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# Open lung biopsy for diffuse interstitial lung disease in children

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*Open lung biopsy for diffuse interstitial lung disease in children. M.E. Coren, A.G. Nicholson, P. Goldstraw, M. Rosenthal, A. Bush. ©ERS Journals Ltd 1999.*

**ABSTRACT: The aim of the study was to investigate the contribution that open lung biopsy makes to the management of children with diffuse interstitial lung disease and to review the procedure-related morbidity in comparison with published literature on other biopsy techniques.**

**The authors reviewed the case notes and histology of patients under 18 yrs who had had an open lung biopsy in 1991–1998 for investigation of diffuse interstitial lung disease.**

**The majority of patients returned from theatre breathing spontaneously and without an intercostal drain. Three out of 27 suffered a complication related to the biopsy that required intervention. A clear histological diagnosis was reached in 25/27 patients resulting in a change of management in 15/27. The most common histological patterns were nonspecific interstitial pneumonitis which generally had a favourable prognosis and follicular bronchiolitis/lymphocytic interstitial pneumonitis where prognosis was largely dependent on that of an underlying systemic disorder.**

**It is concluded that open lung biopsy makes a substantial contribution to the management of diffuse interstitial lung disease in children and considering both diagnostic yield and safety, remains the biopsy technique of choice.**

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The association of persistent severe respiratory distress and diffuse shadowing on chest radiographs represents a diagnostic challenge. There are numerous causes in addition to interstitial lung disease (ILD) including infections, chronic aspiration, cardiac disease and pulmonary vascular disease [1–3]. Noninvasive techniques can diagnose or exclude many of these [1, 2]. ILD is characterized by diffuse interstitial shadowing on computed tomography (CT) scans [2] and in adult patients, a specific diagnosis can frequently be made from the scan appearance alone [4, 5]. In children, the CT appearances are nonspecific and biopsy is often required [2, 6, 7]. There is debate as to the optimum means of obtaining tissue with transbronchial, percutaneous transthoracic, video-assisted thoracoscopic and open lung biopsy techniques available.

The authors describe their experience of open lung biopsy (OLB) in children over a 7 yr period to consider the value to clinical management of this invasive procedure and to describe the spectrum of diseases encountered, correlating histological diagnosis with treatment decisions and subsequent clinical outcome. The authors report the procedure-related morbidity comparing it to published literature on the other techniques.

## *Method*

The children were referred to the tertiary referral paediatric unit of The Royal Brompton Hospital, London, UK between 1991–1998. During that period, there were 27 paediatric lung biopsies for interstitial lung disease with an equal number of males and females. The age range of the children was 5 weeks to 18 yrs with a median of 3 yrs. All patients had severe and progressive respiratory distress and diffuse bilateral infiltrates on imaging. Evaluation prior to biopsy involved a detailed history and examination, chest radiograph and thoracic CT. Other investigations included a minimum of full blood count, sputum culture (where available) and serology looking for specific infections, full evaluation of cellular and humoral immune function and echocardiography (ECHO). Evidence of gastro-oesophageal reflux and specific allergies including avian precipitins was sought where appropriate.

### *Biopsy technique*

A suitable site for biopsy was selected, based upon the CT appearances and the distribution of the radiological abnormality. Areas of dense opacification were avoided as these may show only end-stage fibrosis without diagnostic features. All biopsies were performed under general anaesthesia. After rigid bronchoscopy and lavage for cytology and bacteriology, a single-lumen endotracheal tube was inserted. A short incision was made over the area of interest, incising the underlying intercostal muscles. Depending upon the size of the child this varied from 2–4 cm in length. A clamp was applied across the lung area and the biopsy taken distal to this. The lung was repaired with a continuous suture of polypropylene (Prolene). If the disease was heterogeneous on visualization, biopsies were taken from two areas, one of representative abnormality

and another from the most normal area within the field. An airtight closure was ensured by applying constant airway pressure whilst the lung repair was immersed under saline. The wound was closed in layers evacuating air by the use of a temporary drain through the wound. The drain was removed under anesthesia before the child left the operating theatre. Portions of the biopsy specimen were routinely sent for histological and bacteriological examination.

### *Histology technique and classification*

Haematoxylin and eosin stained slides were reviewed. Patients with an interstitial pneumonitis were classified according to criteria for recognized histological patterns including those of chronic pneumonitis of infancy [8] and nonspecific interstitial pneumonitis [8–10]. Where appropriate, an elastic van Gieson stain was used to look for the presence of fibrosis and periodic acid schiff for alveolar proteinosis-like material. A Perl′s stain was used to look for haemosiderin, Ziehl-Nielsen stain was used to look for acid-fast bacilli and Grocott stain was used to look for fungi. Immunohistochemistry using a standard avidin-biotin technique was used to assess the nature of lymphocytic infiltrates where lymphoma entered the differential diagnosis in patients with reactive pulmonary lymphoid hyperplasia (either lymphocytic interstitial pneumonitis or follicular bronchiolitis).

## Results

There was no mortality related to open lung biopsy. Using the technique described, 15/27 children required neither ventilation nor chest drain following the procedure. Five patients had pneumothoraces noted on chest radiography but were asymptomatic and required no intervention. Seven patients required ventilation following the procedure for a median duration of 24 h. Four of these were infants with severe respiratory failure and two were already ventilated prior to biopsy. Seven patients had a chest drain on return from biopsy of whom two had drains preoperatively and five were on positive pressure ventilation. Three patients required treatment for a complication of the procedure, one pneumothorax requiring drainage, one haemothorax requiring drainage and blood transfusion and one pleural space infection requiring drainage and antibiotics. Details of the individual cases with biopsy findings and follow-up information are listed in table 1.

## Discussion

This series reports the authors′ experience of 27 open lung biopsies in children with diffuse ILD at the time of biopsy. This is a retrospective report, which prevents the authors from providing an accurate denominator with which to compare these 27 cases. It is the experience of the authors, albeit in a tertiary referral centre, that these cases represent the majority of children referred with static or worsening symptoms and a clinical and radiological diagnosis of ILD. Clearly patients with mild symptoms or an improving clinical course may not even be referred and are certainly not subjected to biopsy. A recent prospective analysis of invasive and noninvasive means of diagnosis of paediatric ILD has shown that the introduction of a formal stepwise diagnostic algorithm still results in a biopsy procedure in a high proportion of children with this pattern of disease [11].

The ability to demonstrate that histological diagnosis contributes to the management of these cases has always been fundamental [12–14]. In this series, biopsy resulted in a new intervention in 15/27 patients (56%) and in most of the remainder a suspected diagnosis was confirmed allowing clearer information to be given to families. A course of systemic corticosteroids is the most frequent therapeutic step following the diagnosis of ILD in children and it can be suggested that a therapeutic trial would obviate the need for biopsy in many patients [15]. In fact only 14/27 (52%) of the patients in this series actually commenced systemic steroids and offering them indiscriminately would have exposed all patients, including those whose conditions were found to be inappropriate for steroid therapy, to the risks of side-effects. These patients who have severe and worsening respiratory dysfunction demand a specific diagnosis, informed management decisions and accurate information communicated to the family.

The principal therapeutic decisions following OLB involved a trial of high dose systemic corticosteroids to those with nonspecific interstitial pneumonitis (NSIP) and a detailed look for provoking factors *e.g.* gastro-oesophageal reflux. Additionally the biopsy and concomitant bronchoalveolar lavage allowed the authors to clearly rule out active infection. Patients with lymphocytic interstitial pneumonitis (LIP) or follicular bronchiolitis (FB) associated with connective tissue disease also received high-dose steroids. In LIP or FB associated with immunodeficiency the first step was to look for evidence of specific infection. With primary lymphatic abnormalities, dietary manipulation was the first management step.

Table 1 lists the individual clinical outcomes and whilst the numbers are insufficient to draw firm conclusions about the prognosis for each diagnosis, the clinical associations varied greatly with the different histological patterns as has been described previously [8]. NSIP was first described as a type of interstitial pneumonitis histologically distinct from the patterns described in adults by LIEBOW and CARRINGTON [16] specifically usual interstitial pneumonitis (UIP) which is a very rare diagnosis in children [9, 15]. The aetiology varies but histological parameters have been described and prognosis seems to be much better for NSIP than UIP [9, 17]. In this series, 5/6 cases of NSIP responded well to corticosteroids and all ceased to be oxygen dependent within 18 months. The remaining child had progressive respiratory failure despite systemic steroids and died within a few months. Parents declined post-mortem examination. Clearly the considerable natural variability in NSIP makes it very difficult to be specific about prognosis in individual cases in the absence of precise information about aetiology. There was one case of desquamative interstitial pneumonitis who has remained stable on long term systemic steroids and Azathioprin, one baby with chronic pneumonitis of infancy who died of progressive worsening of respiratory failure and one case of Gaucher′s disease.

LIP is a distinct pattern of diffuse lung disease which currently is grouped together with (FB) as part of the

Table 1. – Clinical details, histology and follow-up

| Sex/Age | Clinical details | Histology | Management/Follow-up |
|---|---|---|---|
| F 12 mo | Progressive respiratory distress with requirement for ≤1 L $O_2 \cdot min^{-1}$ to maintain saturation >92%. Gastrooesophageal reflux. | NSIP | On OS and medical anti-reflux therapy for 12 mo. Gradual improvement in symptoms. |
| F 3 yrs | Recurrent pneumonia. Required 500cc $O_2 \cdot min^{-1} \cdot min^{-1}$ to maintain saturation >92%. | NSIP | Disease progressed despite OS. Died within 6 mo. |
| F 4 yrs | Tachypnoea. Weight loss. Required 1L $O_2 \cdot min^{-1} \cdot min^{-1}$ to maintain saturation >92%. | NSIP | 3 weeks course of OS. Remains well on inhaled steroids. |
| M 2 mo | Expremature (33 weeks). Mild reflux. Required 200–500 cc $O_2 \cdot min^{-1}$ to maintain saturation >92%. | NSIP | OS for 7 mo. Ceased to be $O_2$ dependent within 3 mo. Off all therapy at 2 yrs of age. |
| M 3 yrs | Anorexia and persistent dry cough. Severe tachypnoea but saturation maintained 92% in air at rest. | NSIP | 2 mo OS followed by IS for 1 yr. Well at follow-up. |
| M 6 mo | Recurrent pneumonia. Required 500 cc $O_2 \cdot min^{-1}$ to maintain saturation >92% | NSIP | OS for 6 weeks. Well at follow-up on no treatment. |
| F 5 yrs | Progressive dyspnoea and finger clubbing. Strongly positive Rheumatoid factor. Well saturated at rest but severe dyspnoea on minimal exertion. | LIP | Satisfactory control of symptoms on azathioprin and steroids. |
| F 12 yrs | Persistent tachypnoea following adenovirus pneumonia. Common Variable Immunodeficiency. Severe dyspnoea on minimal exertion. | LIP | Died of underlying disease. |
| F 12 yrs | HIV+. Treated for TB but cough and dyspnoea worsened. BAL-. $O_2$ saturation >92% at rest, desaturation on exercise. | LIP | Lost to follow-up. |
| M 15 yrs | CA. Increasing breathlessness and inability to exercise. Saturation >92% in air at rest. | FB | Failed trial of Azathioprin. Remains reasonably well on OS. |
| M 12 mo | Failure to thrive and respiratory distress. T-cell immunodeficiency (HIV-). Severe tachypnoea but saturation >92% in air at rest. | FB | Remained on IS for some months. Defaulted follow-up. |
| F 3 yrs | DS. Finger clubbing. Immunoglobulin deficiency. Tachypnoea but saturation >92% at rest. | FB | 1 yr on IS. Well at follow-up (on no treatment). |
| F 1 mo | Failure to thrive and recurrent pneumonia. Saturation >92% in air rest. | FB | Symptomatic improvement on high dose IS and intermittent antibiotics. |
| M 6 mo | Failure to thrive and respiratory distress. HIV-. BAL-. Saturation >92% in air at rest. | FBPC | Under investigation for immune deficiency. Commenced on Septrin. |
| F 3 mo | Persistent respiratory distress. Required $O_2$ at rest to maintain saturation >925 | L | Died in infancy at home. |
| M 1 mo | Respiratory failure from birth. Chylous pleural effusions. Required ventilation. | L | Weaned from respiratory support. Fat-free diet. |
| M 7 yrs | Worsening respiratory distress. Pleural and pericardial effusions. Saturation >92% in air at rest. | DPL | Died within 6 mo of respiratory failure. |
| M 9 yrs | Dermatomyositis. Increasing dyspnoea. Required ventilation. | AP | Lung lavage performed. Remains well on OS. |
| M 2 yrs | Failure to thrive. Hepatosplenomegaly. Saturation >92% in air at rest. | GB | Suffers with recurrent infections. Treated with Septrin. |
| F 7 mo | Respiratory distress since birth. Required 200–500 cc $O_2 \cdot min^{-1}$ to maintain saturation >92%. | CPI | Systemic corticosteroids tried but patient died shortly afterwards. |
| F 9 yrs | Progressive anaemia and cyanosis. Saturation >92% in air at rest. | DIP | Stabilized on long term OS and Azathioprin. |
| F 5 yrs | Progressive respiratory distress. Required supplemental $O_2$ to maintain saturation >92% at rest. | PH | Disease stabilized. Remains well on no medication. |
| M 11 mo | Previous repair of TAPVD. Increasing cyanosis. Severe desaturation despite $O_2$ therapy. | VOD | Died shortly afterwards. |
| M 1 mo | Persistent CP. Saturation >92% at rest. | NL | Spontaneous resolution. |
| F 12 yrs | Acute hypoxia with diffuse lung infiltrates. Required 1L $O_2 \cdot min^{-1}$ to maintain saturation >92%. | CAI | Prolonged course of IS. Well at follow-up. |
| F 10 yrs | Recurrent infections. Finger clubbing. Saturation >92% in air at rest. | NDS | Remains asymptomatic on IS despite continuing restrictive lung defect. |
| M 4 yrs | Persistent tachypnoea. Required 200–300 cc $O_2 \cdot min^{-1}$ to maintainsaturation >92%. | NDS | Failed trial of OS. Referred for Fundoplication. |

F: female; mo: months; NSIP: nonspecific interstitial pneumonitis; OS: oral steroids; M: male; IS: inhaled steroids; LIP: lymphocytic interstitial pneumonitis; HIV: human immunodeficiency virus; +: positive; -: negative; BAL: bronchoalveolar lavage; CA: chronic arthritis; FB: follicular bronchiolitis; DS: Down syndrome; PC: pneumocystic carinii; L: lymphangiectasia; DPL: diffuse pulmonary lymphangismatosis; AP: alveolar proteinosis; GB: Gaucher′ disease; CPI: chronic pneumonitis of infancy; SLE: systemic lupus erythematosus; DIP: desquamative interstitial pneumonitis; PH: pulmonary haemosiderosis; TAPVD: total anomalous pulmonary venous drainage; VOD: veno-occlusive disease; CPE: chylous pleural effusion; NL: normal lung; CAI: chronic airway inflammation; NDS: non-diagnostic sample.

spectrum of reactive pulmonary lymphoid hyperplasia [18, 19]. These cases were strongly associated with immunodeficiency states and connective tissue disease as has been described previously [18, 19]. The lung disease per se had a favourable prognosis with outlook related largely to the progression of the underlying disease. Patients with immunodeficiency have repeated pulmonary infections and the decision to biopsy in these cases was related to rapidly worsening symptoms despite treatment for infection or as part of the diagnostic work-up prior to the definitive diagnosis of an immunodeficiency state.

There were three patients with a chylous effusion of which one had diffuse pulmonary lymphangiomatosis (DPL), one had lymphangiectasia and one had a normal biopsy. The child with DPL died shortly afterwards, the child with a normal lung became asymptomatic and the other child with lymphangiectasia remains reasonably well on a fat-free diet. One further neonate, who did not have an effusion at presentation, had a histological diagnosis of lymphangiectasia and died in infancy of respiratory failure. The single case of primary pulmonary veno-occlusive disease died soon after the diagnosis was made.

It was disappointing to have two nondiagnostic samples (7%). One of these patients responded to systemic steroids and has remained stable on a modest dose of inhaled steroids with an improvement in chest radiograph appearance. The other failed to respond to systemic steroids and it has been decided to opt for surgical treatment of severe gastro-oesophageal reflux, which has subsequently been proven, rather than to attempt to rebiopsy. Review of these cases suggests that the decision to biopsy was taken on similar grounds to the others in this series.

The authors compare the results of OLB in this cohort of patients with those of different biopsy techniques published by other groups. It is believed that OLB should be the procedure of choice in the paediatric population on grounds both of diagnostic yield and safety. It provides a large volume of lung tissue allowing the clearest appreciation of lung architecture and distribution of fibrosis and cellular infiltrates. All children requiring lung biopsy need a general anaesthetic (GA) irrespective of the technique. Even bronchoalveolar lavage (BAL), which can occasionally make a clear diagnosis in the setting of diffuse ILD, *e.g.* haemosiderosis [15, 20], usually needs a GA. In general, BAL has been reported as useful only in the diagnosis of infective lung disease in children and would therefore be the first line of investigation in the child with known immunodeficiency who has acute respiratory compromise but not where noninfective parenchymal disease is likely [21]. Using OLB, the authors made a histological diagnosis in 25/27 patients (93%) and with the technique described the incision is small and recovery rapid. Children, especially infants, seem to tolerate the thoracotomy very well and are ambulant on the first postoperative day. Only three patients (11%) in this series required treatment for a complication of the procedure. Seven patients were ventilated post-procedure of whom four were infants and two were older children with the severest respiratory failure. The majority of the patients (15/27) were breathing spontaneously post-procedure and did not require a chest drain.

With regard to the other biopsy techniques, transbronchial biopsy (TBB) certainly has diagnostic uses in paediatrics, for example in follow-up post heart-lung transplant looking for obliterative bronchiolitis and in rare diseases with highly specific features such as pulmonary alveolar microlithiasis [14, 22, 23]. The pieces of tissue are too small to be useful in the context of an undiagnosed interstitial process. Furthermore, TBB is contraindicated where there is pulmonary hypertension.

Percutaneous biopsy would seem the least invasive of the possible transthoracic approaches and has been reported in one series to have a high success rate with minimal complication [24]. Another group reported a diagnostic yield of only 14/24 patients (58%) despite using CT guidance and 17% subsequently required OLB [7]. This procedure may have a role but needs further evaluation.

Video-assisted thoracoscopic surgery (VATS) allows direct visualization of the lung without thoracotomy and comparison with OLB in adults shows it to be equally effective and associated with less pain post-procedure [25–27]. The wider visibility of the lung surface compared to the limited thoracotomy in OLB is cited as an additional advantage but costs are increased [27–29]. The procedure may not be suitable in the smallest patients because of the size of the trocar involved and in paediatric ILD where high proportions of the patients are infants (12/27 in the present series) this limits its applicability [30]. Fan et al. [31] compared OLB and VATS in children and reported similar diagnostic yield from the two techniques but the overall nondiagnosis rate of 48% in this series makes comparison with the current data difficult. Additionally, selection of technique was not random being influenced by the experience of the surgeon and the size of the patient.

It is concluded that open lung biopsy is a safe procedure in children with diffuse interstitial lung disease, has a high diagnostic yield and contributes substantially to the management of these challenging cases. There is a need to minimize the risk of failing to make a clear diagnosis to avoid multiple procedures requiring general anaesthesia. Video-assisted thoracoscopic surgery may have a role in older children, but despite continuing radiological and surgical advances, open lung biopsy should continue to be regarded as the "gold standard" investigation.

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