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Role of bronchoalveolar lavage in children with lung disease

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ABSTRACT: The aim of the present study was to evaluate the clinical role of bronchoscopic and nonbronchoscopic bronchoalveolar lavage (BAL) in the diagnosis of infectious and interstitial lung disease in children.

BAL was performed using three 1 mL·kg^{-1} aliquots of normal saline, with the flexible bronchoscope (Olympus 3.6 or 4.8 mm) wedged in a segmental or subsegmental bronchus of the lobe that showed most abnormality on chest radiograph. In seven children with severe diffuse lung disease who were intubated, a nonbronchoscopic suction catheter lavage was performed. Fluid cultures and cellularity were evaluated using identical methods for both techniques. Between January 1993 and April 1994, 41 BAL were performed in 32 children aged 2 months to 17 yrs (median 8 yrs). Of these lavages, 14 were in heart and heart-lung transplant recipients, 11 in children known to be immunocompromised, and 16 in children who had a lung biopsy for interstitial lung disease or who had presumed infective lung disease. Transbronchial biopsies (TBB) or open lung biopsies were performed coincident with 19 BAL procedures.

In all transplant recipients without clinical symptoms, BAL and TBB cultures were negative and BAL cellularity was normal. TBB did not reveal infection or rejection in any of these patients. A diagnosis of infection was made by BAL in 1 out of 8 transplant recipients with clinical symptoms, and a diagnosis of rejection was made by TBB in 3 out of 8 patients. In 6 out of 11 BAL in immunocompromised children, an infectious agent was found in the BAL fluid. In three other patients who had an open lung biopsy, an interstitial lung disease was diagnosed. In these patients, BAL was abnormal but not diagnostic.

In summary, BAL proved helpful in the diagnosis of infective lung disease, but had little value in the diagnosis of rejection or parenchymal noninfective lung disease in children.

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Bronchoalveolar lavage has been used as a research and clinical tool in adults and children. Whereas standardization papers have been published for adults [1–4], they are lacking for children. We have developed a standardized protocol for performing bronchoscopic bronchoalveolar lavage (B-BAL) and nonbronchoscopic bronchoalveolar lavage (NB-BAL), and have established reference values for children without lung disease [5–7]. Few reports have been published on BAL in healthy children [8–10]. Others have investigated the role of BAL in children with acquired immune deficiency syndrome (AIDS) [11, 12], in immunocompromised children with pneumonia [13, 14], in children following heart-lung and lung transplantation [15], in children with bacterial pulmonary infections [16], and in children with sarcoidosis [17]. NB-BAL using a suction catheter has been performed in intubated neonates and children with respiratory disease [18–20]. NB-BAL appears to be particularly helpful in identifying infectious agents or inflammatory mediators in children with diffuse lung disease who are intubated, particularly if the endotracheal tube is too small to allow the 3.6 mm flexible bronchoscope.

The aim of the present study was to evaluate the clinical role of B-BAL and NB-BAL in diagnosing infectious lung disease, and to assess the cellularity of BAL in infectious and noninfective interstitial lung disease in a major paediatric pulmonary department.

Methods

Subjects

B-BAL was performed in children with presumed infectious lung disease and in children who had a transbronchial biopsy, a computed tomography (CT)-guided transcutaneous needle biopsy or an open lung biopsy, between January 1993 and April 1994. NB-BAL was performed in a selected group of patients who were intubated and ventilated because of severe diffuse infective lung disease.

Forty one BAL procedures were performed in 32 children aged 2 months to 17 yrs (median 8 yrs). Of these, 14 were in heart and heart-lung transplant recipients, 11 in children known to be immunocompromised, and 16

in intubated (n=5) and nonintubated (n=11) children not known to be immunocompromised.

BAL protocol

For B-BAL, three 1 mL·kg^{-1} aliquots of normal saline were instilled into a segment or subsegment of the lobe that showed most abnormality on a chest radiograph *via* a flexible bronchoscope. B-BAL procedures were performed under inhalation general anaesthesia without endotracheal intubation. No premedication was used, and atropine (0.02 mg·kg^{-1}) was given intravenously during induction anaesthesia with 1–5% halothane and oxygen. Liquid lignocaine hydrochloride (2–4%, maximum dose 4 mg·kg^{-1}) was directly applied to the tracheal and laryngeal mucosa. During the procedure halothane and oxygen were given *via* a face mask.

When the disease was diffuse, the right middle lobe was lavaged. A 3.6 mm flexible bronchoscope (Olympus BF3C10) was used for children aged less than 8 yrs, and a 4.8 mm flexible bronchoscope (Olympus BF4B2) for those older than 8 yrs. The bronchoscope was inserted transnasally *via* a face mask or orally *via* a laryngeal mask. In children who were intubated for diffuse lung disease, a NB-BAL was performed. The endotracheal tube had been suctioned before the lavage was performed and the end-whole suction catheter (Vygon CH/F.G. 6-10) was inserted *via* the endotracheal tube with the head of the patient turned to the left. The catheter was advanced until a resistance was felt, and then withdrawn a few millimetres. The same amount of fluid and the same suction pressures (100–150 mmHg) were used as for the bronchoscopic technique. The processing and analysing of the BAL fluid was identical for both techniques. The cells were counted in a haemocytometer and cell differential counts were performed after cytocentrifugation and Giemsa staining [5–7].

Processing of the fluid

The fluid and the tissue were examined using standard cell culture techniques for bacterial, viral, fungal, and mycobacterial pathogens. When indicated, cultures for Legionella and Mycoplasma were used. In addition, immunofluorescence techniques were performed for respiratory viruses and cytomegaloviruses (CMV). Aliquots of the fluid were cytocentrifuged and cells were stained by Ziehl-Neelsen and silver methenamine techniques. Biopsy tissue was also stained with the latter two techniques.

Biopsies

Transbronchial biopsies (TBB) were performed immediately after BAL in heart or heart-lung transplant recipients (n=12). Flexible forceps were inserted through the 4.8 mm bronchoscope and at least six specimens were taken from the upper and lower lobe of the right lung under fluoroscopy. In the one patient with localized disease, a CT-guided transcutaneous needle biopsy and the BAL were performed 2 weeks apart. Open lung biopsy (OLB) followed BAL immediately (n=4) or within 3 days (n=2) in children with infectious or presumptive interstitial lung disease.

Statistical analysis

Cell concentrations·mL^{-1} and percentages of different cell types were not normally distributed (assessed by using normal plots). Therefore, we present the data as medians and interquartile range (first quartile Q1, third quartile Q3) and used nonparametric statistics (Mann-Whitney U test for comparison of cell differentials). The significance level was chosen at $p<0.05$.

Results

Heart and heart-lung transplant recipients

In two heart-lung transplant recipients (D.C. and G.B.), five BAL were performed for symptomatic lung disease. All five lavages were followed by an immediate TBB (table 1). In one child (C.H.) with persistent right upper lobe changes who had a heart transplant, BAL showed

Table 1. – Clinical symptoms, BAL cytology and culture, and biopsy results in heart and heart-lung transplant recipients

Pt	BAL No.	Age yrs	Tx	Clinical signs	BAL cytology TCn	BAL cytology Diff %	BAL culture	Biopsy
D.C.	1	12	HLT	FEV_1 fall	850	N 35	Negative	Moderate rejection
	2	12	HLT	FEV_1 fall	160	L 21	Negative	Mild rejection
	3	13	HLT	Cough	130	N 51	Negative	Mild rejection
	4	13	HLT	FEV_1 fall, cough	1140	N 88	*P. aeruginosa*	Mild fibrosis, *P. aeruginosa*
C.H.	1	2	HT	Focal CXR change	1300	N 45	Negative	ND
	2	2	HT	Focal CXR change	400	N 7	Negative	Organizing pneumonia
C.S.	1	13	HT	Cough, sputum	180	N 6	Negative	Bronchitis
G.B.	1	17	HLT	Cough, FEV_1 fall	650	N 71	Negative	Bronchiolitis obliterans

Pt: patient; BAL: bronchoalveolar lavage; HLT: heart-lung transplant; HT: heart transplant; FEV_1: forced expiratory volume in one second; CXR: chest radiograph; *P. aeruginosa: Pseudomonas aeruginosa.* Tx: transplant; TCn: total count of nucleated cells×10^3·mL^{-1} returned fluid; Diff %: differential cell count as % of total. L: lymphocytes; N: neutrophils; ND: not done.

increased total cellularity and increased neutrophils. Four weeks later, a second BAL again showed similar abnormality and a CT guided needle biopsy 2 weeks later demonstrated organizing pneumonia. The second heart transplant recipient (C.S.), who had a cough productive of yellow sputum, was culture negative and had increased neutrophils. She had been on broad spectrum intravenous antibiotics for 2 weeks. Cellularity in these eight BAL was increased, with a median (1st–3rd quartile (Q1–Q3)) total cell concentration of 750 (228–952) cells $\times 10^3 \cdot mL^{-1}$ of returned BAL fluid, and a median (Q1–Q3) of 48 (27–75)% neutrophils. The median (Q1–Q3) percentage of lymphocytes was 11 (6.5–13)%. A specific agent was identified in the lavage fluid and in the biopsy tissue in one of these procedures. TBB histology revealed acute rejection (n=3), mild chronic rejection (n=1) and non-specific abnormality (n=2) (table 1). Two further transplant recipients (data not shown) underwent six BAL and simultaneous TBB procedures for surveillance. All six BAL showed normal cellularity and yielded negative cultures. None of the TBB showed evidence of rejection or infection.

Table 2. – Underlying disease, clinical symptoms, BAL cytology and culture, lung biopsy and clinical outcome in children known to be immunocompromised

Pt No.	BAL No.	Age months	Diagnosis	Symptoms	BAL cytology TCn	BAL cytology Diff. %	BAL culture	Biopsy
1		38	ALL	Respiratory failure		L 56 N 14	Negative	Pneumonitis
2	1	56	ALL	Respiratory failure		L 67 N 12	RSV	ND
	2		ALL	Respiratory failure		L 59 N 13	RSV	ND
3		95	ALL	Dyspnoea, CXR change		Normal	Negative	ND
4		72	ALL	Cough, CXR change	1030	L 74	Negative	ND
5		47	Neuroblastoma	Cough, CXR change	180	N 18	*P. carinii*	ND
6		24	Neuroblastoma	Focal, CXR change		L 33	Negative	Bronchitis
7		3	SCID	Respiratory failure	275	N 8	*P. cariini*	ND
8		43	ALL	Cough	700	N 11 L 18	Negative	Pneumonitis, mild fibrosis

ALL: acute lymphoblastic leukaemia; SCID: severe combined immunodeficiency; RSV: respiratory syncytial virus; *P. cariini*: *Pneumocystis cariini*. CXR: chest X-ray. For further abbreviations see legend to table 1.

Table 3. – Clinical history, BAL cytology and culture and clinical outcome in children who had a nonbronchoscopic lavage

Pt No.	Age months	History	BAL cytology TCn	BAL cytology Diff. %	BAL culture
1	28	Respiratory failure, ventilated	440	N 24 L 7	Influenza B
2	24	Neuroblastoma, respiratory failure, ventilated	540	N 67 L 4	*P. cariini*
3	12	Trisomia 21, respiratory failure post cardiac surgery	1025	N 75 L 1	*E. coli*
4	9	Respiratory failure, ventilated		N 81 L 2.7	Adenovirus
5	42	ALL, persisting fever post-BMT	450	L 25 N 5	Parainfluenza 1
6	78	Varicella, respiratory failure, ventilated	180	L 46 N 29	*V. zoster*
7	26	Respiratory failure, ECMO	350	N 51 L 5	*S. aureus*

BMT: bone marrow transplant; ECMO: extracorporal membrane oxygenation; *E. coli*: *Escherichia coli*; *V. zoster*: *Varicella zoster*. For further abbreviations see legends to tables 1 and 2.

Table 4. – Initial diagnosis, BAL cytology and culture, lung biopsy and clinical outcome in children not known to be immunocompromised

Pt	Age months	Initial diagnosis	BAL cytology TCn	BAL cytology Diff. %	BAL culture	Biopsy
1	144	? Aspiration		N 11 E 21	Negative	Foreign body granuloma
2	120	Pneumonia		L 35 N 30	*M. pneumoniae*	ND
3	48	Interstitial lung disease	1140	E 20	Negative	Bronchiolitis obliterans
4	204	CF	1850	N 55	*P. aeruginosa*	ND
5	148	Interstitial lung disease	480	N 77	Negative	CMV inclusion bodies
6	78	Interstitial lung disease	1050	N 79	Negative	ND
7	18	TB, ? obstruction		L 63	Negative	ND
8	47	TB meningitis, RML collapse		Normal	Negative	ND
9	36	TB, ? resistance		L 17 N 43	Negative	ND
10	53	Middle lobe syndrome		Normal	Negative	ND
11	108	Varicella		N 17	Negative	ND

CF: cystic fibrosis; TB; tuberculosis; CMV: cytomegalovirus; *M. pneumoniae*: *Mycoplasma pneumoniae*. RML: right middle lobe. E: epithelial cells. For further abbreviations see legend to table 1.

Table 5. – BAL cytology in patients with infection, rejection and in patients without an infectious organism

	Infection n=15	Rejection n=4	No infection n=16
Total number of nucleated cells $\times 10^3 \cdot mL^{-1}$ of returned fluid	350 (270–540)	405 (138–800)	175 (135–800)
Neutrophils % of all leucocytes	30* (18–75)	43 (11.8–66)	7 (3–16.3)
Lymphocytes % of all leucocytes	7 (5–35)	5 (3.3–17.3)	7.4 (5–29.3)

Data are presented as median, and 1st–3rd quartile (Q1–Q3) in parenthesis. *: $p<0.001$ *vs* "no infection", Mann-Whitney U-test. BAL: bronchoalveolar lavage.

Patients known to be immunocompromised

Ten immunocompromised patients underwent 11 BAL (nine B-BAL and two NB-BAL (table 3 patients 2 and 5)) and three open lung biopsies (tables 2 and 3). A specific agent (*Pneumocystis carinii* n=3; respiratory syncitial virus (RSV), n=2; Parainfluenza 1 n=1) was identified in 6 out of 11 lavages (one patient had RSV in two lavages one week apart). Median (Q1–Q3) total cell concentration was 250 (180–700) cells $\times 10^3 \cdot mL^{-1}$ with a median (Q1–Q3) of 25(8–59)% lymphocytes and 11 (5– 14)% neutrophils in these lavages where an organism was found. In three patients who had a negative culture in their lavage, an open lung biopsy was performed within 3 days after BAL. These biopsies revealed a negative culture and a histological diagnosis of nonspecific abnormality. The BAL fluid in these patients showed an abnormal cellularity with either increased lymphocytes or increased neutrophils (table 2).

Patients not known to be immunocompromised

BAL was performed in 13 patients (eight nonintubated (table 4 patients 1, 2, 4, 7–11), five intubated and ventilated (table 3 patients 1, 3, 4, 6 and 7)) with a presumed infective lung disease, and in three patients who underwent an open lung biopsy because of a suspected interstitial process (table 4 patients 3, 5 and 6). Eleven of the 13 patients with presumed infective lung disease had an abnormal BAL cellularity with a median (Q1–Q3) total cell concentration of 325 (230–733) cells $\times 10^3 \cdot mL^{-1}$ and a median (Ql–Q3) of 9 (5–26)% lymphocytes and 30 (10–65)% neutrophils. Seven of the 13 patients with presumed infective lung disease had a positive BAL culture. Of the three patients with suspected interstitial lung disease, biopsy showed intranuclear inclusion bodies suggestive of CMV infection in one child (but negative cultures), foreign body granuloma in the second, and mild bronchiolitis obliterans in the third. All three patients had nonspecific abnormal BAL cellularity (table 4).

Table 5 shows results of BAL cellularity from patients with infection compared to patients without an infectious organism, and compared to heart-lung transplant recipients who had rejection. Neutrophils were significantly higher in patients with infection compared to noninfected patients (30 *vs* 7%; $p<0.001$). Due to low numbers of patients with rejection, the difference in the percentage of neutrophils between patients with rejection and patients without infection did not reach statistical significance (43 *vs* 7%; $p=0.09$). There was no clinically relevant or statistically significant difference in percentage of lymphocytes or total number of cells between these groups. For comparison, our data on BAL in healthy children are shown in table 6 [modified from 7].

Table 6. – BAL cellularity in the pooled second and third aliquots in 18 healthy children

	Pooled aliquots
Return of instillate %	65 (43–72)
Total number of nucleated cells $\times 10^3 \cdot mL^{-1}$ of return	155 (75–258)
Macrophages	
Cells$\times 10^3 \cdot mL^{-1}$ of return	120 (68–213)
% of all leucocytes	91 (84–94)
Lymphocytes	
Cells$\times 10^3 \cdot mL^{-1}$ of return	9.0 (3.3–18.1)
% of all leucocytes	7.5 (4.7–12.8)
Neutrophils	
Cells$\times 10^3 \cdot mL^{-1}$ of return	2.3 (0.5–3.9)
% of all leucocytes	1.7 (0.6–3.5)
Eosinophils	
Cells$\times 10^3 \cdot mL^{-1}$ of return	0.1 (0.0–0.5)
% of all leucocytes	0.2 (0.0–0.3)
Ciliated cells	
Cells$\times 10^3 \cdot mL^{-1}$ of return	0.3 (0.0–1.7)
% of all leucocytes	0.3 (0.0–2.0)
Squamous cells	
Cells$\times 10^3 \cdot mL^{-1}$ of return	0.0 (0.0–0.4)
% of all leucocytes	0.0 (0.0–0.3)

Data are presented as median, with ranges from 25th to 75th percentiles in parentheses. (Modified from [7]).

Safety

Respiratory rate, heart rate and oxygen saturation were monitored in all patients during the procedure and for at least 6 h after the lavage. All patients received supplementary oxygen, routinely during lavage. No clinically important changes in any of these parameters were observed. Of those patients who had been on oxygen before the lavage, none required more oxygen after than before the procedure. BAL did not cause major airway bleeding in any of these patients.

Discussion

The results of this study suggest that BAL is a useful clinical tool in the diagnosis of infective lung disease in children. They further demonstrate that, at present, BAL cannot replace lung biopsy in the diagnosis of acute or chronic rejection in heart-lung or lung transplant recipients and in the diagnosis of noninfectious parenchymal lung disorders in children.

Results of our BAL study on children without lung disease suggested that cellularity, assessed by B-BAL and NB-BAL, was equivalent [6], so that the NB-BAL has been introduced into the present study for selected patients who were intubated for severe diffuse infective lung disease. The NB-BAL appears to be unsuitable in focal lung disease because the site of lavage is unknown and, therefore, a B-BAL lavage was performed in all patients with nondiffuse lung disease. In infective lung disease, the main purpose of performing BAL is to identify the organism responsible. In this study, we cannot compare the diagnostic yield of the NB-BAL with that of the B-BAL, because the patients were substantially different in the severity of their disease.

A high total cell concentration with increased lymphocytes and/or neutrophils suggested abnormality but was nonspecific for infective or noninfective lung disease. The wide range in total cell concentration and in percentage of lymphocytes and neutrophils in these two groups made it impossible to distinguish them. A positive culture was associated with an abnormal total cell count and an abnormal differential count in all patients. In bacterial infection, this increased cellularity supported the diagnosis of lung infection as opposed to bacterial contamination from the upper respiratory tract. BAL total cell concentration and differential count in patients known to be immunocompromised in this study are similar to those found in another study on immunocompromised children [13]. In heart and heart-lung transplant recipients who had an abnormal cell count and negative cultures in their BAL, TBB yielded either nonspecific abnormality or rejection. BAL cell differential was not helpful in differentiating these two groups. Similarly, BAL cellularity was found to be nondiagnostic of infection, rejection and adult respiratory distress syndrome in adult lung transplant recipients [21]. Another study has also concluded that BAL, including assessment of lymphocyte subsets, can only, at present, supplement histological examination of TBB in the diagnosis of complications after heart-lung transplantation in adults [22]. In three other patients, a diagnosis of interstitial lung disease was established by the means of an open lung biopsy. In these patients, also, BAL was abnormal but nondiagnostic. During the study period, no children with sarcoidosis or hypersensitivity pneumonitis were seen. In these rare conditions in children, BAL cellularity might be of greater diagnostic and prognostic value [17].

In symptomatic transplant recipients, BAL results led to a change in management in 1 out of 8 procedures (bacterial infection), and TBB led to a change in 4 out of 6 procedures (acute or chronic rejection). In the remaining two procedures, TBB helped to exclude rejection, which resulted in the decision not to administer high-dose steroids.

BAL appeared to be useful in 6 out of 11 immunocompromised patients because it led to initiation of a specific treatment. An infectious agent was found in these six patients. Three of the five patients with a negative culture had been receiving trimethoprim/sulphamethoxazole high-dose treatment for 2–4 days prior to the BAL. Their treatment was not altered and they improved within a few days after BAL. Thus, it is very likely that these children had a *Pneumocystis carinii* infection. This could have increased the diagnostic yield from 55 to 81%. These results are similar to those found in other studies [13, 14].

In conclusion, BAL (bronchoscopic and nonbronchoscopic) appeared to be a safe procedure because none of the 32 patients experienced any clinically relevant side-effects in 41 procedures. Furthermore, the results of this study demonstrate that BAL culture and cytology are helpful in the diagnosis of infective lung disease in children. In lung and heart-lung transplant recipients, BAL is helpful in the identification of infection but, at present, it cannot replace transbronchial biopsy in the diagnosis of rejection. Following our experience over the past 2 yrs, we now recommend bronchoscopic BAL in those children with focal lung disease. In those with diffuse lung disease, either the bronchoscopic or nonbronchoscopic technique can be used, depending on local facilities.

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