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ORIGINAL ARTICLE

The value of flexible bronchoscopy in pulmonary infections of immunosuppressed children

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Abstract

Objectives: To demonstrate the value of flexible bronchoscopy (FB) and bronchoalveolar lavage (BAL) when determining causes of lung infection in immunocompromised children; to investigate differences in causes and radiological features of lung infections following bone marrow transplantation (BMT) compared to other immunosuppressive conditions; to evaluate the reliability of radiological findings when predicting the pathogen.

Methods: We retrospectively evaluated 132 immunosuppressed children who underwent FB and BAL because pulmonary complications between January 1999 and May 2014 at the Hacettepe University Hospital Pediatric Pulmonology Unit. Two groups, Group I (n = 106) and Group II (n = 26), consisted of patients who had primary or secondary immunodeficiency and those who were immunosuppressed because BMT, respectively. Radiological findings before FB and macroscopic and microscopic findings of the procedure were evaluated.

Results: FB and BAL were diagnostic in 86/132 patients (65.1%) and the antimicrobial treatment changed for 75/132 patients (56.8%). The most common pathogen was bacteria (*Streptococcus pneumoniae* was the leading one). Bacteria were more frequent in Group I than Group II ($P = .008$). No significant difference in radiological findings between Groups I and II was found. Considering all patients, a significant association was detected between viral pathogens and radiologically interstitial infiltration and a ground-glass appearance ($P = .003$). However, no significant association was detected between bacterial and fungal pathogens and the radiological findings.

Conclusion: In immunosuppressed patients, FB and BAL should be evaluated early for clarifying the causative agents. Then, appropriate treatments can be utilised and the side effects and high cost of unnecessary treatment may be mitigated.

KEYWORDS

bronchoscopy, immunosuppression, paediatrics, pulmonary infection

1 | INTRODUCTION

Pulmonary problems constitute a major cause of mortality and morbidity among patients with immunosuppression.[1-3] Currently, flexible bronchoscopy (FB) is included as a routine diagnostic tool for immunosuppressed patients when respiratory findings (clinical or radiological) are present.[4,5]

A special group of individuals with immunodeficiency consists of those who have received bone marrow transplantation (BMT) because diseases such as malignancies, hematological diseases, primary immune deficiencies and other hereditary disorders. Pulmonary infiltration develops in 30% of patients who receive chemotherapy for malignancy and this significantly affects mortality.[6] Lack of early diagnosis and treatment for the aetiology causing the pulmonary problems in these patients adversely affects their prognosis.[7]

The interpretation of pulmonary radiological findings in immunosuppressed patients can also be quite difficult. The appearance of pulmonary infiltration also occurs because noninfectious causes such as the development of graft versus host disease (GVHD) following BMT, disease recurrence or secondary malignancy infiltration, toxicity from chemotherapy or radiotherapy.[8,9] In addition, an impaired inflammatory response as well as other predominant atypical and/or nonspecific aetiologies can cause an accurate aetiology determination to be difficult.[10]

Empirical antibiotic treatment is usually initiated as soon as possible in these patients because of high morbidity and mortality rates, and any delay in treatment can adversely affect the immunocompromised patients' prognosis.[3,11] Many empirical treatment studies have reported that FB and bronchoalveolar lavage (BAL) yield diagnostically valuable results.[10,12] It has also been reported that microorganisms can be found or other diagnoses can be made through FB or BAL in 50-75% of children and adults with immunosuppression.[13] In such patients, the use of FB and BAL can provide a definite diagnosis and as a result, the appropriate treatment can be initiated.

The purpose of the study was to demonstrate the value of FB and BAL in determining the cause of lung infections that develop in immunocompromised children, to investigate differences between the causes and radiological features of lung infections following BMT in comparison to other immunosuppressive conditions and to evaluate the reliability of radiological findings for predicting the causative pathogen.

2 | MATERIALS AND METHODS

2.1 | Patients and FB

Our study retrospectively evaluated the charts of 132 immunosuppressed children whose data were retrieved from 2290 patients who underwent FB and BAL between January 1999 and May 2014.

The patients' demographic features, diagnoses, bronchoscopy indications and the entry route of the bronchoscope, complications because the procedure were all recorded. In addition, preoperative pulmonary radiological findings (direct radiography and/or HRCT), the macroscopic findings of the procedure and the results of the microscopic studies of the BAL were evaluated. The diagnostic yield of FB and its impact on the management were evaluated.

Because the patients experiencing severe respiratory distress and/or thrombocytopenia, we applied FB at the appropriate time, but during the procedure all patients were taking broad-spectrum antibiotics and/or antifungal therapy (all patients were taking multiple antibacterial agents, 30 patients were taking antifungals, 15 patients were taking antivirals). The procedure was conducted with an Olympus® flexible bronchoscope that included 2.2 mm, 3.6 mm, 4.2 mm and 5.0 mm external diameter options. An intubation cannula was used for entry with 2 patients who had already been connected to mechanical ventilators and for the remaining patients, either laryngeal masks (n = 118) or the nasal cavity route were utilised. BAL was performed from the focal area of the radiological pathology when present and the right lung middle lobe when widespread involvement was present.

This study was approved by the Institutional Review Board of the Hacettepe University Faculty of Medicine.

2.2 | Radiological methods

We evaluated the patients' radiological findings (chest X-ray and HRCT) prior to the bronchoscopy, which were categorised as atelectasis, consolidation, ground-glass appearance, interstitial infiltration, nodular infiltration, bronchiectasis, increased aeration/air trapping, mosaic pattern, chronic changes, lymphadenopathy, mass and airway anomaly. A majority of the patients exhibited more than one finding and in these patients, the most significant/difference-making finding was determined for each patient.

2.3 | Laboratory methods

We performed cytological evaluations and microbiological studies of the BAL fluid. Microbiologically, the BAL fluid was evaluated for aerobic bacteria, fungus and tuberculosis (TB). Furthermore, we utilised PCR to evaluate the presence of respiratory viruses (*Bocavirus, coronavirus OC43/HKU1, enterovirus, human rhinovirus, influenza A, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, RSV A, RSV B, metapneumovirus* and *coronavirus 229/NL63*). Any observed pulmonary infection because

CMV was defined as a viral load >10 000 copies in the BAL fluid.[14] Immunofluorescence staining methods were utilised (*indirect fluorescent antibody (IFA)*) to detect PJP.

2.4 | Statistical analyses

We performed the statistical analyses with the IBM SPSS for the Windows Version 21.0 software package. The descriptive statistics were calculated using the data obtained from the analyses (percentage, frequency, mean ± standard deviation and minimum-maximum). In addition, we carried out Chi-square tests to compare the quantitative variables (Pearson's chi-square and Fisher's exact chi-square tests) and a significance level of $P < .05$ was accepted.

3 | RESULTS

We reviewed the hospital records and charts of 132 immunosuppressed patients (57 female and 75 male) who were evaluated with FB and BAL. The age range was 3 months to 22.5 years (mean, 6.1 ± 4.7 y; median 5.3 y). The patients were divided into two groups: Group I (n = 106, 80%) included patients who had exhibited primary or secondary immunodeficiency and Group II (n = 26, 20%) included patients who were immunosuppressed after BMT. To provide more detail, the diagnoses and characteristics of the patients in Groups I and II are presented in Table 1.

TABLE 1 Groups of patients with immune deficiency and the distribution of these patients

	Group I (n = 106)	Group II (n = 26)
Malignant disease (Leukaemia, Lymphoma and Solid Tumours)	16	3
Chronic granulomatous disease	12	–
IgA deficiency	12	–
Undefined immune deficiencies	11	–
Transient hypogammaglobulinemia	10	–
Severe combined immunodeficiency	8	13
Common variable immunodeficiency	7	–
T cell deficiency	6	1
Autoimmune lymphoproliferative disease	6	–
IgG subclass deficiency	4	–
X linked agammaglobulinemia	3	–
Syndromes with immunodeficiency	3	–
Haemophagocytic lymphohistiocytosis	3	1
Ataxia telangiectasia	2	–
Hyper IgE syndrome	1	–
Congenital neutropenia	1	–
Aplastic anaemia	–	3
MHC Class I deficiency	1	–
MHC Class II deficiency	–	1
Metachromatic leukodystrophy	–	1
Thalassaemia major	–	3

Abbreviation: MHC: Major histocompatibility complex

1. Patients in Group I
   - In radiological evaluations prior to FB, consolidation in 31/106 patients, atelectasis in 54/106 patients, diffuse/local nodular infiltration in 19/106 patients, interstitial infiltration in 9/106 patients, a ground-glass appearance in 14/106 patients and bronchiectasis in 17/106 patients were detected. Normal findings were present in the remaining 3/106 patients. Some patients had more than one radiological finding; there were 65/106 patients with only one finding, 35/106 patients with any two of them and 3/106 patients with three of them (detailed radiological results are given in the supplementary table).
   - The macroscopic evaluation of FB provided findings consistent with infection in 70 patients (66%), tracheomalacia was observed in 11 patients, bronchomalacia in 8 patients, airway anomaly in 9 patients, mucosal hyperemia or hemorrhage in 9 patients and normal findings were present in 18 patients.
   - In the microscopic evaluations of BAL, a microbiological agent was detected in 62 patients (58.4%) (Table 2), among which 15 patients exhibited multiple agents (detailed microbiological results are given in the supplementary table). The most common agent was *Streptococcus pneumoniae* (n = 20) both independently as well as along with other agents.
2. Patients in Group II
   - The radiological evaluations for Group II revealed consolidation in 4/26 patients, atelectasis in 8/26 patients, diffuse/local nodular infiltration in 8/26 patients, diffuse interstitial infiltration in 4/26 patients, a ground-glass appearance in 5/26 patients, bronchiectasis in 1/26 patients and normal findings were present in the remaining 1/26 patient. There were 20/26 patients with only one finding and 5/26 patients with any two of them (detailed radiological findings are given in the supplementary table).
   - Macroscopically in the FB, 17 (65.3%) patients had purulent secretion, 2 patients had tracheomalacia, 2 (7.6%) patients had an airway anomaly, 2 (7.6%) patients had hemorrhage and 5 (19.2%) patients presented as macroscopically normal.
   - The BAL results revealed microbiological agents in 14/26 patients (53.8%), among which, 2 patients had multiple agents. Although no statistically significant

TABLE 2 Detection rates and types of microbiological agents detected in immunodeficient patients who underwent FB

	Group I	Group II
Microbiological Studies		
No Pathogen Could Be Demonstrated	44/106 (41.5%)	12/26 (46.1%)
Demonstrated Pathogens	62/106 (58.4%)	14/26 (53.8%)
Streptococcus pneumoniae	20	2
Haemophilus influenzae	10	1
Haemophilus haemolyticus	9	–
Pseudomonas aeruginosa	6	–
Moraxella catarrhalis	4	–
Klebsiella species (pneumonia and oxytoca)	3	–
Stenotrophomonas maltophilia	3	–
Haemophilus parainfluenza	1	–
Escherichia coli	1	–
Staphylococcus aureus	–	1
Enterococcus faecium	–	1
Pneumocystis jiroveci	1	–
Candida albicans	7	2
Aspergillus species	2	1
Cytomegalovirus	5	5
Adenovirus	1	–
RSV A	1	–
Parainfluenzae 1	–	1
Parainfluenzae 3	1	–
Coronavirus OC43/HKU1	–	1
Mycobacterium tuberculosis	2	–

difference was determined for microbiological agents in this group, viral agents were the most common. The microbiological agents detected in the BAL are provided in Table 2.

3. Comparisons of microbiological and radiological findings of patients in Group I and Group II (Table 3)
   - Bacterial pathogens were more prevalent in Group I than in Group II *(P = .008)*, but the results revealed no difference between two groups in regard to the presence of fungi, TB, viruses and PJP.
   - Additionally, no difference was detected between the groups based on the radiological findings (atelectasis, consolidation, nodular infiltration, interstitial infiltration, ground glass and bronchiectasis).
4. One of our aims was to determine the role of radiological findings in predicting the causative pathogen group. When all of the patients were considered together, a significant association was determined between the presence of viral pathogens (including CMV) and the radiological findings of interstitial infiltration and/or a ground-glass appearance *(P = .003)*. However, no significant association existed between the radiological findings and the presence of bacterial or fungal pathogens. In the BAL sample, 14 of 71 patients (19.7%) who were able to be tested for viral agents by a PCR method were found to be positive for viral agents. Of these 14 patients, 10 (71.4%) had interstitial infiltration and a ground-glass appearance. Likewise, 41 of 57 patients (71.9%) with a negative result on the viral PCR study did not have interstitial infiltration and/or a ground-glass appearance. The predictive values of the aetiologic agent based on the radiological findings are provided in Table 4.
5. An evaluation of all diagnostic methods related to FB (macroscopic pathologic findings and demonstration of a microbial agent in BAL) revealed a diagnostic finding in 86 of 132 patients (65.1%). The antimicrobial treatment changed for 75/132 patients (56.8%); it was escalated based on the identified pathogenic agent in 67 of these 132 patients (50.7%):
   - Ganciclovir was given to 10 patients because of pulmonary CMV infection,
   - Anti-TB treatment was started in 2 patients,
   - A new antibacterial was added for 45 patients
   - A new antifungal was added for 10 patients

   However, empirical antibacterial treatment was narrowed in 8 patients because the pathogenic agent not being clearly identified and the competence of the other treatments already in use. Treatment changes because the BAL microbiology results are provided in Table 5.

1. Complications because the FB were procedure presented in 29 of the 132 patients (21.9%), including mild and temporary hypoxia in 27 patients, hemorrhage in 1 patient and temporary bradycardia in 1 other patient that resolved when the procedure was discontinued and did not reoccur during follow-up. No complications from the FB procedure resulted in permanent morbidity and/or mortality.

4 | DISCUSSION

Our results revealed that even though all of the patients received broad-spectrum antibiotics and/or antifungal therapy throughout the procedure, the FB and BAL examinations provided significant data in 75/132 patients (56.8%) that was

TABLE 3 Comparison of groups according to radiological and microbiological findings

	Group I (n = 106)	Group II (n = 26)	*P* value
Radiological Findings			
Consolidation	31/106 (29.2%)	4/26 (15.3%)	.151
Atelectasis	54/106 (50.9%)	8/26 (30.7%)	.065
Diffuse/local nodule	19/106 (17.9%)	8/26 (30.7%)	.146
Interstitial infiltration	9/106 (8.4%)	4/26 (15.3%)	.285[a]
Ground-glass appearance	14/106 (13.2%)	5/26 (19.2%)	.532[a]
Bronchiectasis	17/106 (16%)	1/26 (3.8%)	.105[a]
Normal findings	3 (2.8%)	1/26 (3.8%)	1.000[a]
Distribution of multiple findings			
Only one finding	65/106 (61.3%)	20/26 (76.9%)	.137
Two findings	35/106 (33.0%)	5/26 (19.2%)	.171
Three findings	3/106 (2.8%)	–	–
Microbiological Pathogens			
Bacteria	46/106	4/26	.008
Fungus	8/106	3/26	.695[a]
CMV	5/106	5/26	.307[a]
Other viruses and PJP	3/106	2/26	1.000[a]

[a]Fisher's exact test.

TABLE 4 Sensitivity of radiological findings in predicting the aetiologic agent

Radiological findings	*n*[a]	Microbiological results	*n*[a]	*P* value
Consolidation and/or atelectasis (Cons./At)	84/132	Bacteria	50/132	.119
Bacteria +	36	Cons./At +	36	
Bacteria −	48	Cons./At −	14	
Interstitial Infiltration and/or ground-glass appearance (Int inf./GGA)	26/71	Viruses	14/71	.003
Virus +	10	Int inf./GGA +	10	
Virus −	16	Int inf./GGA −	4	
Nodular Infiltration (Nod inf)	27/121	Fungus	11/121	.261[b]
Fungus +	4	Nod inf. +	4	
Fungus −	23	Nod inf. −	7	

Abbreviations: At, Atelectasis; Cons, Consolidation; GGA, Ground-glass appearance; Int inf, Interstitial infiltration; Nod inf, Nodular infiltration.

[a]Total numbers represent the patient number that could be evaluated for the related pathogen.

[b]Fisher's exact test.

compelling enough to warrant a change in treatment. In the last 5 years, three retrospective studies have been conducted in similar patient groups. In a study published in 2016, the results of 123 patients (75 of them had BMT) who had undergone FB because immunodeficiency and lung findings were reported.[15] Two other studies published in 2017 and 2018 reported the FB and BAL results of 71 adult patients diagnosed with ALL[16] and 117 children[17] with immunodeficiency. In these studies, treatment changes occurred in 74%, 27% and 73% of patients whose BAL samples were positive for microbiological studies, respectively. Likewise, treatment changes were also reported in 65.8%, 17% and 56%, respectively, of the patients whose BAL samples were negative for pathogenic agents. In our study, among all patients whose treatment was changed, 67/75 patients (89.3%) had their treatment increased, whereas only 8/75 patients (10.7%) had their treatment modified to narrow their current treatment (Table 5). In the overwhelming majority of the patients in Group I, the rate of therapy escalation (n = 57, 90.5%) was more prominent, especially the addition of antibiotics (43/57 vs 2/10 patients), because bacterial pathogens were more prevalent in Group I than in Group II *(P = .008)*. Bacterial diversity was high in BAL results and the antimicrobial agents at the time of FB did not cover most pathogens. Other recent

TABLE 5 Treatment changes in groups according to BAL microbiology results

Treatment Changes (n = 75)	Group I (n = 63)	Group II (n = 12)
Escalated Treatments (n = 67, 89.3%)	n = 57 (90.5%)	n = 10 (83.3%)
Antiviral (ganciclovir) addition (n = 10)	5	5
Anti-TB addition (n = 2)	2	–
Antifungal addition (n = 10)	7	3
Anti-bacterial addition (n = 45)	43	2
Narrowing the empirical treatment (n = 8, 10.7%)	n = 6 (9.5%)	n = 2 (16.7%)

reports investigating treatment changes also showed higher escalation as compared to de-escalation[17] and continuation of treatment with nontargeted agents following negative BALs (56.7%)[15], although these differences were not as high as the rates we found. We explain this slight discrepancy because in our immunosuppressed population, after observable positive BAL results, adding therapy seems reasonable, but the cessation of antimicrobial agents is more difficult in this critical population. In addition, we included patients who changed from prophylaxis to a treatment dose for some antibiotics (such as trimethoprim-sulfamethoxazole and ampicillin-sulbactam) and lengthening the duration of current treatment as a treatment change and this would count as an additive effect to our escalation rate. Additionally, these findings point out the overuse of antibiotics and the tendency to continue their use, even in cases without any objective evidence supporting their use.

Our results also provided evidence that BAL evaluation proved to be a very valuable approach for detecting a variety of aetiologic agents such as CMV, TB and resistant microorganisms.

Our research also investigated whether there were differences in aetiological agents and radiologic features according to which pulmonary infections had developed following BMT as well as in other immunodeficiency states. We determined that in the BMT group there were fewer bacterial agents than in the group with other immunodeficiencies, but no difference appeared for other aetiological agents. These results may be related to the protective effect of prophylactic antibiotics that had been administered since the beginning of the BMT process as well as the preparation regimens that cause T-cell depletion in order to prevent the occurrence of graft versus host disease, both of which may play a critical role in the increased frequency of the presence of viral and opportunistic agents in BMT patients. Our results also revealed that bacterial agents, in particular, *S. pneumoniae*, which is recognised as the most common cause of community-acquired pneumonia in patients with immunodeficiency other than BMT, are also extremely important agents to be reviewed.

Another aim of our investigation was to evaluate the sensitivity of HRCT for predicting causative pathogens before FB and BAL had been conducted. In general, practice, bacterial, viral and fungal infections are suspected, respectively, as the causative agents in the presence of consolidation and atelectasis, infiltration and a ground-glass appearance and a nodular appearance. The empirical treatment is determined and initiated accordingly. Our study demonstrated that only interstitial infiltration and a ground-glass appearance on CT were significantly related to CMV and other viral agents in BAL, but their success in showing the bacteria and fungi detected in BAL was low. Importantly, the lack of an expected pathogen because immune dysregulation may have also been the reason for this finding. Studies in recent years on the role of radiological findings in detecting infectious agents have only specified opacities, nodules and a ground-glass appearance as being associated with a pathogenic factor.[16] In addition, Rizik et al.[17] evaluated 117 children with immunodeficiency and determined that although BAL results led to a treatment change in 63% of the cases, the type of radiological findings (focal or lobar vs diffuse, age >1 vs <1) was not ultimately associated with any treatment change.

Therefore, our study appears to be the first to evaluate the reliability of radiological findings in predicting the aetiologic agent in children with immunodeficiency as well as the association of viral aetiologies with radiological findings. According to the data from our study, it is recommended that viral investigations be initiated at an early period of treatment as well as to start early antiviral treatment in patients who present with a ground-glass appearance on the HRCT. Additionally, we recommend that these findings continue to be investigated in studies with larger patient group cohorts.

Limitations of our current study include its retrospective nature as well as the use of prophylactic antibiotics and antivirals by all patients prior to the study; however, previous research in the past and other recent similar investigations were also conducted under empirical treatment conditions.[3,15,17] The fact that we could not evaluate the number of colony-forming units that grew in the BAL is another major limitation of our study. Contamination from the oropharyngeal flora cannot be ruled out, especially in patients with more than one isolated pathogen. However, we have considered these results when managing the therapy.

No serious complications because bronchoscopy have been detected in the juvenile age group among immunocompromised patients as found in our study and reported in the previous literature;[15,17] however, this is not the case in adult patients with immune deficiency, who exhibited a higher incidence of serious complications.[17]

In conclusion, FB and BAL should be done in these patients as soon as possible in order to clarify the causative

agent. In this way, appropriate treatments can be administered and any side effects and high costs that may be attributed to unnecessary treatment regimens may be mitigated.

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CONFLICT OF INTEREST

There are no financial conflicts of interest to disclose.

AUTHOR CONTRIBUTION

N G Eroglu-Ertugrul designed study, performed the study, contributed important reagents, collected data, analysed data and wrote the paper

E Yalcin designed study, performed the study, contributed important reagents and wrote the paper

B Oguz acquisition of data and interpretation, contributed important reagents

T Ocal contributed important reagents

B Kuskonmaz contributed important reagents

N Emiralioglu performed the study and contributed important reagents

D Dogru Ersoz designed the study, performed the study and contributed important reagents

U Ozcelik designed the study, performed the study and contributed important reagents

I Tezcan contributed important reagents

N Kiper designed the study, performed the study and contributed important reagents

ETHICS

Appropriate Ethics Committee approval has been obtained from the Hacettepe University for the research reported.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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