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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Utility of microbiologic testing in surveillance bronchoscopy following lung transplantation: A retrospective cohort study

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Abstract

Background: The utility of surveillance bronchoscopy (SB) for the clinical management of lung transplant recipients (LTRs) is undefined. This study evaluates the role of SB in the monitoring and care of LTRs.

Methods: We retrospectively analyzed all LTRs who had SB at Henry Ford Hospital in Detroit, Michigan between August 2014 and August 2019. Bronchoscopies performed for clinical symptoms, new radiographic abnormalities, and to assess stents or acute rejection were excluded. A total of 107 LTRs and 449 bronchoscopies were analyzed. The primary outcome was the rate of change in clinical care based on microbiologic and pathologic test results. Secondary outcomes were rates of microbiologic and pathologic test positivity and rates of adverse effects.

Results: The most common microbiologic tests performed on bronchoalveolar lavage were bacterial (96.9%), fungal (95.3%), and acid-fast bacillus (95.1%) stains and cultures. Of 2560 microbiologic tests, 22.0% were positive and resulted in therapy changes for 2.9%. Positive galactomannan, acid-fast bacillus tests, and *Pneumocystis jirovecii* antigen/polymerase chain reaction did not result in therapy changes. Of the 370 transbronchial biopsies performed, 82.2% were negative for acute rejection and 13% were positive for A1/A2 rejection. Immunosuppressive therapy changes occurred after 15.8% with reduction in immunosuppression due to positive microbiologic tests in 16.9%. Adverse events occurred in 8.0% of patients.

Conclusion: Diagnostic stewardship is warranted when performing SB in LTRs.

KEYWORDS
antimicrobial stewardship, immunosuppression, lung transplants, rejection, surveillance bronchoscopy

1 | INTRODUCTION

The number of individuals living with lung transplants has been increasing over time. Despite advances in posttransplantation management and therapy, the median survival of lung transplant recipients (LTRs) has remained stagnant: 6.5 years for those who received transplants between 2002 and 2009, and 6.7 years between 2010 and 2017.[1] Bronchiolitis obliterans syndrome remains a significant cause of morbidity and mortality in LTRs, with approximately 90% of recipients developing this condition within 10 years of transplantation.[2,3] Risk factors for developing bronchiolitis obliterans syndrome include not only acute rejection but also infection.[4–6] As such, identifying and treating acute rejection and infection as early as possible has become

Abbreviations: D-/R-, donor and recipient-negative; LTRs, lung transplant recipients; SB, surveillance bronchoscopy; TBBX, transbronchial biopsy.

a focal point to improve outcomes in LTRs. Bronchoscopy with testing of specimens from bronchial alveolar lavage (BAL) and transbronchial biopsy (TBBX) is the most common procedure for diagnosis of infection and acute rejection; however, optimal timing of bronchoscopies and the most appropriate tests to perform during bronchoscopy remain areas of controversy.

According to an International Society for Heart and Lung Transplantation survey, surveillance bronchoscopy (SB) is used by almost 87% of transplantation centers; however, the timing of SB varies from center to center.[7] Several studies have highlighted the clinical utility of prescheduled SB, most specifically for identifying acute rejection and prompting changes in immunosuppressive therapy.[8–10] However, studies specifically detailing surveillance microbiologic testing and the role it plays in the monitoring and care of asymptomatic LTRs are lacking. Therefore, we sought to assess the utility of SB for the clinical posttransplantation management of LTRs.

In this retrospective cohort study, our aim was to characterize SB as a form of diagnostic and therapeutic stewardship and elucidate which surveillance diagnostic tests yielded results that positively affected patient care and those that yielded no valuable information. Understanding which diagnostic tests best contribute to actionable surveillance in LTRs is important to reduce low-yield testing on asymptomatic patients, which should increase value and reduce costs to patients and health care systems.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a retrospective, observational cohort study that examined laboratory test results from SBs performed in LTRs. Medical records for all patients who received lung transplant or heart and lung transplant and who had SB performed at Henry Ford Hospital in Detroit, Michigan between August 2014 and August 2019 were included. Pre-bronchoscopy documentation and post-bronchoscopy documentation were reviewed via the electronic medical record and extracted retrospectively. Patient demographic information was collected, and sex and race/ethnicity designations are described as they were noted in the medical record. SB was defined as a prescheduled protocol bronchoscopy for patients who were not displaying symptoms of acute pathology.[7] This study was approved by the Internal Review Board of Henry Ford Hospital (IRB number: 14494).

SBs were performed in patients under anesthesia at 1 week and 1, 3, 6, 9, 12, and 24 months after transplantation. BAL and/or TBBX were performed during SB, and collected BAL samples were analyzed for bacterial, mycobacterial, viral, and fungal pathogens. Bacterial, fungal, and acid-fast bacillus stain and culture; *Pneumocystis jirovecii* (PJP) antigen performed via direct florescent antibody staining and Quest Diagnostics qualitative polymerase chain reaction (PCR); respiratory viral culture for Influenza A and B, parainfluenza 1, 2, and 3, respiratory syncytial virus, and adenovirus; respiratory viral PCR (BioFire FilmArray nested multiplex PCR); cytomegalovirus (CMV) culture and PCR (Ward Lab qualitative real-time PCR or Quest Diagnostics quantitative real-time PCR, depending on provider ordering preference); and BAL galactomannan (Platelia, positive result defined as index >0.5 per manufacturer cutoff) results were collected and reviewed. Results of bacterial cultures were divided by pathogen, cultures with two or more organisms present and without the presence of *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* were defined as polymicrobial. Adverse events related to bronchoscopy defined as aspiration, systemic inflammatory response syndrome, hospital admission, pneumothorax, blood loss >50 ml, hypoxia, intubation, and chest tube placement were also examined.

Bronchoscopies with the following characteristics were excluded from the analysis: (a) performed for new or worsening respiratory symptoms; (b) showed decline in forced expiratory volume at 1 s ≥10%; (c) revealed new radiographic abnormalities; or (d) were follow-up bronchoscopies to assess stents or recent acute rejection.

Pathologic and microbiologic test results were examined to determine whether they influenced changes in clinical care. Changes in clinical care were defined as follows prescription of antimicrobial therapy and/or reduction of immunosuppressive therapy as prompted by positive microbiologic or pathologic test result.

Rate of change in clinical care based on microbiologic and pathologic test results was the primary outcome. Rates of microbiologic and pathologic test positivity and rates of adverse effects were secondary outcomes.

2.2 | Statistical methods

Data were analyzed with descriptive statistics using SPSS for Macintosh (Version 28.0.1.1). Pearson's chi-square test for nonparametric data was used to analyze categorical data comparing rates observed from SBs performed during the following three timeframes: 0 to <3 months, 3 to 12 months, and >1 year after transplantation. A $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient demographics

A total of 127 patients were analyzed. Twenty patients were excluded because they did not receive SB with 107 included in the final analysis. There were 449 SBs performed in this cohort (Figure S1). Patient characteristics are included in Table S1. The median age at transplantation was 63 years (IQR, 10), and 72 (67%) were male. Regarding ethnicity, 19.6% of patients were Black, 77.6% were White, and 2.8% were listed as Other. There were 92 patients (86.0%) who received double lung transplants, 14 (13.1%) who received single lung transplants, and one (0.9%) heart and lung transplant. The mean Charlson comorbidity index was 4.8 (range 1–12). The median number of SB procedures per patient

TABLE 1 Microbiologic tests performed on surveillance bronchoscopy: timing, rates of testing, and rates of positive results

Timing and rates of tests performed on bronchial alveolar lavage specimens					
	Number (%) of microbiologic tests done from SB after lung transplantation				
Test	All SB $N = 449$	0 to <3 months $n = 137$	3 to 12 months $n = 164$	>1 year, $n = 148$	p-Value[a]
Bacterial assays					
Bacterial culture/stain	435 (96.9)	128 (93.4)	161 (98.2)	146 (98.7)	.02
AFB culture/stain	427 (95.1)	123 (89.8)	159 (97.0)	145 (98.0)	.002
Fungal assays					
BAL galactomannan	206 (45.9)	72 (52.6)	82 (52.0)	52 (46.6)	.01
Fungal culture/stain	428 (95.3)	124 (90.5)	160 (97.6)	144 (97.3)	.01
Total PJP (antigen and PCR)	388 (86.4)	97 (70.8)	153 (93.3)	138 (93.4)	<.001
Viral assays					
All respiratory virus (culture and PCR)	331 (73.7)	93 (67.9)	125 (76.2)	113 (76.4)	.18
All CMV (culture and PCR)	345 (76.8)	84 (61.3)	135 (82.3)	126 (85.1)	<.001
Rates of positive laboratory test results on bronchial alveolar lavage specimens					
	Number positive test results/number tests done (%) from SB done after lung transplantation				
All Microbiologic tests	564/2560 (22.0)	172/721 (23.9)	217/975 (22.3)	175/864 (20.3)	.22
Bacterial assays					
Bacterial culture/stain	338/435 (77.7)	98/128 (76.6)	129/161 (80.1)	111/146 (76.0)	.65
AFB culture/stain[b]	3/427 (0.7)	1/123 (0.8)	2/159 (1.3)	0/145 (0)	.42
Fungal assays					
Total fungal assays	279/1022 (27.3)	93/293 (31.7)	107/395 (27.1)	79/334 (23.7)	.08
BAL galactomannan	166/206 (80.6)	59/72 (81.9)	67/82 (81.7)	40/52 (76.9)	.74
Fungal culture and stain	111/428 (25.9)	33/124 (26.6)	40/160 (25.0)	38/144 (26.4)	.94
PJP antigen and PCR	2/388 (0.5)	1/97 (1.0)	0/153 (0)	1/138 (0.7)	.49
Viral assays					
Respiratory culture	0/82 (0)	0/48 (0)	0/25 (0)	0/9 (0)	n/a
Respiratory PCR	29/249 (11.6)	6/45 (13.3)	9/100 (9.0)	14/104 (13.5)	.57
CMV culture	2/231 (0.9)	0/75 (0)	1/99 (1.0)	1/57 (1.8)	.55
CMV PCR	8/114 (7.0)	0/9 (0)	0/36 (0)	8/69 (11.6)	.06

Abbreviations: AFB, acid-fast bacillus; BAL, bronchial alveolar lavage; CMV, cytomegalovirus; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* antigen; SB, surveillance bronchoscopy procedure.

[a]$p < .05$ considered significant as a difference in rates among the three timeframes .

[b]No *Mycobacterium tuberculosis* isolated.

was 4 (IQR, 4). The plurality of patients (32.7%) was CMV donor and recipient-negative (D-/R-) at the time of transplant, and 22.4% were CMV (D+/R+).

3.2 | Microbiologic results

Of the 449 SBs that were performed, 30.5%, 36.5%, and 33.0% were done at less than 3 months, between 3 and 12 months, and after 1 year post-transplantation, respectively. The most common tests performed per BAL sample were bacterial (96.9%), fungal (95.3%), and acid-fasnt bacillus (95.1%) stains and cultures. Testing for CMV and PJP was more commonly done 3 months or longer posttransplantation ($p < .001$). Of the eight positive CMV BAL PCR tests, one patient was found to have concomitant viremia and represents the only patient in whom management was changed. Full rates of microbiologic testing are shown in Table 1.

Of the 2560 microbiologic tests performed, 564 (22.0%) had a positive result (Table 1). Tests that showed the highest rates of positive results were BAL galactomannan (n = 166/206 tests, 80.6%), bacterial culture and stain (n = 243/433 tests, 55.9%), and fungal culture and stain (n = 111/428 tests, 25.9%). Median BAL galactomannan index was 1.1 with an IQR of 0.73.

All viral assays had low rates of positive results.

The overall rate of antimicrobial prescriptions from all 2560 microbiologic tests was 2.9% (n = 73), and the plurality of prescriptions (4.4%,

TABLE 2 Changes in therapeutic care associated with surveillance bronchoscopy in lung transplant recipients

Test	[a]Number of changes in patient care/number of tests done from SB (%)				
	All SB	0 to <3 months	3 to 12 months	>1 year	*p*-Value[b]
Total changes[c] per SB performed	112/449 (24.9)	47/137 (34.3)	27/164 (16.5)	38/148 (25.7)	.002
Total antimicrobial prescriptions per microbiologic test	73/2560 (2.9)	32/721 (4.4)	18/975 (1.9)	23/864 (2.7)	.006
Antibiotic prescriptions					
Per bacterial culture	55/435 (12.6)	28/128 (21.9)	15/161 (9.3)	12/146 (8.2)	<.001
Per AFB culture	0/427 (0)	0/123 (0)	0/159 (0)	0/145 (0)	n/a
Antifungal prescriptions					
Per all tests for fungal pathogens	7/1022 (0.7)	2/293 (0.7)	1/395 (0.3)	4/334 (1.2)	.31
Per culture and stain	7/428 (1.6)	2/124 (1.6)	1/160 (0.6)	4/144 (2.8)	.34
Per BAL galactomannan	0/206 (0)	0/72 (0)	0/82 (0)	0/52 (0)	n/a
Per PJP antigen and PCR	0/388 (0)	0/97 (0)	0/153 (0)	0/138 (0)	n/a
Antiviral prescriptions					
Per all Viral Tests	11/676 (1.6)	2/177 (1.1)	2/260 (0.8)	7/239 (2.9)	.14
Per respiratory viral culture	0/82 (0)	0/48 (0)	0/25 (0)	0/9 (0)	n/a
Per respiratory viral PCR	8/249 (3.2)	2/45 (4.4)	1/100 (0.7)	4/104 (4.8)	.27
Per CMV culture	2/231 (0.9)	0/75 (0)	1/99 (1.0)	1/57 (1.8)	.55
Per CMV PCR	1/114 (0.9)	0/9 (0)	0/36 (0)	1/69 (1.4)	.72
Immunosuppression changes					
All changes in antirejection and steroid therapy	71/449 (15.8)	28/137 (20.4)	13/164 (7.9)	30/148 (20.3)	.002
Immunosuppression reduced	29/71 (40.8)	14/28 (50.0)	2/13 (15.4)	13/30 (43.3)	.10
Reduction due to positive microbiologic test	12/71 (16.9)	6/28 (21.4)	1/13 (7.7)	5/30 (16.7)	.55
Reduction due to negative biopsy	17/71 (23.9)	8/28 (28.6)	1/13 (7.7)	8/30 (26.7)	.31
Immunosuppression increased	42/71 (59.2)	14/28 (50.0)	11/13 (84.6)	17/30 (56.7)	.10

Abbreviations: AFT, acid-fast bacillus; BAL, bronchial alveolar lavage; CMV, cytomegalovirus; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii*; SB, surveillance bronchoscopy procedure.

[a]Specific changes in patient care varied depending on test results. See Methods for full list of types of care given per the different test results.

[b]$p < .05$ considered significant as a difference in rates among the three timeframes .

[c]Number of SB with at 1 or more changes in therapeutic care including antimicrobial prescription and/or change in immunosuppressive therapy.

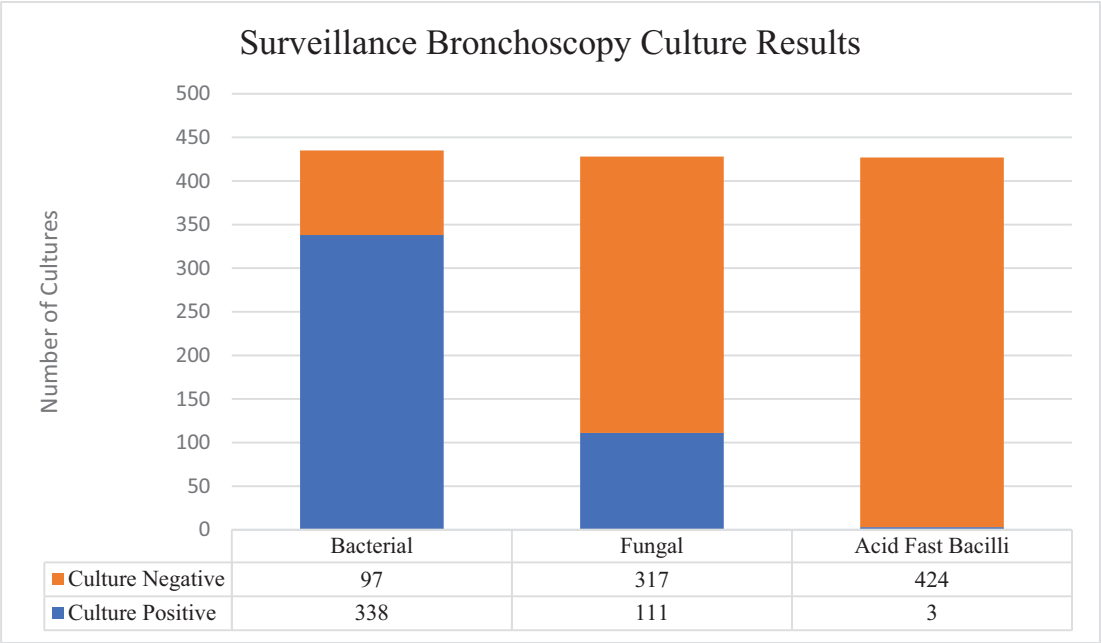
32/721 assays; $p = .006$) occurred within 3 months of transplantation (Table 2). Rates of antimicrobial prescription per laboratory assay were highest after positive bacterial culture and stain results (55/435 assays [12.6%]). A positive BAL galactomannan, acid-fast bacillus culture and stain, PJP antigen/PCR, and respiratory viral cultures did not result in any changes to clinical care. Positive test results from bacterial culture and stain were more likely to elicit antimicrobial prescriptions within the first 3 months after transplantation (21.9%; $n = 28$ changes/128 tests) compared to after 3 months (17.5%; $n = 27$ changes/307 tests) ($p < .001$). Complete results of positive microbiologic tests and changes in therapeutic care are included in Tables 1 and 2.

3.3 | Antibiotic prescriptions

Isolation of *Pseudomonas aeruginosa* accounted for the plurality of antibiotic prescriptions (29.1%, 16/55 prescriptions), and the most common prescribed antibiotic for this infection was inhaled tobramycin (7/16, 43.8%). Polymicrobial flora (23.6% 13/55 prescriptions) and commensal flora (12.7%, 7/55 prescriptions) were the second and third most common culture results that prompted prescriptions of antibiotics. Notably, three prescriptions occurred with a culture negative BAL due to empiric coverage in patients with clinical decompensation. Complete results of bacterial culture data and antibiotic prescriptions are included in Figure 1 and Table 3.

3.4 | Antifungal prescriptions

Isolation of *Aspergillus* species accounted for the plurality of antifungal prescriptions (28.6%, 4/14 prescriptions), and the most common prescribed antifungal for this infection was voriconazole (75.0%, 3/4 prescriptions). Notably, isolation of *Candida* species as well as one bronchoscopy which was culture negative resulted in antifungal prescription due to patient decompensation. Complete results of fungal culture data and antifungal prescriptions are included in Figure 1 and Table 3.



Bacterial Identification (n=338)	**Fungal Identification** (n=118)*
Polymicrobial, 41.7% Commensal Flora, 28.1% Alpha-hemolytic S*treptococcus*, 13.0% *Pseudomonas aeruginosa*, 8.9% *Staphylococcus aureus*, 3.8% Coagulase Negative *Staphylococcus*, 1.5% *Corynebacterium*, 0.6% *Enterococcus faecalis*, 0.6% *Staphylococcus aureus* and *Pseudomonas aeruginosa*, 0.6% *Haemophilus influenzae*, 0.3% *Acinetobacter baumannii*, 0.3% *Klebsiella pneumonia*, 0.3% *Escherichia coli*, 0.3%	*Candida* sp., 53.4% *Penicillium*, 15.3% *Aspergillus* sp., 11.9% *Saccharomyces cerevisiae*, 7.6% Unidentified mold, 5.9% *Cladosporium*, 1.7% *Malbranchea*, 1.7% *Fusarium*, 0.8% *Syncephalastrum*, 0.8% *Paecilomyces*, 0.8%
Acid Fast Bacilli Identification (n=3)	
Mycobacterium gordonae, 66.7% *Mycobacterium avium complex*, 33.3%	

*Fungal Identification number (n=118) is different than fungal culture positive (n=111) due to seven isolates which were polymicrobial.

FIGURE 1 Surveillance bronchoscopy culture results and organism identification

3.5 | Immunosuppressive therapy changes

Of the 449 SBs, test results elicited 71 (15.8%) changes in immunosuppressive therapy. Changes in immunosuppressive therapy were initiated in 20.4% of patients within the first 3 months, in 7.9% between 3 to 12 months, and 20.3% >1 year posttransplantation (p = .002). Immunosuppressive therapy was increased due to a positive biopsy for acute rejection or bronchiolitis in 42 of 71 (59.2%) bronchoscopies. Immunosuppressive therapy was reduced due to a negative biopsy for acute rejection or bronchiolitis in 17 of 71 (23.9%) bronchoscopies. Additionally, immunosuppressive therapy was reduced as a result of positive microbiologic tests in 12 of 71 (16.9%) bronchoscopies. Full results outlining immunosuppressive therapy changes are available in Table 2.

3.6 | Adverse events

Overall, adverse events after SB occurred in 36 of the 449 (8.0%), the most common being hospital admission in nine patients (2.0%).

TABLE 3 Bacterial and fungal culture results with associated antimicrobial prescriptions

Treatment with Antibiotics ($n = 55$)	
Pseudomonas aeruginosa 16/55 (29.1%) ○ Inhaled tobramycin ($n = 7$) ○ Fluoroquinolone ($n = 4$) ○ Cefepime ($n = 2$) ○ Inhaled colistin ($n = 1$) ○ Amoxicillin ($n = 1$) ○ Meropenem ($n = 1$) Polymicrobial 13/55 (23.6%) ○ Fluoroquinolone ($n = 4$) ○ Amoxicillin ($n = 4$) ○ Amoxicillin/Clavulanate ($n = 2$) ○ Doxycycline ($n = 2$) ○ Inhaled tobramycin ($n = 1$) Commensal flora 7/55 (12.7%) ○ Fluoroquinolone ($n = 2$) ○ Cefepime ($n = 1$) ○ Vancomycin ($n = 1$) ○ Doxycycline ($n = 1$) ○ Meropenem ($n = 1$) ○ Cefepime and vancomycin ($n = 1$) *Staphylococcus aureus* 5/55 (9.1%) ○ Linezolid ($n = 2$) ○ Doxycycline ($n = 1$) ○ Amoxicillin/Clavulanate ($n = 1$) ○ Fluoroquinolone ($n = 1$)	Alpha-hemolytic *streptococcus* 4/55 (7.3%) ○ Fluoroquinolone ($n = 2$) ○ Amoxicillin ($n = 1$) ○ Vancomycin ($n = 1$) Culture Negative 3/55 (5.5%)* ○ Vancomycin and piperacillin/tazobactam ($n = 2$) ○ Linezolid ($n = 1$) *Staphylococcus aureus* and *Pseudomonas aeruginosa* 2/55 (3.6%) ○ Inhaled tobramycin ($n = 2$) *Acinetobacter baumanni* 1/55 (1.8%) ○ Meropenem, vancomycin, inhaled colistin ($n = 1$) Coagulase negative *Staphylococcus* 1/55 ○ Fluoroquinolone ($n = 1$) *Enterococcus faecalis* 1/55 (1.8%) ○ Piperacillin/tazobactam, aztreonam, inhaled colistin *Escherichia coli* 1/55 (1.8%) ○ Fluoroquinolone ($n = 1$) *Klebsiella pneumoniae* 1/55 (1.8%) ○ Fluoroquinolone ($n = 1$)
Treatment with antifungals ($n = 7$)	
Aspergillus 4/14 (28.6%) ○ Voriconazole ($n = 3$) ○ Inhaled amphotericin B ($n = 10$) Unidentified mold 1/7 (14.3%) ○ Voriconazole ($n = 1$)	*Candida* sp. 1/63 (1.6%) ○ Fluconazole ($n = 1$) Culture negative 1/317 (0.3%)* ○ Voriconazole ($n = 1$)

*Treatment added empirically due to patient decompensation.

No bronchoscopy-related deaths occurred. All adverse events are included in Table S2.

4 | DISCUSSION

In this study, we observed that most routine laboratory tests, such as those for acid-fast bacilli and viral pathogens, showed extremely low positive test results. Overall, very few adverse events occurred after SB.

Our study echoes other reports that have shown SB prompts changes in care for LTRs, especially within the first 3 months after transplantation. However, these studies have not described details of the specific changes that were instituted and whether or not the changes were appropriate.[8,9,11] We observed that the rate of therapeutic changes were highest (34.3%) within the first 3 months of transplantation and that most changes were for antibiotic prescriptions (~22%) and alterations in immunosuppressive therapy (~20%). Of the 71 changes in immunosuppressive therapy, reduction of immunosuppressive therapy was prompted by positive microbiologic test results in 17%.

Our study reveals many opportunities for diagnostic and therapeutic stewardship. Bacterial testing was the most common test performed and was highly associated with changes in patient care, as noted in other studies.[8,9,12] In our study, bacterial testing was done in 96% of the performed SBs, and antibiotics were administered after positive bacterial test results in 13%. This suggests over-utilization of testing and treatment, as our study included only patients who were asymptomatic at the time of bronchoscopy. Furthermore, immunosuppressive therapy reductions prompted by positive microbiologic tests may represent inappropriate responses to colonization. Recent work by Combs et al. has suggested a relationship between the lung microbiome and the development of chronic rejection and patient mortality, with patient outcomes predicted by both lung bacterial burden and bacterial community composition.[13] Their work showed that patients with "inflammation-associated taxa" (e.g., Pseudomonadaceae and Enterococcaceae) were more likely to develop chronic rejection and had increased mortality.[13] This suggests that inappropriate antimicrobial prescriptions which select for these organisms may be harming patients over and above development of *Clostridioides difficile* infection or simply selection of resistant organisms but may also have an effect on allograft function and patient mortality. An additional study

assessing the utility of *Nocardia* PCR in BAL samples from LTRs similarly noted no episodes of clinical nocardiosis despite positive PCR results, furthering the idea that positive test do not require treatment when there is a lack of clinical symptoms.[14]

Fungal infections after lung transplantation are a common occurrence. One prospective study of 815 LTRs noted an incidence of 19%.[15] *Aspergillus* is one of the most common posttransplant fungal infections, with an incidence of 6.2%, carrying with it a high risk of morbidity and mortality.[16–20] Identification of these infections can be challenging, as fungal cultures have limited sensitivity, and BAL galactomannan has improved sensitivity but limited specificity for invasive disease.[21] There is a paucity of literature evaluating the utility of fungal screening in SB. In our study, fungal culture and stain assays, although positive in almost 26% of 428 tests performed, were associated with therapeutic changes in only 1.6%, as most positive test results were due to nonpathogenic colonizers such as *Candida*, *Penicillium*, or *Saccharomyces* species (seen in 104 of 111 positive cultures). Likewise, BAL galactomannan, while positive in 81% of 206 tests performed, did not lead to changes in patient care in our study because of lack of clinical features of invasive disease, the possibility of positive results due to colonization, or false positive results. Regarding PJP, a retrospective study of 104 LTRs over 10 years reported six cases, all beyond 645 days after transplantation.[22] Similarly, in our study, only two of 388 tests were positive for PJP and did not change patient care.

Nontuberculous mycobacterial culture positivity has been reported in 0.46%–4.19% of LTRs; however, studies do not differentiate the rate of colonization versus true infection.[23–25] Our study showed a nontuberculous mycobacterial positivity rate of only 0.7% of 427 tests performed, all of which were deemed colonization, and none led to changes in patient care.

A previous study of SB reported the incidence of CMV pneumonitis, defined as positive histopathology or positive CMV culture in the presence of allograft dysfunction, to be 2.6%.[26] In our study, 2.9% of 345 CMV tests performed were positive, but patient care was modified in only 0.9%. No biopsy was positive for CMV disease. Community respiratory viruses likewise are uncommon in asymptomatic LTRs. Two studies assessing respiratory viral PCRs in 359 LTRs reported a positivity rate of 2.5%.[27,28] Despite our study yielding slightly higher results, (12% of 249 PCRs performed) only 3.2% led to changes in patient care.

Lastly, complication rates of SBs were low (8.0%) in our study, and serious complications such as blood loss >50 ml, pneumothorax, and chest tube placement occurred in less than 2.0% of patients, which is comparable to what has been seen in other studies of SB.[29,30]

4.1 | Limitations

We were limited by the retrospective design of the study and the use of data from a single institution. It is possible that positive cultures in some cases represented nascent infections. We did not examine the impact of immunosuppressive therapy modifications on long-term outcomes such as development of bronchiolitis obliterans syndrome or mortality. Complications of antimicrobial therapy such as the emergence of subsequent resistance and/or the development of complications such as *Clostridiodes difficile* infection were not evaluated. Cut off for BAL galactomannan set as 0.5 rather than 1.0 as recommended in European guidelines may have led to increased false positive results.[31]

5 | CONCLUSION

Our study suggests that microbial diagnostic testing and consequent antimicrobial therapy may be overutilized as a result of SB during the clinical management of asymptomatic patients who have received a lung transplant. Future prospective studies should examine the role of routine microbiological testing and antimicrobial therapy in asymptomatic LTRs undergoing SB.

AUTHOR CONTRIBUTIONS

Concept and study design: JC, WPD, GA, MR, and TPA. *Drafting of manuscript*: WPD. *Chart review*: TPA, AF, and WPD. *Interpretation of the data*: WPD, GA, and MR. *Critical revisions of manuscript*: WPD, GA, and MA.

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CONFLICT OF INTEREST

All authors concur with submission of the manuscript to *Transplant Infectious Disease* and have no known conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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