

F. Reichenberger  
M. Dickenmann  
I. Binet  
M. Sol  r  
C. Bolliger  
J. Steiger  
F. Brunner  
G. Thiel  
M. Tamm

## Diagnostic yield of bronchoalveolar lavage following renal transplantation

### Key words:

renal transplantation; bronchoalveolar lavage; infection; immunosuppression; mycophenolate mofetil; tacrolimus

**Abstract:** Organ transplant recipients are at high risk of infectious pulmonary complications. In this retrospective study, the diagnostic yield of bronchoalveolar lavage (BAL) was evaluated in renal transplant recipients. The results were analysed in special regard to the clinical presentation of pulmonary infections and the possible impact of new immunosuppressive agents. Over a 5-year period 91 BAL were performed in 71 renal transplant recipients. Microorganisms were isolated from 69% of BAL (63/91): bacteria 32%; cytomegalovirus (CMV) 27%; *Pneumocystis carinii* (PC) 22%; other viruses 9% (HSV; EBV, RSV, adenovirus, HHV8); *Aspergillus fumigatus* 1%. Total cell counts and neutrophil counts in BAL were significantly elevated in bacterial infection, whereas BAL positive for PC showed eosinophilia ( $P<0.05$ ). There was no association between clinical symptoms and the radiological pattern of infiltrates and the type of infection. Immunosuppression containing tacrolimus or mycophenolate mofetil was associated with a significantly higher percentage of PC and CMV infections compared to cyclosporin-based immunosuppression (65% vs. 30%,  $P<0.005$ ). A considerable number of PC and CMV infections occurred beyond 6 months after transplantation. In conclusion, BAL has a high diagnostic yield in renal transplant recipients. Infection with CMV and PC should also be considered beyond 6 months after transplantation, and prophylaxis for opportunistic infections should be given if the immunosuppression is intensified.

### Authors' affiliations:

F. Reichenberger,  
M. Dickenmann,  
I. Binet,  
M. Sol  r,  
C. Bolliger,  
J. Steiger,  
F. Brunner,  
G. Thiel,  
M. Tamm

Divisions of Pneumology and Nephrology, Department of Internal Medicine, University Hospital, Basel, Switzerland

### Correspondence to:

Michael Tamm  
Institute of Respiratory Medicine  
University of Sydney  
PO Box M 77  
Camperdown NSW 2050  
Australia  
Tel: +61 2 9515 8583  
Fax: +61 2 9550 6115  
e-mail:  
michaelt@mail.med.usyd.edu.au

Immunocompromised patients are at high risk of infectious complications, mostly affecting the lungs (1–5). Pulmonary infections are associated with a considerable morbidity and mortality in solid organ transplant recipients (2, 5). Bronchoscopy with bronchoalveolar lavage (BAL) is an established method for detecting pulmonary infectious agents, with a diagnostic yield between 55–85% in immunocompromised patients (2, 3, 6). In organ transplant recipients, a variety of infectious agents have to be considered as pulmonary pathogens. A typical time schedule for the occurrence of pulmonary infectious complications has been described and is often cited (1, 5). Bacterial infections predominantly occur during the first few weeks after transplantation, whereas pulmonary infections with cytomeg-

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alovirus (CMV) or *Pneumocystis carinii* (PC) typically present between the second and sixth months after transplantation.

In the past, high-dose cyclosporin, methylprednisolone, and anti-T-lymphocyte globulin were used whenever an increase of immunosuppression was required. More recently, new potent immunosuppressive compounds, such as tacrolimus (FK 506) and mycophenolate mofetil (MMF), have been widely introduced into clinical practice. These new agents are more efficient at preventing acute graft rejection. Therefore, they are used for rescue therapy in cases of recurrent or resistant graft rejection, but also in primary maintenance immunosuppression. Whether MMF and tacrolimus increase the risk of pulmonary infections is under discussion (7, 8).

In the present study, we analysed the diagnostic yield and the cytological and microbiological findings of BAL performed in renal transplant recipients. Pulmonary infections were analysed according to the presence of clinical symptoms and radiological changes. Furthermore, the impact of new immunosuppressive drugs was assessed concerning the incidence and the time course of pulmonary infections.

## Patients and methods

Over a 5-year period (1994–1998), a total of 91 diagnostic bronchoscopies with BAL were performed in 71 renal transplant recipients. Indications for BAL were fever, respiratory symptoms, and/or infiltrates on chest x-ray. In 11 patients bronchoscopy has been performed twice, and three patients were examined three times. One patient underwent a total of four bronchoscopies. The median time-span between repeated bronchoscopies was 45 days (6–363 days).

Diagnostic bronchoscopy was performed under local anesthesia according to the guidelines of the European Respiratory Society (9). For bronchoalveolar lavage, 3×50 to 3×100 ml of pyrogen-free sterile 0.9% NaCl solution were instilled into the middle lobe or into the segment with the most prominent radiological infiltrate. BAL fluid was recovered by suction or gravity. Ten millilitres of BAL fluid were sent for bacterial, mycobacterial, and fungal culture and another 10 ml for virus culture. Mouth flora and candida grown from BAL were not regarded as relevant pathogens and therefore not included in the analysis. Cytomegalovirus culture was performed by shell vial assay, spinning BAL onto human embryonic fibroblasts and determining the presence of CMV immediate early antigen by immunofluorescence and CMV DNA by *in situ* hybridization after 1 and 5 days, respectively. Conventional cytology was performed with the remaining fluid amount. Following centrifugation the cell pellet was resuspended in cell culture medium, and

**Number and distribution of micro-organisms found in 91 BAL**

Micro-organism	Number of BAL
Bacteria only	15
Bacteria+CMV	9
Bacteria+Pneumocystis	2
Bacteria+CMV+Pneumocystis	2
Bacteria+CMV+Pneumocystis+HSV	1
Bacteria+adenovirus	1
Pneumocystis only	12
Pneumocystis+CMV	3
Pneumocystis+CMV+ HSV	1
CMV only	8
CMV+EBV	1
<i>Aspergillus fumigatus</i>	1
HSV only	3
RSV only	1
HHV 8 only	1
None	30
Total	91

CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; RSV, respiratory syncytial virus; HHV 8, human herpesvirus 8.

**Table 1**

smears were prepared. Routine staining included Grocott for PC and Papanicolaou. Cell differentiation in BAL is shown as absolute numbers of cells and as percentage of total cell count.

Clinical data, including underlying renal disease, type of transplant, actual symptoms, current antimicrobial and immunosuppressive therapy, were obtained from the patient's charts. The types of changes on chest x-ray were analysed blindly by a radiologist unaware of the BAL result.

Statistical analysis was performed using the chi-square test (degree of freedom=1), and the Mann-Whitney U-test with a level of significance at  $P<0.05$ .

## Results

### Patients

A total of 91 diagnostic bronchoscopies with BAL were performed in 71 renal transplant recipients, among them 47 male and 24 female patients with a median age of 54.5 years (19–74 years) at the time of bronchoscopy. The underlying renal diseases were glomerulonephritis ( $n=19$ ), analgesic nephropathy ( $n=11$ ), diabetic nephropathy ( $n=8$ ), vesicoureteral reflux ( $n=8$ ), polycystic kidney disease

**Number and percentage of different bacteria isolated from a total of 30 BAL**

Micro-organism	Number of BAL	Percentage
<i>Hemophilus influenzae</i>	8	26.7%
<i>Staphylococcus aureus</i>	7	23.3%
<i>Streptococcus pneumoniae</i>	2	6.7%
<i>Enterobacter</i>	2	6.7%
<i>Acinetobacter</i>	1	3.3%
<i>Klebsiella pneumoniae</i>	1	3.3%
<i>Legionella pneumoniae</i>	1	3.3%
<i>Pseudomonas aeruginosa</i>	1	3.3%
<i>Hemophilus</i> + <i>Streptococcus</i>	3	10.0%
<i>Hemophilus</i> + <i>Enterobacter</i>	2	6.7%
<i>Hemophilus</i> + <i>Citrobacter</i>	1	3.3%
<i>Staphylococcus</i> + <i>Serratia marcescens</i>	1	3.3%
Total	30	100%

**Table 2**

( $n=7$ ), IgA nephropathy ( $n=6$ ), hypertensive nephrosclerosis ( $n=3$ ), chronic pyelonephritis ( $n=2$ ), nephrectomy for urothelial carcinoma ( $n=2$ ), Alport syndrome ( $n=2$ ), tuberculosis ( $n=1$ ), interstitial nephritis ( $n=1$ ), and idiopathic renal fibrosis ( $n=1$ ). In 23 cases, the transplanted kidney was from a living donor. Seven patients were recipients of a second, and one patient of a third renal transplant. Median age at transplantation was 53 years (16–71 years). Bronchoscopy was performed at a median of 0.5 years after transplantation (4 days to 16 years). Immunosuppression consisted of tacrolimus ( $n=25$ ), mycophenolate mofetil (MMF;  $n=8$ ), or both ( $n=1$ ) in 34 cases.

### Microbiological findings

An infectious organism was isolated in 63 BAL (69%) (Table 1). Bacteria were present in 30 BAL (33%). *Hemophilus influenzae* was found in 14 BAL, including 6 double infections with other patho-

genic bacteria. Other frequently cultured bacteria were *Staphylococcus aureus* ( $n=8$ ), *Streptococcus pneumoniae* ( $n=5$ ), and *Enterobacter* ( $n=4$ ). Other pathological bacteria cultured from BAL were *Acinetobacter*, *Klebsiella pneumoniae*, *Citrobacter*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Legionella pneumoniae*. For details see Table 2.

*Pneumocystis carinii* was detected in 21 cases (23%). Cytomegalovirus was found in 25 BAL (27%). Other viruses included *Herpes simplex* virus ( $n=5$ ), *Adenovirus*, Epstein-Barr virus, and respiratory syncytial virus ( $n=1$  each). Human herpesvirus 8 DNA was detected in the BAL of a patient with transplant-associated pulmonary Kaposi's sarcoma. *Aspergillus fumigatus* was cultured from the BAL of a patient who died with tracheobronchial aspergillosis 2 weeks after transplantation. In 21 BAL multiple infectious agents were present, mostly multiple infections with CMV ( $n=16$ ). No typical or atypical mycobacteria were found. The percentage of eosinophils was significantly increased in BAL positive for *Pneumocystis* ( $P<0.05$ ), whereas total cell and neutrophil counts were significantly elevated in BAL positive for bacteria ( $P<0.05$ ). For details see Table 3.

### Empirical antimicrobial therapy

In 40% of cases bronchoscopy was performed under concurrent antibiotic treatment. Bronchoalveolar lavage was diagnostic in 26 of 36 BAL (72%) in patients on antibiotic therapy. In 35 of 55 patients (64%) without antimicrobial therapy BAL provided a microbiological diagnosis. This difference was not of statistical significance.

### Clinical presentation and radiological changes

Patients presented with cough ( $n=41$ ), dyspnoea ( $n=26$ ), hemoptysis ( $n=4$ ), chills ( $n=3$ ), and nausea ( $n=5$ ) in 70% of cases (64/91). Six BAL were performed in patients ventilated because of respir-

**Total cell count and cell differentiation in BAL according to microbiological findings (median, range)**

Group	Number of BAL	Total count 10 <sup>6</sup> cells/l	Macrophages		Lymphocytes		Neutrophils		Eosinophils	
			%	10 <sup>6</sup> /l	%	10 <sup>6</sup> /l	%	10 <sup>6</sup> /l	%	10 <sup>6</sup> /l
Bacteria	30	322 (35–6978)	50 (2–95)	144 (8–366)	5 (1–86)	17 (1–488)	26 (0–94)	72 (0–6349)	1 (0–4)	2 (0–12)
Pneumocystis	21	124 (43–455)	51 (6–89)	78 (2–341)	25 (1–94)	38 (1–244)	8 (2–46)	10 (4–203)	1.5 (0–28)	2.6 (0–40)
Cytomegalovirus	25	171 (7–1740)	73 (15–97)	124 (6–783)	6 (1–52)	10 (0–63)	21 (0–82)	22 (0–940)	0 (0–2)	1 (0–4)

**Table 3**

**Comparison of the type of micro-organism and radiological changes on chest x-ray**

Group	Number	Diffuse pattern	Localized infiltrates		No infiltrate
			Unilateral	Bilateral	
Bacteria	30	7% (2)	43% (13)	30% (9)	20% (6)
Pneumocystis	21	5% (1)	43% (9)	28% (6)	24% (5)
Cytomegalovirus	25	0	52% (13)	16% (4)	32% (8)
Other viruses	9	33% (3)	33% (3)	11% (1)	22% (2)
<i>Aspergillus fumigatus</i>	1	0	(1)	0	0
No micro-organism	30	0	60% (18)	17% (5)	23% (7)
Total	91	6% (6)	48% (44)	25% (23)	20% (18)

**Table 4**

atory failure. Fever with a mean duration of 3 days (1–14 days) was present in 69% of cases (63/91) at the time of bronchoscopy. Patients with a BAL positive for bacteria, PC, or CMV developed fever (73% vs. 86% vs. 80%), and other clinical symptoms (74% vs. 67% vs. 56%) in comparable percentages. In 73 cases (80%) the chest x-ray showed new infiltrates, either localised in 74% ( $n=67$ ), or with an interstitial pattern in 6% ( $n=6$ ) (Table 4). Infiltrates were present in 80% of bacterial, 76% of PC, 68% of CMV, and 78% of other viral infections. Unilateral infiltrates were present in bacterial, PC and CMV infections in comparable percentages (43% vs. 52% vs. 43%, respectively). Bilateral infiltrates were found in 30% of bacterial, 28% of PC, and 16% of CMV infections. There was no difference in the distribution of radiological changes concerning the num-

ber of micro-organisms found in BAL (single vs. multiple infectious organisms) (data not shown).

### Immunosuppression

Maintenance immunosuppression consisted of cyclosporin A (CyA) combined with azathioprine and/or prednisone in 57 patients when bronchoscopy was performed. Among them 7 patients had received additional anti-rejection therapy with anti-T-lymphocyte globulin or methylprednisolone pulses (12%). Patients at risk for CMV disease had received ganciclovir prophylaxis if they were treated with anti-T lymphocyte globulin for steroid-resistant rejection. Thirty-four BAL were performed in patients under tacrolimus- or MMF-based immunosuppressive regimens. In 19 of them tacrolimus or MMF had been introduced either because of recurrent rejection ( $n=15$ ) or CyA toxicity ( $n=4$ ). Therefore anti-rejection therapy or enhanced immunosuppression for rejection was initiated in a total of 22 patients before respiratory symptoms developed. The diagnostic yield of BAL was 58% under CyA-based immunosuppression compared with 82% under immunosuppression with tacrolimus or MMF ( $P<0.03$ ). The percentage of PC and CMV infections was significantly higher in the group under immunosuppression with tacrolimus or MMF (35% and 41%), compared to CyA-based immunosuppression (16% and 19%, respectively) ( $P<0.005$ ). Data are shown in Table 5.

### Time course of pulmonary infections

Pulmonary infections with PC were found at a median of 4 months after transplantation (range 2 months to 2 years). Cytomegalovirus was detected at a median of 5 months (1 month to 11 years) post-transplant. Bacterial infections were observed at a median of 19 months (1 month to 11 years), significantly later compared to PC and CMV infections ( $P<0.05$ ).

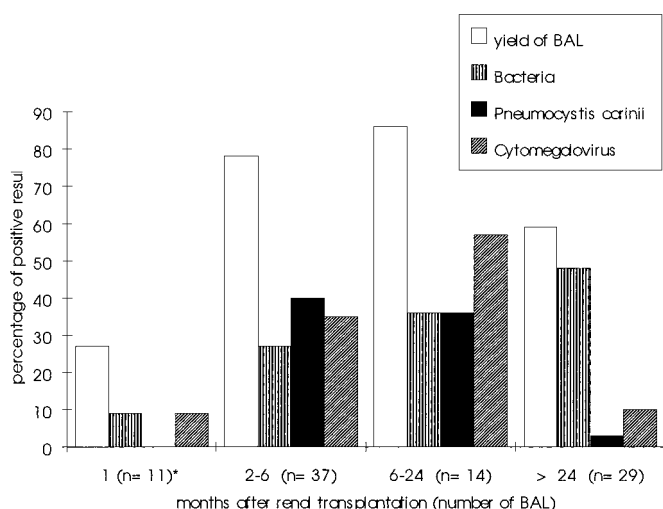
**Comparison of BAL results according to the type of immunosuppression**

Micro-organism	Tacrolimus/MMF	Cyclosporin A
Number of BAL	34	57
Pneumocystis	35% ( $n=12$ ) <sup>a</sup>	16% ( $n=9$ ) <sup>a</sup>
CMV	41% ( $n=14$ ) <sup>a</sup>	19% ( $n=11$ ) <sup>a</sup>
Pneumocystis/CMV <sup>b</sup>	65% ( $n=22$ ) <sup>a</sup>	30% ( $n=17$ ) <sup>a</sup>
Other viruses	2 HSV, 1 Adeno	3 HSV, 1 RSV, 1 HHV8, 1 EBV
Bacteria	44% ( $n=15$ )	26% ( $n=15$ )
<i>Aspergillus</i>	0	1
Positive BAL	76% ( $n=29$ ) <sup>c</sup>	64% ( $n=34$ ) <sup>c</sup>
Multiple infections	32% ( $n=11$ )	17% ( $n=10$ )

MMF, mycophenolate mofetil; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; RSV, respiratory syncytial virus; HHV8, human herpesvirus 8.

<sup>a</sup>  $P<0.005$ , <sup>b</sup> Pneumocystis and/or CMV infection, <sup>c</sup>  $P<0.05$  ( $\chi^2$ -test) comparing tacrolimus/MMF versus cyclosporin A-based immunosuppressive regimens.

**Table 5**



**Fig. 1. Diagnostic yield and microbiological findings in BAL according to the time after renal transplantation.** \* 1 BAL positive for *Aspergillus fumigatus*.

Of 11 bronchoscopies performed within the first month of transplantation only 3 (27%) were diagnostic: one was positive for *Aspergillus fumigatus*, one for respiratory syncytial virus, and another for *Hemophilus influenzae* and CMV.

Between 2 and 6 months after transplantation, the diagnostic yield of BAL was 78% (29 of 37 BAL). *Pneumocystis carinii* was found in 40% ( $n=15$ ), CMV in 35% ( $n=13$ ), and bacteria in 27% ( $n=10$ ) of BAL samples. Two BAL were positive for *Herpes simplex* virus. Within this time period, 18 BAL were performed in patients receiving tacrolimus or MMF (49%).

Between 6 and 24 months after transplantation, 14 BAL were performed. In 86% ( $n=12$ ) a microbiological diagnosis could be made. *Pneumocystis carinii* and bacteria were found in 5 (36%), CMV in 8 (57%), and *Herpes simplex* virus in 2 BAL, respectively. Patients were under immunosuppression with tacrolimus or MMF in 11 cases (78%).

Beyond 24 months after transplantation, BAL was diagnostic in 17 of 29 cases (59%): bacteria were found in 14 BAL (48%), CMV in 3, and other viruses in 4. In one case PC was detected 28 months after transplantation, a patient receiving tacrolimus, azathioprine, and prednisone. Results are shown in Fig. 1.

## Discussion

This study shows a diagnostic yield of BAL of 69% in renal transplant recipients with clinical and radiological signs of pulmonary

infection. While 33% of BAL were positive for bacteria, viruses were found in 36%, most frequently CMV. *Pneumocystis carinii* pneumonia was diagnosed in 23% of cases. In the literature, a comparable incidence of CMV and PC infections in renal transplant recipients has been reported, varying from 22 to 56%, and 10 to 17%, respectively (3, 6, 10, 11). Only a small series by Eriksson et al. found PC in 75% of 17 BAL (12). We observed an increased number of opportunistic infections with PC or CMV in patients treated with tacrolimus or MMF compared to patients receiving immunosuppressive therapy without these agents. However, our patients did not routinely receive prophylaxis against CMV and PC. An increased risk of PC infection in patients treated with tacrolimus has previously been reported (8). Based on the findings of high incidence of PC and CMV respiratory tract infection, these patients should be considered for prophylactic measures. Further factors have to be considered such as an increase in MMF serum concentration when cyclosporin A is switched to tacrolimus associated with a profound immunosuppressive effect.

Detection of CMV in BAL does not prove CMV pneumonitis, especially if other concomitant pathogenic micro-organisms are found. However, if fever, respiratory symptoms and infiltrates develop and CMV can be found in BAL, patients are usually treated with ganciclovir. Cytomegalovirus and PC infection are expected to occur 2–6 months after renal transplantation (5, 10, 13). However, we found a considerable number of these infections later than 6 months after transplantation, predominantly in patients treated with tacrolimus or MMF. The majority of patients has been switched to tacrolimus or MMF because of recurrent rejection. Our results support the statement that prophylaxis against PC and CMV should be prolonged or reintroduced when the immunosuppression is intensified (14). Regarding the increasing use of potent new immunosuppressive agents, the classical time scheme of infectious complications after transplantation should therefore be adapted (4). In patients with respiratory symptoms, PC and CMV infection have to be considered beyond 6 months after transplantation, especially in patients receiving tacrolimus, MMF, or other new immunosuppressive agents. To prevent CMV disease, either prophylaxis can be given or a preemptive approach can be chosen (15).

In our study, clinical symptoms and changes on chest x-ray were not specific for particular infections. Unilateral localised infiltrates on chest x-ray were seen not only in patients with bacterial pneumonia, but also with PC and CMV infection. Surprisingly, CMV infection presented predominantly with localised infiltrates and not with the typical reticular pattern. Literature on the value of clinical and radiological findings identifying the type of pathogens is contradictory (1, 6, 16). In this study, clinical symptoms and chest x-ray were only of limited benefit in the differential diagnosis of pul-



monary infection. Therefore, bronchoscopy with BAL is mandatory for a correct diagnosis in symptomatic transplant recipients irrespective of the radiological pattern.

Total cell and neutrophil counts were higher in BAL of patients with bacterial infections compared with opportunistic pulmonary infections (5, 6). Surprisingly, the percentage of BAL eosinophils was significantly elevated in patients with PC pneumonia, a finding not previously described in organ transplant recipients under im-

munosuppressive therapy. Interestingly blood eosinophilia is also found in patients developing PC pneumonia under immunosuppression with tacrolimus (17).

In summary, bronchoscopy with BAL is an important diagnostic tool in renal transplant recipients with respiratory symptoms, because radiological and clinical signs are not indicative for the type of pulmonary infection. The use of new and potent immunosuppressives is associated with a prolonged risk of infections with PC and CMV.

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