Late Respiratory Infection after Lung Transplantation

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Background: Aiming to improve outcome of lung transplantation (LTx) patients, we reviewed risk factors and treatment practices for the LTx recipients who experienced respiratory infection in the late post-LTx period (>1 month after LTx).

Methods: We analyzed the clinical data of 48 recipients and donors from 61 LTx, who experienced late respiratory infections. Late respiratory infections were classified according to the etiology, time of occurrence, and frequency of donor-to-host transmission or colonization of the recipient prior to transplantation.

Results: During the period of observation, 42 episodes of respiratory infections occurred. The organisms most frequently involved were gram (-) bacteria: Acinetobacter baumannii (n=13, 31.0%), Pseudomonas aeruginosa (n=7, 16.7%), and Klebsiella pneumoniae (n=4, 10.0%). Among the 42 episodes recorded, 14 occurred in the late post-LTx period. These were bacterial (n=6, 42.9%), fungal (n=2, 14.3%), viral (n=4, 28.5%), and mycobacterial (n=2, 14.3%) infections. Of 6 bacterial infections, 2 were from multidrug-resistant (MDR) A. baumannii and one from each of MDR P. aeruginosa, extended spectrum β-lactamase (+) K. pneumoniae, and methicillin-resistant Staphylococcus aureus and Streptococcus pneumoniae. Infection-related death occurred in 6 of the 14 episodes (43%).

Conclusion: Although the frequency of respiratory infection decreased sharply in the late post-LTx period, respiratory infection was still a major cause of mortality. Gram (-) MDR bacteria were the agents most commonly identified in these infections.

Key Words: Lung Transplantation; Respiratory Tract Infections

Introduction

Since the first human lung transplantation (LTx) in 1963, significant progress has been made in this field, From the registry of the International Society for Heart and Lung Transplantation (ISHLT), 3519 LTx for end-stage lung disease were performed in 2010. The median survival for LTx recipients, however, is 5.5 years, disappointing compared to that of other solid organ recipients.

Morbidity and mortality throughout the post-LTx period result primarily from infection; respiratory infections including pneumonia account for approximately 35% of deaths in the first year. Among solid organ transplant recipients, LTx recipients are most susceptible to infection. Several factors unique to the lung may explain this. First, denervation of the allograft decreases mucociliary clearance and the cough reflex, adding to the risks of generalized immunosuppression, the lung is the only allograft continuously exposed to the environment, donor-to-host transmission, and microorganisms colonizing the upper airways.

The various etiologies of respiratory infection in LTx...
patients include opportunistic, hospital- and community-acquired microorganisms, which differ during the time to occurrence. Donor-to-host transmission is one of important risk factors in early respiratory infection following LTx. In the late post-LTx period (>1 month after LTx), the incidence of infectious episodes decreases markedly, despite patients returning to their normal activities at home or work. However, in this late phase, respiratory infection still presents a potentially fatal risk. Better understanding of post-transplantation susceptibility and of patterns of infectious exposure in the patient's environment is urgently required to avert this risk.

The aim of this study is to evaluate the epidemiology of respiratory infection in LTx recipients at our center. In particular, we analyzed the time to occurrence of infection, colonization of the recipient with a relevant infectious agent, donor-to-host transmission of these agents, and the relationship of late-phase respiratory infection to mortality.

Materials and Methods

We analyzed the medical records of 48 LTx recipients treated at our institution between January 2006 and June 2012 for demographic data, primary respiratory disease, microbiological testing before and after transplantation, and episodes of infection throughout the post-transplantation observation period. This study was reviewed and approved by Institutional Review Board at Gangnam Severance Hospital, Yonsei University College of Medicine (IRB no. 3-2012-0223).

1. Pre-transplant screening

Before LTx, sputum samples were cultured for bacteria and fungi, and broncho-alveolar lavage (BAL) fluids from recipient was analyzed by fibrobronchoscopy. Pre-transplant evaluations also included serology for cytomegalovirus (CMV), Epstein-Barr virus, hepatitis A, B and C, herpes virus, and human immunodeficiency virus.

2. Antimicrobial prophylaxis

Postoperative antimicrobial prophylaxis was guided by culture from donor and recipient. For the patients without known colonization, antibacterial prophylaxis was given as either a single agent, piperacillin-tazobactam or a combination of ceftriaxone, isepamicin and metronidazole. Systemic antimicrobial drugs were administered for 7 days if surveillance culture from donor and recipient were both negative. If the cultures were positive, antibacterial prophylaxis was maintained for at least 2 weeks as indicated by the antibiogram. All patients underwent prophylaxis for fungi with fluconazole daily for one year and for *Pneumocystis jirovecii* infection with sulfamethoxazole-trimethoprim. Based on CMV serology, patients at high and moderate risk for CMV infection (recipient [−]/donor [+] and recipient [+] or [−], respectively) were maintained prophylactically with intravenous ganciclovir for two weeks, followed by oral valganciclovir for up to 6 months or one year.

3. Immunosuppressive therapy

Methylprednisolone was used to induce immunosuppression and was followed by maintenance therapy with steroids, calcineurin inhibitor and an antimetabolite. Maintenance immunosuppressive drugs consisted of prednisone, tacrolimus and mycophenolate mofetil.

4. Post-transplant surveillance

Post-transplant evaluation included pulmonary function tests, imaging, periodic sputum cultures, and CMV antigenemia testing. If respiratory infection or rejection was suspected, the patient underwent a chest computed tomography scan, fibrobronchoscopy with alveolar lavage for bacterial and fungal cultures, indirect immunofluorescence tests for viral and *P. jirovecii* infections and mycobacterial polymerase chain reaction, and transbronchial biopsies to assess rejection and infection. Diagnosis of respiratory infection was made if a patient met any of the following criteria: fever (body temperature ≥ 37.8°C), cough, dyspnea, purulent expectora-
tion, chest X-ray showing a new infiltrate, or significant impairment in lung function.

Results

Demographic data for the LTx recipients are presented in Table 1. The mean age of the patients was 48.3 years. Idiopathic pulmonary fibrosis was the most common indication for LTx and most procedures were bilateral.

The microbiological etiology was established in 42 episodes from 48 recipient. Bacterial respiratory infection (73.8%) was more frequent than fungal (11.9%) and viral infection (9.5%). Bacteriological isolates were mostly (67.7%) gram (−) bacteria: A. baumannii (n=13, 31.0%), P. aeruginosa (n=7, 16.7%), and K. pneumoniae (n=4, 10.0%). Fungal infections were diagnosed in 5 recipients, all of them caused by either Candida albicans or Aspergillus species. Two cases of mycobacterial infection were identified, including one non-tuberculous mycobacterium (NTM): Mycobacterium gordonae (Table 2). All 4 patients with viral respiratory infection were

| Table 1, Demographic characteristics of 48 lung transplant recipients |
|---------------------------------------------------------------|
| **Baseline characteristic** | **No. (%)** |
| **Age (range), yr** | 48.3 (22–66) |
| **Sex** | |
| Male | 20 (41.7) |
| Female | 28 (58.3) |
| **Priority of transplant** | |
| Urgent | 3 (6.3) |
| Elective | 45 (93.7) |
| **Disease leading to transplant** | |
| Idiopathic pulmonary fibrosis | 21 (43.8) |
| LAM | 9 (18.8) |
| Bronchiectasis | 5 (10.4) |
| Pulmonary hypertension | 4 (8.3) |
| DAD | 4 (8.3) |
| ARDS | 2 (4.4) |
| COPD | 1 (2.2) |
| Systemic sclerosis | 1 (2.2) |
| Bronchiolitis obliterans | 1 (2.2) |
| **Lung transplant type** | |
| Single lung | 3 (6.3) |
| Double lung | 43 (89.6) |
| Heart-lung | 2 (4.1) |
| **Total** | 48 (100) |

LAM: lymphangioleiomyomatosis; DAD: diffuse alveolar damage; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease.

| Table 2, Microbiological etiologies of respiratory infections after lung transplantation |
|---------------------------------------------------------------|
| **Etiology** | **Time-to-occurrence of lung infection (mo)** |
| **0–1** | **2–12** | **>12** | **Total (n=42)** |
| **Bacteria (n=31)** | |
| Gram (−) bacilli | |
| Acinetobacter baumannii | 11 | 2 | - | 13 |
| Pseudomonas aeruginosa | 6 | 1 | - | 7 |
| Klebsiella pneumoniae | 3 | 1 | - | 4 |
| Escherichia coli | 1 | - | - | 1 |
| Gram (+) cocci | |
| Staphylococcus aureus | 4 | 1 | - | 5 |
| Streptococcus pneumoniae | - | - | 1 | 1 |
| **Fungi (n=5)** | |
| Candida albicans | 2 | 1 | - | 3 |
| Aspergillus species | 1 | 1 | - | 2 |
| **Virus (n=4)** | |
| CMV | - | - | 4 | 4 |
| **Mycobacterium (n=2)** | |
| Mycobacterium tuberculosis | - | 1 | - | 1 |
| NTM (M. gordonae) | - | - | 1 | 1 |

CMV: cytomegalovirus; NTM: nontuberculous mycobacteria.
Table 3. Cytomegalovirus (CMV) serology of 48 lung transplant recipients

| CMV serology       | No. | Episodes |
|--------------------|-----|----------|
| Recipient (−)/Donor (−) | -   | -        |
| Recipient (−)/Donor (+) | 5   | -        |
| Recipient (+)/Donor (−) | 4   | 1        |
| Recipient (+)/Donor (+) | 33  | 3        |
| Recipient or Donor unknown | 6   | -        |

Table 4. Colonization and transmission patterns in lung transplant recipients

| Microorganism            | Donor Colonization | Donor Episodes | Recipient Colonization | Recipient Episodes |
|--------------------------|--------------------|----------------|------------------------|--------------------|
| Gram (−) bacilli         |                    |                |                        |                    |
| *Pseudomonas aeruginosa* | 4                  | 3              | 8                      | 3 (1)*             |
| *Acinetobacter baumannii*| 4                  | 3 (1)*         | 3                      | 1                  |
| *Klebsiella pneumoniae*  | 1                  | 1              | 2                      |                    |
| Other gram (−) bacilli   | 1                  | -              | -                      | -                  |
| Gram (+) cocci           |                    |                |                        |                    |
| *Staphylococcus aureus*  | 7                  | -              | 6                      | -                  |
| Fungi                    |                    |                |                        |                    |
| *Candida albicans*       | -                  | -              | 8                      | -                  |
| *Aspergillus species*    | 1                  | -              | 2                      | -                  |
| Others                   | 2                  | -              | 4                      | -                  |
| Total                    | 20                 | 7              | 33                     | 4                  |

*This episodes occurred in late post-transplant period (>1 month after transplant).

Table 5. Mortality-related respiratory infections in the late post-transplant period (>1 month after transplant)

| Microorganism (n=14) | Infection-related death |
|----------------------|-------------------------|
| Bacteria (n=6)       |                         |
| *Pseudomonas aeruginosa* | 2                      |
| *Acinetobacter baumannii* | 1                      |
| *Klebsiella pneumoniae*  | 1                      |
| *Escherichia coli*    |                         |
| Other gram (−) bacilli |                         |
| *Staphylococcus aureus* |                         |
| *Streptococcus pneumoniae* |                 |
| Fungi (n=2)           |                         |
| *Candida albicans*    |                         |
| *Aspergillus species* |                         |
| Mycobacterium (n=2)   |                         |
| *Mycobacterium tuberculosis* |             |
| NTM (*M. gordonae*)   |                         |
| Virus (n=4)           |                         |
| CMV serology          |                         |
| Recipient (−)/Donor (+) |                     |
| Recipient (+)/Donor (+) or (−) | 1                  |
| Recipient or Donor unknown |                     |
| Total                 | 6                      |

NTM: nontuberculous mycobacteria; CMV: cytomegalovirus.
viral (n=4, 28.5%), and mycobacterial (n=2, 14.3%). Of 6 bacterial infections, 2 were from multidrug-resistant (MDR) A. baumannii and one each from MDR P. aeruginosa, extended spectrum β-lactamase (+) K. pneumoniae, methicillin-resistant S. aureus and S. pneumo-
niae. Among the 14 episodes of late-phase respiratory infection, 6 episodes (43%) resulted in death (Table 5).

Discussion

The most critical risks for mortality in the first month after LTx from infection and posttransplant complic-
ations.8,9 Risk of respiratory infection, typically by noso-
comial organisms, is greatest in this early period. Prophylactic use of antibiotics reduced the risk of post-
LTx pneumonia.10 When immunosuppressive therapy is
at the highest level, opportunistic organisms such as
CMV and fungi account for most of the respiratory
infections. Thereafter, community-acquired bacterial and
viral infections also develop, although infection with
health care-associated organisms remains common.11

In our analysis, the cumulative risk of an episode of
respiratory infection increased sharply during the first 30
days after transplant, when more than half of the epi-
sodes occurred, and continued to increase until it stabi-
lized. Bacterial pneumonia accounted for the largest
proportion of infections followed by viral, fungal, and
mycobacterial infections in the late period. Remarkably,
most of the bacterial infections were gram (−) MDR
and of nosocomial origin. These organisms also ac-
counted for most of the respiratory infection-related
deaths. Thus respiratory infections induced by gram
(−) MDR organisms may predominate over commu-
nity-acquired infection in the late period, Empiric anti-
biotic therapy in the early period after LTx is essential.

CMV infection ranks second to bacterial pneumonia
in incidence in the first year following LTx; however,
our data revealed no episode of CMV in this early
period. In accordance with previous studies, we attrib-
ute this relatively low incidence of early CMV infection
and delay in onset time to the routine prophylactic use
of ganciclovir for up to 6 months or one year.14,15

Recent studies report a reduction in CMV viremia and
infection with prolonged prophylactic regimens; how-
ever, the extended prophylaxis is more likely to delay
the onset of CMV infection than to prevent it.16-19 Other
viruses such as herpes simplex, influenza, and respira-
tory syncytial viruses may cause pneumonia in LTx re-
cipients; however, these did not appear in our study.
In addition, prophylaxis with fluconazole at our in-
sitution proved effective in suppressing fungal infec-
tions. Previous studies show similar suppression of fun-
gal infections as a result of prophylactic strategies.20-23

Other opportunistic microorganisms are far less common.
Mycobacterial infections occur rarely after LTx and
are typically secondary to Mycobacterium tuberculosis.24
However, recent data show a rising incidence of NTM
infections, particularly by M. abscessus, in 3% to 9% of
cases.25-26 Most previous data on pulmonary tuberculosis
come from case reports or small series of patients and
show incidence rates lower than 3%.27,28 In our data,
2 mycobacterium infections occurred in 48 LTx recip-
ients. These results agree closely with findings in other
countries,24-28, where the incidence of tuberculosis is
much lower than in our country (80.7 episodes per
100,000 inhabitants/yr in 2011).29

Data from ISHLT registry show that presence of clin-
ic infection in a donor does not significantly predict
mortality in the recipient in the first year.30 Previous
studies including ours confirm the presence of organ-
isms in 60% to 80% of donor lungs, although these or-
ganisms very infrequently result in respiratory infec-
tions, especially in the late post-LTx period.31-33

This study is limited primarily in the short median fol-
low-up period (338 days), small sample size and retro-
spective design. Additional observation and analysis of
trends in respiratory infection after the first post-LTx
year are needed. Meanwhile, prophylactic strategies
currently in place should be continued.

In conclusion, although antibiotic therapy has sharply
curbed the incidence of respiratory infections following
LTx, respiratory infection still presents a major risk for
mortality in the late post-LTx period. Nosocomial gram
(−) MDR bacteria were most commonly involved in
these episodes,

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