Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

An aggressive systematic strategy for acute respiratory distress syndrome caused by severe pneumonia after renal transplantation

Qiquan Sun, Zhi-Hong Liu, Jinsong Chen, Shuming Ji, Zheng Tang, Zhen Cheng, Daxi Ji and Lei-Shi Li

Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China

Keywords
acute respiratory distress syndrome, continuous renal replacement treatment, immune function, kidney transplantation, pneumonia.

Correspondence
Lei-Shi Li MD, Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, 305 East Zhong Shan Road, Nanjing 210002, China.
Tel.: 86 25 86069034; fax: 86 25 84801992;
e-mail: sunqiquan@yahoo.com

Received: 5 August 2005
Revision requested: 28 August 2005
Accepted: 4 November 2005

doi:10.1111/j.1432-2277.2005.00245.x

Summary

Acute respiratory distress syndrome (ARDS) caused by pneumonia after renal transplantation was usually associated with overimmunosuppression and high mortality rate. We evaluated the efficacy of an aggressive systemic protocol including strategies improving body's immune function. Twenty-one recipients were enrolled in this study. Patients were subjected to a protocol including (i) withdrawal of most immunosuppressants, (ii) early use of immunoenhancers and continuous renal replacement therapy (CRRT), (iii) reasonable administration of antibiotic regimen, (iv) prompt mechanical ventilating strategy, and (v) adequate nutrition. Immunosuppressants were adjusted according to the value of CD4+, CD8+T lymphocytes in peripheral blood. CRRT was conducted at once when patients were admitted to the intensive care unit (ICU), regardless the graft function. Thirteen (62%) survived and eight died finally. This is a high survival rate for this kind of patients. Eighteen patients had received thymosin treatment. All patients who survived experienced renal allograft dysfunction during CRRT, but when CRRT stopped, the function of all grafts gradually recovered. No acute rejection episodes were documented during the treatment. The aggressive systemic protocol including strategies improving the body's immune function and CRRT can improve the outcome of patients with ARDS after renal transplantation. The count of CD4+, CD8+T lymphocytes of peripheral blood is useful in the adjustment of immunosuppressants and the prediction of patient outcome.

Introduction

Organ transplantation is becoming more and more popular for patients with end-stage organ failure, especially for renal transplantation, which has come to be the preferred renal replacement therapy by most patients. Although acute rejection post-transplantation has been significantly reduced by the emerging new aggressive immunosuppressants, pneumonia remains one of the most important complications after organ transplantation [1–4]. Once acute respiratory distress syndrome (ARDS) develops, the mortality is very high. The 28-day mortality rate in subjects with ARDS as a primary diagnosis was 52.1% [5]. The mortality rate is nearly 100% [6–8] in patients on ventilation.

The use of immunosuppressants in transplantation recipients is a double-edged sword. There is no doubt that the development of pneumonia post-transplantation is associated with the overuse of immunosuppressants. We [9] found that once ARDS occurred, the blood CD4+, CD8+ T lymphocyte count decrease significantly, and the recovery of the disease actually meets the recovery course of the body's immune system. Therefore, strategies that can improve the body's immune function may

also help to improve the patient's outcome. Based on this, we developed a systematic aggressive protocol for renal allograft recipients with ARDS caused by severe pneumonia.

Continuous renal replacement treatment (CRRT) has been widely used in the management of critically ill patients, even in patients without renal failure [10,11]. It is reported that CRRT may improve PaO_2/FiO_2 in patients with ARDS [12]. Recently, the immunomodulating function of CRRT was documented [13–15]. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy [16]. In our unit, CRRT has been used in the rescue of critically ill patients for 10 years, and it has also been included in our protocol strategy for ARDS.

Materials and methods

Patients

Four hundred and eighty six cadaveric renal allograft recipients transplanted between January 2001 and April 2005 in Jingling Hospital, Nanjing University were enrolled in this study. All the kidney transplants were performed in recipients with negative pre-transplant crossmatches using standard serological techniques, and later, flow cytometry. The transplant operation was performed in a standard fashion as previously described. Among the patients, 21 were diagnosed as having ARDS caused by severe pneumonia. An aggressive systematic rescue protocol was adopted for the 21 patients. The diagnosis of severe pneumonia was based on: (i) clinical signs of infection such as fever, malaise, asthenia, etc., (ii) hypoxia and infiltrate on the chest X-ray, and (iii) needing hospitalization. ARDS was diagnosed according to the criteria of the American-European Consensus Conference [17]. The research meets the ethical guidelines, including the legal requirements of China. Informed consent was obtained from all patients who underwent the study procedures, and the Human Subjects Committee of Jinling Hospital, Nanjing University School of Medicine approved all study protocols.

Initial immunosuppression

Twelve of the 21 recipients received a primary immunosuppression consisting of cyclosporin A (CsA) plus mycophenolatae mofetil (MMF) plus steroids; nine were treated with tacrolimus plus MMF plus steroids, and among them four recipients also had received two-dose daclizumab (zanapax) induction. The initial dose of MMF was 1.5 g/day, dose of tacrolimus and CsA was adjusted to trough levels (tacrolimus, 8–15 ng/ml during the first half of the year and 5–10 ng/ml during the second half of the year; CsA, 200–300 ng/ml during the first half of the year and 150–250 ng/ml during the second half of the year), A standard corticosteroid tapering regimen was used, consisting of an intravenous bolus of methylprednisolone 500 mg on day 0–day 2, followed by oral prednisone 80 mg/day on day 3, and the dose was tapered from 10 mg/day to 20 mg/day, and then tapered slowly to 5 mg/day thereafter. Once the rejection episode occurred, bolus corticosteroid therapy was selected as the first-line treatment. All the initially prescribed CsA were converted to tacrolimus when diagnosed as acute rejection after 1998.

Rescue strategies

To improve the outcome of ARDS in renal allograft recipients, we developed an aggressive systematic strategy based on rebuilding of patients' immune function. Once patients were admitted to the ICU for ARDS, the following treatments were adopted: (i) withdraw most of the immunosuppressants, leaving only 5 mg prednisolone per day; (ii) monitor the variation of peripheral blood CD4+, CD8+ T lymphocyte count. Once the CD4+ T cell count was below 200/μl, Thymosin was prescribed; if CD4+ T cell count grew to over 600/μl, immunosuppressants were added from low-dose CsA (4 mg/kg/day) or tacrolimus (0.06 mg/kg/day), and MMF (1.0/day) was added 3 days later. All these immunosuppressants should be added gradually to the normal dose in 2 weeks; (iii) include antimicrobial agents against cytomegalovirus (CMV) (ganciclovir) and bacteria (sulbactam/cefoperazon, Sulperazon; Pfizer Inc, Dalian, China, 4–8 g/day) when diagnosed as severe pneumonia. Ganciclovir was used until the serum CMV-DNA turned negative for more than 1 week. If there was evidence of mildew, fluconazol was added; (iv) all patients were mechanically ventilated, in the mode of synchronized intermittend mandatory ventilation (SIMV) + positive end-expiratory pressure (PEEP), and a lung-protective ventilation strategy with small tidal volume (6–8 ml/kg), and limited plateau pressure (<30 cmH_2O) was adopted in all the patients; (v) continuous renal replacement therapy (CRRT) was conducted at once when the patient was admitted to the ICU, even when the graft function was still normal. (vi) Sputum microbiology as well as blood bacteriologic, viral, and fungal standard cultures were performed every 2 or 3 days. Appropriate antibiotics were adjusted according to the results of the microbiology studies. Pulmonary changes were monitored with chest X-rays. (vii) As most patients had anorexia, nutritional support must be strengthened, energy of 35–40 Cal/kg/day should be guaranteed; early enteral feeding was regarded as preferred delivery

routes. A kind of enteral nutrition (Pepti-2000 Variant; Nutricia, Zoetermeer, The Netherlands) was used.

Technical aspects of CRRT

Continous veno-venous hemofiltration (CVVH) with predilution replacement solution at various flow rates ranging from 4000 to 6000 ml/h was adopted in all patients. The CVVH treatment was sustained for at least 72 h using BM25 machines (Baxter Deutschland GmbH, Unterschleissheim, Deutschland). A dual lumen central venous catheter was usually inserted into the internal jugular vein to establish vascular access. An AN69 hemofilter (HOSPAL Industrie, Meyzieu, France) (1.2 m^2) was used and was changed every 24 h or changed whenever a clotting episode occurred. Low-molecular-weight heparin was used as anticoagulant; the dose was adjusted to maintain an activated coagulation time of 160 ± 180 s. The replacement solution used was composed of sodium natrium (140 mmol/l), potassium (2–5 mmol/l), chloride (100–110 mmol/l), bicarbonate (0–24 mmol/l), glucose (11.1 mmol/l) and citrate (7–13.3 mmol/l). The concentration of citrate was adjusted according to the flow rate of replacement solution and blood, and bicarbonate was added to increase the base concentration to 40 mmol/l. In our unit, the CRRT program was performed by a group of skilled nurses and physicians specialized in CRRT. We used Sulperazon 4–8 g/day in most conditions. As most patients experienced decrease of urine volume during CRRT, and CRRT only slightly reduced the half-life of Sulperazon, we did not adjust the dose when patients received CRRT treatment.

T-lymphocyte analysis

Blood samples were drawn from the patients at 6:00 AM on the day of admission to the ICU as ARDS (day 0), day 5, day 10, day 15 post-admission and the day before discharge. T-lymphocyte subsets were analyzed by using an Epics-XL Flow Cytometry (C Beckman, Coulter Inc., Miami, FL, USA). Peripheral blood lymphocytes were exposed to a saturation of concentration of monoclonal antibodies for 15 min at room temperature. Anti-CD4, -CD8 monoclonal antibodies conjugated with fluorescein isothiocyanate and phycoerythrin were purchased from Immunoteck (Marseille, France). Immunoteck control reagent was used as a negative control. We analyzed blood samples from 58 healthy adults, and the normal range of CD4+ was 650 ± 180/μl, CD8+ was 484 ± 137/μl, CD4+/CD8+ was 1.5–2.0.

Statistical analysis

Data are expressed as mean ± SD, Analyses were performed with SPSS 9.0. Student's *t*-test and chi-square test were used as appropriate. $P < 0.05$ was considered to be statistically significant.

Table 1. Patient demographics on admission and clinical course.

Case	Sex/age	Onset of infection (days post-operation)	PaO_2/FiO_2	SAPSII	ALI score	Duration of CRRT (days)	Duration of mechanical ventilation (days)	Survival
1	M/48	83	110	49	3	20	20	Yes
2	F/49	68	116	45	3	13	7	Yes
3	M/23	92	113	38	3	4	7	Yes
4	F/51	69	100	45	3.5	22	20	Yes
5	F/51	78	97	51	3.3	12	11	No
6	M/49	102	113	45	3	21	9	Yes
7	M/44	66	107	53	3.5	21	20	No
8	M/46	70	92	55	4	9	4	No
9	M/45	72	120	47	4	15	14	No
10	F/53	66	103	51	3.5	16	12	Yes
11	M/48	67	108	47	3.5	13	13	No
12	M/38	77	152	42	3	7	3	Yes
13	F/30	95	115	47	3.5	17	9	Yes
14	F/43	75	95	53	4	22	18	No
15	M/54	69	80	59	4	9	8	No
16	F/36	73	130	42	2.5	6	3	Yes
17	F/39	81	117	45	3	22	13	Yes
18	M/53	59	110	49	3.5	10	9	Yes
19	M/39	89	115	47	3.5	14	6	Yes
20	F/54	75	92	55	4	7	7	No
21	F/42	80	133	47	3.5	14	8	Yes

SAPSII, new simplified acute physiology score; ALI, acute lung injury; CRRT, continuous renal replacement treatment/therapy.

Journal compilation © 2006 European Society for Organ Transplantation **19** (2006) 110–116

Results

All 21 patients who received our aggressive systematic rescue protocol met the criteria of ARDS and needed mechanical ventilation. The characteristics of the 21 patients are detailed in Table 1. Eighteen episodes happened in the second or third month post-transplantation, only three happened thereafter. No patient had received CMV prophylaxis therapy before. Ten patients had experienced acute rejection episodes and received bolus corticosteroid therapy. All patients had fever at first, usually accompanied by dry cough and dyspnea. Chest X-ray examination (Fig. 1) showed interstitial pneumonia, which developing rapidly. Microbiologic examinations showed that CMV was responsible for 43% of these episodes, bacteria for 33%, and fungi for 5% (Table 2). Peripheral blood CD4+, CD8+ T-cell counts were routinely monitored. Eighteen of the 21 patients received thymosin because their CD4+ T-cell counts were below 200/μl. Among the 21 patients, 13 survived and the remaining eight patients died during the treatment. The survival rate was 61.9%. All 13 patients who survived experienced renal allograft dysfunction (reflected by a decrease in the level of urine volume and a rise in the level of serum creatinine) during the course of CRRT, but when CRRT stopped, the functioning of grafts gradually recovered and immunosuppressants were added when CD4+ T cells in peripheral blood grew up to 600/μl, none of them returned to dialysis. Despite the aggressive reduction of immunosuppressive therapy, no acute rejection episodes were documented in this patient population during the treatment of pneumonia. Twelve of the 13 patients who survived had normal graft function after 5–36 months

Table 2. Finding of microbiologic examination.

CMV	9 (42.85%)
Bacteria	7 (33.33%)
Fungi	1 (4.76%)
Unknown	4 (19.05%)

CMV, cytomegalovirus.

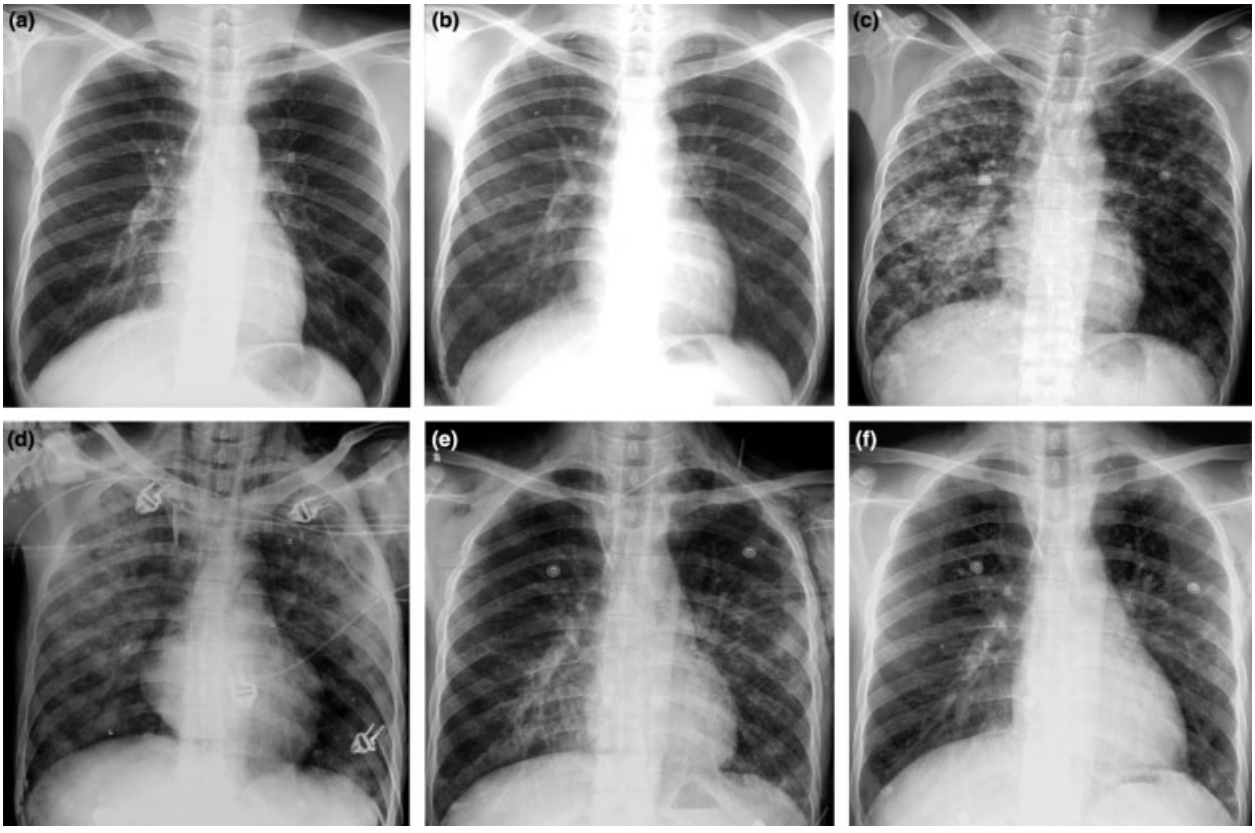

Figure 1 X-ray manifestations during the course of acute respiratory distress syndrome. Picture (a) was taken a month before admission; the patient visited the hospital for 2 days of fever 3 months after renal transplantation (b); three days later, X-ray suggested that severe pneumonia developed (c), and the patient was admitted to the intensive care unit, he was subjected to our rescue protocol immediately, including mechanical ventilation and continuous renal replacement therapy, (d) was taken 2 days after admission; 7 days after admission, the X-ray manifestation was significantly improved and the patient was successfully extubated (e); and (f) was taken 4 days thereafter.

Table 3. The clinical course of ARDS.

	Pre-infection	On admission	Day 5	Day 10	Day 15	Before discharge
Survival group						
Patients survived	13	13	13	13	13	13
PO_2/FO_2	–	117.5 ± 13.8††	238.7 ± 94.1 §	266.9 ± 91.0‡	332.6 ± 64.7**§§§‡‡	NT
SAPS	–	45.5 ± 3.5††	43.1 ± 4.1††	41.6 ± 3.7††§	38.4 ± 2.4††§¶‡‡	NT
ALI score	–	3.2 ± 0.3††	3.1 ± 0.3††	3.0 ± 0.3††	2.6 ± 0.1††§§§‡‡	NT
CD4+	812 ± 325	335 ± 198†	505 ± 210*††	589 ± 273§††	688 ± 326§††	987.5 ± 576‡¶
CD8+	429 ± 221	212 ± 98†	258 ± 67†**	339 ± 83*§††	362 ± 169§**	458 ± 249‡¶
Ratio	1.8 ± 0.6	1.7 ± 0.9	2.0 ± 0.7	1.9 ± 0.7	2.1 ± 0.7	2.4 ± 0.9
Non-survival group						
Patients survived	8	8	8	5	2	0
PO_2/FO_2	–	98.9 ± 12.3	211.3 ± 77.4§	179.8 ± 80.0‡	130.5 ± 78.5	–
SAPS II	–	52.5 ± 4.1	52.0 ± 4.5	55.8 ± 2.9	57.5 ± 0.7	–
ALI score	–	3.8 ± 0.3 g	3.7 ± 0.4	4.1 ± 0.5	4.0 ± 0.0	–
CD4+	764 ± 273	249 ± 146†	185 ± 175†	230 ± 88†	128 ± 32	–
CD8+	533 ± 289	234 ± 198*	134 ± 143†	162 ± 79*	103 ± 34	–
Ratio	1.7 ± 0.7	1.2 ± 0.4	1.4 ± 0.3	1.5 ± 0.3	1.3 ± 0.1	–

ARDS, acute respiratory distress syndrome; NT, not tested; SAPS, simplified acute physiology score; AL1, acute lung injury.
*$P < 0.05$ versus pre-infection.
†$P < 0.01$ versus pre-infection.
‡$P < 0.05$ versus on admission.
§$P < 0.01$ versus d0.
¶$P < 0.05$ versus d5.
**$P < 0.05$ versus non-survival group.
††$P < 0.01$ versus non-survival group.
‡‡$P < 0.05$ versus d10.
§§$P < 0.01$ versus d5.

follow-up; only one patient developed biopsy-proven chronic rejection 31 months after the transplantation (28 months after the ARDS episode).

Compared with pre-infection, the CD4+, CD8+ T lymphocytes decreased very significantly in all the patients when admitted to the ICU ($P < 0.01$), and the ratio of CD4+/CD8+ was also significantly decreased ($P < 0.05$). After admission, all patients underwent our aggressive systemic rescue protocol. In the survival group, the counts of CD4+ lymphocytes kept increasing thereafter. After 10 days of treatment, the CD4+ cell count was significantly higher than that examined on the day of admission ($P < 0.05$). CD8+ cell count exhibited a similar property, but it was not the case for CD4+ T cells. The change in CD4+ lymphocytes was more obvious, resulting in an increasing CD4+/CD8+ ratio. At the same time, the PO_2/FiO_2, new simplified acute physiology score (SAPSII), and acute lung injury (ALI) score were also improved. After 15 days of treatment, the PO_2/FiO_2, SAPS score, and ALI score were significantly improved compared with on admission and the variation were all of statistical significance. On the contrary, in patients in the non-survival group, the counts of CD4+, CD8+ lymphocytes stayed at a low degree, although PO_2/FiO_2 was significantly improved after 5 days of CRRT, and the SAPS and ALI scores were also improved (Table 3).

Discussion

Acute respiratory distress syndrome is associated with mortality rates above 50% in the normal population in most reports [18]. In organ transplantation recipients, the rate is even higher, and a mortality rate of nearly 100% has been documented. ARDS caused by severe pneumonia has turned out to be the major cause of short-term mortality after organ transplantation. We developed an aggressive systematic protocol for this kind of patients including rebuilding the body's immune function. With this protocol, the mortality rate was reduced to <40%.

Management of immunosuppressants after organ transplantation is an art. It is not easy to make a balance between rejection and infection. Previously [9], we found that the number of CD4+, CD8+ T cells significantly decreased when ARDS occurred, which reflected a collapse of the body's immune system, and the variation of CD4+, CD8+ T cell count is a good predictor of patient outcome. The recovery of ARDS in renal allograft recipients was associated with the recovery of the body's

immune ability. We stopped most immunosuppressants during the patients' stay in the ICU, but none of them experienced rejection episodes, and this also reflected a serious immune deficiency status when ARDS developed. Therefore, we think that strategies that can help to rebuild the patient's immune ability may help to improve patient outcome.

Thymosin is regarded as a kind of immunoenhancer which can augment T-cell function [19,20]. It is suggested that TA1 affects thymocytes either by stimulating their differentiation from pluripotent stem cells or by converting them to active T cells [21]. *In vitro* studies suggest that thymosin can increase the ability of T-cell differentiation and maturation; an increase in circulating CD4+, CD8+, and CD3+ cell count was also observed. Immunosuppressed animals administered TA1 experienced a cytoprotective effect that increased survival time and number of survivors [22]. Thymosin (Zadaxin; SciClone Pharmaceuticals, San Mateo, CA, USA) was administered as a kind of immunoenhancer in our protocol.

In this cohort, the variation in CD4+ and CD8+ T cell count was monitored, and was used as an indicator to evaluate the efficiency of the ongoing treatment methods. Immunosuppressants and immunoenhancers were also adjusted according to this indicator. If the levels of CD4+ or CD8+ cells decrease or are maintained at a low degree, more efficient methods need to be considered. On admission of each patient, we stopped most of the immunosuppressants and only excluded low-dose prednisolone. Thymosin was prescribed once the CD4+ T cell count was below 200/ul; if the CD4+ T cell count grew to over 600/ul, immunosuppressants were added from low-dose CsA (4 mg/kg/day) or tacrolimus (0.06 mg/kg/day), and MMF (1.0/day) was added 3 days later. All these immunosuppressants should be added gradually to the normal dose in 2 weeks. None of the patients experienced rejection episodes during their stay in the ICU.

We used CRRT in every patient for no less than 3 days once ARDS developed. The high survival rate of this group may also be associated with the use of CRRT. CRRT had been reported to improve PaO_2/FiO_2 in patients with ARDS. Recently, the immunomodulation function of high volume hemofiltration had turned out to be a hot topic [13–15]. We found that in patients with systemic inflammatory response syndrome (SIRS), CRRT could remove serum systemic inflammatory mediators such as tumor necrosis factor-α, interleukin-6 by convection and absorption [23], and it is well known that these cytokines play important roles in the course of ARDS. Moreover, we also found that CRRT could improve the function of monocytes [24], and might contribute to the recovery of the body's immune function. CRRT is also very helpful in the precise management of fluids. It has been reported that fluid restriction was related to a better outcome of ARDS. In our experience, if the blood pressure can be maintained stably at 110/70 mmHg, negative fluid balance may improve PaO_2/FiO_2 and chest X-ray changes, and reduce the duration of mechanical ventilation. However over fluid deficiency may cause organ failure, such as those of the heart, renal allograft, liver, etc., which in turn may increase the mortality of ARDS. Finally, CRRT may help to control body temperature, and reduce additional oxygen demand caused by fever. CRRT must be managed carefully because of its high precision and complex nature. In our unit, a group of skilled nurses and physicians specialized in CRRT guaranteed an excellent result for the CRRT program. However, the high costs of CRRT limit the extent of its use. A large randomized trial is needed to show a clear benefit.

It was reported that bronchoalveolar lavage (BAL) was useful for early microbiological diagnosis [25]. But when ARDS occurred, in our opinion, few patients could bear BAL examination; it is not rare (19.05% in our study) that microbiological evidence cannot be found out. In this series, CMV was the most frequently detected pathogenic microorganism, followed by bacteria. Pneumocystic carinii pneumonia (PCP) infection is very popular after renal transplantation, but it was not detected in this cohort. So we developed a standard anti-infection strategy. Anti-microbial agents against CMV (ganciclovir), PCP (SMZ) and bacteria (Sulperazon; Pfizer) were included when patients were diagnosed with severe pneumonia, ganciclovir was used until the serum CMV-DNA turned negative for more than 1 week. If there was evidence of mildew, fluconazol was added. As many drugs may cause liver damage, liver-protecting agents should be used routinely.

For a critical syndrome with very poor outcome, a systematic treatment must be strengthened, including strategies to improve the body's immune function, reasonable administration of antibiotic regimens, prompt mechanical ventilating strategy, adequate nutrition, and exact management of fluid. Each portion of this systematic protocol is very important and indispensable. A slight fault in this course may cause serious complication, which can affect the patient's outcome.

As reported [9], the variation of peripheral blood CD4, CD8 count can reflect the body's immune function to some degree, and can be regarded as a predictor of patient outcome. From this study, it is clear that the variation of peripheral blood CD4, CD8 count meet the variation of SAPS and ALI score (Table 2). Therefore, we suggest that during the treatment of ARDS, peripheral blood CD4, CD8 count should be regularly detected, and should be used as an indicator to adjust the use of immunosuppressants and immunoenhancers.

In conclusion, the recovery of ARDS after renal transplantation is actually associated with the recovery of the body's immune function. Early use of immunoenhancers and CRRT may improve the outcome. A systematic treatment must be strengthened, and other treatments involved in our protocol strategy such as reasonable administration of antibiotic regimen, prompt mechanical ventilating strategy, and adequate nutrition are of equal importance. In conclusion, our aggressive systematic protocol based on rebuilding the body's immune function may improve the outcome of ARDS after renal transplantation.

Acknowledgement

We thank Professor Zongjun Zhong from the Department of Radiology for the figure preparation.

References

1. Kasiske BL, Vazquez MA, Harmon WE, *et al.* Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. *J Am Soc Nephrol* 2000; **11**(Suppl. 15): S1.
2. Pazik J, Durlik M, Lewandowska D, *et al.* Pneumonia in kidney allograft recipients. *Transplant Proc* 2003; **35**: 2202.
3. Chang GC, Wu CL, Pan SH, *et al.* The diagnosis of pneumonia in renal transplant recipients using invasive and noninvasive procedures. *Chest* 2004; **125**: 541.
4. Li GS, Ye QF, Xia SS, *et al.* Acute respiratory distress syndrome after liver transplantation: etiology, prevention and management. *Hepatobiliary Pancreat Dis Int* 2002; **1**: 330.
5. Shorr AF, Abbott KC, Agadoa LY, *et al.* Acute respiratory distress syndrome after kidney transplantation: epidemiology, risk factors, and outcomes. *Crit Care Med* 2003; **31**: 1325.
6. Morris DJ. Opportunities for diagnosing cytomegalovirus in pulmonary infections. *Thorax* 1995; **50**: 3.
7. Von Willebrand E, Pettersson E, Ahoner J, *et al.* CMV infection, class II antigen expression and human kidney allograft rejection. *Transplantation* 1986; **42**: 364.
8. Capulong MG, Mendoza M, Chavez J. Cytomegalovirus pneumonia in renal transplant patients. *Transplant Proc* 1998; **30**: 3151.
9. Sun Q, Li L, Ji S, *et al.* Variation of CD4+ and CD8+ T lymphocytes as predictor of outcome in renal allograft recipients who developed acute respiratory distress syndrome caused by cytomegalovirus pneumonia. *Transplant Proc* 2005; **37**: 2118.
10. Ponikvar R. Blood purification in the intensive care unit. *Nephrol Dial Transplant* 2003; **18**(Suppl. 5): v63.
11. van Bommel EF. Should continuous renal replacement therapy be used for 'non-renal' indications in critically ill patients with shock? *Resuscitation* 1997; **33**: 257.
12. Hirasawa H, Sugai T, Oda S, *et al.* Continuous hemodiafiltration (CHDF) removes cytokines and improves respiratory index (RI) and oxygen metabolism in patients with acute respiratory distress syndrome (ARDS). *Crit Care Med* 1998; **26**(Suppl.): 294.
13. Yekebas EF, Eisenberger CF, Ohnesorge H, *et al.* Attenuation of sepsis-related immunoparalysis by continuous veno-venous hemofiltration in experimental porcine pancreatitis. *Crit Care Med* 2001; **29**: 1423.
14. Yekebas EF, Strate T, Zolmajd S, *et al.* Impact of different modalities of continuous venovenous hemofiltration on sepsis-induced alterations in experimental pancreatitis. *Kidney Int* 2002; **62**: 1806.
15. Ronco C, Tetta C, Mariano F. Interpreting the mechanisms of continuous renal replacement therapy in sepsis: the peak concentration hypothesis. *Artif Organs* 2003; **27**: 792.
16. DiCarlo JV, Alexander SR, Agarwal R, Schiffman JD. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. *J Pediatr Hematol Oncol* 2003; **25**: 801.
17. Bernard GR, Artigas A, Brigham KL, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818.
18. Brower RG, Ware LB, Berthiaume Y, Matthay MA. Treatment of ARDS. *Chest* 2001; **120**: 1347.
19. Ancell CD, Phipps J, Young L. Thymosin alpha-1. *Am J Health Syst Pharm* 2001; **58**: 879.
20. Billich A. Thymosin alpha1. SciClone Pharmaceuticals. *Curr Opin Investig Drugs* 2002; **3**: 698.
21. SciClone Pharmaceuticals International. *Thymalfasin Package Insert*. San Mateo, CA: SciClone Pharmaceuticals International, 1998.
22. Liaw Y-F. Current therapeutic trends in therapy for chronic viral hepatitis. *J Gastroenterol Hepatol* 1997; **12**(Suppl.): S346.
23. Xie H, Ji D, Gong D, *et al.* Continuous veno venous hemofiltration in treatment of acute necrotizing pancreatitis. *Chin Med J (Engl)* 2003; **116**: 549.
24. Yu C, Liu Z, Gong D, *et al.* The monocyte dysfunction induced by acute tetramine poisoning and corrected by continuous blood purification. *Arch Toxicol* 2005; **79**: 47.
25. Sileri P, Pursell KJ, Coady NT, *et al.* A standardized protocol for the treatment of severe pneumonia in kidney transplant recipients. *Clin Transplant* 2002; **16**: 450.

