Thorax 1987;**42**:759–765

Value of bronchoalveolar lavage in the management of severe acute pneumonia and interstitial pneumonitis in the immunocompromised child

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ABSTRACT The diagnostic value of 73 bronchoalveolar lavages was assessed in 67 immunocompromised children (aged 3 months to 16 years) with pulmonary infiltrates. Thirty one children had primary and 19 secondary immune deficiency, 14 acquired immunodeficiency syndrome (AIDS), and three AIDS related complex. Bronchoalveolar lavage was performed during fibreoptic bronchoscopy, under local anaesthesia in all but two. One or more infective agents was found in eight of 11 patients with severe acute pneumonia and in 26 of 62 patients with interstitial pneumonitis. In interstitial pneumonitis, the most frequently encountered agents were *Pneumocystis carinii* (12), cytomegalovirus (8), and *Aspergillus fumigatus* (3). The yield was related to the severity of interstitial pneumonitis. The mean cellular count and cytological profile in lavage returns from patients with varying infective agents or underlying pathological conditions showed no significant difference, except in those children with AIDS and AIDS related complex who had appreciable lymphocytosis (mean percentage of lymphocytes 28 (SD 17)). In children with AIDS and chronic interstitial pneumonitis lymphocytosis without pneumocystis infection was observed in eight of nine bronchoalveolar lavage returns and was suggestive of pulmonary lymphoid hyperplasia. Finally, bronchoalveolar lavage produced a specific diagnosis from the microbiological or cytological findings in 44 instances (60%). Transient exacerbation of tachypnoea was observed in the most severely ill children but there was no case of respiratory decompensation attributable to the bronchoscopy. Bronchoalveolar lavage is a safe and rapid examination for the investigation of pulmonary infiltrates in immunocompromised children. It should be performed as a first line investigation and should reduce the use of open lung biopsy techniques.

Interstitial pneumonitis and severe acute pneumonia occur frequently in immunocompromised children, and pose numerous diagnostic and therapeutic problems.[1 2] Two radically different approaches are advocated for the management of these severe, often fatal disorders. Some units prefer to treat empirically with a wide range of treatment regimens, while others prefer positive diagnoses to be obtained first by open lung biopsy if necessary.[3] In the adult bronchoalveolar lavage is currently used not only in the investigation of non-infectious interstitial diseases but also, more frequently, in the diagnoses of pulmonary problems in immunocompromised patients.[4–7] By contrast, in children bronchoalveolar lavage is rarely used and open lung biopsy remains the main diagnostic technique.[8–10] The latter is an invasive procedure, however, which cannot be easily repeated, and does not always lead to the institution of specific treatment.[11] The aim of this study was to develop the non-invasive investigation of pulmonary disorders in immunocompromised children and to attempt to minimise the need for open lung biopsy.

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Accepted 18 March 1987

Methods

PATIENTS

Seventy three fibreoptic bronchoscopies and lavages

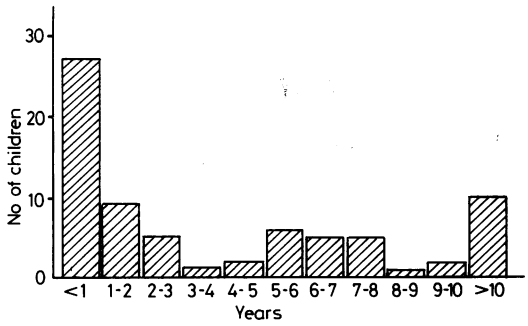

Fig *Age distribution of the children in the study.*

were performed in 67 children (42 boys and 25 girls) from September 1982 to April 1986 at the Hôpital Necker Enfants Malades. Two children had two bronchoalveolar lavages in the course of the same disorder and three children had two or three lavages for different episodes. The mean age was 4 years 4 months (range 3 months–16 years). The figure shows the age distribution. Twenty seven children (41%) were less than 1 year of age, and all were suffering from a primary immune deficiency. Seven of these children had received a bone marrow transplantation from 21 days to two months before the bronchoalveolar lavage.

The type of underlying immune deficiency is summarised in table 1. Thirty one children (46%) had primary immune deficiency, 19 (29%) secondary immune deficiency, 14 (21%) acquired immunodeficiency syndrome (AIDS), and 3 (4%) AIDS related complex (according to the CDC classification[12]).

Sixty two bronchoalveolar lavages were performed for interstitial pneumonitis and 11 for severe acute pneumonia. Patients with interstitial pneumonitis were subdivided into three groups, depending on clinical severity.

Group 1: 37 lavages in 35 children whose clinical condition was good. There was mild tachypnoea, but resting arterial blood tensions were normal. Diagnosis was based essentially on the chest radiograph appearances. Delay between recognition of the interstitial disorder and the bronchoalveolar lavage was long, with a mean of 52 (SD 80) days. Eleven lavages were performed within seven days, eight between eight days and one month, and 18 after one month. This group included seven children (nine lavages) with AIDS and a radiologically significant interstitial pulmonary disorder.

Group II: 18 lavages in 17 children whose clinical condition was moderately severe. Tachypnoea and effort intolerance were accompanied by arterial hypoxaemia (< 9·3 kPa, 70 mm Hg) and hypocapnia. The mean delay between diagnosis and bronchoalveolar lavage was 14 (SD 10) days. Seven lavages were performed before the seventh day, nine from eight days to one month, and two after one month.

Group III: seven lavages in seven children whose clinical condition was poor, with rapid progression towards hypoxaemia (< 8 kPa, 60 mm Hg) requiring oxygen treatment. The mean delay before lavage was 3·8 (SD 2) days. Six children required intubation and assisted ventilation in the course of their interstitial pneumonitis.

In the 11 lavages in 10 children for severe acute pneumonia the mean delay between diagnosis and bronchoalveolar lavage was 7 (SD 4) days (range 2–21 days).

Fifty three lavages (73%) in 49 children were performed while the children were receiving cotrimoxazole treatment. Twenty seven children (27 lavages) were on a therapeutic treatment regimen—sulphamethoxazole 100 mg/kg and trimethoprim 20 mg/kg (for between one day and two months)—and 23 children (26 lavages) were having prophylaxis—sulphamethoxazole 40 mg/kg and trimethoprim 8 mg/kg (for from two days to two months). Forty children (40 lavages, 55%) were receiving erythromycin (for from two days to two months), and 11 children (11 lavages, 15%) were having antifungal treatment, seven by the intravenous route and four orally, at the time of lavage.

Table 1 *Underlying immune deficiencies in 67 children*

		No of patients
PRIMARY IMMUNE DEFICIENCIES		31 (46%, 32 BAL)
Mixed immune deficiency		20
Severe combined immunodeficiency	13	
Wiskott–Aldrich syndrome	3	
Defect in expression of HLA antigens	1	
Miscellaneous	3	
Defects in phagocytic function		7
Chronic granulomatous disease	5	
Defect in adherence proteins	1	
Chediak-Higashi disease	1	
Defects in humoral immunity		2
Familial lymphohistiocytosis		2
SECONDARY IMMUNE DEFICIENCIES		19 (29%, 21 BAL)
Malignancy		14
Acute lymphoblastic leukaemia	8	
Solid tumours	3	
Non-Hodgkin's lymphoma	2	
Hodgkin's disease	1	
Systemic lupus erythematosus		2
Renal transplantation		2
Congenital fetopathy		1
AIDS AND AIDS RELATED COMPLEX		17 (25%, 20 BAL)
Haitian or Central Africa extraction		12
Blood transfusion		3
Haemophilia		1
Maternal drug addiction		1

BAL—bronchoalveolar lavage.

BRONCHOSCOPY

All but two bronchoscopies were performed under local anaesthesia. Premedication usually included atropine (0·01 mg/kg subcutaneously) and droperidol (0·1 mg/kg intramuscularly) one hour before the procedure, and oral or rectal diazepam (0·5 mg/kg) 10–15 minutes before examination. In children less than 6 months of age, or when the respiratory condition was considered too precarious, only atropine and diazepam were given. Furthermore, in cases of hypoxaemia the procedure was done while the patients were receiving nasal oxygen treatment.

Two types of fibreoptic bronchoscope were used, depending on the age and size of the child. In children less than 6 years of age a fibreoptic bronchoscope with an external diameter of 3·6 mm (Olympus BF3C4 and currently 3C10) was used. In children over 6 years of age and of normal size a fibreoptic bronchoscope with an external diameter of 4·8 mm (Olympus BF4B2) was used.

After careful local anaesthesia of the upper airways and larynx with 2% lignocaine the bronchoscope was introduced via the nose. After anaesthesia with 0·5% lignocaine (total dose of lignocaine 5 mg/kg) and inspection of the tracheobronchial tree, the distal extremity of the bronchoscope was wedged in a lobar or segmental bronchus supplying the area of maximal radiological abnormality in the case of acute pneumonia, or at random, most often in the right middle or lower lobe, in the case of diffuse interstitial lesions. A first sample (5–10 ml) of prewarmed physiological saline was injected and reaspirated. This sample was rejected because it was considered to be of bronchial origin and to have oropharyngeal microbiological contamination. Then four to six subsequent equal aliquots (5–30 ml) were instilled slowly until 10–15% of functional residual capacity was reached (that is, in practice a total volume of 20–180 ml, according to the child's size) and gently reaspirated. These samples were used for cytological and microbiological study; immunofluorescence testing (for *Legionella pneumophila*, respiratory syncytial virus, parainfluenza virus, herpes simplex virus, cytomegalovirus, adenovirus); and culture for virus, bacteria, fungi, and mycobacteria. The total duration of the lavage procedure, including anaesthesia, did not exceed 10–15 minutes.

CYTOLOGICAL TECHNIQUE

A total cell count of nucleated cells was performed on lavage fluid and 12 Cytospin preparations were made by cytocentrifugation at 300 rev/min for 10 minutes on a Cytospin 2 (Shandon Southern Instruments, Sewickly, Pennsylvania). These were stained by May-Grünwald-Giemsa, periodic acid-Schiff (PAS), Gram, Grocott, Ziehl, and Perls and examined for cytological evidence of fungal, viral, and parasitic infection, and for the presence of siderocytes. The remaining fluid was cytocentrifuged for 10 minutes at 600 rev/min, the sediment was fixed in Bouin's solution and embedded in paraffin, and histological sections were cut and stained with haematoxylin and eosin, PAS and Grocott stains. In patients with AIDS, extra cytospin preparations were made and fixed in acetone at 4°C for five minutes, and monoclonal antibody staining for OKT4 and OKT8 (Ortho) was performed by the Avidin-Biotin complex method.[13]

STATISTICS

Statistical analysis of the data was performed by using Student's t test and χ^2 analysis. A p value of less than 0·05 was accepted as significant.

Results

INTERSTITIAL PNEUMONITIS

Total cell counts and percentages of macrophages, polymorphonuclear neutrophils and lymphocytes in the disease groups are shown in table 2. In children with AIDS and AIDS related complex, the extent of the lymphocytosis (mean 28% (SD 17%)) was

Table 2 *Cytological data (mean with standard deviations in parentheses) for the total group with interstitial pneumonitis (IP) and for subdivisions according to the underlying immune deficiency*

	Total cells (× 10⁶/l)		*Macrophages (× 10⁶/l) (%)*		*Neutrophils (× 10⁶/l) (%)*		*Lymphocytes (× 10⁶/l) (%)*	
Total IP (n = 62)	362 (330)		246 (238) (68 (23))		62 (72) (17 (19))		54 (60) (15 (15))	
AIDS and AIDS related complex (n = 15)	358 (172)	NS	247 (287) (66 (23))	NS	19 (21) (6 (9))	†	92 (91) (28 (17))	§
Primary deficiencies (n = 28)	513 (456)	NS	384 (278) (72 (22))	NS	96 (107) (19 (19))	§	33 (34) (9 (9))	*
Secondary deficiencies (n = 19)	326 (283)		189 (110) (61 (23))		106 (71) (25 (22))		31 (34) (14 (13))	

Statistical significance of difference between lymphocyte and neutrophil percentages: *p < 0·05; †p < 0·01; §p < 0·001.

significantly greater than in children with primary ($p < 0.001$) and secondary ($p < 0.05$) immunodeficiencies. Six children (eight lavages) with chronic interstitial pneumonitis evolving over two months had a lymphocytosis of over 20%. The mean lymphocyte percentage in all eight patients with chronic interstitial pneumonitis (nine lavages) was 32 (17), whereas it was 22 (18) in six children (six lavages) with acute interstitial pneumonitis, a non-significant difference. Lymphocyte subpopulations were studied in seven cases of AIDS, but only three contained more than 10% lymphocytes. All showed a predominance of OKT8 positive cells with very few OKT4 positive cells, reflecting the inverse OKT4:OKT8 ratio in the blood. A study of lymphocyte subpopulations in a case of T cell lymphoma (human immunodeficiency virus positive) showed 27% lymphocytes, which consisted of a monoclonal cell population ($Leu3a^+$, $OKT4^+$, and TAC^-).

The mean polymorphonuclear neutrophil count for the whole group with interstitial pneumonitis was 17% (19%). It was significantly lower in the children with AIDS and AIDS related complex than in those with the primary ($p < 0.001$) and secondary immune deficiencies ($p < 0.01$). There was, however, no significant relationship between elevation of the neutrophil count and detection of an infecting agent.

Pneumocystis carinii cysts were often accompanied by clumps of cellular debris. Only one of eight cases was associated with concomitant cytomegalovirus infection.

Cytomegalovirus was detected in eight cases by direct immunofluorescence or culture, but characteristic intranuclear inclusions were not seen in any of the cytospin preparations. In one case with negative immunofluorescence and culture, cells with inclusions (non-cytomegalovirus type) compatible with a viral infection were noted.

Severe acute pneumonia

The proportion of macrophages was 84 (12), of lymphocytes 6 (7), and of polymorphonuclear neutrophils 11 (12).

In 10 patients the diagnosis was established from the cytological findings.

MICROBIOLOGY

Severe acute pneumonia

Table 3 shows the microbiological diagnoses. In eight of 11 lavages one or more infectious agents was isolated. *Legionella pneumophila* was detected on two occasions, 15 days apart, in a child whose persistent fever had prompted the second lavage. The second isolation was associated with herpes simplex virus. Bronchoalveolar lavage resulted in the institution of specific treatment for *L pneumophila* in one child, and antiviral treatment with ribavirine in an infant with severe combined immunodeficiency and respiratory syncytial virus.

Table 3 *Microbiological diagnosis in 11 patients having bronchoalveolar lavage for severe acute pneumonia*

	No of patients
Legionella pneumophila	2
Respiratory syncytial virus	3
Herpes simplex virus	1
Adenovirus	1
Clostridium perfringens	1
Mixed infection	1

Interstitial pneumonitis

Table 4 shows microbiological diagnoses. Twenty six lavages (42%) revealed one or more infectious agents. *Pneumocystis carinii* was the most frequently identified pathogen (12 lavages in 12 children). It was an isolated infection in nine cases and associated with another infectious agent in three cases (two cytomegalovirus and one *Aspergillus fumigatus*). Four children with *Pneumocystis carinii* were not receiving co-trimoxazole at the time of the bronchoalveolar lavage; four had been receiving a prophylactic dose for 2, 15, 15, and 21 days, and four had been on a therapeutic regimen for less than 72 hours. Cytomegalovirus was identified in eight lavages returns from seven children. In six it was the only agent; in two cases it was associated with *Pneumocystis carinii* and in one case with adenovirus. *Aspergillus fumigatus* was isolated in three cases, one associated with *Pneumocystis carinii*. Thus four mixed infections were observed.

In interstitial pneumonitis the microbiological yield varied with the severity and nature of the underlying lesion. The severity of the interstitial disease was the most important factor influencing yield. In group I 10/37 lavages (27%) were positive, in group II 11/18 (60%), and in group III five infections and one case of probable viral infection in seven lavages (85%) ($p < 0.05$ between groups I and II, $p < 0.02$ between groups I and III, and $p < 0.01$ between groups I and II + III). No significant difference in yield of individ-

Table 4 *Microbiological diagnosis in 62 lavages for interstitial pneumonitis*

	No of patients
Pneumocystis carinii	12
Cytomegalovirus	8
Aspergillus fumigatus	3
Adenovirus	2
Herpes simplex virus	2
Legionella pneumophila	1
Measles	1
Mycobacterium Calmette-Guérin	1
Mixed infections	4

ual pathogens was found between the different groups. In the primary immune deficiencies group 12/28 lavages were positive (43%), in the secondary deficiencies 9/19 lavages (47%), and in AIDS and AIDS related complex 6/15 lavages (40%). In the patients with primary immune deficiencies, seven of whom had received a bone marrow transplant, cytomegalovirus was isolated in only one case. Six children (two in group I, three in group II, and one in group III) whose bronchoalveolar lavage fluid produced no pathogen underwent an open lung biopsy. The open lung biopsy revealed two cases in which the bronchoalveolar lavage fluid had yielded false negatives, with the detection of tuberculous lesions without demonstration of acid fast bacilli in one case and isolation of cytomegalovirus in one case. In the four other cases non-specific inflammation was seen. Interestingly, in group I 14 lavages were performed within 15 days of the onset of the pulmonary problem, and there were only four positive results (28%). In the 10 cases where the bronchoalveolar lavage was non-diagnostic the children had been treated with co-trimoxazole and erythromycin treatment from the onset of the interstitial disorder. None of these children had had an open lung biopsy. All have been cured completely. In interstitial pneumonitis the result of the bronchoalveolar lavage led to a change of treatment in 13 cases: the start of treatment with co-trimoxazole or modification of dose (eight times) and the start of treatment with erythromycin and rifampicin (one case), an antifungal drug (three cases), and an antimitotic agent (one case).

TOLERANCE

No case of respiratory decompensation was attributable to bronchoscopy or bronchoalveolar lavage. Transient exacerbation of the tachypnoea was seen in the most severely ill patients, but no patient required transfer to the intensive care unit. No appreciable haemorrhages were observed, even in patients with thrombocytopenia (10–30 $\times$ 10^6/l). A transient febrile spike occurred four to six hours after the bronchoalveolar lavage in 40% of the children.

Discussion

Although bronchoalveolar lavage is widely used in adults, its application in children is still infrequent, and so far no large series of its use in children has been reported. Our results emphasise the value of this technique in the investigation of interstitial pneumonitis and severe acute pneumonia in the immunocompromised child. The miniaturisation of fibreoptic bronchoscopes has now made the practice of fibreoptic bronchoscopy possible even in infants,[14 15] and in our study 27 children out of a total of 67 were less than 1 year of age. In the hands of a skilled operator fibreoptic bronchoscopy is a safe, rapid test, which is well tolerated by the patient. Hypoxaemia due to the pulmonary pathology may be aggravated, especially in the youngest patients, by the passage of the fibreoscope into the tracheobronchial tree. Oxygen therapy, however, administered by nasal catheter via the opposite nostril, prevents aggravation of hypoxaemia. In the most hypoxic children a temporary increase in tachypnoea was noted. No prolonged respiratory decompensation could, however, be attributed to the procedure itself. The febrile spike, often seen in the four to six hours following the procedure, is also observed in adult patients after bronchoscopy and bronchoalveolar lavage.[4] One of the main advantages of local anaesthesia is the absence of respiratory depression, which occurs during general anaesthesia. Furthermore, the duration of the procedure is short, as the technique itself takes only a few minutes. Endoscopy is usually performed via the nasal airways. In a child of more than 5 years of age, however, when the severity of the pneumonia has necessitated intubation and artificial ventilation, bronchoscopy can be performed by passing the fibrescope through the endotracheal tube.

The causes of severe acute pneumonia and interstitial pneumonitis in the immunocompromised child are most often opportunistic infections, especially in children who have primary immune deficiencies. In a few cases, however, interstitial pneumonitis is secondary to non-infectious causes, such as malignant disease, radiotherapy, or chemotherapy.[16] Several modes of investigation have been proposed: aspiration biopsy, fine needle lung biopsy, and blind bronchial brushing.[17–20] These techniques, however, either have a low diagnostic yield or are potentially dangerous. Thus open lung biopsy is still the definitive test, advocated as the first line of investigation by many groups. The diagnostic yield of open lung biopsy varies from 61% to 100% in the various studies.[8–10] In a recent series of 46 open lung biopsies in 44 immunodeficient children with an acute diffuse pulmonary infiltrate, Prober and colleagues[10] showed that open lung biopsy produced a diagnosis in 35/46 cases (76%)—an infectious cause in 33 children (72%) and malignant infiltration on two occasions (4%). Our yields of infective agents in 62 cases of interstitial pneumonitis are lower, since in our series infection was documentated in 27/62 (44%) and specific infiltration once (1·6%). These results are probably at least partly due to the varying severity of illness in our patients. In fact, the severity of the interstitial pneumonitis is the most important factor influencing the yield of the bronchoalveolar lavage fluid. In our 25 acutely ill patients (groups II and III) the microbiological and cytological yield was 68%,

approaching the results of Prober and colleagues, after open lung biopsy. It is of course difficult to dissociate the importance of the severity of the interstitial pneumonitis, the delay between the diagnosis of interstitial pneumonitis and the lavage, and the dose and duration of treatment received. Whenever an interstitial pneumonitis was well tolerated the diagnosis was often made at a later stage, sometimes in the course of routine chest radiography. Some children were referred to us only secondarily for bronchoalveolar lavage, after empirical treatment or even when the clinical and radiological signs were improving. On the contrary, an interstitial pneumonitis poorly or moderately tolerated was rapidly recognised and the child referred for bronchoalveolar lavage with a minimum of delay.

Among the infective agents identified, *Pneumocystis carinii* was still the most frequent (12 cases). Its incidence has diminished, however, as a prophylactic dose of co-trimoxazole has been used more regularly.[21] It is interesting, however, that *Pneumocystis carinii* was detected in three children who had been receiving prophylactic doses for 15–21 days. Furthermore, *Pneumocystis carinii* was detected in four children, one with AIDS, who had been receiving full high dose regimens for 72 hours before lavage. Cytomegalovirus was detected eight times, either by immunofluorescence or by culture. It was isolated on only one occasion among the seven children who had received a bone marrow transplantation. This incidence is in agreement with current publications.[22]

An infective cause of interstitial pneumonitis in the immunocompromised child is generally due to a viral or opportunistic pathogen. Bacterial infections are rarely documented but bronchoalveolar lavage also may provide some false positive bacterial results.[23] In fact, oropharyngeal contamination is unavoidable during the passage of the bronchoscope and only the use of a doubly protected catheter can overcome this problem.[24] Unfortunately, the diameter of the fibrescope most often employed (Olympus BF3C10) does not allow the passage of these catheters. This therefore limits the interpretation of results for an acute severe pneumonia, whenever an opportunistic agent such as *Legionella pneumophila* or a viral agent such as adenovirus or RSV is not identified. In fact, in our series detection of seven opportunistic or viral agents in 11 lavages highlights the value of the bronchoalveolar lavage even in severe acute pneumonia.[25]

Although the main aim of the bronchoalveolar lavage in the investigation of lung disease in the immunocompromised child is the microbiological examination, our results also emphasise the value of cytological data. Demonstration of malignant cells or study of lymphocyte subpopulations by monoclonal antibodies can identify a specific disease process. For example, in a child with a T cell lymphoma, human immunodeficiency virus positive, and with extensive alveolar-interstitial lung disease, bronchoalveolar lavage showed a monoclonal lymphocyte population. In this child, the radiological signs have regressed after immunosuppressive treatment. In general, however, a specific cause is less frequently detected by bronchoalveolar lavage than by open lung biopsy or transbronchial biopsy in the adult.[26] The latter technique, which requires the use of bronchoscope BF4B2, cannot be easily performed in children less than 8 years of age, and is still used infrequently above that age.[27]

The study of total cell count and cytological profile was usually of little diagnostic value. No significant difference was noted in lavage returns from patients with different infections or underlying pathological conditions except for those children with AIDS or AIDS related complex and interstitial pneumonitis, who had a significant increase in lymphocytes.[28 29] Seven children with AIDS had chronic interstitial pneumonitis. Although none had an open lung biopsy, the clinical and radiological features and slow evolution were compatible with pulmonary lymphoid hyperplasia as recently described.[30] The mean lymphocytosis in this group was higher than in six cases of acute interstitial pneumonitis (five AIDS and one AIDS related complex)—32% (SD 17%) *v* 22% (18%)). Yet this difference was not significant ($p = 0{\cdot}07$). Furthermore, lymphocytosis, per se, is not specific for pulmonary lymphoid hyperplasia as we have encountered it in two children with AIDS and acute interstitial pneumonitis due to *Pneumocystis carinii*. This has also been reported in adults.[31] A failure to recognise a viral infection cannot be excluded, but open lung biopsy performed in similar cases[30 32 33] did not disclose any viral agent, except Epstein-Barr virus in one case.[34] In practice, a lymphocytosis and sterile bronchoalveolar lavage fluid in a child with AIDS and chronic interstitial pneumonitis provides a valuable argument for avoiding open lung biopsy.

In summary, bronchoalveolar lavage made possible a specific diagnosis based on microbiological or cytological data in 44 out of 73 cases (60%). It should therefore be advocated as an early line of action. Open lung biopsy should be reserved for cases where the bronchoalveolar lavage fluid remains sterile and where the clinical condition of the patient deteriorates.

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