ORIGINAL ARTICLE

Bronchoalveolar lavage in children with inflammatory and non inflammatory lung disease

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Abstract

Background: Bronchoalveolar lavage (BAL) is a useful bronchoscopic technique. Studies in "normal" children are limited.

Aim: To provide data on BAL reference values from Greek children and compare BAL cellular and noncellular components in children with inflammatory and non-inflammatory lung diseases.

Methods: Seventy two children, aged 2.5 months to 16 years, underwent diagnostic bronchoscopy and BAL. Patients were divided in two groups whether lung inflammation was absent or present. Differential cytology, flow cytometry for lymphocyte subsets and cytokine and chemokine measurements were performed on BAL fluid.

Results: Alveolar macrophages were the predominant cellular population in normal children. Patients with inflammatory pneumonopathies had significantly more neutrophils. There was no difference in lymphocyte subpopulations. Values of CD4+/CD8+ ratio in BAL was similar to that reported in adults. Levels of IL-8 and TNF- α were significantly higher in children with inflammatory lung diseases.

Conclusion: This study provides the first data on BAL of "normal" Greek children. BAL from patients with pulmonary inflammation was characterised by neutrophilia. Finally, we propose that measurement of IL-8 and TNF-a levels in BAL could help in early identification of inflammation in the tracheobronchial tree. Hippokratia 2010; 14 (2): 109-114

Key words: bronchoalveolar lavage, bronchoscopy, lymphocyte subsets, cytokines

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Bronchoalveolar Lavage (BAL) in children is indicated in several inflammatory and non inflammatory lung disorders. By this procedure we have the opportunity to sample the endobronchial environment and expand our knowledge regarding this environment in various pneumonopathies of children[1,2]. However, there are restrictions in using BAL for research purposes, one of the major ones being the limited number of studies which deal with normal values for BAL components. Therefore, it has been proposed that each centre should establish its own reference values for BAL cellular and non cellular components.

The aim of our study was: 1) to assess the cellular components and some of the common inflammatory mediators in BAL of children with inflammatory and non inflammatory respiratory problems, and 2) to compare our findings with those of relevant studies in children and adults.

Material-Methods

The study material was collected from 74 children (22 female), aged 2.5 months to 16 years who had an indication for a diagnostic or therapeutic bronchoscopy. All children underwent physical examination, thorough haematologic work up, chest radiograph plus chest CT when clinically indicated and allergy testing (RAST or skin prick testing) when personal or family history of atopy was positive. Parental informed consent was obtained for all children prior to bronchoscopy[3].

Bronchoscopy was performed according to international standards[3].

BAL was obtained from the right middle lobe (90% of patients) or lingula (10% of patients) according to ERS guidelines[4]. Total cell counts were performed on uncentrifuged BALF using a Malassez haemocytometer. Differential cytology was performed following centrifugation (centrifugation speed was 500g for 5 min) and staining of air-dried slides with May-Grunwald Giemsa. Samples were further analysed by three colour flow cytometry (FITC, PE and PE-Cy5) for assessment of lymphocyte subpopulations[5].

Cytokine (TNF-a, IL-4, IL-5, IL-18) and chemokine (IL-8 and eotaxin) levels in BALF were measured by using a commercial enzyme linked immunosorbent assay (R&D systems, UK). The kits were able to detect concentrations as low as 4 pg/mL of IL-8 and TNF-a, 12.5pg/ml of IL-18, 3.2 pg/ml of IL-5 and 0.12pg/ml of IL-4. All samples were run in duplicate, and the mean values were used for statistical analysis.

Statistical analysis

Data were analysed with statistical package SPSS version 15.0. Data distribution was checked by Kolmogorov-Smirnov test. In data normally distributed student's t test was used. In non parametric data Mann-Whitney U test was employed. Data are expressed, when appropriate, in percentages, median values, standard deviation and range.

Results

Of the 74 children initially enrolled in the study, 22 were excluded due to unacceptable BAL samples. A sample was considered to be unacceptable for analysis when fluid recovery was less than 40%, contained more than 5% of epithelial cells, or when there was excessive mucous –despite filtration through a gauge- that rendered microscopic examination impossible. Finally, 52 children whose BAL samples were acceptable for analysis were studied. The 52 children were allocated to 2 groups (A & B) on the basis of clinical diagnosis prior to bronchoscopy and the bronchoscopic findings. Group A consisted of 20 children with no clinical or laboratory indication of pulmonary inflammation. All children of this group were apyrexial and had normal haematologic work-up. Absence of inflammation was confirmed bronchoscopically. Data regarding children of Group A are summarised in Table 1. This group was considered as control group. Group B consisted of 32 children with clinical and laboratory findings indicative of pulmonary inflammation. Bronchoscopy confirmed inflammation of the tracheobronchial

Table 1: Demographic data, chest roentgenogram (CXR), indication for bronchoscopy and bronchoscopic findings of children of Group A (controls.

	Sex	Age (years)	Weight (Kgrs)	CXR	Indication for bronchoscopy	Bronchoscopic findings
1	F	5	16.5	Left lower lobe atelectasis	Left lower lobe atelectasis	Foreign body in the left lower lobe
2	M	3	15	Streaky changes	Recurrent viral infections	Normal findings
3	F	0.92	12	Normal	Foreign body suspicion	Normal findings
4	M	1.5	9.5	Left lung hypoplasia. Right pneumocoele	Left lung hypoplasia. Right pneumocoele	Flattening of the subsegments of the left main bronchus
5	F	10	33	Left hilar lymphadenopathy	Mantoux 27mm	Normal findings
6	M	4.5	19	Right upper lobe atelectasis	Right upper lobe atelectasis. Foreign body suspicion	Mucous plug.
7	M	2.66	14	Normal	Foreign body suspicion	Normal findings
8	M	0.468	5.5	Normal	Stridor and wheezing	Severe laryngotracheomalacia
9	M	6	34	Normal	Acute lymphoblastic Leukaemia	Normal findings
10	M	8.08	26	Left sided infiltration	Left sided infiltration	Normal findings
11	M	10.3	30	RML,RLL Consolidation	Recurrent pneumonias	Normal findings
12	M	1.66	10	Pulmonary sequestration	Pulmonary sequestration (post op)	Constriction of the orifice of the LLB
13	M	2.5	5.5	Enlarged thymus	Stridor	Laryngomalacia
14	F	0.3	5.7	Normal	Stridor	Laryngomalacia
15	M	14	95	Normal	Post removal of endotracheal tumor	Residual subglottic stenosis
16	M	11.2	49	Dextrocardia	Dextrocardia	No inflammation
17	M	0.25	6.5	Normal	Stridor	Laryngomalacia
18	M	5.75	17	Normal	Chronic cough	Scarred right arytenoid
19	F	9.83	33	Normal	Tick cough	Normal findings
20	M	0.33	5.1	Normal	Stridor	Laryngomalacia

Table 2: Demographic data, chest roentgenogram (CXR), indication for bronchoscopy and bronchoscopic findings of children of Group B.

	Sex	Age (years)	Weight (Kgrs)	CXR	Indication for bronchoscopy	Bronchoscopic findings
1	F	6	17	Bilateral bronchiectases (CT)	Chronic Lung Disease. Pseudomonas on throat swab	Inflammation of the tracheobronchial tree (mainly left)
2	M	6	25	Mild hyperinflation	Chronic cough-no response to bronchodilators	Airway hyperaemia, short epiglottis
3	F	2.5	13	Right lung hyperinflation (expiration)	Foreign body suspicion. Lung infection	Constriction of the left main bronchus. Abundant secretions
4	F	12.75	63	Bilateral bronchiectases (CT)	Chronic Pulmonary Failure. Eosinophilic syndrome	Erythematous airways. Abundant sticky secretions
5	M	12	24	Steaky changes	CF	Mild inflammation
6	F	7	21	RML consolidation	RML syndrome	RML syndrome
7	M	5.5	25	RUL atelectasis	RUL atelectasis. Recurrent pneumonias	Mucous plug
8	F	6	16.5	Hyperinflation of the lower zones	Chronic lung disease. Frequent infections	Inflamed airways
9	F	3.5	13.5	Mild hyperinflation	CF	Mild inflammation
10	M	0.83	8.5	RUL atelectasis	RUL atelectasis. Post tracheooesophageal fistula repair	Scarred posterior wall of the trachea
11	M	7	19	Bilateral bronchiectases (CT)	Chronic Lung Disease	Inflammation of the tracheobronchial tree
12	M	8.7	29	Persistent consolidation of RML and RLL	Right sided pneumonia	RML syndrome
13	M	1.6	8	Normal	Stridor. Post tracheotomy removal	Left arytenoids subluxation
14	M	11	35	Consolidation (L)	Recurrent pneumonias. Corrected congenital heart disease	Constriction of the left main bronchus
15	M	0.2	3.5	Hyperinflation	Larynomalacia. Cerebral Palsy	Laryngomalacia-Inflammation
16	F	1.2	9	RML consolidation	Atelectasis. History of choking	Inflammation
17	M	12	30	Hyperinflation. Bronchiectases	CF	Mild Inflammation
18	M	4.5	19	Streaky changes	CF	Mild Inflammation
19	M	5.5	16	Normal	Obstructive apnoea	Severe inflammation
20	M	0.4	9	Normal	Recurrent croup, cyanotic spells	Tracheobronchomalacia with severe inflammation
21	F	6	18	Mild hyperinflation, streaky changes	CF	Abundant secretions
22	M	0.7	10	Left lung hyperlucense	Left sided hyperinflation	Left main bronchus constriction. Bronchomalacia
23	M	1.5	15	Left lung hyperinflation	Foreign body suspicion	Foreign body (nut)
24	M	8	25	CF characteristic	CF, positive Mantoux test	Severe inflammation
25	M	7	19	Hyperinflation. Bronchiectases	CF	Severe inflammation
26	F	5.5	15	Peribronchial thichening	CF, failure to thrive	Abundant secretions
27	F	5.75	25	Peribronchial thickening	Kartagener syndrome	Severe inflammation
28	F	10	18	Consolidation of the LLL	Persistent consolidation of the LLL	Inflammation
29	M	0.25	4.6	Peribronchial thichening	Cyanotic spells during feeding	Laryngomalacia-inflammation
30	M	3.16	16	Consolidation of the RML	Persistent consolidation of the RML	Inflammatory constriction of the Right middle bronchus
31	M	3	16	Normal	Aspiration of gum	Foreign body (gum)
32	M	10.75	48	Normal	Stridor	Ai rway inflammation

Table 3: Cellular analysis of BAL of children of Group A and B.

Group	A	B
N	20	32
Age range (years)	0.25-14	0.21-12.75
No aliquots	3	3
Volume saline	3 ml/kg	3 ml/kg
Recovery (%)		
Mean.±SD	61.21±10.21	55.18±9.91
Median	62.18	53.65
Range	40-81	40-75
TCC (cells 10^4/ml)		
Mean± SD	17.92±8.12	55.038±78.29
Median	15	28.95
Range	5.8-33.5	8.9-305
Macrophages %		
Mean± SD	93.33±4.56	42.59±23.32
Median	95	40
Range	84-99	8-81
Lymphocytes %		
Mean± SD	3.93±3.08	5.94±5.36
Median	3.25	5
Range	0.3-12	1-24
Neutrophils %		
Mean± SD	2.94±2.82	49.59±26.72
Median	2	57.5
Range	0.3-11.5	3-89

tree (mucosal erythema and abundant secretions) in all children of this group. Data regarding these 32 children are summarised in Table 2. Groups A and B were comparable in terms of sex distribution (p=0.476), age and weight (p=0.598 and p=0.756 respectively). Children of the 2 groups were also comparable regarding personal and family history of atopy and blood levels of IgE.

Safety & Complications

No serious complications occurred during or after bronchoscopy. Thirteen and a half per cent of children had episodes of oxyhaemoglobin desaturation that were reversed with temporary removal of the bronchoscope and oxygen supplementation. Seven per cent of children developed fever within 24 h following bronchoscopy.

Fluid Recovery

Fluid recovery was significantly lower (p: 0.043) in Group B (53.65±9.61%) compared to Group A (62.8±10.61%).

BAL cultures

All BAL cultures of children in Group A were sterile while 8 cultures from 8 children of group B were positive with the following isolates: staphylococcus aureus in 4, haemophilus influenzae in 1, pneumococcus in 1, staphylococcus aureus plus aspergillus in 1and staphylococcus aureus plus pseudomonas aureginosa in 1.

Cellular components

Results of BAL cellular analysis in children of groups A and B are shown in Table 3. The median value of Total Cell Concentration (TCC) in BAL of children in Group A was 15.10^4cells/ml. The predominant cell population was alveolar macrophages (mean±SD=93.33±4.56%) while lymphocytes and neutrophils were found in very low percentages (mean±SD=3.93±3.08% and mean±SD=2.94±2.82% respectively). In children of Group B (children with inflammatory lung diseases) TCC as well as percentage of neutrophils were significantly higher compared to Group A (median value $28.95.10^4$ cells/ml, p=0.008 and mean±SD=49.59±26.72%, p<0.001 respectively), whereas the percentage of alveolar macrophages (mean±SD=42.59±23.32%) was significantly lower (p<0.001). There was no significant difference between the 2 groups in the percentage of lymphocytes.

Lymphocyte subsets

No significant difference was found between the 2 groups regarding lymphocyte subpopulations measured by flow cytometry (total B, T, NK cell numbers and T cell subsets). The ratio of helper to cytotoxic T cells (CD4+/CD8+) in group A ranged between 1.02 to 3.8 (median 1.7).

Cytokines/Chemokines

Measurement of inflammatory mediators and cytokines that promote type 2 immune response (atopy) are shown in table 4. IL-8 and TNF-α levels were significantly higher in Group B compared to Group A (p=0.017 and 0.012 respectively). Eotaxin was detected only in children of Group B with bronchoalveolar lavage eosinophilia (range 28.8 to 36.8pg/ml), while it was undetectable in all children of Group A. There was no significant difference between the 2 groups regarding levels of IL-18 (p=0.447), IL-4 (p=0.061) and IL-5 (p=0.913).

Discussion

Studies on BAL in children mainly refer to patients with respiratory problems, whereas BAL studies in normal children are few in the literature for ethical reasons. Some investigators have approached the problem by collecting data from children that were subjected to fiberoptic bronchoscopy for various reasons without evidence of respiratory tract infections (stridor, chronic cough, evaluation of the stenosis of a main bronchus and follow-up of foreign body aspiration). Others, have used children undergoing elective surgery under general anaesthesia for non pulmonary illnesses[4]. In our study we opted to follow the former approach in order to overcome the possible effect of perioperative stress.

No serious complications were observed in our study.

Table 4: Cytokine and chemokine levels (pg/ml) in children of groups A and B.

	Group A	Group B
IL-8		
Mean ± SD	234.9±528.44	685.83±766.18
Median (Range)	97 (37 – 2453)	336 (26 – 2421)
TNF-a		
Mean ± SD	60.2±72.59	220.73±322.02
Median (Range)	35 (18 – 306)	56 (18 – 1211)
IL-18		
Mean ± SD	54.76±28.94	55.81±53.65
Median (Range)	36.10 (36.10 – 112)	36.10 (36.10 – 268)
IL-4		
Mean ± SD	1.10±3.43	6.03±12.15
Median (Range)	0.13 (0.13 – 13.0)	0.13 (0.13 – 44.23)
IL-5		
Mean ± SD	7.78±5.53	15.56±14.74
Median (Range)	6.30 (6.30 – 27.0)	6.30 (6.30 – 44.80)

We believe that this can be attributed to the careful selection of patients and to the judicious attention to safety procedures. Oxygen desaturation occurred in 13.8% of our patients.

Median BAL fluid recovery in our children was 57.49%. It was significantly higher (p: 0.043) in children of Group A (62.80%) than in children of group B (53.65%). We think that this difference is due to the increased viscosity of the secretions in the tracheobronchial tree of children with inflammed lungs. De Blic et al reported similar findings in children with obstructive lung diseases[4] and Kim et al in children with bronchiolitis[6].

Our study provides the first data on BAL among Greek children without inflammatory pulmonary conditions. Although these children cannot be considered as "normal", they may be regarded as an approximation of "healthy" children, since they were apyrexial, had normal full blood counts and bronchoscopy revealed absence of inflammation. Total cell concentration (TCC) in this group of children (group A or control group) was 15 x 10^4 cells / ml. This is similar to what has been reported in previous studies regarding children and adults[7-9].

Alveolar macrophages were the predominant cellular population, while lymphocytes and neutrophils were found in very low proportions. Slight variations regarding BAL cellular components in our population compared to reports from previous studies may be attributed to different inclusion criteria and technical details[4].

In children of Group B, TCC was significantly higher than in children of group A. Marguet et al have also reported an increase of TCC in children with cystic fibrosis, chronic cough, asthma and recurrent wheezing[1]. Moreover, patients of this group had significantly more neutrophils compared to controls ($p<0.001$). This was expected due to infection and inflammation process in the tracheobronchial tree of these 32 children. BAL cultures were positive in only 8 out of 32 patients; this can be explained by previous administration of antibiotics[10] or non homogeneous distribution of microorganisms in the different lobes[11]. Neutrophilic predominance in BAL has also been described in children with recurrent wheezing[12], with RSV bronchiolitis[6] and mild to moderate persistent asthma[13], conditions with coexistent inflammation.

Measurements of lymphocyte subsets in our patients showed no significant difference between the 2 groups. Few studies have dealt with this subject in the paediatric population[4]. Interestingly, the ratio of helper to cytotoxic T cells (CD4+/CD8+) in our control group was higher than in 2 previous papers dealing with "normal" children (median=1.7 - range=1.02 to 3.8)[7,14]. Our findings are similar to what has been reported in adults regarding lymphocyte subsets in BAL[15], as well as lymphocyte subsets in peripheral blood of children. We believe that this difference could be attributed to multiple factors that could have increased CD8+ T lymphocytes in BAL of children considered to be "normal" in the aforementioned studies. Some of these factors might be viral infections, preoperative stress and general anaesthesia. More studies should be carried out in order to clarify this discrepancy since this ratio is extremely important in the diagnosis of certain lung diseases, such as sarcoidosis[16], histiocytosis and hypersensitivity pneumonitis[4].

Regarding cytokines and chemokines (Table 4) measured in BAL of our patients it was found that levels of IL-8 were significantly higher (p: 0.017) in group B than in group A (controls). This was expected since group B patients had inflammatory pneumonopathies characterised by BAL neutrophilia. Similar increases in IL-8 levels have also been reported in other inflammatory lung diseases such as CF[17-19], measles bronchiolitis obliterans[20], respiratory problems secondary to gastroesophageal reflux[21], and chronic cough due to subclinical infection[22].

TNF- α levels were also significantly higher in Group B patients compared to controls (p=0.012). This cytokine promotes chemotaxis of neutrophils and also increases the levels of IL-8[23]. Taggart et al also found increased levels of this cytokine in BAL of CF patients[24]. We believe that these 2 cytokines must be measured in BAL of children with respiratory tract problems as they could be important markers of inflammation, especially when BAL cultures are negative.

IL -18 is a cytokine that structurally resembles IL-1 and functionally IL-12. It promotes inflammation[25] and enhances the activity of Natural Killer cells and CD8+ cytotoxic T cells. There are very few papers on IL-18 in BAL in adults[26-28] and none in the paediatric literature. We found no difference in IL-18 levels between the 2 groups (p: 0.447); this reflects the absence of difference between the 2 groups in the percentages of NK cells (p=0.383) and cytotoxic T lymphocytes (p =0.899).

IL-4 and IL-5 participate in Th2 immune response[29,30].

We found no difference in IL-4 and IL-5 levels between the 2 groups (p=0.061 and p=0.913 respectively). This was somehow expected, since the patients of the 2 groups did not differ in terms of personal and family history of atopy nor in IgE levels.

In conclusion, this study provides the first data on BAL of "normal" Greek children. Our results could contribute towards creating a database of "reference values" in the paediatric population. BAL from all our patients with clinical or laboratory evidence of pulmonary inflammation was characterised by neutrophilia. Interestingly, we found that values of CD4+/CD8+ ratio in BAL of children of both groups was similar to that reported in adults and not lower as previously found in two other studies. There was no difference in lymphocyte subpopulations between children with inflammatory and non inflammatory lung conditions. Therefore, we propose that measurement of IL-8 and TNF-a levels in BAL (an easy and quick ELISA test) could help in early identification of inflammation in the tracheobronchial tree.

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