Original Article

Diagnostic Utility of Bronchoalveolar Lavage in Immunocompromised Patients with Lung Infiltrates

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Abstract

Introduction: Lung infections are associated with a high mortality rate in immunocompromised patients. Achieving an accurate and rapid diagnosis is vital to help guide management, and thus improve survival.

Objective: To establish the diagnostic yield, clinical value, and safety of bronchoscopy with bronchoalveolar lavage (BAL) in immunocompromised adult patients with pulmonary infiltrates.

Methods: This retrospective study included all immunocompromised adult patients who underwent bronchoscopy with BAL for investigation of radiologically confirmed pulmonary infiltrates at a tertiary care hospital between January 01, 2014, and June 30, 2021. Clinically significant findings of BAL were defined as a positive microbiological result of a potential pathogen determined using routine culture, acid-fast bacilli smear, mycobacterial culture, tuberculosis PCR, fungal culture, *Aspergillus* antigen, and multiplex PCR panel and/or positive cytology.

Results: A total of 103 unique patients were included (mean ± SD age: 44.5 ± 14.1 years), of which the majority were male (60.2%). The BAL diagnostic yield was 52.4% (95% CI: 42.6–62.2%). In the multiple logistic regression model, positive BAL was predicted by symptom of sputum (*a*OR 4.01, 95% CI: 1.27–12.70, $P = 0.018$). Almost half of the procedures (43.7%, 95% CI: 33.9–53.4%) resulted in a change in the management plan, with positive BAL findings more than twice as likely to result in a change (OR 2.39, 95% CI: 1.07–5.33, $P = 0.033$). Only three (2.9%) procedures resulted in complications and required ventilator support and/or oxygen escalation.

Conclusions: BAL is a safe clinical tool that can be useful in impacting clinical management in a significant proportion of immunocompromised patients with pulmonary infiltrates.

Keywords: Bronchoalveolar lavage, bronchoscopy, immunocompromised, lung infection, lung infiltrates

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INTRODUCTION

Lung infection is a leading cause of morbidity and mortality in immunocompromised populations. Therefore, early diagnosis of patients presenting with fever and pulmonary infiltrates is vital.[1,2] Noninvasive microbiological sampling is often nondiagnostic, and lung infiltrates have noninfectious

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causes in up to 30% of immunocompromised patients, such as drug toxicity, pulmonary edema, and interstitial lung disease.[3,4]

Bronchoscopy with bronchoalveolar lavage (BAL) is performed widely in immunocompromised patients with pulmonary infiltrates to help establish diagnosis, guide patient management, and limit antimicrobial resistance.[5] BAL involves the instillation of sterile saline into a target area of the lung, which is then collected for analysis. The risk of major complications following BAL is significantly lower (0.5%) than after transthoracic approaches and transbronchial biopsy (6.8%).[6] In previous studies, the microbiological yield of BAL has been reported to range from 31% to 83%, depending on the population studied. Importantly, the results from BAL analysis can lead to changes in clinical management plans in a significant proportion of patients.[7,8]

Because of the reported wide variability of the BAL yield, this study aimed to confirm and establish the diagnostic yield in immunocompromised patients with pulmonary infiltrates at a tertiary care center in Saudi Arabia. Data on predictors of BAL findings and the impact of BAL on clinical management are limited. In the real world, performing early BAL (within 48 h) after the identification of pulmonary infiltrates in immunocompromised patients might be challenging because of the busy schedule of the endoscopy unit and pulmonologists. In addition, most patients are likely to be initiated on empirical antimicrobials to avoid pulmonary complications associated with delayed treatment until the results of BAL. Hence, this study also aimed to explore whether early versus late BAL had an impact on BAL microbiological yield and to identify the predictors of positive BAL.

MATERIALS AND METHODS

Study design, setting, and subjects

This retrospective study included all immunocompromised adult patients who underwent bronchoscopy with BAL at King Fahad Specialist Hospital, Dammam, Saudi Arabia, for the investigation of radiologically confirmed pulmonary infiltrates between January 01, 2014, and June 30, 2021. The classification of immunocompromised patients was according to 2013 Infectious Diseases Society of America (IDSA) definition.[9] Mechanically ventilated patients and those with transbronchial biopsies taken during bronchoscopy were excluded from the study.

The IDSA clinical practice vaccinations define highly immunocompromised groups as follows: patients with HIV infection with a CD4 T-lymphocyte count <200 cells/mm, patients receiving daily corticosteroid therapy with a dose ≥20 mg of prednisone or equivalent for ≥14 days, patients receiving certain biologic immune modulators such as tumor necrosis factor-alpha (TNF-α) blocker or rituximab, patients receiving cancer chemotherapy, individuals who previously received a solid organ or hematologic transplant, and patients with hematologic malignancies.

Bronchoscopy with bronchoalveolar lavage

Board-certified pulmonologists performed bronchoscopy with BAL from the radiologically involved area in cases of focal infiltrates and from either the lingula or middle lobe if the infiltrates were diffuse. Five to six aliquots of 20–30 ml normal saline were used for lavage after wedging the scope into the bronchial segment of the targeted pulmonary parenchyma. Approximately at least 30% of the infused amount was considered an adequate return of the BAL.

Data collection

Predefined clinical data were extracted retrospectively from medical notes and laboratory reports. The data comprised age, gender, cause(s) of immunosuppression, comorbidities, antimicrobial medications (prophylactic and empirical) in the 7 days prior to the procedure, self-reported symptoms, clinical status before bronchoscopy, chest radiological findings, and complete blood counts. Cytology and microbiology BAL laboratory reports were extracted, including bacterial and fungal cultures, acid-fast bacilli smear and culture, tuberculosis PCR, multiplex PCR (for respiratory bacteria, viruses, and *Pneumocystis jirovecii*), and the *Aspergillus*-galactomannan antigen assay.

BAL results were recorded as positive if clinically significant findings were reported, defined as microbiology reporting a causative pathogen rather than a contaminant/colonizer, or cytology showing noninfectious causes, such as malignancy or alveolar hemorrhage.

Impacts or alterations to the clinical management plan recorded following the BAL results were defined as discontinuation of antimicrobials within 7 days of the procedure, antimicrobials commenced within 7 days of the procedure and/or treatment of a nonmicrobial etiology.

The safety of the procedure was assessed by collecting data on related complications occurring within 24 hours, such as cardiac events, pneumothorax, respiratory tract bleeding,

commencement or escalation of oxygen supplementation or ventilatory support.

All data were entered into a REDCap database. The study received ethical approval from the Institutional Review Board of King Fahad Specialist Hospital, Dammam, and was conducted according to ICH-GCP and the 2013 Declaration of Helsinki.

Statistical analysis

Descriptive statistics are presented as the mean (standard deviation, SD) for continuous variables and number (proportion) for all categorical variables. Binomial distribution was used to measure the prevalence of diagnostic yield (i.e., the number of BAL with a positive diagnostic finding divided by the total number of patients) with a 95% confidence interval. Bivariate analysis was performed using independent sample *t* tests, Mann–Whitney *U* tests, Pearson Chi-square tests and Fisher's exact tests (χ^2), as appropriate, to compare demographic and clinical characteristics between patients with a positive BAL and those with a negative BAL.

Multiple logistic regression was used to identify significant predictors of diagnostic yield after adjusting for potentially confounding factors. The results are expressed as an adjusted odds ratio (*a*OR) with a 95% confidence interval. Two-sided *P* values of < 0.05 were considered statistically significant. All statistical analyses were performed using Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Subjects

A total of 116 bronchoscopy procedures were reviewed, of which 13 were repeat bronchoscopy with a BAL procedure that occurred >7 days apart, and thus the final study sample consisted of 103 unique patient records. The mean age (SD) of the patients was 44.5 (14.1) years, and the majority were male (*n* = 62; 60.2%).

Table 1 summarizes the clinical characteristics of the subjects. The most frequently reported symptoms were cough (59.2%), fever (44.7%), dyspnea (39.8%), sputum (23.3%), and chest pain (6.8%). Nearly a quarter of the patients (24.3%) were receiving supplemental oxygen on the day of bronchoscopy.

Diagnostic yield of BAL

Overall, the diagnostic yield of BAL was 52.4% (95% CI: 42.6–62.2%), with 54 of 103 procedures resulting in positive microbiology (*n* = 50) and/or cytology (*n* = 9) findings [Table 2]. The median time between chest radiology and bronchoscopy was 6 days (IQR 3–11). A quarter (*n* = 28, 23.5%) of the bronchoscopies were performed within 2 days of chest radiology.

Table 1: Clinical characteristics of the patients (*N*=103)

Variables	*n* (%)
Cause of immunosuppression*	
HIV	2 (1.9)
Cancer chemotherapy	19 (18.4)
≥20 mg prednisone or other corticosteroid for ≥14 days	8 (7.8)
Biological immunomodulatory therapy	16 (15.5)
Solid organ transplant	22 (21.4)
Kidney	20 (19.4)
Liver	2 (1.9)
Hematologic transplantation	25 (24.3)
Hematologic malignancy	65 (63.1)
Leukemia	31 (30.1)
Lymphoma	29 (28.2)
Myeloma	5 (4.8)
Comorbidity*	
Chronic pulmonary disease	6 (5.8)
Chronic heart disease	2 (1.9)
Chronic kidney disease	8 (7.8)
Chronic liver disease	3 (2.9)
Diabetes	18 (17.5)
Antimicrobials treatment within 7 days prior to procedure	
Antibiotic†	80 (77.7)
Antiviral‡	52 (50.5)
Antifungal	47 (45.6)

*More than one cause of immunosuppression or comorbidity in some subjects, †15/80 (18.8%) were on prophylactic cotrimoxazole, ‡33 (63.5%) were on prophylactic acyclovir, 5 (9.6%) were on prophylactic valaciclovir, and 2 (3.8%) were on prophylactic valganciclovir

Using bivariate analyses and simple binary logistic regression, diagnostic yield (i.e., BAL positive or BAL negative) was compared by demographic and clinical characteristics, including age, sex, cause(s) of immunosuppression, comorbidities, self-reported symptoms, clinical status before bronchoscopy, chest radiological findings, antimicrobial medications in the 7 days prior to the procedure, complete blood counts, macroscopic findings from bronchoscopy, and the time between chest radiology and bronchoscopy. Six characteristics showed significance in the bivariate analysis. The comorbidity of diabetes (OR 3.94, 95% CI: 1.20–12.94, $P = 0.024$) and the self-reported symptoms of sputum prior to bronchoscopy (OR 3.58, 95% CI: 1.29–9.98, $P = 0.015$) were associated with a positive BAL. Chronic pulmonary disease ($P = 0.010$), prior antiviral usage (OR 0.31, 95% CI: 0.14–0.70, $P = 0.005$), and immunosuppression due to hematologic malignancy (OR 0.42, 95% CI: 0.18–0.96, $P = 0.040$) were associated with a negative BAL. In particular, treatment with acyclovir was associated with a decreased likelihood of a positive BAL (χ^2 4.93, $P = 0.026$). In addition, the mean number of antimicrobials prescribed among patients was 2.95 (95%

CI: 2.53–3.37; median = 3.0). Patients who were classified as BAL positive received significantly fewer antimicrobials than patients who were BAL negative ($\beta = -0.87$, 95% CI: −1.69 –−0.05, $P = 0.038$).

The six variables that were significant in the bivariate analyses were modeled using multiple logistic regression, which revealed that only self-reported sputum retained significance as a predictor of diagnostic yield [Table 3] and explained 14.4% of the observed variance. BAL procedures among patients who self-reported the presence of sputum prior to the procedure were four times as likely to produce clinically significant findings as among patients who did not report this symptom (*a*OR 4.01, 95% CI: 1.27–12.71, $P = 0.018$). The Pearson Chi-square goodness-of-fit test showed that the data in the multivariate model fit well (χ^2 35.45, $P = 0.542$).

Table 2: Clinical findings of bronchoalveolar lavage by type (*N*=103)

Variables	BAL positive, *n* (%)	BAL negative, *n* (%)	Not available (missing), *n* (%)
Microbiology findings			
Culture and sensitivity*	26 (25.2)	70 (68.0)	7 (6.8)
AFB stain	1 (1.0)	93 (90.3)	9 (8.7)
Mycobacterial culture†	6 (5.8)	88 (85.4)	9 (8.7)
TB-PCR	3 (2.9)	91 (88.3)	9 (8.7)
Fungal culture‡	6 (5.8)	84 (81.6)	13 (12.6)
Aspergillus antigen	2 (1.9)	25 (24.3)	76 (73.8)
Respiratory multiplex panel§	27 (26.2)	21 (20.4)	55 (53.4)
Cytology findings‖	9 (8.7)	65 (63.1)	29 (28.2)

**Aspergillus* (*n*=3), *Escherichia coli* (*n*=1), *Enterobacter* (*n*=1), *Haemophilus influenzae* (*n*=2), *Klebsiella* (*n*=1), *Moraxella catarrhalis* (*n*=2), *Pseudomonas* (*n*=2), *Staphylococcus aureus* (*n*=8), *Stentrophomonas* (*n*=2), *Streptococcus* (*n*=2), other (*n*=2); †*Mycobacterium tuberculosis* (*n*=3), nontuberculous mycobacteria (*n*=3); ‡*Aspergillus* spp. (*n*=5), other mold species (*n*=1); §Adenovirus (*n*=4), Coronavirus (*n*=3), *Enterovirus* (*n*=1), *Haemophilus influenzae* (*n*=3), Influenza (*n*=2), *Moraxella catarrhalis* (*n*=1), Mycoplasma (*n*=1), PJP (*n*=9), Rhinovirus (*n*=5), *Staphylococcus aureus* (*n*=8), *Streptococcus pneumoniae* (*n*=3); ‖GMS stain (*n*=7), Viral cytopathic changes (*n*=1), lymphocytosis (*n*=1), severe acute inflammation (*n*=1). BAL – Bronchoalveolar lavage; AFB – Acid-fast bacteria; TB – Tuberculosis; PCR – Polymerase chain reaction; PJP – *Pneumocystis jirovecii* pneumonia; GMS – Grocott's methenamine silver

Table 3: Multivariate analysis of predictors of diagnostic yield of bronchoscopy with bronchoalveolar lavage (*N*=97)*

Variables	OR (95% CI)	*P*
Comorbidity of diabetes	3.13 (0.83–11.81)	0.092
Antiviral treatment prior to procedure	0.47 (0.15–1.53)	0.211
Sputum production	4.01 (1.27–12.70)	0.018
Immunosuppression due to hematologic malignancy	0.83 (0.28–2.51)	0.748
Number of antimicrobials prescribed prior to procedure	0.90 (0.67–1.20)	0.470

*Chronic pulmonary disease was included as a confounder but did not produce an aOR estimate because there were no patients with chronic pulmonary disease who were considered BAL positive. aOR – Adjusted Odds ratio; CI – Confidence interval; BAL – Bronchoalveolar lavage

Impact of BAL on the management plan of pulmonary infiltrates

Almost half of BAL procedures ($n = 45$, 43.7%, 95% CI: 33.9–53.4%) resulted in a change in the patient management plan within 7 days of the procedure. BAL procedures with clinically significant findings were more than twice as likely to result in a change than procedures without such findings (OR 2.39, 95% CI: 1.07–5.33, $P = 0.033$), although almost one-third of negative BAL procedures also resulted in a change in the management plan.

Among BAL-positive patients, two-thirds of the management changes ($n = 19$, 65.5%) involved the initiation of a new antimicrobial, while 10 procedures (34.5%) resulted in the discontinuation of an antimicrobial, and 2 changes (6.9%) resulted in the management of an alternate diagnosis. Similar results were seen among BAL-negative patients, where two-thirds of changes ($n = 11$, 68.7%) involved the initiation of a new antimicrobial, although higher proportions of patients who were BAL-negative had a discontinuation of an antimicrobial ($n = 7$, 43.7%) and management of an alternate diagnosis ($n = 4$, 25.0%) than those who were BAL-positive.

Safety of BAL procedure

Only three (2.9%, 95% CI: 0.0–6.2%) bronchoscopies with BAL resulted in a complication within 24 hours. Two patients (1.9%) required ventilatory support, and one (1.0%) required the start or escalation of oxygen supplementation. No bleeding or mortality related to the procedure occurred.

DISCUSSION

This study demonstrates that bronchoscopy with BAL is a useful and relatively safe clinical tool in immunocompromised patients with pulmonary infiltrates. Almost half of the patients studied had changes in their management, and only a few experienced complications following the procedure. Our study demonstrated a diagnostic yield that is similar to that reported in the literature (31%–83%), despite the majority of the patients being treated with antimicrobials.[7,8,10] We suspect that the yield may have been higher if more nonculture-based tests were performed, which were only recently introduced to our center. These tests improve sensitivity and provide faster results, allowing for more rapid adjustment in antimicrobial therapy, and thus, potentially improving outcomes.[11,12]

The median time between chest imaging and bronchoscopy was 6 days, with only a quarter occurring within 2 days.

Despite the delay in performing BAL, unexpectedly, it did not show a statistically significant association with the diagnostic yield. This may be due to the relatively small sample size of the study. In previous studies, early bronchoscopy has been shown to have an increased yield, as much as 2.5-fold higher when performed within 4 days, and early BAL-driven treatment (within 7 days) is associated with improved survival.[2,13,14] Furthermore, achieving a microbiological diagnosis is becoming increasingly important due to higher incidences of infections caused by multidrug-resistant organisms. Prescribing targeted treatment is vital to improve the clinical response and to reduce the risk of antimicrobial resistance and toxicities.[10]

Advances in cancer treatment and immunomodulatory agents that affect the immune system on different levels have led to a significant increase in the risk of infection with opportunistic and rare organisms with variability in clinical presentations that have made it more challenging to reach a specific diagnosis. Using noninvasive techniques, generally, has inferior sensitivity and specificity than bronchoscopy with BAL. Such infections include invasive fungal infections, *P. jirovecii* pneumonia (PJP), cytomegalovirus, and mycobacteria.[15] Although a high-resolution CT scan is a vital investigation and can give plausible differential diagnoses, changes in imaging can be late in the patient's presentation, and often, are nonspecific. Induced sputum cytology for *P. jirovecii* has a low yield of approximately 50%, particularly in non-HIV immunocompromised patients. Serum beta-D-glucan is sensitive but can be elevated in other fungal infections.[16] In contrast, BAL testing has a higher sensitivity of >90%, especially when combined with PCR.[17,18]

Invasive pulmonary aspergillosis is the most common invasive fungal infection in immunocompromised patients, and biopsy is usually required to confirm the diagnosis. Less invasive tests, such as bronchoscopy with BAL, would be of great value in supporting such a diagnosis and optimizing the therapeutic approach.[19] CT scans, which could show suggestive radiological findings such as the "halo sign" or "reversed halo sign" and nodular lesions, have a low sensitivity in detecting invasive aspergillosis. BAL galactomannan has a high sensitivity of 91.3% compared with 50% and 53.3% for culture and microscopy, respectively.[20] Unfortunately, in our study, the detection of *Aspergillus* antigen was not available in the majority of BAL samples, as the test was only recently introduced at our center. The lack of a uniform panel of testing may have resulted in the antigen inadvertently not being requested. BAL is also vital to guide management, as empirical treatments for fungal infections, which typically include amphotericin B and/or azoles, have potential toxicity and are expensive.

Our study revealed that the presence of sputum was independently associated with a positive BAL. Sputum is likely to represent high microbial load and inflammation. A prior study found that positive sputum culture is associated with positive BAL but unclear if it yielded the same organisms from both upper and lower respiratory tracts.[21] Factors such as the number of antimicrobials, comorbidities, or underlying cause of immunosuppression were not predictive of the BAL yield in the multivariate analysis. The diagnostic yield of BAL might be higher in HIV patients, but in our group, there were only two patients with HIV infection. Most subjects (63.1%) had hematologic malignancy, reflecting the type of patients our center provides clinical care to.

Although bronchoscopy with BAL is a safe procedure and complications are generally self-limiting, critically ill immunocompromised patients have a higher rate of intubation than other groups; therefore, it is better to proceed with bronchoscopy early on, potentially avoiding further respiratory deterioration.[22] In our study, only three (2.9%) patients required an escalation of their oxygen therapy within 24 hours of the procedure, with two patients requiring intubation and mechanical ventilation. Both patients who required intubation were on high flow oxygen before the procedure (>5 L/per minute), suggesting that patients on high-flow oxygen are at high risk of deterioration post-bronchoscopy.

Strengths and limitations

The strength of this study is that it provides real-world data from a tertiary care center in Saudi Arabia about the clinical value of BAL in immunocompromised patients with pulmonary infiltrates, the majority of whom had been on empirical and prophylactic antimicrobials. Despite the majority of patients being on prophylactic/empirical antimicrobials, BAL results impacted management in a positive way.

Limitations of this study include its retrospective design and the lack of a uniform panel of investigations. However, data were collected in a standardized format. Furthermore, the study was carried out in a single tertiary center with a heterogeneous group of immunocompromised patients, and the sample size was not large enough for a minimum power of 80%. Another limitation is the lack of a uniform protocol regarding the sampling technique and the timing of BAL. As mentioned, nonculture-based assays have only started to be used recently, and we suspect that earlier

introduction may have increased the diagnostic yield of this study. We did not study the impact of BAL-driven changes in management on the clinical outcomes of morbidity and mortality. Our study lacked a control group of immunocompromised subjects with lung infiltrates who did not have bronchoscopy but undergo noninvasive testing, which would be useful in future studies.

CONCLUSIONS

BAL in immunocompromised patients is a useful investigative tool with a reasonable diagnostic yield. Importantly, it has an impact on the clinical management of patients. The impact on clinical outcomes (i.e., morbidity and mortality) needs to be explored in a prospective clinical trial comparing BAL to noninvasive culture and diagnostic molecular tests.

Ethical considerations

The study was approved by the Institutional Review Board of King Fahad Specialist Hospital, Dammam (Ref. no.: PUL0001), on July 8, 2021. The study was conducted in accordance with the ICH-GCP and the Declaration of Helsinki, 2013.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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