SURVEILLANCE BRONCHOSCOPY IN CHILDREN DURING THE FIRST YEAR AFTER LUNG TRANSPLANTATION – IS IT WORTH IT?

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ABSTRACT

Since January 2002, routine surveillance bronchoscopy with broncho-alveolar lavage (BAL) and trans-bronchial biopsy has been performed in all paediatric recipients of lung and heart-lung transplants at Great Ormond Street Hospital using a newly revised treatment protocol. It was the aim of this study to report the prevalence of rejection and bacterial, viral or fungal pathogens in asymptomatic children and compare with the prevalence in symptomatic children.

The study population included all paediatric patients undergoing single lung transplantation (SLTx), double lung transplantation (DLTx) or heart-lung transplantation (HLTx) between January 2002 and December 2005. Surveillance bronchoscopies were performed at 1 week, 1, 3, 6 and 12 months post-transplant. Bronchoscopies were classified according to whether subjects were symptomatic, defined on presence of cough, sputum production, dyspnoea, malaise, decrease in lung function or chest radiograph changes. Results of biopsies and BAL were collected, procedural complications recorded.

23 transplant operations were performed, 12 DLTx, 10 HLTx, 1 SLTx (15 female patients). Median patient age: 14.0 years (range 4.9 -17.3). 15 patients had cystic fibrosis. 95 surveillance bronchoscopies were performed. Rejection (≥A2) was diagnosed in 4% of biopsies of asymptomatic, and 12% of biopsies of symptomatic recipients. Potential pathogens were detected in 29% of asymptomatic, and 69% of symptomatic patients. The overall diagnostic yield was 35% for asymptomatic, and 85% for symptomatic children (p<0.0005). The complication rate for bronchoscopies was 3.2%.

Many children have silent rejection or sub-clinical infection in the first year following lung transplantation. Routine surveillance bronchoscopy allows detection and targeted therapy of these complications.
Lung transplantation has become an accepted treatment option for end-stage lung disease even in children, but overall survival remains poorer compared to other solid organ transplants. The majority of early deaths is related to overwhelming infection in the immunocompromised host, accounting for almost 50% of deaths within the first year post-transplant. The International Society of Heart and Lung Transplantation (ISHLT) Eighth Official Registry Report 2005 showed that infection remains a significant cause of mortality throughout the entire follow-up period, even if CMV is excluded. Acute cellular rejection (ACR) accounts for 4% of deaths up to one year post-transplant, but bronchiolitis obliterans (BO) is the major cause of death by five years post-transplant (>40%).

Several authors have reported an association between an increased frequency and severity of ACR and the subsequent development of BO, while non-alloimmunologic factors, such as bacterial, viral, and fungal infection may also play a role. Early detection and treatment of ACR and/or infection allows prevention of irreversible graft damage and may therefore have a positive impact on long-term survival following lung transplantation.

Fiberoptic bronchoscopy with broncho-alveolar lavage (BAL) and transbronchial biopsy has become the most valuable tool used to monitor the lung transplant recipient and detect ACR and infection. The procedure provides direct visualisation of the airway and anastomoses and the ability to obtain lung tissue and broncho-alveolar specimen, even in the paediatric age group.

In the beginning of 2002, all our treatment protocols for children following lung transplantation were revised, and a new triple immunosupression therapy including tacrolimus and induction therapy with basiliximab and new guidelines for drug monitoring were implemented. Routine surveillance bronchoscopies with BAL and biopsies on five occasions within the first year post-transplant have been performed in all recipients of lung and heart-lung transplants at Great Ormond Street Hospital for Children since. It was the aim of this study to report the prevalence of ACR and bacterial, viral or fungal pathogens detected in asymptomatic children after lung transplantation and to compare this with the prevalence in symptomatic children since implementation of our new treatment protocols in 2002.

Some of these results have previously been reported in abstract form at the International Society for Heart and Lung Transplantation 2006 Annual Meeting in Madrid, Spain.

**METHODS**

The study population comprised all paediatric patients undergoing single lung (SLTx) or double lung (DLTx) or heart-lung (HLTx) transplantation at Great Ormond Street Hospital for Children over a four-year period from January 2002 to December 2005. Data collected included demographics (sex, age), patients’ underlying diagnosis, and type of transplant. All transplants were ABO-matched, and none was human leucocyte antigen (HLA)-matched.

This study was approved by the Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee, London, United Kingdom.

Transplant surgery was performed in standard fashion. All patients received basiliximab as induction therapy, then triple immunosuppression with tacrolimus, azathioprine and prednisolone according to our standard protocol (available from the authors on request). We aim for tacrolimus trough levels of 12-15ng/ml within the first three months post-transplant, followed by target levels of 10-12ng/ml for up to one year post-transplant, and 8-10ng/ml thereafter. Prednisolone is tapered down to 0.5mg/kg/day within the first six weeks post-transplant, then down to 0.25mg/kg/day.
for six months and maintained on 0.1-0.15mg/kg/day indefinitely. A minimum of two anti-pseudomonal antibiotics was used in transplant recipients with cystic fibrosis (CF) based on the recipient’s most recent sputum culture results pre-transplant. Intravenous liposomal amphotericin was used in all transplant recipients with CF for the first week post-transplant. CF patients with isolation of atypical mycobacteria pre-transplant were started on appropriate anti-mycobacterial therapy peri-operatively. In addition, all transplant recipients received teicoplanin on induction of anaesthesia and early post-transplant. All patients were commenced on anti-infective prophylactic treatment with co-trimoxazole and acyclovir, which were continued indefinitely, and nystatin for the first three months post-transplant. In addition, oral itraconazole and nebulised colistin or amikacin were used for three to six months post-transplant in recipients with CF. All our patients at high risk for CMV infection (defined as positive recipient or donor serology) received prophylaxis with oral ganciclovir (or valganciclovir since 2003) for a minimum of three months post-transplant. All children had routine CMV monitoring in peripheral blood performed weekly for the first three months, then monthly up to one year post-transplant using qualitative polymerase chain reaction (PCR) in the early part of the study (until 2002), and quantitative real-time PCR thereafter (since 2003).

Surveillance bronchoscopies with BAL and biopsies were routinely performed in all transplant recipients during the first year after transplantation (one week, and one, three, six and twelve months post-transplant). Surveillance bronchoscopies with BAL and biopsies are not performed beyond 12 months post-transplant in our institution. Bronchoscopies were classified according to whether subjects were asymptomatic or symptomatic at the time of the surveillance procedure, defined on presence of cough, sputum production, dyspnoea, malaise, chest radiograph changes or more than 10% decline in forced expiratory volume in one second (FEV₁). Laboratory spirometry was performed according to our laboratory protocols, which are based upon adult American Thoracic Society (ATS) and European Respiratory Society (ERS) standards for spirometry. Spirometry was performed weekly in the first three months post-transplant and at least monthly thereafter. In addition, any suspicious clinical changes post-transplant prompted bronchoscopy with BAL and biopsies as well, but these clinically indicated procedures were not included in this study.

Two operators (P. Aurora and C. Benden) performed all bronchoscopies. Nearly all cases were carried out under general anaesthesia through a laryngeal mask. An adult-size fiberoptic bronchoscope with a 4.9-mm outer diameter (Olympus BF Type P40, Olympus Medical Systems, Tokyo, Japan) was used and biopsies were obtained with an alligator jaw-step biopsy forceps (Olympus FB-211D). Only for eight bronchoscopies of children with less than 25 kg of body weight, a paediatric bronchoscope with a 3.6-mm outer diameter (Olympus BF Type 3C40) and a small biopsy forceps (Olympus FB-15C) through the 1.2-mm instrument channel had to be used.

Biopsies were performed under fluoroscopic guidance from the lung periphery of either the right or the left lower lobe. We aimed to obtain at least five specimen of tissue for histopathologic evaluation. The tissue specimen were fixed in 10% formaldehyde solution, and then serially sectioned and routinely stained with haematoxylin and eosin, elastic van Gieson, periodic acid-Schiff, reticulin and Grocott. The histopathologic diagnosis of acute cellular rejection was based on the working formulation for the classification of pulmonary allograft rejection from the Lung Rejection Study Group of the ISHLT: grade A0 = no significant abnormality; grade A1 = minimal; grade A2 = mild; grade A3 = moderate; and grade A4 = severe. In addition, further aspects of pulmonary allograft rejection were also graded according to the above ISHLT criteria: grade B0 = active airway damage without scarring; B1 = lymphocytic bronchitis; grade B2 = lymphocytic bronchiolitis.
BAL was performed by wedging the tip of the bronchoscope in the right upper lobe, right middle lobe or in the lingula. 10-20 ml of sterile 0.9% sodium chloride was instilled as one aliquot and retrieved by manual suction. BAL fluid was collected in a sterile container and processed. BAL fluid was examined microscopically as direct wet preparation and after gram and Ziehl-Nielsen staining. BAL fluid was cultured semi-quantitatively for bacteria and fungi including specific culture for mycobacteria and *Legionella pneumophilia*. The isolation of coagulase negative staphylococci on BAL culture was considered as of doubtful clinical significance unless the pathogen was simultaneously cultured on peripheral blood culture. Isolation of viridans streptococci (normal mouth flora) was not regarded as of clinical relevance. *Candida albicans* and *Candida species (non-albicans)* were considered clinically significant if there was additional evidence of invasive fungal infection (positive histopathology and/or blood culture). Blood cultures were only taken from children with clinical signs of sepsis, defined as pyrexia (peripheral body temperature > 37.5°C), raised blood inflammatory markers or malaise.

Immunofluorescence technique was used for detection of *Adenovirus*, *Influenza Virus Type A* and *B*, *Para-Influenza Virus Type 1,2* and *3*, *Respiratory Syncytial Virus* and *Pneumocystis carinii* in the BAL fluid. Early antigen fluorescent foci (DEAFF) test was used for the detection of CMV in this study. Supplementary testing for viral DNA (CMV, Epstein-Barr Virus (EBV), Adenovirus) by PCR was performed if indicated, using qualitative polymerase chain reaction (PCR) in the early part of the study (until 2002), and quantitative real-time PCR thereafter (since 2003).

All procedural complications were recorded.

**Statistical analysis**

The diagnostic yield of bronchoscopies in the two groups of subjects was compared using the Chi-squared test incorporating Yates’ correction for continuity. Statistical significance was accepted for P < 0.05.

**RESULTS**

**Study population**

A total of 23 lung transplant operations were performed between January 2002 and December 2005, of which 12 (52%) were DLTx, 10 (43%) HLTx and one (4%) SLTx. The SLTx was a boy with CF who had previous pneumonectomy. The median age at transplant was 14.0 years (range 4.9-17.3 years); there were 15 (65%) female and 8 (35%) male patients.

Seventeen (74%) had CF, of which 14 were ΔF508-homozygous. Five (22%) patients had primary or secondary pulmonary hypertension (PH) and one (4%) end-stage lung disease secondary to post Adenovirus lung damage and chronic aspiration pneumonia in infancy. Six CF patients had chronic lung infection with *Pseudomonas aeruginosa*. Three CF patients chronically grew *Pseudomonas aeruginosa* and *Staphylococcus aureus*, one CF patient *Staphylococcus aureus* only, one CF patient *Methicillin-resistant Staphylococcus aureus*, and one CF patient had chronic lung infection with *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. Three transplant recipients with CF grew atypical mycobacteria pre-transplant on sputum culture, of which one isolated *Mycobacterium avium*
intracellulare and two isolated Mycobacterium abscessus. One transplant recipient with CF had chronic lung infection with Burkholderia multivorans pre-transplant. No patient died within the first twelve months post-transplant. However, one male CF patient died at the age of 17.2 years 23 months post left SLT due to fungal sepsis, and one female patient aged 16.7 years died 27 months post DLTx for CF due to chronic graft failure.

Trans-bronchial biopsy and BAL results

A total of 95 bronchoscopies with biopsies and BAL were performed as routinely scheduled surveillance procedures, of which 69 (73%) were performed in subjects classified as asymptomatic and 26 (27%) in symptomatic subjects. A median of five biopsies were performed per patient (range 2-5).

ACR ≥ A2 was diagnosed in 3/69 (4%) of biopsies of asymptomatic subjects, and 3/26 (12%) of biopsies of symptomatic subjects (Table 1). These episodes of ACR were treated with a minimum three-day course of high dose intravenous methylprednisolone (10mg/kg/day). In addition, ACR = A1 was diagnosed in 5/69 (7%) of biopsies of asymptomatic, and 4/26 (15%) of biopsies of symptomatic children. In response to these results, maintenance immunosuppression was tapered down more slowly. In one case, a grade A1 rejection in an asymptomatic patient one week post-transplant progressed to a grade A2 rejection on surveillance biopsy follow-up one month post-transplant. At that time, the child presented with respiratory symptoms and decreased lung function.

In nine cases, biopsy samples revealed lymphocytic bronchitis/bronchiolitis (grade ≥ B1). However, immunosuppression was not augmented in these cases.

Due to small biopsy sample size, no grading (ISHLT Lung Rejection Study Group classification of pulmonary allograft rejection) was given in eleven cases. However, there was no histological evidence of ACR in any of these cases. Seven of the subjects were classified as asymptomatic, four as symptomatic. If these eleven cases were excluded from the analysis, ACR ≥ A2 was diagnosed in 3/62 (5%) of biopsies in asymptomatic subjects, and 3/22 (14%) of biopsies of symptomatic subjects. Only in one of these cases a paediatric bronchoscope was used.

Bacterial, viral and/or fungal pathogens were detected in 20/69 (29%) of asymptomatic children, and 18/26 (69%) of symptomatic children (Table 1). More than one pathogen was detected in eleven cases.

Bacteria were the most frequently isolated pathogens in BAL fluid. Bacterial pathogens was detected in 16/69 (23%) of asymptomatic, and 17/26 (65%) of symptomatic children. The different bacterial pathogens are listed in Table 2. More than 95% of bacterial pathogens were detected in lung transplant recipients with CF; No bacteria were detected in blood cultures taken simultaneously. All children with isolation of bacterial pathogens in BAL fluid were treated with either an appropriate oral or intravenous antibiotic course even if infection was sub-clinical.

Viral pathogens were detected in 4/69 (6%) of asymptomatic, and 4/26 (15%) of symptomatic children. Viral pathogens are listed in Table 2. All children with CMV detection in BAL fluid were donor-recipient CMV mismatches; two children had a breakthrough CMV infection despite oral prophylactic ganciclovir or valganciclovir. All patients with CMV detection received a two- to three-week course of intravenous ganciclovir followed by oral ganciclovir or valganciclovir for further three months. CMV monitoring in peripheral blood was performed up to twice weekly in these cases until CMV DNA was undetectable.
Fungi were detected in four cases, two asymptomatic and two symptomatic children respectively. Fungal species are listed in Table 2. None of the fungal pathogens were related to invasive fungal infection.

There was detection of *Pneumocystis carinii* in one case only of an asymptomatic child six month post-transplant; this female patient with PH received a sequential bilateral lung transplant at the age of 4.9 years. In this case, co-trimoxazole prophylaxis had been withheld for two months due to drug-induced neutropenia. The patient was treated with high dose co-trimoxazole (120mg/kg/day) for three weeks following detection of *Pneumocystis carinii* in the BAL fluid. Airway complications that needed interventional therapy were detected in two cases (one anastomotic airway stenosis, one bronchomalacia of left main bronchus). Balloon dilatation was successfully performed to overcome the anastomotic stenosis; a stent insertion was required to improve the airway obstruction due to bronchomalacia.

The overall diagnostic yield was 24/69 (35%) for asymptomatic children and 22/26 (85%) for symptomatic children respectively (P < 0.0005).

No lethal complications occurred due to surveillance bronchoscopies. One patient had moderate bleeding post-biopsy (estimated blood loss 100-200 ml), but no blood transfusion was indicated. A pneumothorax requiring chest tube insertion occurred in one case. One patient had a minor aspiration post-anaesthesia in the recovery room while sitting upright. A chest radiograph showed radiological features compatible with right lower lobe aspiration pneumonia in this case, but no treatment was required. The overall complications rate was 3.2%.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute rejection (≥ A2)</strong></td>
<td>3 (4)</td>
<td>3 (12)</td>
</tr>
<tr>
<td><strong>Acute rejection (= A1)</strong></td>
<td>5 (7)</td>
<td>4 (15)</td>
</tr>
<tr>
<td><strong>Isolation of pathogen</strong></td>
<td>20 (29)</td>
<td>18 (69)</td>
</tr>
<tr>
<td><strong>ACR / isolation of pathogen</strong></td>
<td>24 (35)</td>
<td>22 (85) *</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>69</td>
<td>26</td>
</tr>
</tbody>
</table>

*Table 1.* Results of trans-bronchial biopsy (TBB) and broncho-alveolar lavage (BAL) in asymptomatic subjects (Group 1) and symptomatic subjects (Group 2).  
*P < 0.0005  ACR: acute cellular rejection*
Table 2. Bacterial/viral/fungal pathogens detected in broncho-alveolar lavage (BAL) specimen of all 95 bronchoscopies performed in the study.

*Including two Methicillin-resistant Staphylococcus aureus (MRSA)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>18</td>
</tr>
<tr>
<td>Staphylococcus aureus*</td>
<td>11</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>3</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>3</td>
</tr>
<tr>
<td>Pandoraea species</td>
<td>2</td>
</tr>
<tr>
<td>Achromobacter xylosoxidans</td>
<td>1</td>
</tr>
<tr>
<td>Ralstonia pickettii</td>
<td>1</td>
</tr>
<tr>
<td>Burkholderia multivorans</td>
<td>1</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>1</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5</td>
</tr>
<tr>
<td>Viridans Streptococci</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>4</td>
</tr>
<tr>
<td>Parainfluenza Virus–2</td>
<td>1</td>
</tr>
<tr>
<td>Influenza Virus A</td>
<td>1</td>
</tr>
<tr>
<td>Influenza Virus B</td>
<td>1</td>
</tr>
<tr>
<td>Candida albicans/non albicans</td>
<td>3</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
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</tr>
</tbody>
</table>

DISCUSSION

To the authors’ knowledge, this is the first study to compare the prevalence of ACR and sub-clinical graft infection in asymptomatic and symptomatic pediatric lung transplant recipients in the era of modern immunosuppression in a single centre applying a uniform management approach. This retrospective analysis has demonstrated that many children have silent rejection or sub-clinical infection in the first year following lung transplantation.

Transplantation has been employed as therapy for end-stage lung disease since the early 1980s, and has by now become an accepted therapeutic option, even in the paediatric age group. Despite improved short-term survival due to improved surgical techniques, organ preservation and intensive care, long-term outcome following lung or heart-lung transplantation remains poor. The major obstacles to improved long-term survival are ACR and infection, and the subsequent development of BO. The underlying mechanism of this graft deterioration is unknown, but many risk factors are reported. The single, most important factor for the development of BO is the frequency and severity of ACR. However, non-alloimmunologic factors, such as bacterial, viral, and fungal infections may also play a role. It remains uncertain whether ACR in children is more frequent compared to adults. It is important to recognize, that differentiation between ACR and infection in children and adults is nearly impossible, as clinical signs and symptoms are non-specific in both groups. However, it is unknown, whether children report symptoms
less frequent compared to adults. As there is a lack of a valuable surrogate marker to reliably distinguish ACR from infection, bronchoscopy with biopsy and BAL has remained the ‘gold standard’.4,13,14

By means of routine surveillance bronchoscopies one aims to reduce the incidence of BO due to earlier detection of ACR and subsequent augmentation of immunosuppression. However, the role of surveillance bronchoscopies with biopsy and BAL in asymptomatic lung transplant recipients has remained a controversial issue up to now. Valentine et al estimated, that more than 50% of adult lung transplant centres in the ISHLT perform regularly scheduled bronchoscopies.15 According to a recent informal survey of pediatric lung transplant centres participating in the International Paediatric Lung Transplant Collaborative; three-quarters of the centres perform routine surveillance bronchoscopies for at least the first year post-transplant. Three centres continue surveillance bronchoscopies for an extended period longer than one year (A. Faro, personal communication).

To our knowledge, there are eleven published studies (four prospective, seven retrospective) regarding the role of trans-bronchial biopsies in lung transplant recipients. The studies have different study designs, end points, and length of follow-up.16-20 Taking these studies together, surveillance biopsies detected ACR (≥ grade A2) in approximately 13.6% of clinically silent cases, the majority within the first four to six months post-transplant.21 Previous studies by Valentine et al and Tamm et al reported success of lung transplantation in adult recipients without surveillance biopsies, although these studies have limitations. Valentine et al used pooled data from the ISHLT Registry as their control group and therefore not a homogeneous cohort.15 Tamm et al used historical controls instead.18

There is only one published study investigating the role of surveillance bronchoscopies to detect ACR in children following lung transplantation. Visner et al from the University of Florida reported the incidence of ACR (≥ grade A2) in 393 biopsy procedures performed in paediatric lung transplant recipients. Only 25% of biopsies were performed for surveillance, but 38% as ACR treatment follow-up, and 37% in symptomatic patients. ACR was found in 24% of surveillance procedures. Results of BAL to rule out infection were not reported. The incidence of complications in this study was 1.8%.7

We found an incidence of ACR (≥ grade A2) of 12% in symptomatic children compared to 4% in asymptomatic children. In addition, the incidence of ACR (grade A1) was 15% in symptomatic, and 7% in asymptomatic patients. The importance of grade A1 ACR remains controversial, although a previous prospective study from Toronto reported, that 22% of grade A1 rejection episodes progressed to a higher-grade ACR within three months.22 We found progression of grade A1 ACR to a higher-grade ACR in one case only.

In our study, we detected lymphocytic bronchitis/bronchiolitis (≥ grade B1) in nine biopsies, just more than half in asymptomatic children. The relevance of lymphocytic bronchitis/bronchiolitis is unknown. Yousem et al reported previously the likelihood of ACR preceding the development of lymphocytic bronchitis, which responds to augmented immunosuppression, but further details are not known.23

We report evidence of infection (bacterial, viral and/or fungal) in more than two third of symptomatic children, but also isolation of pathogens in nearly one third of asymptomatic children. Without the use of routine surveillance bronchoscopies with BAL, sub-clinical infection would have remained undetected in many cases.

Apart from CMV, infection accounts for 37% of deaths during the first year post-transplant, and 19% between three to five years post-transplant respectively.6 The risk of infection is much higher following lung transplantation compared to any other type of solid organ transplantation. In addition, the potential role of pathogens in the pathogenesis of BO remains unclear. Bacterial and fungal infections are not known to directly contribute to the pathogenesis of BO, although it may increase the risk of ACR.24 Pseudomonas aeruginosa is frequently isolated from lung transplant
recipients. It has been suggested, that infections caused by pathogens such as Pseudomonas aeruginosa may be linked to BO but this remains uncertain. In contrast, CMV pneumonitis was correlated with the development of BO in previous studies.\textsuperscript{25}

Our study has some limitations. The sample size of our study population is small, and there is a lack of long-term follow-up. Despite this, our study offers the unique opportunity to show the positive impact of modern immunosuppression and a uniform management approach including routine surveillance bronchoscopy on short-term results in children post lung transplantation. The impact of routine surveillance bronchoscopy on long-term graft survival remains unproven though. Only 13 bronchoscopies with BAL and biopsies were performed in children at 12 months post-transplant. The majority of subjects were asymptomatic (10/13). Nevertheless, five asymptomatic children had silent rejection and/or sub-clinical infection. The small number of subjects precludes statistical analysis, but these data suggest that surveillance bronchoscopy at 12 months post transplant is justified. It could also be argued that the role of surveillance bronchoscopy in monitoring children, who are more than 12 months post-transplant, should be re-examined.

In this study, DEAFF test was routinely used for the detection of CMV in BAL fluid, and supplementary testing of quantitative viral load by real-time PCR in plasma if indicated. However, Westall et al recently demonstrated that quantitative PCR analysis of CMV load in BAL fluid and the application of a diagnostic threshold are a better predictor for the presence of histologically proven CMV infection, compared with detection of viral load in plasma.\textsuperscript{26} In our institution, quantitative measurements of CMV load by real-time PCR in BAL fluid are now routinely performed.

In conclusion, our data suggest that many children have silent rejection and/or sub-clinical infection in the first year following lung transplantation. Routine surveillance bronchoscopy allows detection and targeted therapy of these complications and might therefore improve long-term outcome post-transplant.

COMPETING INTEREST STATEMENT
The authors do not have any competing interests to declare.

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