Int J Clin Exp Med 2015;8(1):1324-1332
www.ijcem.com /ISSN:1940-5901/IJCEM0003873

*Original Article*

# Early- and late-onset severe pneumonia after renal transplantation

Guowei Tu[1], Minjie Ju[1], Yijun Zheng[1], Ming Xu[2], Ruiming Rong[2], Duming Zhu[1], Tongyu Zhu[2], Zhe Luo[1]

*[1]Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, P. R. China; [2]Department of Urology, Zhongshan Hospital, Fudan University, Shanghai, P. R. China*

Received November 15, 2014; Accepted January 8, 2015; Epub January 15, 2015; Published January 30, 2015

**Abstract:** Background: The aim of this study was to clarify the distinctions in the clinical characteristics and outcomes between early- and late-onset severe pneumonia after renal transplantation requiring ICU admission. Methods: The data were retrospectively collected in consecutive renal recipients with severe pneumonia from January 1, 2009, to December 31, 2013, in a tertiary ICU. We classified the patients according to the time of pneumonia onset as follows: early-onset severe pneumonia (E-SP) corresponded to a pulmonary infection occurring during the first year following the transplantation, and late-onset severe pneumonia (L-SP) corresponded to a pulmonary infection occurring after the first year following the transplantation. Results: In the E-SP patients, fungi (42.1%) and viruses (31.6%) were the most common pathogens. Twenty-three (71.9%) patients received non-invasive ventilation (NIV), 15 (65.2%) of whom were intubated. The median duration of the ICU and hospital stays was 11 ± 5 and 19 ± 4 days, respectively. In the L-SP patients, bacteria (42.1%) and viruses (26.3%) were the predominant pathogens. Four of 15 (26.7%) patients failed NIV treatment. The median duration of the ICU and hospital stays was 9 ± 3 and 16 ± 3 days, respectively. The ICU mortality among the E-SP patients was 18.8% (6 of 32), compared with 7.1% (2 of 28) in the L-SP group ($P$ = 0.264). Conclusions: Early-onset severe pneumonia in renal transplant recipients resulted in a more serious condition, higher rate of NIV failure, longer duration of mechanical ventilation, and increased length of ICU and hospital stays.

**Keywords:** Renal transplantation, severe pneumonia, non-invasive ventilation, mechanical ventilation

## Introduction

Pneumonia is a frequent complication after renal transplantation, whereas severe pneumonia is a life-threatening condition that may frequently require admission to the intensive care unit (ICU) or lead to significant morbidity and mortality [1]. The risk of pulmonary infection in renal transplant patients is determined by a semi-quantitative relationship between the following two factors: the epidemiological exposures of the individual and the "net state of immunosuppression" [2, 3]. Epidemiological exposures are divided into the following four overlapping categories: donor- and recipient-derived infections and community and nosocomial exposures. The net state of immunosuppression is a complex function determined by the interactions of several factors (including the intensity of the immunosuppression, underlying diseases, comorbid conditions, neutropenia, and metabolic conditions) [4].

Although the traditional time course of infections post-transplant was compiled to guide the differential diagnosis and empirical anti-infectious treatment in solid organ transplant recipients, it focuses principally on the causative pathogens rather than on the entire clinical course [3]. A large cohort of renal transplant recipients indicated that the infection-related mortality during the first 3 months post-transplantation was higher than that after 2 years post-transplantation [5], which suggested the presence of separate early- and late-onset infection subtypes among renal transplant recipients. Additionally, patients with severe pneumonia frequently require comprehensive management involving immunosuppressant adjustment, mechanical ventilation support, fluid management, other life support treatments, and anti-infectious treatment. Few studies have been conducted to elucidate the differences in the clinical features of and response to interventions between early- and late-onset pneumonia in transplant recipients.

**Table 1.** Summary of standardized approach for renal transplant recipients with severe pneumonia

| Major Areas | Major Recommendation |
|---|---|
| Microbiological diagnosis | |
| (1) Non-invasive diagnosis | Blood, urine and sputum culture |
| | Serum antibodies of virus and mycoplasma; G test; GM test; T-SPOT. TB |
| (2) Invasive diagnosis | Fiberoptic bronchoscopy with bronchoalveolar lavage |
| Treatment | |
| (1) Empirical antibiotic therapy | < 12 months: TMP-SMX + moxifloxacin + ganciclovir |
| | > 12 months: moxifloxacin + ganciclovir |
| (2) Glucocorticoids | Methyprednisolone 1 mg/kg is started every 12 h intravenously |
| | The dosage of methyprednisolone is adjusted according to chest radiographic findings and oxygen saturation |
| (3) Immunosuppressants | All immunosuppressants are discontinued on admission to ICU |
| | Immunosuppressants are started at a low dose when the dosage of intravenous methylprednisolone is reduced to 1.0 mg/kg/d |
| (4) Nutrition | Early enteral feeding is preferred to parenteral or delayed enteral nutrition. |
| | Parenteral nutrition is used if calorie goals are not achieved in 3 days in ICU |
| (5) Fluid management | Conservative fluid management is employed relieves the pulmonary edema |
| (6) Hemodynamic monitoring | FloTrac/Vigileo™ or PiCCO is used in persistent haemodynamic instability |
| (7) Ventilation | NIV: $PaO_2/FiO_2$ < 200 mm Hg while breathing oxygen delivered by a face mask at a maximal concentration |
| | MV: severe hypoxia or increasing shortness of breath |
| (8) ECMO | For severe hypoxemia, uncompensated hypercapnia, or the presence of excessively high plateau pressure |

TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole; ICU, intensive care unit; PiCCO, pulse indicator continuous cardiac output; NIV, non-invasive ventilation; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

We aimed to clarify the distinctions in clinical characteristics and outcomes between early- and late-onset pneumonia after renal transplantation requiring ICU admission based on our 5-year experience.

## Methods

### *Patients*

We retrospectively studied all the consecutive renal transplant recipients hospitalized in a medical/surgical ICU of Zhongshan Hospital of Fudan University from January 1, 2009, to December 31, 2013. This study was approved by the Ethics Committee of Zhongshan Hospital of Fudan University and was in compliance with the institutional requirements. The patients provided informed consent.

The initial diagnosis of pneumonia was mainly based on clinical manifestations and radiography. All the patients received high-resolution computed tomography (HRCT) examinations before ICU admission and during the course of treatment in the ICU. Severe pneumonia was defined as a pulmonary infection warranting admission to the ICU. The need for ICU care is suggested by the presence of one of two major criteria (septic shock requiring vasopressors and acute respiratory failure requiring intubation and mechanical ventilation) or at least three of the following nine minor criteria: (1) respiratory rate ≥ 30 breaths/min; (2) $PaO_2/FiO_2$ ratio ≤ 250; (3) multilobar infiltrates; (4) confusion/disorientation; (5) uremia (blood uric nitrogen level ≥ 20 mg/dL); (6) leukopenia (white blood cell count < 4000 cells/$mm^3$); (7) thrombocytopenia (platelet count < 100,000 cells/$mm^3$); (8) hypothermia (core temperature < 36°C); and (9) hypotension requiring aggressive fluid resuscitation [6]. The clinical diagnosis of acute respiratory distress syndrome (ARDS) was made in accordance with the 2012 Berlin definition [7]. Acute rejection was diagnosed based on histological examination of the biopsy specimen.

We classified the patients according to the time of pneumonia onset as follows: early-onset severe pneumonia (E-SP) corresponded to a

**Table 2.** Patient baseline demographics

| Patient characteristics | E-SP (n = 32) | L-SP (n = 28) | *P* value |
|---|---|---|---|
| Age (yrs ) | 52 (41-60) | 55 (47-67) | 0.210 |
| Male gender, n (%) | 23 (71.8%) | 13 (46.4%) | 0.065 |
| IS regimens before admission | | | |
| CsA + MMF + Pred, n (%) | 12 (37.5%) | 12 (42.9%) | 0.793 |
| TAC + MMF + Pred, n (%) | 19 (59.4%) | 12 (42.9%) | 0.301 |
| Rapa + MMF + Pred, n (%) | 1 (3.1%) | 4 (14.3%) | 0.175 |
| Comorbidities | | | |
| Diabetes mellitus, n (%) | 2 (6.3%) | 7 (25%) | 0.069 |
| Hypertension, n (%) | 10 (31.3%) | 14 (50%) | 0.189 |
| Congestive heart failure, n (%) | 2 (6.3%) | 4 (14.3%) | 0.403 |
| Symptoms at presentation | | | |
| Fever, n (%) | 32 (100%) | 28 (100%) | 1.000 |
| Cough, n (%) | 9 (28.1%) | 13 (46.4%) | 0.183 |
| Scanty sputum, n (%) | 24 (75.0%) | 20 (71.4%) | 0.778 |
| Time of onset post renal transplant (months) | 3 (2-6) | 96 (60-144) | <0.001 |
| Acute rejection history, n (%) | 5 (15.6%) | 4 (14.3%) | 1.000 |
| Severity | | | |
| $PaO_2/FiO_2$ at admission (mmHg) | 156 ± 60 | 250 ± 84 | < 0.001 |
| Apache-II | 22 ± 5 | 15 ± 7 | < 0.001 |
| SAPS-II | 43 ± 15 | 29 ± 10 | < 0.001 |
| ARDS criteria, n (%) | 25 (78.1%) | 10 (16.7%) | 0.002 |

Results expressed as mean ± standard deviation, median (25%-75% interquartile range), n (%). E-SP, early-onset severe pneumonia; L-SP, late-onset severe pneumonia; IS, immunosuppression; CsA, cyclosporin A; MMF, mycophenolate mofetil; TAC, tacrolimus; Rapa, rapamycin; Pred, Prednisone; Apache-II, Acute Physiology and Chronic Health Evaluation II; SAPS-II, Simplified Acute Physiology Score II; ARDS, acute respiratory distress syndrome.

pulmonary infection occurring during the first year following transplantation, and late-onset severe pneumonia (L-SP) corresponded to a pulmonary infection occurring later after the first year following transplantation [8, 9].

*Standardized approach for renal transplant recipients with severe pneumonia (**Table 1**)*

The standardized clinical approach for renal transplant patient recipients with severe pneumonia included microbiological diagnostic and therapeutic approaches that were described in our previous study [10].

*Microbiological diagnostic approach:* Non-invasive diagnostic tests were routinely implemented in all the patients, including blood, urine, and sputum cultures, as well as serum antibodies against Epstein-Barr virus (EBV), cytomegalovirus (CMV), *Legionella, and Mycoplasma*. Additionally, the G test, GM test, and T-SPOT. TB test were used for the indirect diagnoses. It was recommended that the patients with negative findings undergo aggressive diagnostic procedures, principally fiberoptic bronchoscopy with bronchoalveolar lavage (BAL).

*Therapeutic approach:* The empirical antibiotic therapy included moxifloxacin, ganciclovir, and trimethoprim-sulfamethoxazole (TMP-SMX) for early-onset pneumonia patients and moxifloxacin plus ganciclovir for late-onset pneumonia patients. Antifungal drug therapy was administered in cases of suspected or confirmed fungal infection. The dosages of all the drugs were adjusted based on the allograft function. The antibiotics were adjusted within 24 h after the results of the microbiological cultures and serum tests became available.

All the immunosuppressants were withdrawn on admission to the ICU, and methylprednisolone (1 mg/kg every 12 h) was initiated, followed by gradual tapering [11]. Calcineurin inhibitors were started at a low dose when the intravenous methylprednisolone dose was reduced to 1.0 mg/kg/d.

**Table 3.** Baseline laboratory tests of renal transplant patients with severe pneumonia

| Patient Characteristics | E-SP (n = 32) | L-SP (n = 28) | *P* value |
|---|---|---|---|
| Hb (g/L) | 110 (104-124) | 105 (100-128) | 0.821 |
| PLT ($10^9$/L) | 220 (201-264) | 212 (200-257) | 0.803 |
| WBC (× $10^9$/L) | 6.8 (3.8-13.3) | 6.3 (4.3-8.8) | 0.616 |
| ANC (× $10^9$/L) | 8.2 (6.4-11.5) | 8.4 (7.1-13.4) | 0.871 |
| ALC (× $10^9$/L) | 0.7 (0.5-0.8) | 0.6 (0.4-0.8) | 0.875 |
| Creatinine (μmol/L) | 116 (92-159) | 114 (94-174) | 0.960 |
| Albumin (g/L) | 30 (26-40) | 30 (25-37) | 1.000 |
| Glucose (μmol/L) | 7.5 (5.8-10.8) | 8.4 (6.3-12.2) | 0.766 |
| Bilirubin (μmol/L) | 8.1 (4.4-15.5) | 8.7 (4.7-17.4) | 0.654 |
| NT-proBNP (pg/mL) | 705 (434-1245) | 774 (307-1534) | 0.724 |
| PCT (ng/mL) | 0.3 (0.2-0.4) | 0.3 (0.2-0.4) | 1.000 |

Results expressed as median (25%-75% interquartile range). E-SP, early-onset severe pneumonia; L-SP, late-onset severe pneumonia; Hb, hemoglobin; PLT, platelets; WBC, white blood count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCT, procalcitonin.

**Table 4.** Microbiological isolates of severe pneumonia in the study

| Microorganism | E-SP (n = 19) | L-SP (n = 19) |
|---|---|---|
| Bacteria | 4 (25.1%) | 8 (42.1%) |
| *Streptococcus hemolyticus* | 0 | 2 |
| *Staphylococcus aureus* | 1 | 0 |
| *Mycobacterium species* | 0 | 1 |
| *Escherichia coli* | 2 | 2 |
| *Klebsiella pneumoniae* | 1 | 1 |
| *Pseudomonas aeruginosa* | 0 | 2 |
| Virus | 6 (31.6%) | 5 (26.3%) |
| *Cytomegalovirus* | 4 | 3 |
| *Adenovirus* | 1 | 2 |
| *Epstein-Barr virus* | 1 | 0 |
| Fungi | 8 (42.1%) | 2 (10.5%) |
| *Pneumocyst carinii* | 4 | 0 |
| *Non-Pneumocyst carin*ii | 4 | 2 |
| *Mycoplasma* | 1 (5.3%) | 3 (15.8%) |
| *Legionella* | 0 | 1 (5.3%) |

E-SP, early-onset severe pneumonia; L-SP, late-onset severe pneumonia.

Non-invasive ventilation (NIV) was considered the first treatment choice if the $PaO_2/FiO_2$ ratio was < 200 mm Hg and consisted of oxygen delivery by a conventional face mask at the maximum concentration. NIV success was defined as avoidance of intubation and clinical improvement leading to discharge to the general ward. Endotracheal intubation was considered in the following patients: ① patients unable to clear airway secretions; ② patients unable to protect the airway; ③ patients failing to maintain a $PaO_2/FiO_2$ of 100 mm Hg despite optimal standard medical management or NIV with a respiratory rate (RR) of > 30 breaths/min and a blood pH < 7.3 within 4-8 h; and ④ patients with hemodynamic instability. The decision regarding endotracheal intubation and extubation was made at the discretion of the attending physician.

The management of other aspects of care, such as blood glucose control, nutritional support, thromboembolic prophylaxis, sedation, and analgesia, was performed according to the current guidelines [12].

*Data collection*

The following data were recorded:

(1). Baseline demographic data (age, gender, immunosuppression regimens before admission, comorbidities, symptoms at presentation, time of onset post-renal transplantation, and acute rejection history).

(2). Patients' degree of disease severity ($PaO_2/FiO_2$ ratio, Acute Physiology and Chronic Health Evaluation II [APACHE II] score, and Simplified Acute Physiology Score II [SAPS II]).

(3). Baseline laboratory tests (hemoglobin, platelets, white blood count [WBC], absolute neutrophil count [ANC], absolute lymphocyte count [ALC], creatinine, albumin, glucose, bilirubin, N-terminal pro-brain natriuretic peptide [NT-proBNP], and procalcitonin [PCT]).

(4). Microbiological isolates in patients with severe pneumonia.

(5). Clinical outcome of patients (mechanical ventilation support, renal replacement therapy, length of stay in the ICU, length of stay in the hospital, ICU mortality, and hospital mortality).

*Statistical analysis*

The normally distributed data were reported as the means ± standard deviation (SD) and were compared between the groups using an

**Table 5.** Clinical outcomes of patients with early and late-onset severe pneumonia

| Patient characteristics | E-SP (n = 32) | L-SP (n = 28) | *P* value |
|---|---|---|---|
| Mechanical ventilation support | | | |
| NIV required, n (%) | 23 (71.9%) | 15 (53.6%) | 0.183 |
| NIV success, n (%) | 8 (34.8%) | 11 (73.3%) | 0.045 |
| Intubation required, n (%) | 16 (50%) | 5 (17.9%) | 0.014 |
| Duration of mechanical ventilation (days) | 9 ± 2 | 6 ± 3 | < 0.001 |
| Renal replacement therapy required, n (%) | 1 | 3 | 0.303 |
| Duration of IS withdrawal (days) | 10 ± 3 | 8 ± 3 | < 0.001 |
| Length of stay in ICU (days) | 11 ± 5 | 9 ± 3 | 0.039 |
| Length of stay in hospital (days) | 19 ± 4 | 16 ± 3 | 0.002 |
| ICU mortality, n (%) | 6 (18.8%) | 2 (7.1%) | 0.264 |
| Hospital mortality, n (%) | 7 (21.9%) | 3 (10.7%) | 0.312 |

Results expressed as mean ± standard deviation, median (25%-75% interquartile range), n (%). E-SP, early-onset severe pneumonia; L-SP, late-onset severe pneumonia; NIV, non-invasive ventilation; IS, immunosuppression; ICU, intensive care unit.

unpaired *t*-test. The non-normal data were reported as the medians (25-75% interquartile range) and compared between the groups using the Mann-Whitney U test. The chi-square test or Fisher's exact test was applied to compare the categorical variables as expressed in the form of numbers and percentages. All the probabilities were 2-tailed, and values of $P < 0.05$ were considered significant. All the statistical analyses were performed with SPSS for Windows (version 11.5; SPSS, Inc., Chicago, IL, USA).

## Results

### *Baseline demographics*

During the study period, 60 recipients were admitted to the ICU with a primary diagnosis of severe pneumonia. The median age was 55 (43-60) years. The average duration between the kidney transplant and the onset of pneumonia was 43 (3-62) months. All the patients presented with fever; 22 (36.7%) presented with coughing; and 44 (73.3%) presented with scanty sputum. The mean APACHE II and SAPS II scores on admission were 22 (14-23) and 36 (20-40), respectively. The baseline immunosuppressive regimens included cyclosporine A (CsA), tacrolimus (TAC), mycophenolate mofetil (MMF), rapamycin (Rapa), and prednisone (Pred), which were used in different combinations, namely, CsA + MMF + Pred in 24 patients, TAC + MMF + Pred in 31 patients, and Rapa + MMF + Pred in 5 patients. Five (15.6%) patients in the E-SP group and four (14.3%) patients in the L-SP group had the acute rejection history as confirmed by the biopsy.

Of the 60 patients, 32 (53.3%) patients were admitted with E-SP and 28 (46.7%) with L-SP. There were no significant differences between these two groups with respect to age, gender, baseline serum creatinine, acute rejection history, comorbidities, and symptoms at presentation. The average duration between kidney transplantation and pneumonia onset was 3 (2-6) months in E-SP and 96 (60-144) months in L-SP ($P < 0.001$) patients. The condition of the E-SP patients was more severe, as evidenced by the $PaO_2/FiO_2$ on admission (156 ± 60 vs. 250 ± 84, $P < 0.001$), the Apache-II score (22 ± 5 vs. 15 ± 7, $P < 0.001$), the SAPS-II score (43 ± 15 vs. 29 ± 10, $P < 0.001$), more extensive radiological findings, and a greater number of ARDS criteria met (78.1% vs. 16.7%, $P = 0.003$) (**Table 2**).

As shown in **Table 3**, the results of the baseline biochemical tests, including hemoglobin, platelets, WBC, ANC, ALC, serum creatinine, albumin, glucose, bilirubin, NT-BNP, and PCT, were not significantly different between the two groups.

### *Microbiological findings*

Sixteen (26.7%) patients had a definitive microbial diagnosis based on the non-invasive diagnostic tests. In the remaining 44 patients, BAL was performed in 40 patients, with positive findings in 15 patients.

Among the E-SP patients, 15 (46.9%) patients had definite microbiological findings. The cultures of the sputum, pleural fluid, blood, and BAL fluid showed that 8 (42.1%) patients had infections caused by fungi, 6 (31.6%) by viruses, 4 (25.1%) by bacteria, and 1 (5.3%) by *Mycoplasma*. Four patients presented with more than one underlying pathogen, as follows:

CMV + *Pneumocyst carinii* (n = 2), adenovirus + *Mycoplasma* (n = 1), and *Streptococcus hemolyticus* + CMV (n = 2). Sixteen (57.1%) patients in the L-SP group had definite microbiological findings. Of the 19 isolates, 8 (42.1%) were bacterial, 5 (26.3%) were viral, 2 (10.5%) were fungal, 3 (15.8%) were caused by *Mycoplasma*, and 1 (5.3%) was caused by *Legionella*. Three cases of co-infection were identified as follows: CMV + EBV (n = 1), adenovirus + *Mycoplasma* (n = 1), and CMV + fungi (n = 1). No pathogens were isolated in the remaining 29 patients (48.3%) with severe pneumonia (**Table 4**).

*Clinical outcomes*

(1) Mechanical ventilation support

All the patients received oxygen therapy via a facemask on admission, 38 (63.3%) of whom received non-invasive ventilation (NIV) due to progressive hypoxia. Two patients underwent endotracheal intubation immediately after admission to the ICU because of severe hypoxia and hemodynamic instability. In the E-SP group, 23 (71.9%) patients received NIV, 15 (65.2%) of whom were intubated. In the L-SP group, 4 of 15 (26.7%) failed NIV. The total duration of mechanical ventilation was longer in the E-SP group than in the L-SP group (9 ± 2 vs. 6 ± 3 days, $P < 0.001$) (**Table 5**).

Four patients with E-SP developed pneumothorax during NIV treatment, three of whom died in the ICU. These four patients suffered from severe pulmonary interstitial damage during the course of the disease. One patient succeeded in weaning from mechanical ventilation after adequate gas drainage and was discharged from the hospital in good condition. None of the patients developed pneumothorax in the L-SP group.

(2) Renal graft function

Immunosuppression medications were completely withdrawn in the 60 patients on day 1 of admission to the ICU. The total duration of the immunosuppressant withdrawal was 10 ± 3 days in the patients in the E-SP group and 8 ± 3 days in the patients in the L-SP group ($P < 0.001$). Despite aggressive withdrawal or reduction of immunosuppressant therapy, the patients did not experience clinically evident acute rejection episodes during hospitalization. The level of serum creatinine in the E-SP group was 91 (78-133) μmol/L at ICU discharge, which was similar to the mean renal function on ICU admission (116 [92-159] μmol/L, $P = 0.167$). In the L-SP group, the mean level of serum creatinine at ICU discharge was 109 (94-174) μmol/L, which was comparable to the mean level on ICU admission (114 [98-185] μmol/L, $P = 0.138$). These patients were followed up for 6 months and did not exhibit any acute allograft rejection. Four patients required renal replacement therapy (RRT) during the ICU stay. Three patients in the L-SP group were considered to have developed chronic allograft nephropathy (CAN) despite the absence of a transplant renal biopsy; one of these patients died in the ICU, and two were dialysis-dependent at ICU discharge. One patient in the E-SP group presented with a pulmonary infection and delayed graft function (DGF) on ICU admission. The function of the allograft gradually recovered after RRT, and a transplant renal biopsy revealed acute tubular necrosis (ATN). The patient did not require RRT at ICU discharge. Length of stay and mortality.

(3) Length of stay and mortality

The median duration of the ICU stay was 11 ± 5 days in the E-SP group and 9 ± 3 days in the L-SP group ($P = 0.039$). The median total hospital stay was 19 ± 4 days in the E-SP group and 16 ± 3 days in the L-SP Group ($P = 0.002$). The ICU mortality rate among the E-SP patients was 18.8% (6 of 32), compared with 7.1% (2 of 28) in the L-SP group ($P = 0.264$) (**Table 5**). Two patients developed severe hypoxemia after returning to the general ward; subsequently, they both refused intubation and died of respiratory failure.

## Discussion

The findings of this study indicate that the condition of the renal transplant recipients with E-SP was more severe, as evidenced by the $PaO_2/FiO_2$ on admission, the Apache-II scores, the SAPS-II scores, and the greater number of ARDS criteria met compared with the L-SP patients. The patients with E-SP required longer mechanical ventilation, ICU stay, and hospitalization durations. As expected based on the previous study [1], the ICU and hospital mortalities in the E-SP group were higher than those in the L-SP group, although no statistically signifi-

cant differences were achieved because of the limited sample size in this study.

Immunosuppressive agents have agent-specific side effects [13]; however, they share the adverse consequences of the impairment of normal immunity that are associated with infection. The first year post transplantation is a time of rapid change in immunity status and the time during which immunological complications are most common. Enhanced immunosuppression is associated with an increased risk of infection by opportunistic microorganisms, such as *Pneumocystis carinii*, CMV, *Aspergillus*, *Cryptococcus*, and EBV, due to the alteration of the expression of inflammatory mediators and cytokines by a complex interrelated cascade [14]. After 1 year following transplantation, the net state of immunosuppression of patients with stable and reduced levels of immunosuppression is typically similar to the general population, whereas those who require intensified immunosuppression are at an ongoing risk for opportunistic infections [15]. The "net state of immunosuppression" is the internal cause of the differences between early- and late-onset pneumonia. In the cohort of patients in the present study, the immunosuppressants were discontinued at ICU admission. Aggressive reduction of immunosuppressants is considered extremely important because it allows a timely recovery of immunity [16]. The two groups of patients in our study underwent immunosuppressant withdrawal for 10 ± 3 and 8 ± 3 days; however, their renal function at ICU discharge was comparable to baseline, and they did not experience acute allograft rejection within a mean duration of 6 months of follow-up after ICU discharge. This finding provided further evidence that such aggressive immunosuppressant withdrawal was life-saving and that the associated long-term risk of acute rejection was minimal.

Our study revealed that 48.3% of the patients had no microbiological diagnosis despite aggressive investigations, which was similar to the results of a previous study [5]. Determining the potential pathogens and administering improper empirical treatment may be perilous and adversely influence the outcome. The traditional time course of post-transplant infections indicated that infectious processes tend to occur at relatively specific times during the post-transplant course [3]. The patterns of infection in the post-transplant period have been altered by the increased identification of organisms and by antibiotic prophylactic therapy [4]. The microbial findings and guidelines are typically based on an analysis of a general population other than selected patients with severe pneumonia who required ICU admission. In this study, fungi and viruses were the most commonly found pathogens in E-SP patients, whereas bacteria and viruses were the predominant pathogens in L-SP patients. The types of causative pathogens specifically found in severe pneumonia patients after renal transplantation appeared consistent with the time course of post-transplant infections.

Four cases of PCP were confirmed in the E-SP group, whereas no PCP was diagnosed in the L-SP group, demonstrating that the empirical use of TMP-SMX on admission served as an early and appropriate option against *Pneumocystis carinii* in E-SP patients. Gordon et al. found that, after the first year, 1 of 534 renal transplant patients on PCP prophylaxis developed an infection [17]. The late presentation of PCP is rare, with occurrence typically related to the intense immunosuppression associated with acute rejection [18]. Although all the renal transplant recipients at our center received regular CMV prophylaxis by oral ganciclovir or valganciclovir for at least 3 months post-transplant, there were 4 cases of CMV pneumonia in the E-SP group and 3 cases in the L-SP group. Previously, CMV disease was considered to occur at one to four months post-transplantation in the absence of antiviral prophylaxis. Santos et al. recently found that delayed-onset CMV disease (occurring > 100 days post-transplant) occurred more commonly than early-onset CMV disease and that it was associated with inpatient death [19]. Previous transplant failure or rejection, lymphocyte-depleting therapy, and high-dose steroid administration were the major risk factors for delayed-onset CMV disease [19-21].

In this study, we found that patients in the E-SP group have a higher rate of NIV failure and a longer duration of mechanical ventilation support than L-SP patients, which implied a poorer response to NIV in E-SP patients. Four patients with E-SP developed pneumothorax during NIV treatment, and only one of them survived to hospital discharge. Concerns have been raised regarding the high mortality rate among

patients who fail NIV and the possibility that an unnecessary delay in intubation results in excess mortality [22]. Although we are unable to identify the risk factors for NIV failure and ventilator-induced lung injury (VILI) in the small sample of this single-center study, research to determine the predictors of response to NIV may be warranted.

Some limitations of this study should be acknowledged. The major limitation is that the study is a single-center study with a relatively small number of patients. Second, the retrospective design of the study may have higher risks of bias. Third, bronchoscopy with BAL was not performed in all the patients. The microbiological etiology of the infection remained unknown in nearly half of the patients despite aggressive investigation, which prevented us from drawing definite conclusions regarding the microbiological findings.

## Conclusion

In renal transplant recipients, E-SP resulted in a more serious condition, a higher rate of NIV failure, a longer duration of immunosuppressant withdrawal, a longer duration of mechanical ventilation, and an increased length of ICU and hospital stay. Our findings merit further study with larger trials to evaluate the clinical feature and outcome differences between E-SP and L-SP.

## Acknowledgements

This article was supported by grants from the research funding of Zhongshan hospital (2012ZSQN/42 and 2013ZSQN/29).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Tongyu Zhu, Department of Urology, Zhongshan Hospital, Fudan University, Shanghai 200032, P. R. China. Tel: +86-21-64041990-2953; E-mail: tyzhu@fudan.edu.cn; Dr. Zhe Luo, Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai 200032, China. Tel: +86-21-64041990-3659; E-mail: luo.zhe@zs-hospital.sh.cn

## References

[1] Linares L, Cofan F, Cervera C, Ricart MJ, Oppenheimer F, Campistol JM, Moreno A. Infection-related mortality in a large cohort of renal transplant recipients. Transplant Proc 2007; 39: 2225-2227.

[2] Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357: 2601-2614.

[3] Fishman JA. Infections in immunocompromised hosts and organ transplant recipients: essentials. Liver Transpl 2011; 17 Suppl 3: S34-37.

[4] Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect 2014; 20 Suppl 7: 4-9.

[5] Hoyo I, Linares L, Cervera C, Almela M, Marcos MA, Sanclemente G, Cofan F, Ricart MJ, Moreno A. Epidemiology of pneumonia in kidney transplantation. Transplant Proc 2010; 42: 2938-2940.

[6] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 Suppl 2: S27-72.

[7] Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307: 2526-2533.

[8] Perez-Ordono L, Hoyo I, Sanclemente G, Ricart MJ, Cofan F, Perez-Villa F, de la Bellacasa JP, Moreno A, Cervera C. Late-onset Pneumocystis jirovecii pneumonia in solid organ transplant recipients. Transpl Infect Dis 2014; 16: 324-328.

[9] Schober T, Framke T, Kreipe H, Schulz TF, Grosshennig A, Hussein K, Baumann U, Pape L, Schubert S, Wingen AM, Jack T, Koch A, Klein C, Maecker-Kolhoff B. Characteristics of early and late PTLD development in pediatric solid organ transplant recipients. Transplantation 2013; 95: 240-246.

[10] Tu GW, Ju MJ, Zheng YJ, Zhu DM, Xu M, Rong RM, Zhu TY, Luo Z. An interdisciplinary approach for renal transplant recipients with severe pneumonia: a single ICU experience. Intensive Care Med 2014; 40: 914-915.

[11] Tu GW, Ju MJ, Han Y, He HY, Rong RM, Xu M, Xue ZG, Zhu TY, Luo Z. Moderate-dose glucocorticoids as salvage therapy for severe pneumonia in renal transplant recipients: a single-center feasibility study. Ren Fail 2014; 36: 202-209.

[12] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR,

Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013; 39: 165-228.

[13] Meyer KC, Decker C, Baughman R. Toxicity and monitoring of immunosuppressive therapy used in systemic autoimmune diseases. Clin Chest Med 2010; 31: 565-588.

[14] Danovitch GM. Handbook of kidney transplantation. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2010.

[15] Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. Infect Dis Clin North Am 2010; 24: 273-283.

[16] Yang CY, Shih CJ, Yang WC, Lin CC. Aggressive immunosuppressant reduction and long-term rejection risk in renal transplant recipients with Pneumocystis jiroveci pneumonia. Exp Clin Transplant 2012; 10: 344-349.

[17] Gordon SM, LaRosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-LaRosa L, Longworth DL. Should prophylaxis for Pneumocystis carinii pneumonia in solid organ transplant recipients ever be discontinued? Clin Infect Dis 1999; 28: 240-246.

[18] Muhammad Iqbal AH, Lim SK, Ng KP, Tan LP, Chong YB, Keng TC. Pneumocystis jirovecii pneumonia 13 years post renal transplant following a recurrent cytomegalovirus infection. Transpl Infect Dis 2012; 14: E23-26.

[19] Santos CA, Brennan DC, Fraser VJ, Olsen MA. Delayed-onset cytomegalovirus disease coded during hospital readmission after kidney transplantation. Transplantation 2014; 98: 187-194.

[20] Cordero E, Casasola C, Ecarma R, Danguilan R. Cytomegalovirus disease in kidney transplant recipients: incidence, clinical profile, and risk factors. Transplant Proc 2012; 44: 694-700.

[21] Hibberd PL, Tolkoff-Rubin NE, Conti D, Stuart F, Thistlethwaite JR, Neylan JF, Snydman DR, Freeman R, Lorber MI, Rubin RH. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. Ann Intern Med 1995; 123: 18-26.

[22] Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, Alcazar M, Torres A. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. Intensive Care Med 2012; 38: 458-466.