Diagnostic Yield of Bronchoalveolar Lavage in Immunocompromised Children With Malignant and Non-Malignant Disorders

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Summary. Background: The diagnostic yield of bronchoalveolar lavage (BAL) in the Immunocompromised pediatric population has ranged from 28% to 68%. We hypothesized that the diagnostic yield of BALs would be higher in more recent years due to new diagnostic assays. Methods: A retrospective case series was performed among immunocompromised children ≤18 years old who underwent BALs from 2001 to 2012, to assess the yield of microbiologic diagnostic studies and to determine the impact of BAL findings on antimicrobial management. Results: In all, 123 subjects underwent 174 BALs (mean age 9.9 years). Underlying diagnoses included both malignant (n = 79) and non-malignant (n = 44) disorders, and 75 (61.0%) subjects were hematopoietic stem cell transplant (HSCT) recipients. Fifty-four (31.0%) of 174 BAL were positive for ≥1 potential pathogen (n = 58 microorganisms). The diagnostic yield of BALs performed from 2001 to 2006 versus 2007–2012 was similar (40.5% vs. 26.6%, respectively, $P = 0.07$). Most subjects (86.2%) were on ≥1 antimicrobial at the time of BAL. Most (65.8%) negative BALs were associated with narrowing antimicrobial therapy, while most (74.1%) positive BALs were associated with continuing or changing to targeted antimicrobial therapy. Conclusions: In this study population, the diagnostic yield of BAL was similar to that previously described and unchanged in more recent years. Both negative and positive BALs were associated with changes in antimicrobial management. Summary: A 10-year retrospective review of bronchoalveolar lavage in 123 immunocompromised children determined that the rate of isolation of potential pathogens was 31% in this population. The majority of BAL was associated with a change in antimicrobial therapy. **Pediatr Pulmonol. 2017;52:820–826.**   © 2017 Wiley Periodicals, Inc.

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Conflict of interest: None

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INTRODUCTION

Lower respiratory tract infections (LRTIs) result in substantial morbidity and mortality for immunocompromised children.[1,2] Approximately 25% of children undergoing hematopoietic stem cell transplant (HSCT) will develop a LRTI.[1,3] Improving detection of pathogens from BAL specimens is critical to guide antimicrobial management, direct infection prevention and control strategies, understand potential changes in epidemiology, and avoid more invasive diagnostic interventions, for example, lung biopsy. Prior studies of BAL performed in immunocompromised children have reported detection of pathogens in 28–68% (mean 50%) of procedures using a variety of case definitions and patient populations.[2,4–10] However, few recent studies have examined the diagnostic yield of BAL in the immunocompromised pediatric population and compared the yield of different diagnostic assays.

Thus, the primary aim of this study was to determine the overall diagnostic yield of BALs in immunocompromised children over the past decade, and to compare the rates of isolation of bacterial, fungal, viral, and mycobacterial pathogens in the early (2001–2006) versus later (2007–2012) years of the study period. We hypothesized that the diagnostic yield of BALs performed in the earlier years of the study would be lower than BALs performed during the later years due to improvements in diagnostic assays. The secondary aim was to determine if BAL results were associated with changes in antimicrobial therapy.

METHODS

Study Design, Site, and Subjects

A retrospective case series of immunocompromised pediatric patients undergoing BAL from 2001 to 2012 was performed at NewYork-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, New York, New York. The decision to perform BAL was made by the patient's primary team in consultation with the pediatric pulmonology service. Eligible subjects were ≤18 years of age at the time of BAL and had multiple underlying diagnoses (Table 1). To identify cases, the BAL procedure records of the Pediatric Pulmonology division were reviewed. If a subject underwent more than one BAL during the study period, all procedures were included. Flexible bronchoscopy was performed to obtain BAL specimens in patients who were intubated endotracheally, or less commonly, via laryngeal mask airway (LMA). Sites for BAL were chosen based on chest imaging, usually CT scan, and by findings at the time of bronchoscopy. BAL was performed at multiple sites if there were multiple areas of involvement on imaging, or by bronchoscopic

appearance. The institutional review board of Columbia University Medical Center approved the conduct of this study with a waiver of informed consent.

BAL Assays

The results of all microbial studies performed on each BAL were reviewed, including bacterial cultures, fungal cultures, AFB smear and culture, and viral diagnostic studies (cultures, direct fluorescence assay [DFA], and/or enzyme-linked immunoassays [EIAs], and polymerase chain reaction [PCR]). In May 2012, a multiplex reverse transcriptase (RT)-PCR assay was introduced (FilmArray, Biofire Diagnostics, Inc., Salt Lake City, UT)[11] comprising 20 viral and bacterial targets (adenovirus, four coronaviruses, human metapneumovirus, rhinovirus/enterovirus, five subtypes of influenza A/B, four subtypes of parainfluenza, respiratory syncytial virus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*). Results of cytologic staining for *Pneumocystis jiroveci* cysts, acid-fast organisms, viral inclusions or evidence of cytologic transformation, and the Platelia *Aspergillus* galactomannan from BAL (Bio-Rad, Hercules, CA)[12] introduced in September 2012 were also reviewed. *Legionella* cultures were not routinely sent. Quantitative BAL was not introduced at our institution's microbiology lab until after the end of the study period.

Pathogen Case Definition

Potential pathogens were defined as any detection by PCR or growth in culture of respiratory viruses (e.g., RSV or parainfluenza), cytomegalovirus (CMV), herpes simplex virus (HSV), nontuberculous mycobacteria (NTM), pathogenic bacteria, or fungal organisms (e.g., *Aspergillus*, *Pneumocystis*, or *Mucor* spp.). Coagulase-negative staphylococci (CoNS) or mixed commensal flora were not considered pathogens in this study. Quantitative BAL was not performed during the study.

Antimicrobial Management

Pharmacy records in the electronic medical record (EMR) were reviewed to assess whether BAL results were associated with changes in antimicrobial therapy. To assess changes in antimicrobial therapy, we recorded the treatment initiated during the 72 hr prior to BAL through the 7 days following BAL. For patients who grew mycobacteria, pharmacy records were reviewed for 60 days following bronchoscopy. Intravenous and inhaled antimicrobial agents and adjunctive agents, for example, CMV- or RSV-specific immunoglobulin, were collected.

TABLE 1—Demographic and Clinical Characteristics of Immunocompromised Children With and Without Potential Pathogens Detected by BAL, 2001–2012

Characteristic	Patients (n = 47) with potential pathogen isolated from BAL N (%)	Patients (n = 76) without potential pathogen from BAL N (%)	P
BAL	84 (48)	90 (52)	
Mean age at 1st BAL (range)	9.4 years (0.7–18.5)	10.2 years (0.4–18.9)	0.45
Sex			
M	28 (59.6)	50 (65.8)	0.56
Race/ethnicity			
White non-Hispanic	13 (27.6)	25 (64.8)	0.68
Black	4 (8.5)	7 (9.2)	1.00
Hispanic	13 (27.6)	19 (25.0)	0.83
Asian	2 (4.3)	4 (5.3)	1.00
Other	1 (2.1)	1 (13.2)	1.00
Unknown	14 (29.8)	20 (26.3)	0.68
Underlying diagnosis			
Acute myelogenous leukemia	8 (17.0)	14 (18.4)	1.00
Acute lymphocytic leukemia	13 (27.6)	17 (22.3)	0.52
Aplastic Anemia	2 (4.3)	11 (14.4)	0.12
Chronic myelogenous leukemia	2 (4.3)	0	0.14
Hemophagocytic lymphohistiocytosis	4 (8.5)	5 (6.6)	0.73
Hodgkin disease	2 (4.3)	2 (2.6)	0.63
Other malignant disorders	5 (10.6)	16 (21.0)	0.70
Other nonmalignant disorders[1]	11 (23.4)	11 (14.5)	0.23
HSCT Prior to BAL	31 (70.0)	44 (57.9)	0.44
Time from 1st HSCT to 1st BAL			
≤30 d	8 (25.8)	15 (34.1)	
>30 d	23 (74.2)	29 (65.9)	0.61
Degree of myeloablation			
Myeloablative	16 (51.6)	25 (56.8)	0.81
Reduced toxicity	7 (22.6)	13 (29.5)	0.60
Reduced intensity	8 (25.8)	6 (13.6)	0.23
Received anti-thymocyte globulin	17 (54.8)	21 (47.7)	0.64
Received alemtuzumab	5 (16.1)	10 (22.7)	0.57
Time period			
2001–2006	28 (59.6)	30 (39.5)	
2007–2012	19 (40.4)	46 (60.5)	0.041

HSCT, hematopoietic stem cell transplant.
[1]Underwent HSCT prior to BAL. Other malignant and non-malignant indications for HSCT included neuroblastoma, Langerhans cell histiocytosis, adrenoleukodystrophy, myelodysplastic syndrome, thalassemia, pansclerotic morphea and Wiskott–Aldrich syndrome.

Doses of antimicrobials were reviewed to differentiate prophylactic from treatment regimens.

The EMR notes of the patient's primary team or intensive care team were reviewed to determine the rationale for changes in antimicrobial therapy. Antimicrobial therapy was categorized as *targeted* or *non-targeted*. *Targeted* therapy was defined as antimicrobials that treated an identified bacterial pathogen based on susceptibility results. *Non-targeted* therapy was defined as antimicrobials that did not treat an identified pathogen or that were continued for a negative BAL. Antimicrobial therapy was further categorized as follows:

(1) narrowing therapy (discontinuation of ≥1 non-targeted antimicrobial or discontinuation of second targeted antimicrobial, i.e., duplicate therapy);
(2) continuing targeted therapy (continuing ≥1 targeted antimicrobial for >5 calendar days);
(3) changing to targeted therapy (adding ≥1 targeted antimicrobial continued for ≥5 calendar days);

(4) continuing non-targeted therapy (continuing ≥ 1 nontargeted antimicrobial for ≥ 5 calendar days); or

(5) no antimicrobial therapy recorded.

Treatment could reflect ≥ 1 category.

Data Collection

Demographic and clinical characteristics were collected from the EMR. In patients who underwent autologous HSCT followed by a planned allogeneic HSCT, the date and degree of myeloablation[13] of the first HSCT were used in the analysis. Radiographic findings suggestive of LRTI, for example, nonspecific "opacities," "nodules," and "ground glass opacities" were abstracted from attending radiologists' electronic reports of computed tomography (CT) performed within 10 days of BAL (when available) or chest radiographs (if a recent CT had not been performed). Radiographic findings reported for <5% of subjects (i.e., scarring, mass, reticulations, increased attenuation) were excluded from analysis, as the study was not powered to detect an association between such findings and potential pathogens.

Statistical Analysis

To analyze potential factors associated with isolation of pathogens from BAL, we assessed binary variables such as sex and transplantation status using chi-square (or Fisher's exact test) or Student's t-test, when applicable. Factors associated with positive BAL findings in the bivariate analysis (P-value ≤ 0.2) were further assessed by multilogistic regression. P-values ≤ 0.05 were considered significant.

The proportion of specimens sent for each test during the years 2001–2006 versus 2007–2012, as well as the overall yield of BALs performed during each period, was compared via test of proportions. The types of microorganisms, that is, bacterial, fungal, NTM, and/or viruses detected during these two time intervals were similarly analyzed. Additionally, the yield from the first versus second BAL performed within 30 days of the first BAL was compared for subjects in whom BAL was performed more than once. Radiographic findings associated with isolation of potential pathogens were compared via Fisher's exact test. Statistical analysis was performed using SAS version 9.3 (Cary, NC).

RESULTS

Study Subjects

During the study period, 123 subjects (mean age 9.9 years, range 0.4–18.9 years) underwent 174 BALs. The demographic and clinical characteristics of subjects, including their underlying diagnoses, are shown in Table 1. The majority of subjects (n = 75, 60.9%) had
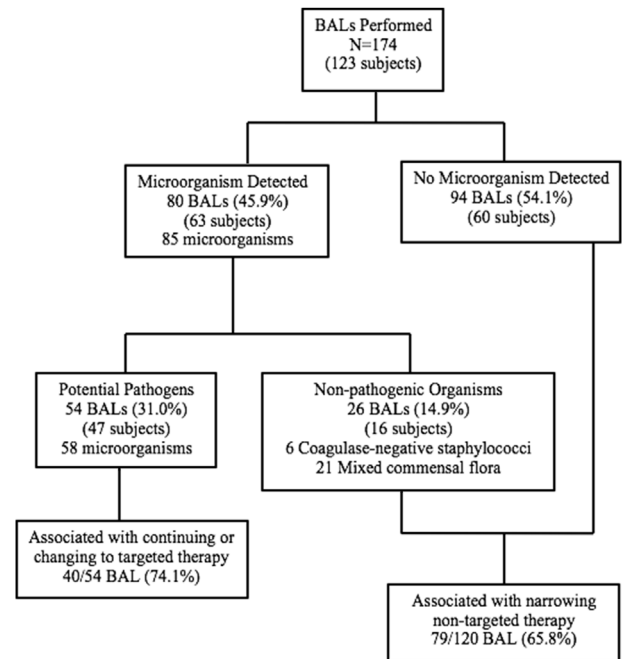

Fig. 1. Diagnostic yield of BAL.

undergone HSCT prior to their BAL and the mean time from first HSCT to BAL was 123 days (range 1–625 days). No factors, including HSCT transplant status or degree of myeloablation, predicted detection of potential pathogens. Thirty-one subjects had >1 BAL performed. Among those who had a second BAL within 1 year of the first, the mean time to second BAL was 163 days (range 9–316 days).

BAL Findings

Overall, 80 (45.9%) of the 174 BALs yielded 85 microorganisms (Fig. 1), of which 54/174 (31.0%) were positive for 58 potential pathogens and 26/174 (14.9%) were positive for non-pathogenic organisms. The diagnostic yield of BALs performed from 2001 to 2006 versus 2007–2012 was similar (40.5% vs. 26.6%, respectively, $P = 0.07$), as shown in Table 2. In addition, the types of microorganisms detected in the earlier versus later era were similar. Overall, the most commonly isolated organisms were gram-negative bacilli (GNB), CMV and *Candida* species. All cultures for anaerobic pathogens (n = 82), *Legionella* (n = 135), *Actinomyces* (n = 46), *Nocardia* (n = 49), and *Mycoplasma* (n = 80) were negative.

There was a significant increase in obtaining fungal and CMV cultures during the years 2007–2012, when compared to the earlier years of the study ($P < 0.01$). Additionally, in the later years of the study, there was a decrease in viral cultures ($P = 0.05$) and an increase in viral comprehensive panels ($P = 0.012$) as the former was supplanted by the latter at our institution. The proportion

TABLE 2— Yield of BAL for Potential Pathogens, 2001–2006 Versus 2007–2012

Diagnostic assays obtained	2001–2006, N = 84	2007–2012, N = 90	P
Mean antimicrobial duration prior to BAL (range)	4.6 d (1–15)	5.6 d (0–24)	0.42
Negative BAL	40 (47.6%)	54 (60.0%)	0.13
CoNS or mixed commensal flora	12 (14.3%)	15 (16.7%)	0.68
Potential pathogens isolated	34 (40.5%)	24 (26.6%)	0.07
Bacteria (all)	11 (13.1%)	6 (6.7%)	0.20
Gram-negative bacilli	6	5	
Gram-positive cocci	5	1	
Viruses (all)	9 (10.7%)	7 (7.8%)	0.60
CMV	5	3	
Adenovirus	2	2	
RSV	1	1	
Other[1]	1	1	
Fungi or molds (all)	11 (13.1%)	10 (11.1%)	0.81
Candida spp.	6	7	
Pneumocystis	3	1	
Aspergillus spp.	1	1	
Other[2]	1	1	
Mycobacterium avium complex	3 (3.6%)	1 (1.1%)	0.36

CoNS, coagulase-negative staphylococci; CMV, cytomegalovirus; RSV, respiratory syncytial virus.
[1]Parainfluenza type 3 and HSV.
[2]*Trichosporon* and *Mucor* spp.

of BALs sent for bacterial culture, AFB culture, and cytologic examination was similar over time.

Twelve subjects had a second BAL performed within 30 days of their first BAL. The yield of the first BAL was 50% (6/12) while the diagnostic yield for the second BAL was 33% (4/12). Three of the second BALs detected new microorganisms including *Candida krusei*, *Aspergillus niger*, and *Pseudomonas aeruginosa*.

Radiographic Findings

The majority of BALs (166, 95.4%) were preceded by abnormal findings on CT scan (n = 134, 77%) or chest radiography. Nonspecific opacities (n = 32), nodules

TABLE 3— Radiographic Findings Associated With BAL

Radiographic findings	Potential pathogen isolated from BAL, n = 58 (%)	Negative or non-pathogen (CoNS or mixed commensal flora), n = 116 (%)	P
Nonspecific opacity	32 (55.2)	32 (27.6)	<0.001
Nodule	30 (51.7)	26 (22.4)	<0.001
Atelectasis	16 (27.6)	33 (28.4)	1.00
Ground glass opacity	21 (36.2)	22 (19.0)	0.016
Effusion	12 (29.7)	29 (25.0)	0.575
Consolidation	15 (25.9)	15 (12.9)	0.054

CoNS, coagulase-negative staphylococci.

(n = 30), and ground glass opacities (n = 21) were significantly associated with the detection of potential pathogens (Table 3).

Antimicrobial Therapy

The majority of study subjects (106 subjects, 86.2%) were receiving ≥1 antimicrobial agent at the time of BAL; 13.2%, 64.2%, and 22.6% were receiving one, 2 or >3 agents, respectively. The mean duration of antimicrobial therapy prior to BAL was 5.3 days (range, 0–24 days).

Therapy was narrowed (i.e., at least one non-targeted agent was discontinued) following 79 (65.8%) of 120 negative BALs. However, a non-targeted agent was also continued following 68 (56.7%) negative BALs. Following the 54 positive BALs, therapy was continued for 13 (32.5%) or changed to targeted therapy for 27 (67.5%). Of the 13 positive BALs resulting in continuation of targeted therapy, 10 (76.9%) had a bacterial or fungal organism identified. Of the 27 positive BALs resulting in changing to targeted therapy, 17 (63.0%) had a viral or mycobacterial organism identified.

DISCUSSION

In this study, we describe a large cohort of immuno-compromised children who underwent BAL over a 12-year period and found that the infectious diagnostic yield of BAL was 31%. We did not identify demographic or clinical risk factors associated with detection of a potential pathogen. Subjects who had undergone HSCT and/or who had received more myeloablative conditioning regimens were not more likely to have a detectable pathogen. However, radiographic findings of nonspecific opacities, ground glass opacities and nodules were more likely to be associated with isolation of a potential pathogen; the presence of such findings may therefore have clinical utility in the decision to perform BAL in immunocompromised children.

The rate of positive BALs in previous studies has ranged from 28% to 68%, as shown in Table 4,[4–5,7–10,14–16] and this variability likely reflects institutional differences in patient populations, BAL testing modalities, and local epidemiology of pathogens.[4,14] Perhaps more importantly, the case definitions for pathogenic microorganisms has varied; in contrast to the current study, some studies have included CoNS and mixed commensal flora as pathogenic.[4,5] Yet others have variously excluded isolates of CMV, *Candida* spp., NTM and *Aspergillus* spp. as airway contaminants.[4,6,9]

Contrary to our hypothesis, the rate of isolation of potential pathogens was higher in the earlier years of the study than in later years, although not statistically significant, despite the fact that significantly more samples were submitted for fungal and CMV cultures

TABLE 4— Case Series of BAL Findings in Immunosuppressed Children

Ref.	Study period	Subject n/BAL N	Underlying diagnoses	BAL yield n/N[1] (%)	Bacteria (%)	Viruses (%)	Fungi[2] (%)	NTM
Current study	2001–2012	123/174	Hematologic malignancies, HLH, aplastic anemia, cancer, HSCT	54/174 (31)	29.3	27.5	36.2	6.9%
[4]	2000–2009	33/44	Hematologic malignancies, HSCT	22/44 (55)	32.3[3]	35.3	32.3	0
[7]	2000–2004	58/62	Primary immunodeficiency, cancer, HSCT	33/62 (53)	59.6[3]	26.9	13.4	0
[9]	1995–2003	89/92	Cancer, HSCT	41/92 (45)	24.4	24.4	51.2	0
[10]	1990–2002	78/78	HSCT	53/78 (68)	52.3	13.6	6.8	0
[5]	1993–2003	54/68	Leukemia, HSCT, AIDS, OHT, cancer, SLE	25/36 (37)	56.7[3]	16.2	27.0	0
[8]	1988–1998	53/53	Cancer	15/53 (28)	20.0	26.7	46.7	6.7%
[14]	1995–1999	52/86	Cancer, HSCT, SCID	27/86 (31)	24.9	24.9	41.2	0
[15]	1990–1996	28/31	HSCT	16/31 (52)	37.5	50.0	12.5	0
[19]	1985–1990	27/29	HSCT	15/29[3] (52)[4]	0	75.0	25.0	0

HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; AIDS, acquired immunodeficiency syndrome; OHT, orthotopic heart transplant; SLE, systemic lupus erythematosus; SCID, severe combined immunodeficiency.
[1] n = pathogenic microorganism(s) detected; N = number of BALs.
[2] Fungi includes: yeast, mould, and *Pneumocystis*.
[3] Included coagulase-negative staphylococci and/or viridans-group streptococci as pathogenic microorganisms.
[4] *Toxoplasma* isolated from one BAL.

in the later study period. Our results indicate that the majority of patients were on multiple antimicrobials at the time of BAL, and this may have affected culture results. Additionally, during the last two decades, isolation of viral microorganisms from BAL has decreased overall,[5,15] which may reflect improving antiviral prophylaxis in patients who are CMV-seropositive. The decreasing incidence of *Pneumocystis* pneumonia due to prophylaxis against this organism is also well documented.[17] Furthermore, negative BALs may have reflected non-infectious causes of lower tract disease such as graft-versus-host disease or pulmonary fibrosis, as has been previously described.[2,10,16,18–19] Recent comparison studies have suggested that lung biopsy may elucidate noninfectious diagnoses in a manner superior to that of BAL,[20–22] though this procedure is associated with higher morbidity and mortality than BAL.

Our study supports the observations made in prior series that a positive result from BAL impacts treatment decisions.[4,8,20] We found that most negative BALs were associated with discontinuing at least one non-targeted antimicrobial, although often another non-targeted agent was continued. In addition, the majority of positive BALs were associated with changing to targeted antimicrobials for viral or mycobacterial pathogens. Thus, prescribing was improved following 119 (68.4%) of 174 BALs.

Limitations

This single center retrospective study had limitations. Not all diagnostic tests were performed for every BAL and we were unable to consistently determine the reason for this. We also did not examine whether indication for bronchoscopy (e.g., fever, worsening respiratory status, radiographic findings) was associated with detection of potential pathogens. Furthermore, we could not assess the usefulness of RT-PCR for respiratory viral pathogens as our institution introduced this technology in May 2012; nor could we assess the usefulness of *Aspergillus* galactomannan as so few tests were sent. Furthermore, quantitative BAL analysis was unavailable during the study period. The study was not sufficiently powered to detect the association of relapse, refractory disease, type of chemotherapy, or different conditioning regimens, on the yield of BALs. We did not analyze the association of neutropenia with the yield of BAL or with radiographic findings. Finally, we could not conclusively determine providers' rationale for continuing non-targeted therapy or discontinuing targeted therapy.

CONCLUSIONS

BAL contributes to treatment decision-making in immunocompromised patients with presumed LRTI, and continues to have a role in the care of this population. A multicenter study should be performed to validate a case definition for positive BALs, to examine the relative contribution of newer diagnostic modalities, and to further assess the impact of BALs on antimicrobial management.

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