Pulmonary complications in 110 consecutive renal transplant recipients

C. L. Edelstein, J. C. Jacobs, M. R. Moosa

The pulmonary complications in 110 consecutive renal transplant recipients on cyclosporin and low-dose steroid immunosuppression were studied retrospectively. The pulmonary complications were: acute pulmonary oedema in 19 patients, pneumonia in 18, tuberculosis in 9, acute pulmonary embolism in 5, and lung abscess in 1. Sixty-nine patients (62,7%) had no pulmonary complications; 69% of the complications occurred in the first 4 months after the transplant. Pulmonary tuberculosis became evident later. The mean age, period of follow-up, human leucocyte antigen (HLA) B/DR mismatches, mean serum urea and serum creatinine concentrations, systolic and diastolic blood pressures, and cyclosporin dosage did not differ between the groups with no complications, infectious complications and non-infectious complications. The number of rejection episodes treated with bolus steroids was significantly higher in the infectious and non-infectious complications groups compared with the group with no complications.

The incidence of pulmonary complications after renal transplantation, especially pneumonia and tuberculosis, was still high despite the use of low-dose steroids and cyclosporin. Pulmonary complications were the commonest cause of death in the first 3 years after the transplant. A high index of suspicion for pulmonary tuberculosis and pulmonary embolism in these patients is necessary.

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Patient and renal allograft survival at Tygerberg Hospital has improved dramatically over the past decade with the use of cyclosporin A (CyA). Ninety-four per cent of recipients are still alive at 1 year, and graft survival is over 70% for cadaver kidneys.[1]

However, renal transplantation is followed by a variety of complications that may cause significant morbidity and mortality. In a recent 'state of the art' review, pulmonary complications were reported to occur in 18 - 24% and pneumonias in 8 - 16% of renal allograft recipients.[2] The studies reviewed were from the pre-CyA era. We could find only two major studies of pneumonias after renal transplantation in the CyA era.[3,4] It is unknown whether the incidence of pulmonary complications after renal transplantation has changed in the CyA era, and it is controversial whether the incidence of pneumonias has changed.

Tuberculosis is still endemic in the Cape Town area. The incidence of pulmonary tuberculosis after renal transplantation in endemic areas is high.[5] The incidence of pulmonary complications post-renal transplantation in a tuberculosis-endemic area is not known.

The aims of our study were: (*i*) to describe the pulmonary complications in a group of renal transplant patients on CyA and low-dose steroid immunosuppression; and (*ii*) to analyse the factors that influence the development of these pulmonary complications.

Material and methods

One hundred and ten consecutive patients who underwent renal transplantation between October 1988 and November 1991 were studied retrospectively in November 1992.

Follow-up information was recorded either until the patient died, or until the immunosuppression was stopped and dialysis was resumed.

Atelectasis or respiratory depression occurring in the first postoperative week was regarded as an anaesthetic complication and was not included in this study.

Patients received the following immunosuppressive regimen: (*i*) methylprednisolone 500 mg intravenously immediately pre-operatively and on day 1 postoperatively. Methylprednisolone 250 mg intravenously was given on day 2 postoperatively and 125 mg intravenously on day 3 postoperatively; (*ii*) oral methylprednisolone 24 mg per day, irrespective of body mass, was started on day 2 postoperatively. At 1 month postoperatively it was tapered by 4 mg every 2 weeks until a dose of 8 mg was reached; (*iii*) azathioprine 50 mg per day, irrespective of body mass, was started on day 2 postoperatively; (*iv*) CyA 10 mg/kg/day was started immediately pre-operatively and then adjusted to keep whole blood levels between 400 and 600 ng/ml (fluorescent polarisation immunoassay) in the first 6 months and between 200 and 400 ng/ml after 6 months; and (*v*) rejection episodes were treated with an intravenous bolus of methylprednisolone 500 mg followed by 250 mg on 2 further consecutive days.

All patients received prophylactic cefoxitin 1 g intravenously immediately pre-operatively followed by 1 g 8-hourly for three doses postoperatively.

Definitions

1. **Acute pulmonary oedema**: (*i*) fluid overload on clinical examination plus a radiological picture of pulmonary oedema; and (*ii*) clinical or radiological improvement with diuretic therapy, treatment of rejection, or dialysis.

2. **Acute pulmonary embolism**: (*i*) clinical picture compatible with pulmonary embolism, e.g. acute dyspnoea, pleural rub, hypoxia; and (*ii*) a ventilation/perfusion lung scan highly suggestive of pulmonary emboli.

3. **Pneumonia**: (*i*) clinical signs and symptoms, e.g. cough, sputum production, focal area of crepitations, or

Renal Transplant Unit, Department of Internal Medicine, University of Stellenbosch and Tygerberg Hospital, Tygerberg

C. L. Edelstein, M.B. CH.B., M.MED.

J. C. Jacobs, M.B. CH.B., M.MED.

M. R. Moosa, M.B. CH.B., F.C.P. (S.A.)

bronchial breathing; and (*ii*) opacity, consolidation or nodule on chest radiology.

4. **Pulmonary tuberculosis**: (*i*) the presence in sputum, or pleural fluid or tissue of acid-alcohol-fast bacilli; (*ii*) the culture of *Mycobacterium tuberculosis* from sputum or pleural fluid; or (*iii*) the presence of caseating granuloma in lung tissue.

Statistical analysis

Variables between the control group and the infectious and non-infectious groups were analysed by means of the unpaired Student's *t*-test.

Results

Over the 3-year period 110 patients underwent renal transplantation. The mean period of follow-up for the whole group was 632 days (range 1 - 1 487). No patients were lost to follow-up.

Ninety-two per cent of the complications occurred in the first year and of these 69% occurred in the first 4 months post-transplant (Table I).

Table I. Pulmonary complications post-renal transplant

	No.	%	Mean time (days)
No complication	69	62,7	
Infectious complications			
Pneumonia	18	16,3	91
Lung abscess	1	0,9	90
Tuberculosis	9	8,2	297
Non-infectious complications			
Acute pulmonary oedema	19	17,3	85
Pulmonary embolism	5	4,5	116

Some patients had more than one complication.

The actual 1-year graft survival rate of the whole group was 71%. The 1-year patient survival rate was 93,7%. Pulmonary complications were the commonest cause of death in the 3-year period (Table II).

Eighteen patients (16%) developed 22 episodes of pneumonia at a mean time of 91 days post-transplant (Table III).

Pulmonary tuberculosis developed in 9 patients (8,2%) at a mean time of 150 days post-transplant (Table IV). Two out of the 9 patients died of pulmonary tuberculosis.

Table II. Deaths post-renal transplant

Patient	Time (days)	Cause of death
1st year		
1	1	Surgical
2	4	Myocardial infarct
3	43	Pulmonary embolism
4	55	Myocardial infarct
5	60	Gastro-intestinal bleeding
6	144	Pulmonary embolism
7	201	Pulmonary tuberculosis
2nd year		
8	400	Unknown
9	540	Stroke
10	690	Pulmonary tuberculosis
3rd year		
11	930	Bacterial septicaemia

Table III. Pneumonia post-renal transplant

Patient	Time (days)	Lobe	Sputum culture	Anti-biotics	Outcome
1 (H)	28	RLL	-	P, A	Cured
2 (H)	58	RLL	-	C, Clox	Cured
3 (H)	5	RLL	*S. aureus*	C	Cured
(H)	21	RLL	-	CTZ	Cured
(C)	120	LLL	*N. meningitidis*		Cured
4 (H)	7	LLL	-	CEF	Cured
5 (H)	31	LLL	-	CTX	Cured
6 (H)	30	RUL		CTX	Recurred
(C)	60	Unknown	*S. aureus*	A, Cip, Clox	Cured
7 (C)	60	3 Lobe	*K. pneumoniae*	A, CEF, Clox	Cured
8 (H)	2	LLL		CEF, Co	Cured
9 (C)	90	RUL	-		Cured
10 (C)	240	LUL	*H. influenzae* *S. faecalis*	C	Cured
(C)	660	RUL	-	A, CEF	Cured
11 (H)	7	RLL	-	CTX	Cured
12 (H)	6	RLL	-	CTX	Cured
13 (C)	350	RLL	*P. aeruginosa* *S. pneumoniae*	CTZ	Cured
14 (H)	4	RLL	*E. coli*	C	Prolonged
15 (C)	134	3 Lobe	*E. coli*	CEF, Clox	Cured
16 (C)	124	RML, RLL	-	A, P	Cured
17 (H)	7	Unknown	*S. pneumoniae*	C	Cured
18 (H)	60	RLL	-	C, Gen, Clox	Cured

P = piperacillin, A = amikacin, Gen = gentamicin, Clox = cloxacillin, C = cefoxitin, CTZ = ceftazidime, CTX = ceftriaxone, CEF = cefotaxime, Cip = ciprofloxacin, Co = co-trimoxazole; (H) = hospital acquired, (C) = community acquired; RLL, RML, RUL = right lower, middle, upper lobe; LLL, LUL = left lower, upper lobe.

Table IV. Pulmonary tuberculosis post-renal transplant

Patient	Complication	Microbiology	Time (days)	Outcome
1	Effusion	Pleural biopsy: (+)AFB and granulomas	210	Cured
	Bronchopneumonia	Postmortem (+)ZN	690	Died
2	Nodule	(+)tuberculosis culture	270	Cured
4	Nodule	ZN(–), (+)tuberculosis culture	180	Cured
5	Bronchopneumonia	(+)tuberculosis culture	90	Cured
6	Miliary tuberculosis	(+)bone marrow granulomas (–)ZN	120	Graft loss
7	Bronchopneumonia	Post mortem (+)ZN	150	Died
8	Bronchopneumonia	(+)ZN	150	Cured
9	Pleural effusion	(+)ZN	90	Graft loss

ZN = Ziehl-Neelsen staining.

The commonest cause of acute pulmonary oedema post-renal transplant was acute renal allograft rejection (Table V).

Table V. Acute pulmonary oedema post-renal transplant

Cause	Patients	%	Mean time (days)
Acute rejection	9	47	56
Non-function of graft	3	16	5
Unknown	3	16	32
Chronic rejection	2	10,5	435
Cardiac	2	10,5	92

Five patients developed pulmonary embolism post-renal transplant (Table VI). One case was diagnosed only at post-mortem, and in 2 cases it was thought to be the cause of death.

Table VI. Acute pulmonary embolism post-renal transplant

Patient	Time (days)	Diagnosis	Outcome
1	390	Lung scan	Alive
2	60	Lung scan	Alive
3	43	Postmortem	Died
4	84	Lung scan	Died
5	6	Lung scan	Alive

The number of rejection episodes, treated with high-dose bolus steroids in the first year, was significantly higher in both the infectious and non-infectious complications groups compared with the control group without complications (Table VII).

Table VII. Pulmonary complications in the three groups

	No complication	Infectious complication	Non-infectious complication
M/F	1,6:1	1,5:1	1,3:1
Age (yrs)	37	39	37
Follow-up (days)	656	615	573
B/DR HLA mismatches	2,8	2,6	2,6
Rejection episodes	1,7	2,56*	2,52†
Mean urea (mmol/l)	15,7	15,7	19
Mean creatinine (μmol/l)	322	235	354
Mean SBP (mmHg)	144	146	147
Mean DBP (mmHg)	87	88	86
Mean CyA dose (mg/kg)	5,9	5,2	6,2

*P-value = 0,02.
†P-value = 0,026.
Mean values = mean of 1st year.
SBP/DBP = systolic/diastolic blood pressure.

Monthly income and unemployment rates at the time of assessment for the renal replacement programme were used as crude objective parameters of socio-economic status. The mean monthly income (R) and unemployment status (% of the total patients) was R630 and 29% in the group without pulmonary complications, R694 and 18% in the infectious pulmonary complications group, and R703 and 0% in the non-infectious pulmonary complications group.

Discussion

A recent 'state of the art' review of pulmonary complications after transplantation quotes an 18 - 24% incidence of pulmonary complications and an 8 - 16% incidence of pneumonias after renal transplantation.[2] The studies reviewed were from the pre-CyA era when very high doses of steroids were used and it is unknown whether the incidence of pulmonary complications has changed in the CyA, low-dose steroid era.[6-9] There have only been two studies of pulmonary infections in the CyA era.[3,4] The Minnesota randomised prospective trial of CyA versus azathioprine/antilymphocyte globulin for immunosuppression in renal allograft recipients[3] found that the CyA group had fewer pneumonia episodes than the azathioprine antilymphocyte globulin-treated group (3,7% v. 9,2%). However, the Canadian Multicentre Transplant Study Group[4] found that pneumonia occurred equally in the CyA and conventionally treated groups (6% in both groups). We found pulmonary complications in 37% of our renal transplant patients and pneumonias in 16,3%. Although our patients received CyA and low-dose steroids the incidence of pulmonary complications is high and comparable with studies from the pre-CyA era. The infectious and non-infectious complications groups did not have lower monthly incomes or higher unemployment rates than the control group.

The high incidence of pulmonary tuberculosis in our renal transplant patients is disturbing, although not surprising as tuberculosis is still endemic in the Cape Town area. This high incidence of tuberculosis was present despite the fact that transplant patients with either a previous history of tuberculosis or any old scarring on chest radiographs are prescribed prophylactic isoniazid. Four out of the 9 patients with tuberculosis either died or lost their grafts. Pulmonary tuberculosis therefore remains an important problem in renal transplant recipients in developing countries, especially in endemic areas.[5]

Positive microbiological culture was obtained in less than 50% of the episodes of pneumonia. However, all patients responded to the second- or third-generation cephalosporin in combination with either an aminoglycoside or cloxacillin or both. Bronchoscopies were not routinely done, and no patients developed *Pneumocystis carinii* pneumonia, CMV pneumonia or fungal pneumonia. However, pulmonary tuberculosis took the form of a bronchopneumonia in 5 patients, and was first diagnosed at postmortem examination in 2 cases.

Although the incidence of pulmonary embolism is much reduced in uraemia, renal transplantation re-establishes the risk.[2] Improved surgical technique and earlier postoperative mobilisation have reduced the risk of pulmonary embolism after renal transplantation.[10] Superinfection in infarcted lung is well described,[8] and occurred in 1 of our patients who developed a lung abscess in an area of infarcted lung.

Pulmonary disease has been described as the most important single cause of mortality after renal transplantation.[2] This was confirmed in our study in the first 3 years post-transplant. However, pulmonary tuberculosis and pulmonary embolism as opposed to pneumonia were the commonest causes of death. It should be noted that 2

cases of pulmonary tuberculosis and 1 case of pulmonary embolism were first diagnosed at postmortem examination, suggesting that one should have a high index of suspicion for these conditions post-renal transplant.

The patients with no pulmonary complications had fewer rejection episodes. The increased amount of bolus steroid therapy in the infectious complications group may have contributed to the increased incidence of pulmonary infections in this group. Acute allograft rejection treated with bolus steroids was the commonest cause of acute pulmonary oedema in the non-infectious group. This may account for the fact that the non-infectious group received more bolus steroids than the control groups.

Conclusions

Our incidence of pulmonary complications after renal transplantation, especially pneumonia and tuberculosis, is still high, despite the use of low-dose steroids and CyA. Most of these complications occurred in the first year after the transplant. Pulmonary complications, especially pulmonary tuberculosis and pulmonary embolism, contributed significantly to the mortality of our renal allograft recipients.

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