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Microbiologic yield of bronchoalveolar lavage specimens from stem cell transplant recipients

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Abstract

Purpose: Stem cell transplant (SCT) recipients commonly undergo bronchoalveolar lavage (BAL) collection as an infectious pulmonary work-up. Previous studies report the utility and overall diagnostic yield of fiberoptic bronchoscopy with BAL in this vulnerable population, though none focused purely on microbiologic yield or made comparisons with less invasive means of pathogen detection. We sought to determine and elaborate on the microbiologic yield of BAL in SCT recipients, assess a correlation between BAL studies and less invasive means of pathogen detection, and assess the utility of repeating a BAL within 30 days.

Methods: Between January 1, 2009, and July 31, 2013, we reviewed medical records of 125 SCT recipients who underwent 179 BALs. In addition to demographic information and details pertaining to their SCT, a comprehensive review of their microbiologic data was performed and recorded.

Results: Our study showed an overall BAL microbiologic yield of 40%, despite 92% of patients receiving broad-spectrum antimicrobial therapy at the time of the BAL procedure.

Conclusions: Although an initial BAL sample in this population provides crucial microbiologic information, repeating the procedure within 30 days may have minimal additional microbiologic yield. BAL continues to be an essential diagnostic tool in SCT recipients undergoing an infectious pulmonary work-up.

KEYWORDS

bone marrow transplant, bronchoalveolar lavage, fiberoptic bronchoscopy, immunocompromised, immunosuppressed, stem cell transplant

1 | INTRODUCTION

Stem cell transplant (SCT) is a well-recognized and accepted treatment for certain hematologic and nonhematologic cancers. However, infectious and noninfectious pulmonary complications are reported to occur in 40%-60% of all SCT recipients.[1] Infectious pulmonary complications are a major cause of morbidity and death in SCT recipients.[2]

However, the clinical presentation and radiologic appearance of noninfectious complications—such as drug and radiation toxicity, bronchiolitis obliterans, pulmonary graft-versus-host disease, diffuse alveolar damage, pulmonary hemorrhage, pulmonary edema (cardiogenic and noncardiogenic), acute respiratory distress syndrome, and idiopathic noninfectious pulmonary syndrome—can mimic infectious pneumonias.[3,4] Microbiologic diagnosis of infectious pulmonary complications

Abbreviations: AspAg, *Aspergillus* antigen; BAL, bronchoalveolar lavage; cocci, *Coccidioides* species; CT, computed tomography; EBV, Epstein-Barr virus; FARP, FilmArray Resipiratory Panel; FOB, fiberoptic bronchoscopy; GGO, ground-glass opacity; ICH, immunocompromised host; MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nasopharyngeal; NS, nasal swab; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SCT, stem cell transplant.

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often requires both computed tomography (CT) and fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL). FOB with BAL has generally been considered a safe and valuable procedure for evaluation of pulmonary complications in SCT recipients undergoing an infectious pulmonary work-up.[3–6] The BAL specimen is evaluated with an array of diagnostic microbiologic studies targeting various pathogens, including bacteria, mycobacteria, fungi, and viruses.

Prior published studies have reported a diagnostic yield of BAL ranging from 31% to 80%.[2,3,5–13] The data often combine the diagnostic yield of both infectious and noninfectious pulmonary complications in SCT recipients. Few reports focus exclusively on the microbiologic yield of BAL in SCT recipients. We therefore sought to determine and elaborate the overall microbiologic yield of BAL in recipients of autologous (auto-SCT) and allogeneic (allo-SCT) SCTs, who underwent an infectious pulmonary work-up at our institution.

2 | PATIENTS AND METHODS

2.1 | Patient population

The study cohort consisted of 125 SCT recipients who underwent 179 BAL procedures between January 1, 2009 and July 31, 2013, at our institution as part of their infectious work-up for fever, respiratory symptoms, or new pulmonary radiographic abnormalities. For patients who had multiple bronchoscopy procedures, each encounter was considered as an independent procedure. Patients who had an auto-SCT before receiving an allo-SCT were counted toward the allogeneic dataset.

2.2 | Immunocompromised host (ICH) BAL order set

The ICH BAL order set at our institution during the study period consisted of the following tests: bacterial Gram stain and culture, fungal smear and culture, acid-fast bacilli smear and culture, *Aspergillus* antigen (AspAg), *Coccidioides* species (cocci) polymerase chain reaction (PCR), *Legionella* species culture and PCR, *Pneumocystis jirovecii* smear and PCR, cytomegalovirus culture, herpes simplex virus culture, varicella culture, Epstein-Barr virus (EBV) PCR, viral respiratory culture, and cytologic evaluation. The BAL AspAg test was incorporated into the ICH BAL panel in May 2011.

2.3 | Data collection

The following data were collected for each BAL: age; gender; date, type, and indication of SCT; date of FOB with BAL; presence of graft-versus-host disease at time of BAL; neutropenia, defined as absolute neutrophil count of $<500\times10^9$/L at 48 hours before BAL; corticosteroid use; specific empirical antimicrobial therapy at least 48 hours before BAL; radiographic findings (chest CT or chest radiograph, or both); sputum cultures; serum cytomegalovirus PCR; methicillin-resistant *Staphylococcus aureus* (MRSA) nasal swab (NS); nasopharyngeal (NP) influenza PCR; *Legionella* urinary antigen within 7 days of BAL; serum cocci serologic testing; and serum AspAg at 7 days before and 4 weeks after BAL. In addition, detailed information regarding the ICH BAL test results was collected for each patient.

2.4 | Chest CT and radiographic criteria

Chest CT and chest radiograph findings were grouped into the categories diffuse or focal, consolidations, ground-glass opacities (GGOs), nodules (solid or ground glass), cavitations, and bronchial impaction. These categories were not mutually exclusive. *Diffuse* was defined as bilateral involvement or abnormalities extending beyond 1 lobe of a lung.[6]

2.5 | Antimicrobial therapy

Empirical broad-spectrum antimicrobial therapy administered within 48 hours before collection of the BAL specimen was recorded. Prophylactic antimicrobial regimens were not included in the analysis. *Empirical antimicrobial therapy* was defined as any broad-spectrum antibacterial, anti-mold, or cytomegalovirus-specific therapy.

2.6 | Microbiologic yield of the BAL specimen

Candida, coagulase-negative *Staphylococcus*, and EBV were excluded from the microbiological yield analysis. Pathogens were grouped into the primary categories of bacteria, fungi, viruses, and mixed. Data were analyzed to (i) determine and elaborate the microbiologic yield of BAL in SCT recipients, (ii) assess a correlation between BAL studies and less invasive means of pathogen detection, and (iii) evaluate the utility of repeating a BAL within 30 days.

The Mayo Clinic Institutional Review Board approved this study.

3 | RESULTS

In total, 179 BALs were performed on 125 SCT recipients between January 1, 2009 and July 31, 2013. Among the 179 BALs, 43 (24%) and 136 (76%) underwent an auto- or allo-SCT respectively. There were 9 BALs (5%) from patients who underwent an auto-SCT followed by an allo-SCT and were counted toward the allogeneic category. The demographic data are elaborated in Table 1.

3.1 | Empirical antimicrobial therapy

Among patients who underwent 166 BALs and were receiving empirical antimicrobial therapy, 154 (93%), 110 (66%), and 37 (22%) were taking broad-spectrum antibacterial, antifungal, and antiviral therapies respectively (Table 1).

3.2 | Microbiological yield

Of the 179 BALs, 92 (51%) had a microorganism identified; 71 BAL isolates (40%) were identified as true pathogens. When divided into auto- and allo-SCT subgroups, 14/43 BALs (33%) and 57/136 BALs

TABLE 1 Demographic characteristics of 125 SCT recipients who underwent BAL for infectious pulmonary work-up

Characteristic	Value
Total no. of BALs	179
Allogeneic, no. (%)	136 (76)
Autologous, no. (%)	43 (24)
Male to female ratio	2:1
Age, years	
Mean	50
Median (range)	53 (19-77)
Post-transplant period, median, days	
Allogeneic SCT	155
Autologous SCT	187
All	161
Indication for SCT, no. of patients	
Acute myelogenous leukemia	32
Myelodysplasia or myeloproliferative neoplasm	20
Multiple myeloma	20
Non-Hodgkin lymphoma	14
Acute lymphoblastic leukemia	13
Hodgkin lymphoma	7
T-cell leukemia	4
Chronic myelogenous leukemia	3
Chronic lymphocytic leukemia	3
Aplastic anemia	2
Testicular carcinoma	2
POEMS syndrome	1
Amyloidosis	1
Pure red cell aplasia	1
Pleuropulmonary blastoma	1
Burkitt lymphoma	1
ANC >500×10^9/L, no. (%)	138 (78)
ANC ≤500×10^9/L, no. (%)	25 (14)
BALs per patient, no. of patients	
1	92
2	22
≥3	11
Patients receiving empirical antimicrobial therapy 48 hours before BAL, ratio (%)	
Total	166/179 (92)
Antibacterial	154/166 (93)
Antifungal	110/166 (66)
Antiviral	37/166 (22)
Patient death during index hospitalization, no. (%)	22 (12)

BAL, bronchoalveolar lavage; SCT, stem cell transplant; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; ANC, absolute neutrophil count.

(42%) identified a true pathogen respectively. The microorganisms isolated from BAL samples from both auto- and allo-SCT recipients are listed in Table 2. Of the true pathogens isolated, 31% were

TABLE 2 Microorganisms detected in BAL specimens

	Positive BAL Test, no.	
	Auto-SCT	Allo-SCT
Bacterium (n=39)		
Pseudomonas aeruginosa	2	12
Methicillin-resistant *Staphylococcus aureus*	0	5
Legionella pneumophila	2	3
Streptococcus pneumoniae	1	2
Escherichia coli	0	1
Mycobacterium kansasii	0	1
Stenotrophomonas maltophilia	1	0
Mycobacterium canariasense	0	1
ESBL *Klebsiella pneumoniae*	0	1
Mycobacterium avium complex	1	0
Mycobacterium gordonae	0	1
Nocardia brasiliensis	0	1
Moraxella catarhallis	1	0
Actinomyces	0	1
Rhodococcus equii	0	1
Virus (n=33)		
Parainfluenza 3	2	12
Respiratory syncytial	0	5
Cytomegalovirus	0	5
Influenza A/B	3	2
Coronavirus	0	2
Adenovirus	0	2
Herpes simplex	0	1
Fungus (n=42)		
Aspergillus species	5	15
Pneumocystis jirovecii	3	5
Penicillium species	0	3
Saccharomyces species	0	3
Rhizopus species	0	3
Coccidioides species	0	3
Paecilomyces species	0	1
Trichoderma species	0	1

BAL, bronchoalveolar lavage; Auto-SCT, autologous stem cell transplant; Allo-SCT, allogeneic stem cell transplant; ESBL, extended spectrum β-lactamase–producing.

bacteria, 24% fungi, 24% viruses, and 21% were mixed organisms. Of the BALs in which a true pathogen was identified, 92% of the patients had received broad-spectrum antimicrobial therapy in the 48 hours before BAL collection. Empirical antimicrobial therapy prior to BAL was administered to 88% and 94% in the auto-SCT and allo-SCT subgroups respectively.

The following pathogens were evaluated in more detail: MRSA, *Pseudomonas* speies, *Legionella* species, *Aspergillus* species,

Pneumocystis jirovecii, *Coccidioides* species, and viruses. Table 3 summarizes the clinical information of patients with these pathogens.

3.2.1 | Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA was isolated in 5 BAL cultures. All 5 were obtained from allo-SCT patients. Four had a concordant MRSA sputum culture. Two of the 5 BALs with positive MRSA cultures were receiving anti-MRSA therapy. Eighty cases had a MRSA NS test. One MRSA NS was found to be positive and also had a concordant positive MRSA BAL culture. The 79 other negative MRSA NSs had concordant negative BAL specimens and, when testing was performed, had negative sputum cultures as well (negative predictive value, 100%). The other 4 positive MRSA BAL cultures, in addition to the 4 positive MRSA sputum cultures, did not have a NS tested. All cases involved chest CT findings of diffuse consolidations and 2 patients had cavitations.

3.2.2 | *Pseudomonas* species

Fourteen BAL cultures revealed *Pseudomonas*—2 were collected from auto- and 12 from allo-SCT recipients. One of these had a concurrent sputum culture with *Pseudomonas*. There were 12 cases where antipseudomonal antimicrobial therapy was administered before the BAL collection, of which 11 cases had appropriate therapy based on susceptibility testing. The period of antipseudomonal therapy before BAL ranged from 1 to 11 days (median [interquartile range], 1 [1-4] day). Thirteen cases had a chest CT before BAL collection; the most common CT finding was consolidations (77%), followed by GGO (38%). Seven had diffuse abnormalities. Two cases showed cavitary lesions, and these cases also had concurrent detection of *Aspergillus*.

3.2.3 | *Legionella* species

Legionella was isolated in 5 BAL cultures—2 were retrieved from auto- and 3 from allo-SCT. All 5 had a concurrent positive BAL *Legionella* PCR. Two cases were diagnosed within 5 days of each other (one on the day of admission and requiring intensive care unit admission; the other, 5 days later). The other cases were separated in time by at least 8 months. Two cases were receiving anti-*Legionella* therapy within 48 hours of BAL collection. *Legionella* urinary antigen was obtained in 3 cases, of which 2 were positive (*Legionella pneumophilia* serogroup 1 [n=1] and an unspecified *L pneumophilia* group [n=1]). The 1 case with a negative urinary antigen test involved a BAL culture that showed *Legionella bozemanii*. Four cases had a chest CT, and the most common radiographic abnormality observed was dense lobar or segmental consolidations.

3.2.4 | *Aspergillus* species

Twenty BALs were positive for *Aspergillus* species—5 were from auto- and 15 from allo-SCT patients. Three different methods were used to assess for the presence of *Aspergillus*: BAL culture, BAL AspAg, and serum AspAg. Table 4 lists the frequency of each test and the concordance between them. The numbers of BAL fungal culture, BAL AspAg, and serum AspAg tested were 179, 67, and 97 respectively. Positive results were noted in 8, 12, and 5 samples for BAL culture, BAL AspAg, and serum AspAg respectively. The only concordance seen among the 3 tests was between a positive BAL culture and serum AspAg. Of the 20 BALs with *Aspergillus* identified with both BAL AspAg and BAL fungal culture, 10 patients were receiving anti-*Aspergillus* therapy and 7 were taking anti-*Aspergillus* therapy for longer than 7 days before BAL collection. In addition, *Aspergillus* was found in 5 BALs (25%), along with another pathogen.

Of the patients who had BALs with a positive *Aspergillus* result, 19 had a chest CT; the most common radiographic feature was GGO with areas of consolidations (42%). Three cases were found to show cavitary lesions on chest CT. Of these, 2 were identified with BAL AspAg and the other had a positive BAL culture.

3.2.5 | *Pneumocystis jirovecii*

Eight positive results were detected for BAL *P. jirovecii* PCR—3 were detected from auto- and 5 from allo-SCT patients. All 8 cases had a BAL *P. jirovecii* fluorescent smear tested and 1 tested positive.

TABLE 3 Computed tomography (CT) findings, absolute neutrophil count (ANC), and presence of concurrent GVHD in patients with commonly isolated pathogens

	Finding, no. (%)		
Organism, CT	**ANC <500**	**Concurrent GVHD**	**Predominant radiographic findings on chest CT**
MRSA (n=5), 5	2 (40)	5 (100)	Diffuse, 5 (100); consolidations, 5 (100); cavitation, 2 (40)
Pseudomonas (n=14), 13	2 (14)	12 (86)	Focal, 7 (54); consolidations, 10 (77); GGO, 5 (38); cavitary lesions, 2 (15)
Legionella (n=5), 4	1 (20)	3 (60)	Diffuse, 2 (50); lobar/segmental consolidation, 4 (100)
Aspergillus species (n=20), 19	3 (15)	13 (65)	Focal, 10 (53); consolidations, 14 (74); GGO, 12 (63); GGO with consolidation, 8 (42); cavity, 3 (16)
Pneumocystis jirovecii (n=8), 8	0 (0)	3 (38)	Diffuse 8 (100); GGO, 8 (100)
Coccidioides (n=3), 3	1 (33)	2 (66)	Diffuse 2 (66); GGO with consolidation 3 (100)
Parainfluenza (n=14), 14	2 (14)	10 (71)	Diffuse, 9 (64); GGO, 12 (86%); nodularity, 7 (50%); consolidation, 3 (21%)

GVHD, graft-versus-host disease; GGO, ground-glass opacity; MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 4 Methods used to detect *Aspergillus* infection and concordance

Methods	Concordance
Tests performed, No. (%)	179 (100)
Serum AspAg	97 (54)
BAL AspAg[a]	67 (37)
BAL culture	179 (100)
Positive results per test performed, ratio (%)	
Serum AspAg	5/97 (5)
BAL AspAg[a]	12/67 (18)
BAL culture	8/178 (4)
Concordance rate, no. (%)	
BAL culture vs. serum AspAg	1 (100)
BAL culture vs. BAL AspAg[a]	0 (0)
BAL AspAg vs. serum AspAg	0 (0)

[a]BAL AspAg introduced as part of BAL immunocompromised host order set in May 2011.
BAL, bronchoalveolar lavage; AspAg, *Aspergillus* antigen.

High-dose corticosteroid therapy was given in 2 cases and 3 cases received *P. jirovecii* prophylaxis (2 pentamidine and 1 trimethoprim-sulfamethoxazole). The most common CT finding among the 8 cases was diffuse GGO (88%).

3.2.6 | *Coccidioides* species

Coccidioides species can be detected in the BAL with fungal smear, culture, or PCR. There were 3 positive cocci results on BAL PCR, of which 1 had a concurrent positive BAL culture (and negative serum cocci serology). All 3 positive BAL cocci PCRs were from allo-SCT patients. Serum cocci serologies were tested in 88 cases; 4 had positive cocci serologic results, of which 1 had a concordant BAL PCR. The most common radiographic finding on chest CT was consolidations with GGO.

3.2.7 | Viruses

The most common viruses detected were EBV (n=16), followed by parainfluenza virus (n=14; 2 were isolated from auto- and 12 from allo-SCT patients) and respiratory syncytial virus (RSV) (n=5). The clinical significance of a positive EBV PCR in the BAL is unknown, and it is not included in our analysis. All positive EBV results were detected with BAL PCR; parainfluenza and RSV were isolated through the BAL viral respiratory shell vial culture. The most common radiographic pattern for parainfluenza, RSV, and influenza was diffuse GGO with occasional areas of nodularity and consolidations. Of the composite of 23 BALs with parainfluenza, RSV, and influenza, 8 BALs (35%) identified a bacterium or fungus in addition to the virus. All 5 cases with RSV were treated with ribavirin.

3.2.8 | Mixed organisms

Fifteen BAL specimens had 2 or more concurrent pathogens, and the most common combination was bacterium and fungus (n=7), followed by fungus and virus (n=4) and by bacteria and virus (n=3). The other BAL specimen isolated all 3 of these pathogens.

3.3 | Repeat BAL

A total of 33 patients underwent 2 or more BALs. The total number of repeated BALs was 53. The number of repeated BALs ranged from 1 (n=22) to 5 (n=1). Twenty-four repeated BALs were performed within 30 days of each other, none of which showed a new pathogen. Median interval between repeated BALs for the remaining 29 was 90 days (range, 35-705 days). Four repeated BALs showed persistence of an organism isolated from the first BAL, despite administration of appropriate antimicrobial therapy. The 4 persistent organisms noted were MRSA (n=1); *Pseudomonas* (n=1); *Aspergillus* (n=1) identified with BAL culture; and parainfluenza 3 (n=1).

4 | DISCUSSION

In this vulnerable population, FOB with BAL is considered to be a well-tolerated, safe, and accurate procedure.[3] Complication rates of FOB with BAL in SCT recipients can be as low as 0%.[5] If transbronchoscopic lung biopsies are performed in addition to BAL, complication rates can be as high as 7%-15%.[4,6] The safety profile and low complication rate of BAL[3] make it the most commonly used diagnostic tool in SCT recipients undergoing an infectious pulmonary work-up.[14] The major limitations to obtaining an acceptable sputum sample include patient effort and cooperation, quality of samples, colonization and contaminations, and an overall low yield of positive culture.[15] Sputum cultures infrequently have a positive impact on clinical care, and for these reasons, the routine ordering of sputum cultures in patients with pneumonia is controversial.[15] Our study showed that of the 26 sputum cultures collected, 10 yielded a true pathogen, of which only 3 correlated with what was retrieved from the BAL. This finding supports the notion that obtaining a BAL specimen is a critical part of the infectious work-up of SCT recipients and provides valuable microbiologic information.

The combined infectious and noninfectious diagnostic yield of BAL in SCT recipients is between 31% and 80%.[2,3,5–13] Reasons for such variable microbiologic yields of BAL from prior studies include different patient populations, empirical antimicrobial regimens that differed among health care institutions, and various testing protocols and methodologies on the BAL sample. Our study reports an overall microbiologic yield of 40% from BAL specimens obtained from SCT recipients undergoing an infectious pulmonary work-up.

Administration of prophylactic or preemptive antimicrobial therapy is common in SCT patients because empirical antimicrobial therapy is associated with improved clinical outcomes.[16] However, early and aggressive use of such empirical regimens is conceptually thought to decrease the microbiologic yield of a BAL sample. In our cohort of patients who had a true pathogen identified on BAL, 92% had treatment with broad-spectrum antimicrobial therapy initiated at least 48 hours before BAL collection. In addition, 62% of our cohort with

39 BALs, who had detection of MRSA, *Pseudomonas*, or *Aspergillus*, or a combination of these, was taking appropriate therapy targeting these specific pathogens. Therefore, receipt of concurrent antimicrobial therapy should not dissuade the operator from performing a BAL in this patient population.

MRSA pneumonia is associated with poor outcomes and frequently necessitates empirical antibiotic therapy. A recent study reported that a negative MRSA on PCR from a NS specimen had a 99% negative predictive value for MRSA pneumonia.[17] We report similar findings wherein 80 MRSA NSs were performed and 79 were negative. All 79 BAL and sputum cultures that were negative in these cases were negative for MRSA. The 1 patient who had a positive MRSA PCR with NS also had MRSA growth on BAL culture (MRSA PCR by NS: positive predictive value, 100%; negative predictive value, 100%). Given similar findings from the present study, a negative MRSA PCR from NS may be used to de-escalate anti-MRSA antimicrobial therapy in SCT recipients.

In an immunocompetent patient, isolation of *Aspergillus* from sputum and BAL samples in the absence of compatible clinical signs and symptoms is thought to represent airway contamination or colonization. However, in the immunocompromised patient, *Aspergillus* has emerged as an important cause of morbidity and death.[18,19] The recovery of *Aspergillus* in respiratory secretions in SCT recipients has been reported to have a positive predictive value as high as 80%-90%,[20] and most isolates require treatment. We report our observations based on microbiologic data, realizing that any positive *Aspergillus*-related study would be considered significant in this immunosuppressed cohort until proven otherwise. Our study found 8 positive BAL cultures and 12 positive BAL AspAg. No concordance was observed between the two tests. The only concordance seen was between a positive BAL culture and serum AspAg. The lack of concordance among the various methods to detect *Aspergillus* was indeed surprising and encourages clinicians to use multiple modalities to identify the presence of *Aspergillus* species as a cause of pulmonary infiltrates in this vulnerable population.

Our institution is located in the desert southwestern United States, where coccidioidomycosis is endemic. Coccidioidal illness most commonly manifests as a respiratory illness, and thus we evaluated the performance of cocci BAL PCR in SCT recipients. Since SCT recipients routinely receive azole prophylaxis to prevent invasive *Candida* and mold infections, this practice also likely reduces the incidence of coccidioidomycosis in the cohort. We had 1 BAL sample with isolation of *Coccidioides* species and a concordant positive BAL PCR. Among 2 additional cocci BAL PCRs, 1 had a concordant positive cocci serologic test. Overall, 4 patients had positive cocci serologic tests, among whom only 1 had a concurrent positive BAL PCR. Immunosuppressed hosts have lower rates of seroconversion after infections, and this fact likely contributed to the low prevalence of positive cocci serologies in this population. Therefore, multiple modalities might be necessary to diagnose coccidioidomycosis in SCT recipients, in similarity with *Aspergillus* infection.

Although EBV was the most common virus detected in BAL, the clinical significance of a positive BAL EBV PCR is not known and does not offer any meaningful clinical information in SCT recipients. We have since eliminated BAL EBV PCR from our BAL ICH bundled order sets. Thus, we considered parainfluenza as the most common "real" viral pathogen isolated in our cohort. Notably, we observed that 11 of 12 BAL parainfluenza isolated between May 2012 and May 2013 were during a local parainfluenza outbreak. The FilmArray Respiratory Panel (FARP; BioFire Diagnostics, Inc, Salt Lake City, UT USA), which assesses the presence of 17 respiratory viruses and 3 atypical bacterial pathogens via PCR, was introduced at our institution at the end of our study period and was not part of our data collection. We are therefore unable to comment on whether a NP FARP or a BAL FARP would have provided additional information in our cohort. Azadeh et al.[21] compared the yield of concurrent NP vs BAL FARP at our institution and concluded that if a pathogen is identified by NP FARP, a BAL FARP is unlikely to add new microbiological information. Conversely, a BAL FARP may identify causative respiratory pathogens if performed within 7 days of a negative NP swab. Going forward, it would be interesting to study the utility of NP vs BAL FARP in our SCT population.

Thirty-three patients underwent multiple BALs. Although the sample size was small, we observed that repeating a BAL within 30 days provided no additional microbiologic information but, rather, revealed the persistence of the original pathogen despite appropriate therapy. In this series, 174 of 179 cases (97%) had a chest CT within 48 hours of FOB. Chest CT scans may be more sensitive than chest radiographs, and CT is now the standard diagnostic tool in the initial assessment of invasive pulmonary aspergillosis and other opportunistic pulmonary infections in SCT recipients.[22,23] This was a retrospective study and thus has its inherent limitations. We did not assess the impact of BAL results on antimicrobial therapy (ie, alteration or initiation), morbidity, or death, because our study was designed only to analyze the microbiologic yield of BAL. Specific complication rates of FOB were not collected. This also was a single-institution study and the results may not be generalizable to SCT patients in other institutions or regions.

To our knowledge, this is the largest retrospective study to date that looks at the microbiologic yield of FOB with BAL in SCT recipients. We were able to demonstrate that sputum cultures are unreliable in detecting pulmonary pathogens in this population. In addition, obtaining a BAL sample despite the patient receiving antimicrobial therapy for at least 48 hours before sample collection continues to be a valuable diagnostic test to consider in this immunosuppressed cohort.

BAL is an essential diagnostic tool in SCT recipients undergoing an infectious pulmonary work-up. Our study showed an overall BAL microbiologic yield of 40% despite 92% of this group having received empirical broad-spectrum antimicrobial therapy before BAL collection. Although an initial BAL sample can provide critical microbiologic information, repeating a BAL within 30 days may not have additional diagnostic yield.

AUTHOR CONTRIBUTIONS

K.K.S.: Research concept/design, data collection, analysis, and interpretation, drafting article, critical revision of article, and approval of article; C.K.: Data collection, analysis, critical revision of article, and

approval of article; K.B.: Data collection, critical revision of article, and approval of article; T.G., J.S., and L.W.: Data analysis and interpretation, critical revision of article, and approval of article; H.R.V.: Research concept/design, data analysis and interpretation, critical revision of article, and approval of article.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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