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**Original Article**

# Clinical Usefulness of Bronchoalveolar Lavage in the Management of Pulmonary Infiltrates in Adults with Hematological Malignancies and Stem Cell Transplantation

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**Abstract.** ***Introduction:*** **Pulmonary complications are frequent in patients with hematologic malignancies and stem cell transplantation. Regardless of the microbiological usefulness of bronchoalveolar lavage (BAL), little information exists on both its benefits as a guide for therapeutic decisions and its impact on patients' clinical outcome.**
***Methods:*** **A prospective observational single-center study was performed between July 2011 and July 2016. Consecutive episodes of pulmonary infiltrates were analyzed in subjects over 18 years of age who presented hematologic malignancies and underwent chemotherapy or stem cell transplantation.**
***Results:*** **Ninety-six episodes of pulmonary infiltrates were analyzed. Acute leukemia was the most frequent underlying condition. Thirty-seven patients (38.5%) received a stem cell transplant. Sixty-one (62.9%) were neutropenic at the moment of inclusion in the study. A definitive etiologic diagnosis was obtained in 41 cases (42.7%), where infection accounted for the vast majority of cases (33 cases, 80.5%). Definitive diagnosis was reached by non-invasive methods in 13 cases (13.5%). BAL was performed in 47 cases and led to a diagnosis in 40.4% of the cases. BAL results led to therapeutic changes in 27 cases (57.4%), including the addition of new antimicrobials to empiric treatments in 10. Regarding BAL's safety, two patients experienced minor adverse events and one a severe adverse event; no procedure-related deaths were observed.**
***Conclusions:*** **Infection was the leading cause of pulmonary infiltrates in patients with hematologic malignancies and stem cell transplantation. BAL was a useful decision-making diagnostic tool, with minor adverse events.**

**Keywords:** Bronchoalveolar lavage; Pulmonary infiltrate; Hematologic malignancy; Stem cell transplantation.

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**Introduction.** Pulmonary complications are frequent in patients with hematological malignancies and stem cell transplant recipients.[1-4] Infections account for the vast majority of these complications, followed by alveolar hemorrhage, drug toxicity, graft-versus-host disease, pulmonary edema, and transfusion-related injury.[5] Early diagnosis and appropriate antimicrobial treatment are crucial in reducing morbidity and mortality.[6]

In addition to invasive methods,[7,8] microbiological non-invasive diagnostic tests, such as sputum culture, nasopharyngeal swab for respiratory virus detection and a serologic test for fungal and viral detection, have shown diagnostic usefulness, especially in patients with respiratory failure where bronchoalveolar lavage (BAL) performance may be harmful due to unstable clinical setting.[9,10]

Bronchoalveolar lavage fluid analysis has been widely used as a diagnostic tool for the diagnosis of pulmonary infiltrates (PI) in immunosuppressed patients, with a variable diagnostic yield among different series (31-80%).[11-15] However, there is scarce robust evidence for its usefulness as a tool for therapeutic decision-making (even with positive microbiological culture results) and its impact on patients' outcome and continues to be investigated.[6,12,16,17,18]

The main purpose of the present study was to describe the etiology of PI in patients with hematological malignancies under chemotherapy or stem cell transplantation. Secondary objectives were to assess BAL diagnostic yield and usefulness as a therapeutic decision approach, and finally to describe BAL safety in this subset of patients.

**Methods.** A prospective observational study was carried out at a university hospital in Buenos Aires, Argentina, which is specialized in the diagnosis and treatment of hematological malignancies and stem cell transplant recipients. All subjects over 18 years of age with a diagnosis of PI (defined as abnormal parenchymal finding in chest X-ray or CT-scan) and hematological malignancies under chemotherapy treatment or stem cell transplantation were consecutively included between July 2011 and July 2016. Multiple cases of PI in the same subject were independently analyzed. Palliative-care patients were excluded.

According to the treating physician´s best judgment, non-invasive (sputum culture, nasopharyngeal swab for respiratory virus detection, urinary pneumococcal antigen, serum galactomannan index, blood cultures, cytomegalovirus (CMV) viral load) and/or invasive (BAL, transbronchial lung biopsy, surgical lung biopsy) diagnostic methods were performed. BAL was performed under propofol or remifentanil sedation through laryngeal mask access with mechanical ventilation support. Lavage was performed using six 20ml saline solutions syringes. Our routine microbiological research for BAL fluid consists of culture for bacteria, Nocardia, mycobacteria and fungi, galactomannan index, PCR, and shell vial detection for CMV and Gram Weigert's technique for *Pneumocystis jirovecii* detection. Respiratory syncytial virus (RSV), adenovirus, Influenza A and B, and parainfluenza (1-3) diagnosis by direct antigen detection by immunofluorescent assay with monoclonal antibodies (Millipòre) in smears of respiratory samples. RSV, human metapneumovirus, adenovirus, rhinovirus, and Influenza A detection by real-time PCR: nucleic acid was extracted by total nucleic acids from 200 ul of the original sample using the automated MagNA Pure LC 2.0 with the MagNA Pure Compact Nucleic Acid Isolation Kit I extraction kit from Roche. Real-time PCR was performed with 5ul of nucleic acid eluate using for Influenza A/H1N1, adenovirus, and human metapneumovirus commercial assay set (TibMolbiol, Roche) and the enzyme LightCycler Multiplex RNA Master Virus in the Light Cycler 2.0 device as manufacturer's instruction. For RSV and rhinovirus detection, a homebrew real-time PCR was used.[19,20] The same viral detection techniques were used for nasopharyngeal swab samples. The serum galactomannan index was performed by enzyme immunoassay (Platelia®Aspergillus Bio-Rad, France) and considered positive with two independent samples ≥0.5 optical density index value. Instead, positive BAL fluid was considered positive, with one sample ≥1 optical density index value.[21] Early BAL was defined as the one performed within 4 days after the diagnosis of PI.[6,22] Patients were followed for 30 days after the diagnosis of PI.

Predominant abnormal radiologic patterns were defined as uni or bilateral alveolar consolidation, nodular, "ground glass" opacity, or "tree-in-bud" pattern, according to radiologists' descriptions. The presence or absence of pleural effusion was also recorded.

Etiologies of PI were classified as either infectious or non-infectious. Infectious etiologies could be bacterial pneumonia (defined as a significant positive culture in sputum or BAL fluid of pathogenic bacteria or blood culture and sputum culture with the growth of the same microorganism), invasive pulmonary mycosis according to EORTC/MSG 2008,[23] a viral infection caused by RSV, Influenza, Parainfluenza, Adenovirus or Rhinovirus detected by indirect immunofluorescence

or PCR in nasopharyngeal swabs or BAL, and CMV pneumonia defined by shell vial detection or identification of intranuclear/intracytoplasmatic inclusion bodies.[23,24] Non-infectious etiologies could be alveolar hemorrhage (defined as more than 20% hemosiderin-loaded macrophages or bloody tube progression in BAL fluid in the absence of infection), congestive heart failure (defined as abnormal radiological images and clinical signs ameliorated by diuretic therapy), a pulmonary manifestation of hematological cancer (biopsy-proven), transfusion-related acute lung injury, engraftment syndrome (noncardiogenic pulmonary edema during neutrophil recovery) and graft-versus-host disease (clinical and laboratory or biopsy-proven).[26,27]

Complications during or following BAL were classified as minor (mild hypoxemia enhancement and self-limited hemorrhage) or major (severe hypoxemia, hemorrhage requiring specific intervention, arterial hypotension requiring vasopressor therapy or death). According to institutional protocols, patients with a platelet count lower than 50,000/mm$^3$received platelet infusion during the procedure.

Therapeutic modifications were defined as any change, addition or discontinuation of antibiotics, antifungal, or antiviral therapy according to BAL fluid findings.

Data were analyzed using descriptive statistics. Continuous variables were described according to their median, whereas categorical variables were described according to their number and percentage. For statistical analysis, Mann-Whitney *U*-test (for continuous variables) and Fischer's exact test (for categorical variables) were used.

The Ethics Committee at our hospital approved the study. An informed consent form was obtained from each patient.

**Results.** A total of 96 episodes of PI were analyzed in 77 patients. **Table 1** shows demographic characteristics. The mean age was 56.4 years (range 25-81). Acute leukemia was the most frequent hematological cancer, accounting for 59 cases (61.5%). Thirty-seven patients (38.5%) were stem-cell transplant recipients (20 autologous and 17 allogenic). Sixty-one patients (62.9%) were neutropenic upon inclusion.

**Table 1.** Patients' basal characteristics (n= 96).

| Variable | Number of cases n=96 (%) | BAL YES n=47 (49%) | BAL NO n=49 (51%) | *p* |
|---|---|---|---|---|
| **Mean Age** (years) | 56 | 54 | 58 | *0.32* |
| Min-max (years) | 25-81 | 25-76 | 30-81 | |
| **Gender** | | | | |
| Male | 69 (71.9) | 31 (65.9) | 38 (77.6) | *0.25* |
| **Oncohematologic disease** | | | | |
| Leukemia | 59 (61.5) | 34 (72.3) | 25 (51) | *0.03* |
| Lymphoma | 21 (21.8) | 10 (21.3) | 11 (22.4) | *1* |
| Multiple Myeloma | 10 (10.4) | 1 (2.1) | 9 (18.4) | *0.01* |
| Others | 6 (6.3) | 2 (4.3) | 4 (8.2) | *0.67* |
| **Stem-cell transplant** | 37 (38.5) | 16 (34) | 21 (42.9) | *0.40* |
| Autologous | 20 | 6 | 14 | *0.07* |
| Allogenic | 17 | 10 | 7 | *0.42* |
| **Immunosuppression** | | | | |
| Chemotherapy 3 months before hospitalization | 68 (70.8) | 35 (74.5) | 33 (67.3) | *0.50* |
| Fludarabine | 10 (10.4) | 8 (17) | 2 (4.1) | *0.04* |
| High-dose steroids | 22 (22.9) | 12 (25.5) | 10 (20.4) | *0.63* |
| GVHD | 11 (11.5) | 8 (17) | 3 (6.1) | *0.11* |
| **Neutropenia** | 61 (62.9) | 29 (61.7) | 32 (65.3) | *0.66* |
| **Clinical variables found upon PI diagnosis** | | | | |
| Fever | | | | |
| Hypoxemia | 88 (91.7) | 41 (87.2) | 47 (95.6) | *0.15* |
| Breath rate > 20/min | 35 (36.5) | 16 (34) | 19 (38.8) | *0.67* |
| | 56 (58.3) | 25 (53.2) | 31 (63.3) | *0.67* |
| **Clinical severity** | | | | |
| APACHE [41] score <10 | 74 (77) | 36 (76.6) | 38 (77.6) | *1* |
| APACHE score 10-20 | 20 (21) | 11 (23.4) | 9 (18.4) | *0.61* |
| APACHE score>20 | 2 (2) | 0 (0) | 2 (4) | *0.49* |
| **Predominant pulmonary infiltrate** (n=95) | | | | |
| Nodular | | | | |
| Alveolar | 28 (29.5) | 22 (46.8) | 6 (12.8) | *<0.001* |
| Ground-glass opacities | 26 (27.4) | 10 (21.3) | 16 (34) | *0.16* |
| Tree-in bud | 29 (30.5) | 11 (23.4) | 18 (38.3) | *0.11* |
| | 12 (12.6) | 4 (8.5) | 8 (17) | *0.21* |

**Table 2.** Non-invasive diagnostic methods used

| Diagnostic method | Positive/total performed (%) | Definitive diagnosis, n |
|---|---|---|
| Blood culture | 7/96 (7.3%) | 2 |
| Nasopharyngeal swab | 12/64 (18.8%) | 7 |
| Sputum culture | 8/25 (32%) | 4 |
| Serum galactomannan | 3/52 (5.8%) | 1 |
| Urinary pneumococcal antigen | 0/31 (0%) | 0 |

**Table 3.** BAL microbiologic results

| Isolated Microorganism | n |
|---|---|
| Bacterial culture | |
| *Pseudomonas aeruginosa* | 3 |
| *Acinetobacter* spp | 2 |
| *Enterococccus faecium* | 1 |
| *Neisseria meningitidis* | 1 |
| *Escherichia coli* | 1 |
| MRSA | 1 |
| Respiratory viruses | |
| Adenovirus | 2 |
| Respiratory Syncytial Virus | 1 |
| Influenza | 1 |
| Parainfluenza | 2 |
| Rhinovirus | 1 |
| Positive galactomannans | 5 |
| Fungal culture | |
| *Aspergillus terreus* | 1 |

PIs were diagnosed by CT-scan in 94 episodes (97.9%) and by X-ray in 2. Sixty-eight (72.3%) had bilateral infiltrates. Alveolar pattern was present in 36 cases (37.5%), ground-glass opacities in 42 (43.8%), nodular in 37 (38.5%) and "tree-in-bud" pattern in 21 (22.3%). There was more than one abnormal CT pattern in 42 cases (43.8%).

Results from non-invasive diagnostic methods are shown in **Table 2**. Sputum culture had the highest diagnostic yield (32%), followed by nasopharyngeal swab (18.8%), blood culture (7.3%), and serum galactomannan (5.8%). All urinary pneumococcal antigen tests performed were negative. Differences between positive tests and definitive diagnosis are explained by co-infection (for the case of nasopharyngeal swabs), the clinical relevance of microbiological findings (for sputum cultures), or false-positive results according to clinical and radiological criteria (for serum galactomannan).

As far as CMV infection is concerned, serum viral load was performed in 8 patients with risk factors for CMV infection,[28-30] 2 of whom were positive. No BAL Shell vial or pathology sample yielded positive results for CMV infection.

BAL was performed in 47 (49%) episodes, 40 of which (85%) occurred in a new fashion, and 38 of which (81%) were under an empirical antimicrobial therapy. There was a microbiological diagnostic yield of 40.4% (19 positive cultures, 5 of which with more than one pathogen identified). The results are shown in **Table 3**. All positive BAL results were considered diagnostic. BAL was not performed in 49 cases for the following reasons: good response to empirical treatment started at 48h (51%), a serious clinical condition making procedure unsafe (18.4%), non-invasive diagnosis obtained (22.4%) and non-infectious alternative diagnosis (8.2%). BAL was more frequently performed in patients with acute leukemias and under fludarabine regimes.

We did not find a significant correlation between pulmonary imaging abnormalities and etiologic diagnostic yield (**Table 4**); however, noteworthy is the fact that the majority of BAL performed was in cases presenting with nodular lesions. BAL fluid results led to therapeutic changes in antimicrobial drug and its duration in 27 episodes (**Table 5**). In those cases evidencing negative BAL, and based on the BAL fluid galactomannan negative results, 4 antifungal treatments could be discontinued. Seven wide-spectrum antibiotic treatments against multi-resistant organisms were also discontinued. All patients (n=11) in which treatment was discontinued had a favourable outcome with the resolution of pulmonary infection. As far as outcome is concerned, 16 (34%) patients had oxygen saturation lower than 90%, and 25 (53.2%) had a platelet count $<50{,}000/mm^3$ (3 of which had $<10{,}000/mm^3$) at the time of bronchoscopy. Breath rate and oxygen saturation were 20 (12-26) vs 20 (12-26), ($p$ = 0.41) and 95 (64-100) vs 95 (86-98), ($p$ = 0.74) before and after bronchoscopy, respectively. BAL-related complications consisted of two minor (mild hypoxemia) and one major (respiratory failure requiring mechanical ventilation assistance) events, with no procedure-related deaths.

Of all the 97 PIs herein included, a definitive etiology was obtained in 41 (42.7%) cases (**Table 6**). The following results were obtained: infection in 33 cases (80.5%), fluid overload in 4 (9.7%), alveolar hemorrhage in 2 (4.8%), underlying hematological malignancy in 1 (2.5%) and graft-versus-host-disease in 1 (2.5%). Fourteen patients required ICU admission, and thirteen (13.5%) died during the 30 days following the initial respiratory event, 6 of them being directly

**Table 4.** Predominant pulmonary infiltrate and diagnostic yield.

| Predominant pulmonary infiltrate | Number of cases n=94 | Definitive diagnosis YES | Definitive diagnosis NO | *p* |
|---|---|---|---|---|
| Nodular | 28 (29.5) | 11 (26.8) | 17 (32.1) | *0.58* |
| Alveolar | 26 (27.4) | 11 (26.8) | 15 (28.3) | *0.87* |
| Ground glass | 29 (30.5) | 14 (34.1) | 15 (28.3) | *0.54* |
| Tree-in bud | 12 (12.6) | 5 (12.2) | 7 (13.2) | *1* |

**Table 5.** Therapeutic changes following BAL results.

| | Total BAL performed n=47 | BAL with microbiologic positive results n=19 | BAL without microbiologic positive results n=28 |
|---|---|---|---|
| Therapeutic change | 27 (57.4%) | 16 (84.2%) | 11 (39.3%) |
| Antibiotic withdrawal | 12 | 5 | 7 |
| Antifungal withdrawal | 8 | 4 | 4 |
| Antibiotic started | 2 | 1 | 1 |
| Antifungal started | 4 | 2 | 2 |
| Antibiotic change (to lower spectrum agent) | 6 | 6 | 0 |
| Antiviral started | 4 | 4 | 0 |

**Table 6.** Etiology of pulmonary infiltrates in patients with a definitive diagnosis.

| | Number of cases n=41 (%) |
|---|---|
| Infection | 33 (80.5) |
| Bacterial infection | 12 |
| Viral infection | 14 |
| Fungal infection | 4 |
| Coinfection | 3 |
| Fluid overload | 4 (9.7) |
| Alveolar hemorrhage | 2 (4.8) |
| Underlying hematological malignancy | 1 (2.5) |
| Graft-versus-host disease | 1 (2.5) |

related to PI event.

**Discussion.** This study evidences the results of a local series of PI. As in previous reports, we found a diagnostic yield of around 40% with BAL, which allowed the identification of bacterial, viral, and also fungal infections. However, 80.6% of BAL was performed under empirical antimicrobial treatment. In almost half of the cases, BAL results, either positive or negative, determined a modification in therapeutic regimes, including the addition of an antimicrobial agent not included in the empirical treatment in 22.7% of the cases. Since patients' survival in this selected population is significantly determined by early and appropriate treatment,[6] this finding is highly relevant. Furthermore, negative cultures in BAL fluids allowed antimicrobial de-escalation or even withdrawal in 11 cases. Broad-spectrum antibiotics such as colistin, tigecycline, daptomycin, and linezolid were part of empiric treatments accounting for multidrug-resistant organisms and local microbiology; negative BAL analysis allowed their discontinuation, therefore minimizing both adverse events and probably the occurrence of multidrug-resistant bacteria outbreaks..[31]

In four cases, Aspergillus galactomannan in BAL was negative, leading to discontinuation of antifungal treatment. *Aspergillus* galactomannan in BAL is known to have an excellent negative predictive value.[21,32] Locally, we have found that *Aspergillus* spp was the most frequent mold isolate in immunosuppressed patients, whereas Zygomycetes accounted for less than 6 % of the cases.[33]

In contrast with other reports,[34,35] we did not find significant differences in diagnostic yield according to pulmonary imaging patterns. We believe this may be, in part, explained by our low total cases number or by the lack of randomization according to radiographic findings.

BAL appeared to be safe in our cohort, with only 1 severe adverse event related to the procedure. 53.2% of cases had significant thrombocytopenia, and 34% had hypoxia at the time of BAL, with no procedure-related mortality. These numbers are lower than those reported in the literature.[12,17,36]

Non-invasive diagnostic methods led to 30 positive microbiological results, mainly respiratory virus-positive swabs or sputum culture. However, BAL was performed in 9 of these cases, mainly due to the high possibility of co-infections in this group of patients.[37] Only 14 out of 96 cases could be diagnosed through non-invasive methods.

In the absence of serum galactomannan positive tests, positive galactomannan in BAL let to the diagnosis of pulmonary aspergillosis in a small number of patients. This finding is similar to previous reports evidencing a sensitivity gap of over 60% when comparing BAL fluid with positive serum tests.[38-40]

This study has many limitations. Firstly, the lack of randomization of patients undergoing BAL leads to probable selection bias towards the group of patients in which BAL was performed. However, no significant clinical differences were observed between patients. There was also a selection bias toward more immunosuppressed patients and specific imaging patterns since BAL was mainly performed in patients with a diagnosis of acute leukemia, those treated with fludarabine, and patients presenting nodular pulmonary lesions. Given the design of the study, the clinical outcome and management changes between groups of patients could not be compared.

The multidisciplinary approach to the management of these patients (including internists, oncologists, pneumologists, and infectious diseases specialists) leads to discrepancies in the usefulness of BAL in this setting.[41] In a recent study, Marchesi *et al.* observed

that a BAL-driven antimicrobial approach has a positive impact on clinical outcome and mortality.[18]

We believe our findings enlarge the still scarce body of evidence that will help determine more precise algorithms for the diagnosis and treatment of pulmonary infiltrates in patients with hematological malignancies. Future comparative randomized studies are required to determine the actual impact of BAL and the timing of performance on the management of this complex group of patients.

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