Comparison of Bronchoalveolar Lavage and Mini-Bronchoalveolar Lavage in the Diagnosis of Pneumonia in Immunocompromised Patients

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Key Words

Bronchoalveolar lavage • Mini-bronchoalveolar lavage •
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Abstract

Background: Pneumonia is a major cause of morbidity and mortality in immunocompromised patients. Bronchoalveolar lavage (BAL) is commonly used to help diagnose and characterize pneumonia in these patients. Mini-BAL is a less-invasive, less-costly and less-cumbersome diagnostic tool than BAL. **Objectives:** In this study, we compared the diagnostic value of BAL and mini-BAL in the evaluation of pneumonia in immunocompromised patients with respiratory failure. **Methods:** Sixty-four respiratory samples were collected from 32 immunocompromised patients admitted to our respiratory intensive care unit with a clinical diagnosis of pneumonia and respiratory failure requiring invasive mechanical ventilation. A single BAL sample and a single mini-BAL sample were collected from each patient. Samples were examined for bacteriologic, mycologic, mycobacteriologic, and viral organisms. **Results:** The mean age of the patients was 56.0 ± 14.4 years. Of the 32 BAL samples, bacterial iso-

lates were detected in 11 patients (34.4%) and on the other hand bacterial isolates were detected in 10 patients (31.3%) of the mini-BAL samples. Fungal isolates were detected in 11 patients (34.4%) from BAL samples and 13 patients (40.6%) from mini-BAL samples. Our analysis demonstrated a strong positive correlation between the results of BAL and mini-BAL testing ($r = 0.850$ and $r = 0.821$, respectively). **Conclusion:** In this study, we demonstrated a strong correlation between the isolation rates of bacteria and fungi in BAL and mini-BAL samples obtained from immunocompromised patients with pneumonia and respiratory failure. The data strongly support the use of mini-BAL sampling in such patients as a less-invasive, less-costly and simpler alternative to traditional BAL.

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Introduction

Respiratory infection, particularly pneumonia, is a common cause of morbidity and mortality in immunocompromised patients [1, 2]. Evidence suggests that the mortality of such patients may reach up to 50–80% if the

diagnosis of pneumonia is accompanied by respiratory failure that requires mechanical ventilation [3]. Early, accurate diagnosis and the use of appropriate antibiotic therapy can reduce mortality rates in these patients. Diagnostic modalities including flexible bronchoscopy with bronchoalveolar lavage (BAL) and protected-specimen brush have been traditionally used to help guide the early and appropriate therapy in critically ill patients presenting with pneumonia and the effectiveness of these modalities has also been demonstrated in several studies [4–8].

Although bronchoscopic methods have high diagnostic yields, such sampling methods are costly and generally require highly experienced operators to perform them; on the other hand, the bronchoscopy itself has high risk in patients presenting with thrombocytopenia and hypoxemia. Furthermore, these invasive procedures can turn out to be complicated for reasons such as bleeding, specimen contamination, hypoxemia, airway spasm and arrhythmia [9–11].

Based on the above observations, new and less-invasive diagnostic methods such as mini-BAL and endotracheal aspiration (ETA) have been evaluated over the recent years, particularly in the diagnosis of ventilator-associated pneumonia (VAP) [12–15].

Mini-BAL was first used successfully in 1989 for the diagnosis of hospital-acquired pneumonia in a series of 59 patients [16]. Yet, there is insufficient data regarding the diagnostic value of mini-BAL and ETA compared to BAL and other bronchoscopic procedures in immunocompromised patients with pneumonia. For this reason, there is an increasing interest in the feasibility and diagnostic utility of these less-invasive methods, particularly the mini-BAL. This prospective study evaluates the diagnostic value of mini-BAL compared to BAL in immunocompromised patients with pneumonia and respiratory failure requiring mechanical ventilation. Secondly, we compare the results of BAL and mini-BAL sampling to those of ETA.

Methods

Patients

From September 2007 to September 2009, we enrolled 32 immunocompromised patients in this study, who were hospitalized in our respiratory intensive care unit (ICU) with bilateral pneumonia, respiratory failure, and treatment with invasive mechanical ventilation. The infiltrates were documented with chest X-ray in ICU. As the study population consisted of intubated and mechanically ventilated patients, it was impossible to perform computed tomography of the thorax. Apart from this, the long distance between the Department of Radiology and ICU was another factor.

The mini-BAL catheter is usually directed into the right lung; however, in one third of the patients it may be inserted into the left lung [13]. It was difficult to perform chest X-ray after the procedure. For these reasons, patients with bilateral pneumonia were included in the study.

Criteria for classification as ‘immunocompromised’ included: current presence of hematologic malignancy or solid organ tumor, a history of chemotherapy in the 6 months prior to enrollment, active long-term corticosteroid use (≥ 20 mg/day prednisone equivalent for ≥ 2 weeks), a history of high-dose corticosteroid use (≥ 60 mg/day prednisone equivalent for ≥ 2 weeks in the 3 months prior to enrollment), a history of hematopoietic stem cell or solid organ transplantation, ongoing use of cytotoxic treatment, and HIV positivity.

In the immunocompromised patients, a constellation of suggestive clinical features, a demonstrable infiltrate by chest X-rays, with or without supporting microbiological data, is considered for the diagnosis of pneumonia [17].

Isolated fungal agents from respiratory samples were considered as proven, probable or possible fungal infections due to criteria stated by the revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group [18].

Comprehensive analyses of patient demographics, comorbid medical conditions, types of immunocompromised states, and severity of illness by APACHE II scores were performed.

The study was approved by the local ethics committee and informed consent was obtained from the patients’ relatives. On the first day at ICU, respiratory specimens were sequentially collected by ETA, mini-BAL and BAL from all patients by the same physicians (M.S.T., F.B.). The microbiological results of these samples were investigated prospectively. The samples collected by all three methods were processed by bacteriology, mycology, virology and mycobacteriology laboratories. Apart from these, CMV antigenemia was investigated in the blood samples of all patients.

Mini-BAL

Invasive mechanical ventilation FiO_2 value was set to 1.0 and enteral feeding was discontinued 30 min prior to the procedure. In the first place, a lavage catheter (Combicath™; Plastimed, Saint-Leu-La Forêt, France) (fig. 1) was advanced into the endotracheal tube until gentle resistance was met. Then, the protective sheath at the distal end of the catheter was detached and the catheter was advanced further along the tracheobronchial tree. Radiological confirmation of catheter placement was felt to be unnecessary due to the presence of extensive bilateral infiltrates in all study subjects. Finally, 20 ml 0.9% NaCl was injected through the catheter and then aspirated by the same injector.

Bronchoalveolar Lavage

Following mini-BAL, FiO_2 value remained at 1.0 and parameters such as oxygen saturation, pulse, or blood pressure were continuously monitored. Using a flexible bronchoscope (Olympus CLE-10, USA), we performed BAL by serial 20-ml fractions of 0.9% NaCl to a total volume of 120–150 ml. About 60% lavage volume return was assumed, an amount which we managed to obtain in our patients.

Endotracheal Aspiration

Respiratory samples were obtained through the endotracheal tube by protected, sterile catheter method (MucoSafe®; Unoplast-Maersk Medical, Denmark).

Microbiologic Examination

A quantitative culture threshold of 10^4 CFU/ml was considered significant for BAL; 10^5 CFU/ml was considered significant for mini-BAL and ETA. The identification of bacterial isolates and antibiotic susceptibility testing were performed according to CLSI guidelines by an automated system (VITEK 2; BioMérieux Inc., Marcy-l'Etoile, France) and by conventional culture methods [19]. A mycological investigation was conducted by conventional methods. Samples were examined for fungal structures by direct microscopy and then cultivated on Sabouraud dextrose agar plates incubated at 26 and 35°C for 10 days. For any given study subject, a finding of >5 CFU on at least 2 different respiratory samples was accepted to represent fungal infection. Yeast species were identified on the basis of conventional methods, including germ tube and appearance on Tween 80 agar plate, or an automated system (ID32; BioMérieux Inc.). Samples were sent to the mycobacteriology laboratory for acid-fast bacilli smear and culture. In addition, virology tests of samples were done serologically in the virology laboratory.

Statistical Analysis

Spearman's nonparametric correlation analysis was used to assess the correlation between the various methods of respiratory sampling. Correlations were scored as weak ($r = 0-0.49$), moderate ($r = 0.5-0.74$), or strong ($r = 0.75-1$). Student's *t* test and the χ^2 test were used to compare the laboratory and clinical parameters of subjects in whom microbiological agents were isolated and in whom no microbiological agents were isolated, respectively ($p < 0.05 = \text{significant}$).

Results

Thirty-two immunocompromised patients with bilateral radiographic infiltrates, clinically suspected pneumonia, and respiratory failure requiring invasive mechanical ventilation were included in this study. The mean age of study subjects was 56.0 ± 14.4 years. Twenty-three (71.9%) subjects were male. The demographic, clinical, and laboratory data for all subjects at the time of admission to the ICU are shown in table 1. Of 32 BAL samples, bacteria were isolated in 11 (34.4%) and fungi were isolated in 11 (34.4%). Of 32 mini-BAL samples, bacteria were isolated in 10 (31.3%) and fungi were isolated in 13 (40.6%) (table 2). Both bacteria and fungi were isolated in 5 BAL samples and in 5 mini-BAL samples of the same patients. Overall, microbiological agents were detected in 17 of 32 BAL samples (53.1%) and in 18 of 32 mini-BAL samples (56.3%) (table 3). The correlation coefficients amongst the different sampling methods are

Fig. 1. Mini-BAL catheter (Combicath; Plastimed).

shown in table 4. We demonstrated strong correlations for bacterial and fungal detection between BAL and mini-BAL ($r = 0.850$ and $r = 0.821$, respectively). In view of detecting bacterial agents, ETA correlated weakly both with BAL and mini-BAL ($r = 0.477$ and $r = 0.430$, respectively) whereas there were no correlations to detect fungal agents. Mycobacterial and viral agents were not isolated in any of the samples.

Mortality was seen in 23 subjects (71.9%). There was no mortality difference between subjects in whom respiratory pathogens were isolated compared to subjects in whom no respiratory pathogens were isolated. There were no complications associated with any of the sampling methods.

Discussion

Our study compared the relative performance of BAL and mini-BAL for the detection of respiratory pathogens in immunocompromised patients with pneumonia and respiratory failure. We demonstrated a strong correlation between the two methods.

BAL and other bronchoscopic methods are frequently used to help diagnose pneumonia in immunocompromised patients. A prior study of 104 immunocompromised patients with pneumonia showed a microorganism isolation rate of 38% by BAL [4]. Another study of 199 patients with hematological malignancy, fever, and pulmonary infiltrates on chest imaging demonstrated an isolation rate of 59% for bacterial and/or fungal organ-

Table 1. Demographic, clinical and laboratory data of patients on admission

Age, years	56.0 ± 14.4
Sex (male), n	23 (71.9%)
Reasons for immunosuppression, n	
Hematological malignancy	16 (50.0%)
Solid tumor	10 (31.3%)
Corticosteroid treatment	5 (15.6%)
HIV(+)	1 (3.1%)
Comorbidities, n ¹	
Diabetes mellitus	13 (40.6%)
Atherosclerotic cardiac disease	5 (15.6%)
Chronic renal failure	5 (15.6%)
Chronic liver disease	1 (3.1%)
No comorbidities	11 (34.4%)
APACHE II	23.6 ± 7.1
Sepsis, n	25 (78.1%)
PaO ₂ /FiO ₂	167.2 ± 79.1
Fever, °C	37.0 ± 1.1
Leukocytes, /mm ³	12,400 ± 17,864
CRP, mg/dl	20.8 ± 13.2
Procalcitonin, ng/dl	4.1 ± 5.6
Albumin, g/dl	2.7 ± 0.6
Creatinine, mg/dl	1.4 ± 1.5

Values are given as number with percentage in parentheses or as mean ± SD. APACHE II = Acute Physiology and Chronic Health Evaluation II; CRP = C-reactive protein.

¹ Three patients have more than one comorbidity.

Table 2. Bacteriological and mycological results of BAL and mini-BAL samples

	BAL (n = 32)	Mini-BAL (n = 32)
Bacteriological results		
<i>Acinetobacter baumannii</i>	4	4
<i>Streptococcus pneumoniae</i>	2	2
MSSA	2	2
<i>Cupriavidus pauculus</i>	1	1
<i>Enterococcus faecium</i>	1	–
<i>Pseudomonas aeruginosa</i>	1	1
Yeast	3	2
No agent	18	20
Mycological results		
<i>Candida</i> spp.	11	12
<i>Aspergillus</i> spp.	–	1
No agent	21	19

Both bacteriological and mycological pathogens were detected in 5 BAL samples and in 5 mini-BAL samples from the same patients. MSSA = Methicillin-sensitive *Staphylococcus aureus*.

isms by BAL [5]. A similar study of 93 neutropenic patients revealed respiratory microorganisms in 49% of BAL samples [6]. Yet another study demonstrated a microorganism isolation rate of 63% for BAL in a series of 57 allogeneic bone marrow transplant recipients with pneumonia [20]. Such studies support the utility of BAL in helping to characterize pneumonia pathogens in immunosuppressed patients. Our demonstration of a 53.1% isolation rate of bacterial and/or fungal pathogens by BAL in similarly immunosuppressed patients is congruent with previous findings.

Despite its high diagnostic performance in immunocompromised patients, BAL has inherent disadvantages in such patients, including the requirement for highly experienced operators and special equipment, possible complications, and high cost. However, we did not observe any complications related to the flexible bronchoscopy.

The main concern in patients with hematological malignancy is thrombocytopenia. This fact implies that BAL is not always applicable in the highest-risk patients. Although a few studies comparing bronchoscopic and non-bronchoscopic methods to evaluate immunocompromised patients with pneumonia demonstrated the diagnostic utility of both types of tests, there is a paucity of literature comparing invasive and noninvasive methods [8].

In 1989, Rouby et al. [16] used mini-BAL in the diagnosis of nosocomial pneumonia. They concluded that mini-BAL is an easily applicable, repeatable, inexpensive, and highly efficacious alternative diagnostic tool to bronchoscopic methods of respiratory sampling. Similarly, Kollef et al. [14] utilized mini-BAL in the evaluation of patients with VAP. They isolated at least one respiratory pathogen in 46.2% of cases. Another study compared the diagnostic performance characteristics of ETA and mini-BAL in 82 patients with probable VAP and demonstrated that mini-BAL was significantly more specific than ETA for the microbiological diagnosis of pneumonia [21]. No patients experienced complications attributable to the mini-BAL procedure. The observations prompted the authors to conclude that mini-BAL is an effective, safe, sensitive, specific, and inexpensive tool for the serial evaluation of pneumonia in mechanically ventilated patients. Ost et al. [22] compared endotracheal aspirates, flexible bronchoscopy with protected brush or BAL, and mini-BAL procedures in the diagnosis of VAP. The use of mini-BAL did not improve survival but did decrease costs and antibiotic use in their patients.

Table 3. Pathogens detected in BAL and mini-BAL samples (n = 19 patients)

Age/ sex	Underlying condition	Bacteriology		Mycology	
		BAL	Mini-BAL	BAL	Mini-BAL
60/F	Steroid treatment	MSSA	MSSA	–	–
43/F	H. malignancy	<i>A. baumannii</i>	<i>A. baumannii</i>	–	–
54/M	H. malignancy	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>Candida</i> spp.	<i>Candida</i> spp.
74/M	H. malignancy	–	–	–	<i>Candida</i> spp.
21/M	Solid tumor	–	–	<i>Candida</i> spp.	<i>Candida</i> spp.
70/M	H. malignancy	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>Candida</i> spp.	<i>Candida</i> spp.
81/F	H. malignancy	Yeast	Yeast	<i>Candida</i> spp.	<i>Candida</i> spp.
63/F	H. malignancy	<i>A. baumannii</i>	<i>A. baumannii</i>	<i>Candida</i> spp.	<i>Candida</i> spp.
63/M	Solid tumor	Yeast	Yeast	<i>Candida</i> spp.	<i>Candida</i> spp.
45/M	HIV(+)	Yeast	–	<i>Candida</i> spp.	<i>Candida</i> spp.
65/F	Solid tumor	<i>A. baumannii</i>	<i>A. baumannii</i>	<i>Candida</i> spp.	<i>Candida</i> spp.
47/F	Solid tumor	<i>C. pauculus</i>	<i>C. pauculus</i>	–	–
24/F	H. malignancy	–	–	<i>Candida</i> spp.	<i>Candida</i> spp.
63/M	Solid tumor	–	–	<i>Candida</i> spp.	<i>Candida</i> spp.
57/M	Solid tumor	MSSA	MSSA	<i>Candida</i> spp.	<i>Candida</i> spp.
50/F	H. malignancy	<i>E. faecium</i>	–	–	–
49/F	Steroid treatment	<i>A. baumannii</i>	<i>A. baumannii</i>	–	–
58/M	H. malignancy	–	–	–	<i>Aspergillus</i> spp.
53/M	Solid tumor	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	–	–

H. malignancy = Hematological malignancy; MSSA= methicillin-sensitive *Staphylococcus aureus*; *A. baumannii* = *Acinetobacter baumannii*; *S. pneumoniae* = *Streptococcus pneumoniae*; *C. pauculus* = *Cupriavidus pauculus*; *E. faecium* = *Enterococcus faecium*; *P. aeruginosa* = *Pseudomonas aeruginosa*.

Finally, in a prior study conducted in our hospital, the performance characteristics of ETA and mini-BAL were compared in 31 patients clinically suspected of having VAP [13]. Mini-BAL demonstrated a greater microorganism isolation rate in patients admitted to the hospital with lower respiratory infection, and a greater recovery of purulent secretions in cases of suspected VAP.

Although studies have demonstrated the usefulness of mini-BAL in VAP, there is insufficient case experience to characterize the utility of the test in immunocompromised hosts. Our study compared the performance of BAL versus mini-BAL in such patients and here we demonstrate a strong correlation between the isolation rates of bacterial and fungal organisms in the two methods: we detected bacteria and/or fungi in 53.1% of BAL samples and in 56.3% of mini-BAL samples. On the other hand, our data demonstrate a weak correlation between BAL and ETA for bacterial and/or fungal isolation. The cost of flexible bronchoscopy with BAL was approximately 3-fold higher than the mini-BAL in our study (EUR 125 vs. EUR 40, respectively).

Table 4. Correlation of the methods

		Correlation coefficient (r)
BAL bacteriology	mini-BAL bacteriology	0.850
BAL bacteriology	ETA bacteriology	0.477
Mini-BAL bacteriology	ETA bacteriology	0.430
BAL mycology	mini-BAL mycology	0.821
BAL mycology	ETA mycology	0.095
Mini-BAL mycology	ETA mycology	–0.176

An evaluation of 249 BAL samples collected from the bronchoscopic examinations of 199 febrile patients with hematological malignancy and pulmonary infiltrates showed the isolation of fungal pathogens in 46 samples [5]. Another study detected fungal pathogens by BAL in 23 of 135 immunocompromised patients with pulmonary infiltrates [8]. In our study, the use of BAL and mini-BAL led to the isolation of *Candida albicans* in 12

patients and *Aspergillus fumigatus* in 1 patient. All 13 patients with fungal pathogens isolated by BAL or mini-BAL were considered to have probable fungal pneumonia based on careful consideration of host factors, clinical criteria, and mycological criteria [18]. Although they did not have 'proven fungal disease', antifungal therapy was given to all 13 patients. They were critically ill, mechanically ventilated and immunosuppressed subjects. Furthermore, both direct and indirect mycological evaluations (culture and antigenemia) were positive. Therefore, we had to start immediate treatment with the antifungal agents.

The contribution of the results of diagnostic bronchoscopic methods to survival in immunosuppressed patients is debatable. Prior work demonstrated that the information gained from BAL had no effect on the survival of neutropenic patients with pneumonia [6]. A previous investigation in our hospital showed no relationship between the results of mini-BAL testing and survival rates in patients with VAP [13]. Our current study shows no difference in the rates of survival between patients in whom respiratory pathogens were isolated and those in whom they were not isolated.

The number of subjects in our current study is small due to the highly specific characteristics of this group of immunocompromised patients with bilateral pneumonia who have manifested respiratory failure and a need for invasive mechanical ventilation.

In conclusion, we show a strong correlation between BAL and mini-BAL methods to isolate bacterial and fungal pathogens. Taken in combination, the overall rate of pathogen detection by the two methods in our study was 59.4%, but this high diagnostic rate did not impact survival. Our study suggests that mini-BAL is an efficient, easily applicable, comparable, less-invasive and cost-efficient method, an alternative to BAL for the early diagnostic evaluation of pneumonia in immunocompromised patients with respiratory failure. These data should be validated in a prospective manner at multiple centers with greater numbers of cases.

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