computerized hospital records. For patients who had undergone multiple bronchoscopies, each bronchoscopy was considered independently. The study included patients at the Brigham and Women's Hospital, a 635-bed tertiary care center, and the Beth Israel-Deaconess Medical Center, a 535-bed tertiary care center, each with active, accredited HSCT programs.

Clinical Characteristics

The medical records of each identified patient were reviewed, and the data were recorded on standardized forms. The collected data included the following: (1) general information (*ie*, age, gender, date of HSCT, and indication for HSCT); (2) information related to the time of bronchoscopy (*ie*, nature and duration of symptoms, number and duration of antimicrobial agents used, vital signs, routine blood testing results, chest radiographic results, and microbial culture data for sputum and blood); (3) findings related to bronchoscopy (*ie*, a description of visual findings, BAL culture, BAL cytology, and endobronchial and transbronchial biopsy (TBBx) pathology results; and (4) clinical outcomes (*ie*, changes in therapy related to bronchoscopy, complications related to bronchoscopy, and hospital mortality).

The vital signs recorded included heart rate, BP, respiratory rate, and an estimate of blood oxygenation. The variability in oxygen requirements were normalized by the use of an arterial oxygen saturation (Sa_{O_2})/fraction of inspired oxygen (F_{IO_2}) ratio. To determine the F_{IO_2} for patients receiving oxygen therapy by nasal cannula, each liter of supplemental oxygen was multiplied by 0.02 and was added to the room air F_{IO_2} (0.21). For intubated patients or patients requiring supplemental oxygen by face mask, the F_{IO_2} setting was considered to be the absolute F_{IO_2}. For example, for a patient with an Sa_{O_2} of 100% while breathing room air, the ratio was recorded as 1.0/0.21 = 4.76. For a patient with an Sa_{O_2} of 90% while breathing oxygen at 4 L/min by nasal cannula, the ratio was 0.90/0.29 = 3.1. Radiographic infiltrates were categorized as diffuse, focal, or nodular, according to the final report.

Bronchoscopic Findings

There was no standard protocol for the evaluation of pulmonary infiltrates in HSCT patients at either medical institution. Bronchoscopy in HSCT patients was performed at the discretion and direction of individual pulmonary consultants at each institution. The identification of potential pathogens was recorded from final microbiological laboratory reports. The reports included the results of routine microbiological cultures (bacterial, fungal, and viral), in addition to stains for acid-fast bacilli and special stains for organisms such as Pneumocystis sp. Reports for cytologic diagnosis were examined for the identification of nuclear inclusion bodies for CMV and hemosiderin-laden macrophages (for hemorrhage). The diagnosis of diffuse alveolar hemorrhage (DAH) was considered with the demonstration of a progressively bloody return of fluid at the time of BAL. For bronchoscopic biopsy specimens, pathologic diagnoses were obtained from the final pathology report. Medical records also were reviewed for surgical and/or autopsy lung pathology reports related to the same episode of illness.

Clinical Utility and Outcomes

Medical records were reviewed to identify changes in patient management in response to information obtained with bronchoscopy. Specific changes included the addition or discontinuation of therapy with antimicrobial agents, systemic glucocorticosteroid agents, or antineoplastic agents. Complications of bronchoscopy included the development of any of the following within 24 h of the procedure: (1) pulmonary hemorrhage requiring intubation; (2) respiratory distress and the need for assisted ventilation (either invasive or noninvasive); (3) pneumothorax requiring chest tube placement; (4) sustained oxygen desaturation (*ie*, unable to resume prebronchoscopy level of supplemental oxygen) requiring ICU monitoring as judged by the treating physicians; or (5) death.

Statistical Analysis

Comparisons of nonparametric data (such as the number of days post-HSCT) utilized the Mann-Whitney *U* test. Comparisons of nominal data (such as the presence of mechanical ventilation vs mortality) utilized χ^2 analysis, or in the case of small numbers, the Fisher exact test. A p value of < 0.05 was considered to be significant.

Results

Identification of HSCT Patients

Over the period January 1997 to September 2001, the study identified a total of 1,163 HSCT patients, including 591 auto-HSCT patients and 572 allo-HSCT patients. Over the same time period, a total of 169 bronchoscopies were performed to assess pulmonary infiltrates, including 44 bronchoscopies in 39 auto-HSCT patients and 125 bronchoscopies in 107 allo-HSCT patients. Most bronchoscopies were performed in hospitalized patients, including 38 of 44 bronchoscopies (86%) in auto-HSCT patients and 116 of 125 bronchoscopies (93%) in allo-HSCT patients. Overall, 12.5% of HSCT patients required bronchoscopy to assess pulmonary infiltrates, including 6.6% of auto-HSCT patients and 18.7% of allo-HSCT patients. Baseline characteristics at the time of bronchoscopy comparing auto-HSCT and allo-HSCT patients are outlined in Table 1.

Table 1—*Baseline Characteristics of Auto-HSCT and Allo-HSCT Patients at Time of Bronchoscopy

Characteristic	Auto-HSCT	Allo-HSCT	p Value
Total bronchoscopy, No.	44	125	
Mean age,† yr	48	44	< 0.001
Male/female ratio	1.8:1	1.7:1	NS
Solid tumor	77%	14%	< 0.001
PcP prophylaxis	41%	82%	< 0.001
CMV/HSV prophylaxis	59%	68%	NS
Days post-HSCT†	501	330	< 0.05
Immunosuppressive agents	23%	82%	< 0.001
Days of prior symptoms,†	16.8	14.0	NS
Receiving antibiotics	72%	92%	< 0.01
Antibiotic therapy,† d	7.9	4.0	< 0.001
PcP therapy	30%	45%	< 0.05
Antifungal agents	16%	46%	< 0.001

*NS = not significant; HSV = herpes simplex virus; PcP = Pneumocystis pneumonia.
†Mean.

Findings at Bronchoscopy

Bronchoscopy reports were available for all study patients identified, and $> 90\%$ of procedures had BAL fluid samples submitted for complete testing, including bacterial, fungal, viral, and mycobacterial cultures as well as special stains for acid-fast bacilli and for Pneumocystis sp.

For allo-HSCT patients, a potential infectious etiology was identified in 51% of BAL specimens (Table 2). Recognizing that Candida sp rarely cause disease in the lungs (Candida was specifically treated in only two of the cases identified in this study), if Candida species were excluded from the analysis, the overall infectious yield was 40%, with bacteria being the most frequently identified potential pathogens. Bacterial isolates included *Pseudomonas aeruginosa* (n = 11) and *Staphylococcus aureus* (n = 3). In comparison, a potential infectious etiology was identified in 41% of BAL specimens from auto-HSCT patients. If Candida sp are excluded, the yield for the BAL fluid samples was 27%, with bacterial isolates, including *S aureus* (n = 3) and *Klebsiella pneumoniae* (n = 1), being the most frequent isolated potential pathogens. A total of three cases of Pneumocystis pneumonia were identified, including two patients who had not received prior Pneumocystis prophylaxis and one who had received inhaled pentamidine.

BAL fluid cytology yielded findings in 9 of 125 allo-HSCT specimens (7%), and included hemosiderin-laden macrophages (n = 4), the visualization of fungal forms (n = 3), and cytopathic changes consistent with CMV (n = 2). BAL fluid cytology yielded findings in 2 of 44 of auto-HSCT specimens (5%), and included hemosiderin-laden macrophages (n = 1) and the visualization of fungal forms (n = 1). For allo-HSCT and auto-HSCT patients, all BAL cytology findings were confirmed by findings at the time of bronchoscopy (*eg*, the return of progressively bloody BAL fluid suggesting alveolar hemorrhage), or BAL fluid culture results.

TBBxs were performed in 71 patients, including 51 of 125 allo-HSCT patients (41%) and 20 of 44 auto-HSCT patients (45%). Adequate tissue samples were obtained in the majority (94%) of cases. For allo-HSCT patients, the most frequent pathologic findings were nonspecific (82% of all TBBx reports). Infectious etiologies included tissue culture demon-

Table 2—*Diagnostic Findings by Bronchoscopy*

Findings	Allo-HSCT	Auto-HSCT
BAL, No.	125	44
Infectious disease, %	51	41
Fungal	27	30
Candida sp	15	25
Aspergillus sp	10	2
Pneumocystis	2	2
Bacterial	25	16
Gram-negative	11	5
Gram-positive	10	11
Atypical mycobacteria	4	0
CMV	6	0
Other viral	9	7
Other	3	7
Noninfectious disease, %		
DAH	10	0
Nondiagnostic (including Candida), %	50	66
TBBx, No.	51	20
Infectious disease, %	4	0
Infection suspected	4	0
Noninfectious disease	6	15
Hypersensitivity pneumonitis	2	0
Chemotherapy-related injury	4	5
Malignancy	0	10
Non-specific (non-diagnostic)	82	82
Inadequate specimen	6	5
Endobronchial biopsy, No.	3	0
Infectious, %	67	0
Recurrent malignancy, %	33	0

strating the presence of Actinomyces (n = 1) and inclusion bodies the were consistent with CMV infection (n = 1). Similar to allo-HSCT patients, for auto-HSCT patients the most frequent pathologic finding was nonspecific (82% of all TBBx reports). In contrast to allo-HSCT patients, no potential infectious etiologies were identified in auto-HSCT patients, and 10% of TBBx specimens demonstrated malignancy, including Hodgkin disease (n = 1) and multiple myeloma (n = 1). None of the TBBx specimens in either group yielded a diagnosis of Pneumocystis pneumonia, including two TBBx specimens from two patients with BAL fluid samples demonstrating the presence of Pneumocystis by use of a special stain. Three endobronchial biopsies were reported in allo-HSCT patients revealing endobronchial Aspergillosis infection (n = 2) and recurrent non-Hodgkin lymphoma (n = 1).

Factors Associated With Identification of Potential Pathogens by Bronchoscopy

In auto-HSCT patients, the identification of a potential pathogen by bronchoscopy (excluding Candida sp) was more likely in patients who were receiving therapy with immunosuppressive agents (42% vs 17%, respectively; p = 0.07), but was not influenced by the number of days post-HSCT, the duration of symptoms, or the number of or the duration of therapy with antimicrobial agents at the time of bronchoscopy. In comparison, for allo-HSCT patients, bronchoscopy was more likely to identify a potential pathogen in patients who were further removed from the original HSCT (median, 218 vs 139 days, respectively; $p < 0.001$) or were receiving therapy with fewer antimicrobial agents (mean number of agents, 2.6 vs 3.2, respectively; p = 0.048) at the time of bronchoscopy. For both auto-HSCT and allo-HSCT patients, there was no difference in the bronchoscopic yield with regard to the type or distribution of infiltrates on routine chest radiographs or CT scans (data not shown).

Influence of Bronchoscopy Results on Treatment

For auto-HSCT patients, the findings at the time of bronchoscopy resulted in no change in pharmacologic therapy in the majority of patients (64%) [Table 3]. No significant differences in therapeutic decisions were apparent when comparing auto-HSCT patients with a specific diagnosis suggested by bronchoscopy compared to patients without a specific diagnosis. For allo-HSCT patients, the findings at the time of bronchoscopy resulted in no change in pharmacologic therapy in 50% of patients. However, allo-HSCT patients with a specific diagnosis provided by bronchoscopy were more likely to have a change in therapy (the addition of either antimicrobial agents or steroids) compared to those without a specific diagnosis.

Complications Associated With Bronchoscopy

In the 169 bronchoscopies performed, there were a total of 15 complications (overall complication rate,

Table 3—*Influence of Specific Diagnosis From Bronchoscopy Results on Clinical Decisions Related to HSCT Patient Management

Patient Management	All	Specific Diagnosis	No Specific Diagnosis
Auto-HSCT	44	15	29
D/C antimicrobial agents	8 (20)	3 (20)	5 (17)
Add antimicrobial agents	1 (2)	0	1 (3)
Add steroids	5 (11)	1 (7)	4 (14)
Other	2 (5)	0	1 (3)
No change	28 (64)	10 (67)	18 (62)
Allo-HSCT	125	63	62
D/C antimicrobial agents	25 (20)	14 (23)	11 (17)
Add antimicrobial agents	23 (18)	20 (32)	3 (5)
Add steroids	22 (18)	16 (26)	6 (10)
Other	4 (3)	3 (5)	1 (2)
No change	62 (50)	18 (30)	44 (70)

*Values given as No. (%). D/C = discontinued.

9%), including 11 complications in allo-HSCT patients and 4 complications in auto-HSCT patients. The complications included sustained oxygen desaturation requiring ICU monitoring (n = 5), respiratory failure necessitating assisted ventilation (n = 3), pulmonary hemorrhage (n = 3), pneumothorax (n = 2; both requiring chest tube), arrhythmia (supraventricular tachycardia; n = 1), and inadvertent extubation (n = 1). There were no deaths within 24 h of bronchoscopy. TBBx was associated with 4 complications (8% of all TBBxs) in allo-HSCT patients, including hemorrhage requiring intubation (n = 2) and pneumothorax (n = 2), and 1 complication (5% of all TBBxs) in auto-HSCT patients (hemorrhage requiring intubation). There were no differences in the complication rates for bronchoscopy with or without TBBx in either group (data not shown). For the clinical factors examined, only tachycardia at the time of bronchoscopy was associated with an increased risk for any complication from bronchoscopy (heart rate, 112 vs 95 beats/min; p = 0.006). The risk of complications from bronchoscopy was not influenced by the presence of mechanical ventilation, systolic BP, Sao_2/Fio_2 ratio, platelet count, or prothrombin time (PT).

Association of Bronchoscopic Findings With Hospital Mortality

The overall in-hospital mortality rate for allo-HSCT patients (n = 116) and auto-HSCT patients (n = 38) who underwent bronchoscopy was similar (38% vs 27%, respectively; p = 0.25). For both allo-HSCT and auto-HSCT patients, the mortality rate was not influenced by whether bronchoscopy provided a specific diagnosis, identified a potential pathogen, or resulted in a change in therapeutic management (Table 4).

Table 4—*Influence of Bronchoscopy-Related Clinical Factors on In-Hospital Mortality Rate for HSCT Patients

Clinical Factor	Mortality Rate, %		p Value
	If Factor Present	If Factor Absent	
Auto-HSCT patients			
Specific diagnosis established	36	22	NS
Potential pathogen identified	38	15	NS
Therapy changed	29	24	NS
Allo-HSCT patients			
Specific diagnosis established	43	33	NS
Potential pathogen identified	42	34	NS
Therapy changed	38	38	NS

*See Table 1 for abbreviation not used in the text.

Characteristics at the Time of Bronchoscopy Associated With In-Hospital Mortality

A review of select patient characteristics at the time of bronchoscopy revealed that for auto-HSCT patients nonsurvivors had significantly elevated mean PTs at the time of bronchoscopy compared to survivors (14.2 vs 12.8 s, respectively; p = 0.04). There were no significant differences in age, number of days post-HSCT, hypoxemia ratio, or platelet count. In comparison, for allo-HSCT patients nonsurvivors had significantly elevated mean PTs (13.5 vs 12.7 s, respectively; p = 0.02) and worse hypoxemia ratios (2.4 vs 3.8, respectively; p < 0.0001), and were further removed from the original HSCT (median time, 177 vs 132 days, respectively; p = 0.02) compared to survivors. In addition, nonsurvivors had a trend toward lower platelet counts compared to hospital survivors (88 vs 111 cells/μL, respectively; p = 0.06).

A review of select clinical factors for auto-HSCT patients revealed a higher in-hospital mortality rate for patients receiving empirical antifungal agents (71% vs 14%, respectively; p = 0.006) at the time of bronchoscopy. A trend toward a greater in-hospital mortality rate was observed in auto-HSCT patients who required mechanical ventilation (57% vs 19%, respectively; p = 0.06) at the time of bronchoscopy. In comparison, for allo-HSCT patients, the increased in-hospital mortality rate was associated with the use of mechanical ventilation (77% vs 24%, respectively; p < 0.0001) or empirical antifungal agents (55% vs 21%, respectively; p < 0.0001) at the time of bronchoscopy. In addition, the in-hospital mortality rate was higher in allo-HSCT patients with DAH at bronchoscopy (67% vs 34%, respectively; p = 0.02) or in patients who experienced a bronchoscopic complication (82% vs 34%, respectively; p = 0.003).

Surgical Lung Biopsy and Autopsy Data

Surgical lung biopsy (SLB) and autopsy data were available for only a few select patients. For the 44 auto-HSCT patients who had undergone bronchoscopy, 8 subsequently underwent SLB. Specific pathologic diagnoses were available for four patients (50%), and findings included Aspergillus (n = 1), metastatic malignancy (n = 2), and pulmonary veno-occlusive disease (n = 1). The pathologic findings were nonspecific in the remaining specimens. Only one autopsy had been performed among the auto-HSCT patients (a patient who had undergone both SLB and autopsy), and pathologic findings confirmed the diagnosis of pulmonary venoocclusive disease that previously had been established by SLB. For all eight auto-HSCT patients who had undergone SLB or autopsy, one of the prior bronchoscopies had yielded the presence of herpes simplex virus

1 and one had revealed the presence of Aspergillus sp. Neither infection was confirmed by SLB, and none of the specific diagnoses identified by SLB had been identified by prior bronchoscopy.

For the 125 allo-HSCT patients who had undergone bronchoscopy, 19 patients (15%) also had undergone SLB following bronchoscopy, and pathology data were available for all 19 patients. A specific diagnosis was reported for 9 of the 19 patients (47%), including invasive aspergillosis (n = 2) and nocardiosis (n = 1). Other specific diagnoses included thromboembolic disease (n = 2), posttransplant lymphoproliferative disorder (n = 1), recurrent Hodgkin disease (n = 1), DAH (n = 1), and bronchiolitis obliterans organizing pneumonia (n = 1).

In addition, 19 of the 125 allo-HSCT patients who had undergone bronchoscopy (15%) also had undergone a postmortem examination (*ie*, autopsy) within 1 month of the bronchoscopy. A review of pathology reports revealed a specific diagnosis in 15 patients (79%), including invasive aspergillosis (n = 3) and mucormycosis (n = 1). Additional specific diagnoses included DAH (n = 8), graft-vs-host disease of the lung (n = 2), and obliterative bronchiolitis (n = 1). Eighteen of 19 patients had pathologic evidence of diffuse alveolar damage (DAD).

For the allo-HSCT patients, these 19 SLBs and 19 autopsies were performed on 35 patients (3 patients had undergone both procedures). Of the nine patients (26%) in whom prior bronchoscopy had identified a potential pathogen (excluding Candida sp), only one of the 9 (Aspergillus sp; 11%) had infection confirmed by SLB or autopsy pathology. In contrast, among the seven patients who had pathologic evidence for lung infection (including Aspergillus sp, five patients; Mucor, one patient; and nocardia, one patient) only one had been identified by prior bronchoscopy. For noninfectious diagnoses, among the seven patients with evidence for DAH obtained by bronchoscopy, only four (57%) had DAH confirmed by SLB or autopsy pathology. In contrast, among seven patients with DAH that had been identified by SLB or autopsy, only four (57%) had been diagnosed by prior bronchoscopy. For the three patients who had undergone both SLB and autopsy examination, all revealed nonspecific lung disease.

Discussion

This retrospective review demonstrated that diagnostic bronchoscopy may be useful in the evaluation of adult allo-HSCT and auto-HSCT recipients with pulmonary infiltrates. Bronchoscopy was performed in 12.5% of all HSCT patients and was requested more often in allo-HSCT patients (18.7%) than in auto-HSCT patients (6.6%). Findings at bronchoscopy provided a specific diagnosis more frequently in allo-HSCT patients (50%) than in auto-HSCT patients (34%). For both allo-HSCT and auto-HSCT patients, BAL alone provided most diagnoses, whereas TBBx provided additional specific information in $< 10\%$ of cases. Furthermore, information obtained from bronchoscopy influenced clinical decisions more often in allo-HSCT patients (50%) than in auto-HSCT patients (36%), allowing for the discontinuation or addition of antimicrobial, corticosteroid, or neoplastic agents to therapy. Complications from bronchoscopy occurred in 9% of all HSCT patients, and complications were associated with a significantly higher in-hospital mortality rate for allo-HSCT patients (82%) than for auto-HSCT patients (50%). The overall in-hospital mortality rates for allo-HSCT and auto-HSCT patients were similar (38% vs 27%, respectively; $p = 0.25$), but, importantly, establishing a specific diagnosis by bronchoscopy was not associated with an improved in-hospital mortality rate for either auto-HSCT or allo-HSCT patients.

The observation that bronchoscopy provided diagnostic information in 34 to 50% of HSCT patients was consistent with those of prior publications. The finding that bacteria represented the most commonly isolated potential pathogens for both allo-HSCT and auto-HSCT patients in the current study was similar to that reported by Dunagan et al.[6] Whereas prior studies frequently isolated CMV,[8,9] the lower frequency for the isolation of CMV and Pneumocystis sp in the current study likely reflects changes in standards of care, including the increased use of CMV antigen monitoring and Pneumocystis chemoprophylaxis. Recognizing that the isolation of a microbe by bronchoscopy may not represent a true pathogen, 27% of patients for each HSCT group received antimicrobial treatment directed against the isolated pathogen, results that were similar to those reported in prior studies of White et al[8] (25%) and Feinstein et al[9] (31.6%). The likelihood of isolating a potential pathogen in allo-HSCT patients was higher in the presence of treatment with fewer empirical antimicrobial agents, in contrast to the use of more immunosuppression therapy in auto-HSCT patients. There was no influence of preceding antimicrobial therapy duration on pathogen isolation for either group.

The observation that findings from bronchoscopy did not influence mortality was consistent with those of other investigations of bone marrow transplant recipients.[6,8,9] The lack of apparent benefit from diagnostic bronchoscopy may be multifactorial, including a nonstandardized approach to the evaluation of

HSCT patients, the variable timing of diagnostic bronchoscopy relative to the onset of respiratory symptoms, the number and duration of concurrent antimicrobial agents, the prescription of prophylactic agents, the level of pharmacologic immunosuppression, the lack of ability to distinguish true pathogens from colonizing organisms or contaminants, and the limited sensitivity of bronchoscopy for specific diagnoses, among other factors. Further studies are required to optimize the specific role of diagnostic bronchoscopy in allo-HSCT and auto-HSCT patients who develop respiratory complications.

The reported limited sensitivity of bronchoscopy for certain diagnoses such as invasive fungal infections or DAH is illustrated by the current study. For the diagnosis of fungal pneumonia, the observation that bronchoscopy may not be as sensitive as SLB or autopsy data was consistent with those of other studies[11–13] that have shown the sensitivity of bronchoscopy for invasive fungal pneumonia to be 30 to 56%. Similarly, the diagnosis of DAH by bronchoscopy may have low sensitivity and specificity (compared to the available SLB and autopsy data), and is consistent with findings from Agusti et al,[14] in which 54% of bronchoscopies showing DAH were falsely positive and 50% of patients with DAH determined by autopsy had negative bronchoscopy findings. The limited sensitivity in establishing these diagnoses by bronchoscopy may contribute to a lack of influence on mortality.

The observation in the current study that bronchoscopy is often requested well into the clinical course of illness (range, 14.0 to 16.8 days) suggests that the underlying disease state may be well-advanced into a stage of diffuse lung injury, and may be less likely to respond to specific therapeutic interventions by the time bronchoscopy is performed. The high mortality rate for patients with diffuse lung injury is supported in part by the observation that autopsy findings demonstrated evidence for DAD in 18 of 19 patients (95%). This concept is further supported by the observation of high mortality rates in patients receiving mechanical ventilation (who are at the highest risk of developing DAD) vs those not receiving ventilation (77% vs 24%, respectively).

The apparent lack of mortality benefit gained from the information obtained by bronchoscopy may in part also reflect the nature and severity of the underlying infections, as illustrated by the cases of Aspergillus infection. For the 14 patients in whom Aspergillus had been identified by either bronchoscopy or SLB, only 7 (50%) survived hospitalization. In addition, 4 of 19 autopsies (21%) identified invasive fungal infections, a rate that is much higher than that of the general population of HSCT patients, suggesting a high mortality rate in patients with fungal infection. These findings are consistent with the study by Wald et al,[15] in which the 1-year survival rate for HSCT patients with invasive Aspergillus infection was only 7%. Perhaps aggressive investigations to establish the diagnosis of Aspergillus infection at an earlier clinical stage in these patients may provide additional benefit, although prospective investigations would be required to evaluate this strategy.

This study was the first to directly examine the utility of diagnostic bronchoscopy comparing allo-HSCT patients to auto-HSCT patients with pulmonary radiographic abnormalities. Although many similarities were observed, certain differences were noted. Although the microbial spectrum of bacteria was similar for the two HSCT groups, the bronchoscopic isolation of specific pathogens such as Aspergillus sp, CMV, and atypical mycobacteria was limited to allo-HSCT patients. Furthermore, allo-HSCT patients were more likely to sustain a complication related to bronchoscopy, and complications in allo-HSCT patients were associated with a high in-hospital mortality rate. Although an explanation for the observed differences comparing allo-HSCT to auto-HSCT patients was not established, the differences may have clinical implications in the approach and empirical management of HSCT patients who develop pulmonary symptoms and radiographic abnormalities.

The relatively low yield of TBBx in the current study was similar to that reported in prior investigations. Only 4% of biopsy specimens revealed a specific infection in the allo-HSCT group, and no specific infection was found in the auto-HSCT group. In the auto-HSCT patients, two biopsy specimens (10%) did reveal recurrent malignancy. These results are in accord with those of the study by White et al[8] that reported 1 of 42 biopsy specimens (2%) demonstrating a specific infection. In our study, the rate of complications from TBBx was 8% in allo-HSCT patients and 5% in auto-HSCT patients. The overall bronchoscopy complication rate of 9% was similar to that reported by Dunagan et al[6] (9% rate of major complications) and White et al[8] (15% rate of major complications). Although platelet count, PT, and Sao_2/Fio_2 ratio were risk factors for death, they were not risk factors for complications. The data suggest that differences in the baseline severity of illness may not explain the increased risk for complications. Although the rates of complications from bronchoscopy were similar with or without TBBx, the finding that complications related to bronchoscopy may be associated with higher mortality together with the limited yield of specific

diagnoses, the routine of use of TBBx in this patient population needs to be carefully reviewed in prospective studies.

Several additional limitations of the current study are noteworthy. The retrospective nature of this review precludes establishing cause-and-effect relations with certainty. Thus, relationships between factors such as bronchoscopic findings and mortality cannot be firmly established. In order to address whether bronchoscopy truly affects patient outcomes, a randomized controlled trial would be required comparing empirical treatment to treatment based on bronchoscopy findings. Mortality data examining patients who had bronchoscopy-associated complications were also limited, as the numbers were small and the presence of complications may be confounded by advanced underlying severity of illness contributing to an increased mortality. The comparison of clinical outcomes related to HSCT patients who had pulmonary infiltrates but did not undergo bronchoscopy was also not available. The current study represents the largest report of bronchoscopy in HSCT patients, although the limited numbers of patients in subgroups did not allow for a subgroup analysis. With the observed lower rate of bronchoscopy in our institutions compared to those in published studies,[96,8] our results may not be applicable to other institutions, although the lower rate of bronchoscopy may reflect the increased use of chemoprophylaxis in our patients. Definitive comparisons of bronchoscopy results to SLB or autopsy data were not possible as few SLB or autopsy data were available.

A major fundamental goal of diagnostic bronchoscopy is to establish a specific diagnosis that will allow targeted therapeutics and improve survival. The discontinuation of unnecessary treatment with pharmacologic agents would reduce the associated morbidity, reduce costs, and reduce the development of antibiotic resistance. The absence of any apparent benefit of bronchoscopy on mortality in the current study may reflect the absence of a standardized approach to the evaluation of HSCT patients with pulmonary radiographic abnormalities, and may also reflect the requests for diagnostic evaluations, which may come too late into the clinical course of illness either to establish the diagnosis or to change the outcome. The lack of apparent benefit may also reflect the controversy related to the definition of specific diagnoses such as DAH. The problem is further confounded by the fact that not all allo-HSCT and auto-HSCT patients undergo diagnostic bronchoscopy, so that the identification of specific patients who may benefit from bronchoscopy remains to be established.

In conclusion, diagnostic bronchoscopy can provide a potential etiology for the development of pulmonary infiltrates in both adult allo-HSCT and auto-HSCT patients. Furthermore, the information obtained from diagnostic bronchoscopy often influences decisions that are related to therapeutic pharmacology for both allo-HSCT and auto-HSCT patients. However, in the current diagnostic approach the information related to bronchoscopy did not influence outcomes such as in-hospital mortality rate. In addition, although complications occur in 9% of cases, for allo-HSCT and auto-HSCT patients who experience complications the associated in-hospital mortality rate was 50 to 82%. Further prospective studies are required to define the specific role of diagnostic bronchoscopy in allo-HSCT and auto-HSCT patients, and to establish the optimal time for the performance and utility of this procedure. Recognizing the complication risks related to bronchoscopy and the limited sensitivity for certain diagnoses, caution should be exercised in the selection of patients for diagnostic bronchoscopy.

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