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Original Article

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Infections in Lung Transplant Recipients during and after Prophylaxis

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ABSTRACT

Background: The timeline of infections after lung transplantation has been changed with the introduction of new immunosuppressants and prophylaxis strategies. The study aimed to investigate the epidemiological characteristics of infectious diseases after lung transplantation in the current era.
Materials and Methods: All patients who underwent lung or heart–lung transplantation at our institution between October 29, 2008 and April 3, 2019 were enrolled. We retrospectively reviewed the patients' medical records till April 2, 2020.
Results: In total, 100 consecutive lung transplant recipients were enrolled. The median follow-up period was 28 months after lung transplantation. A total of 127 post–lung transplantation bacterial infections occurred. Catheter-related bloodstream infection (25/84, 29.8%) was the most common within 6 months and pneumonia (23/43, 53.5%) was the most common after 6 months. Most episodes (35/40, 87.5%) of respiratory viral infections occurred after 6 months, mainly as upper respiratory infections. The remaining episodes (5/40, 12.5%) mostly manifested as lower respiratory tract infections. Seventy cytomegalovirus infections observed in 43 patients were divided into 23 episodes occurring before and 47 episodes occurring after discontinuing prophylaxis. Of 10 episodes of cytomegalovirus disease, four occurred during prophylaxis and six occurred after prophylaxis. Of 23 episodes of post–lung transplantation fungal infection, 7 were aspergillosis and all occurred after the discontinuation of prophylaxis.
Conclusion: Lung transplant recipients experienced a high burden of infection even after 6 months, especially after the end of the prophylaxis period. Therefore, these patients should be continued to be monitored long-term for infectious disease.

Keywords: Infection; Lung transplantation; Prophylaxis

INTRODUCTION

Infectious diseases are a major cause of early and late deaths after lung transplantation (LT) [1]. Post-LT infectious diseases generally follow a predictable time to onset [2], but with new

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Conflict of Interest
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potent immunosuppression strategies and more effective prophylactic antibiotic agents, the frequencies and temporal patterns of infections after LT have changed [3]. In addition, compared with other solid organ transplants, LT has a higher posttransplant infection rate [4], which is characterized by a higher multidrug-resistant (MDR) bacterial infection rate [5], a higher cytomegalovirus (CMV) infection burden [6], and a higher invasive fungal infection rate, particularly invasive aspergillosis [7]. Prophylactic duration of CMV infection in LT recipients is usually from 6 months to more than 1 year according to CMV seropositivity, but it is still controversial because of the occurrence of late-onset CMV diseases [8]. Many LT centers have generally used prophylactic strategies targeting *Aspergillus* species, but the optimal antifungal agent and duration of prophylaxis are still unclear [9].

Therefore, it is important to know the epidemiological changes of infectious diseases after LT and the pattern of infectious diseases during and after the prophylaxis periods to prevent and treat infections after LT. Relatively few studies have assessed recent changes of post-LT infections [10]. One study reported the recent burden and timeline of infectious diseases during the first year after transplantation in 2,761 solid organ recipients in Switzerland [4], but it was limited to understanding the difference between during and after prophylaxis of each infectious disease. Some studies have reported the incidence of certain infections after LT, but they only estimated the relative incidence and frequency of certain pathogens [7, 11]. Therefore, we investigated the epidemiological characteristics of clinically relevant infections after LT and the changes during and after the prophylaxis through comprehensive and consistent long-term follow-up over the past decade.

MATERIALS AND METHODS

1. Patient population

The study population consisted of all patients who received lung or heart–lung transplantation at our institution between October 29, 2008 and April 3, 2019. Data were censored at death, loss of follow-up, or April 2, 2020. We retrospectively reviewed the medical records of all patients. The immunosuppressive regimen consisted of induction therapy with basiliximab and triple therapy with tacrolimus, mycophenolate mofetil, and prednisone. Tacrolimus was given to a target trough level of 10 - 15 ng/mL for the first 6 months and 8 - 12 ng/mL thereafter. This study was approved by the institutional review board of the Asan Medical Center (2020-0994).

2. Pre-transplant screening

Before the LT procedure, recipient and donor sputum samples were cultured for bacteria, mycobacteria, and fungi. We also performed serological tests in recipients and donors for herpes viruses, hepatitis viruses (hepatitis A, B, and C), and human immunodeficiency virus. Latent tuberculosis was screened by the tuberculin skin test and QuantiFERON-TB Gold test (Cellestis, Carnegie, Australia) in recipients.

LT candidates without hepatitis A or B antibodies were vaccinated before transplantation. All LT candidates and recipients were recommended to receive annual influenza vaccinations. Since April 2010, a 13-valent protein-conjugated pneumococcal vaccine was used for priming before LT, followed 8 weeks later by a 23-valent polysaccharide vaccine.

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3. Prophylaxis strategies

Antibacterial prophylaxis was guided by donor and recipient sputum cultures and cefepime was administered intravenously for patients who were sputum culture negative. Regardless of the CMV serostatus of recipients and donors, intravenous ganciclovir was given for antiviral prophylaxis at a dosage of 5 mg/kg every 24 hours for 4 weeks after the LT. Oral valganciclovir was administered at a dosage of 900 mg once daily up to 6 months thereafter. CMV viremia was monitored regularly at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 weeks after LT, and then monthly or bi-monthly untill 1 year after LT. We changed the CMV monitoring method from CMV antigenemia (Chemicon, Temecula, CA, USA) to quantitative real-time polymerase chain reaction (Abbott Molecular Inc., Des Plaines, IL, USA) in June 2017. After the prophylaxis period, asymptomatic patients with more than 20 antigen-positive cells or viral load of more than 5,000 IU/mL were preemptively treated until clearance of CMV viral load (at least 2 weeks).

Voriconazole was administered intravenously at a dosage of 4 mg/kg every 12 hours for antifungal prophylaxis, and the target trough level was 1.5 to 5.5 mg/dL. We changed to oral voriconazole when the recipient was able to resume a normal diet. If voriconazole was poorly tolerated or adverse effects occurred, it was replaced by itraconazole. The total duration of antifungal prophylaxis was 6 months. Galactomannan (Platalia Aspergillus; Bio-Rad, Hercules, CA, USA) assays were performed regularly at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 weeks after LT, and then monthly or bi-monthly until 1 year after LT. Patients with 0.5 or greater optical density index of galactomannan assay were followed up more frequently (weekly or bi-weekly). If two consecutive positive galactomannan assays were seen, thoracic computed tomography scanning was performed for the patient. Oral trimethoprim/sulfamethoxazole (160/800 mg) was administered every other day for lifetime *Pneumocystis jirovecii* pneumonia prevention. If intolerable adverse effects of trimethoprim/sulfamethoxazole were seen, it was changed to dapsone.

4. Clinical definitions

The definitions of bacterial, viral, and fungal infections are based on the recommendations of the American Society of Transplantation [12]. Bloodstream infections were defined as primary when the focus could not be defined. Catheter-related bloodstream infections were defined as follows: positive simultaneous blood cultures from the central venous catheter and peripheral vein yielding the same organism along with either (1) the presence of significant catheter-tip colonization with 15 colony-forming units or more of the same organism isolated from the blood culture or (2) when the blood culture drawn through the central venous catheter became positive at least 120 minutes earlier than a positive culture drawn simultaneously from a peripheral vein [13].

Rejection was diagnosed via biopsy and classified according to the International Society for Heart and Lung Transplantation guidelines [14]. Pulmonary function tests were performed at every outpatient visit (every 1 - 3 months) for diagnosis and functional grading of chronic airway rejection. Chronic lung allograft dysfunction was diagnosed as a persistent decline in forced expiratory volume in 1 second of at least 20% compared with the two best postoperative values, in the absence of other causes [15].

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RESULTS

A total of 100 consecutive patients were enrolled in this study (88 bilateral lung and 11 heart–lung transplantation from deceased donors and 1 living donor lobar LT from her parents). The median follow-up period was 28 months (interquartile range [IQR], 13 - 60 months) after LT. **Table 1** shows the demographic and clinical characteristics of these patients. The median age of the patients was 51 years (IQR, 31 - 60 years), and the study series included 15 pediatric patients (age range, 1 - 16 years). The most common reason for LT was interstitial lung disease (58%). Most of the recipients (97%) and donors (96%) were seropositive for CMV before the LT. Antiviral prophylaxis was prematurely terminated in 37 patients (median duration, 84 days; range, 14 - 160 days), antifungal prophylaxis was prematurely terminated in 14 patients (median duration, 45 days; range, 6 - 130 days), and anti-pneumocystis prophylaxis was prematurely terminated in 15 patients (median duration, 151 days; range, 29 - 768 days). A total of 33 LT recipients died, and 21 recipients had infection-related mortality. The survival rates using the Kaplan-Meier method were 78%, 67%, and 63% at 1 year, 3 years, and 5 years, respectively.

Table 1. Demographic and clinical characteristics of the study population

Characteristics	n = 100
Median age, years (interquartile range)	51 (31 – 60)
Male sex	66
Disease leading to transplantation	
Interstitial lung disease	58
Bronchiolitis obliterans	13
Acute respiratory distress syndrome	11
Pulmonary hypertension	6
Cystic fibrosis	2
Bronchiectasis	2
Chronic obstructive pulmonary disease	1
Others	7
Transplantation type	
Bilateral lung	88
Heart–lung	11
Living donor lobar lung	1
Cytomegalovirus seropositivity	
Recipient	97
Donor	96
Premature termination of antiviral prophylaxis	37
Leukopenia	25
Thrombocytopenia	16
Others	2
Premature termination of antifungal prophylaxis	14
Elevation of hepatic enzymes	6
Hallucination	3
Drug interaction	2
Others	3
Premature termination of antipneumocystis prophylaxis	15
Elevation of creatinine	4
Hyperkalemia	2
Hyponatremia	2
Leukopenia	1
Thrombocytopenia	2
Others	4
Acute rejection	9
Chronic lung allograft dysfunction	12
Infection-related mortality	21
Overall mortality	33

Data are numbers of patients, unless otherwise indicated.

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1. Bacterial infections

A total of 127 episodes of post-LT bacterial infections were observed in the 57 patients during the study period. Thirty-one (24.4%) occurred within 1 month of the LT, 53 (41.7%) between 1 and 6 months, and 43 (33.9%) after 6 months (**Table 2**). Catheter-related bloodstream infection was the most common bacterial infection within 1 month of LT (8 out of 31 episodes, 25.8%) and between 1 and 6 months (17 out of 53, 32.1%). Pneumonia was the most common bacterial infection after 6 months (23 out of 43, 53.5%). *Mycoplasma pneumoniae* was only observed at 6 months after LT. MDR bacteria, such as methicillin-resistant staphylococci, vancomycin-resistant enterococci, and carbapenem-resistant or extended-spectrum ß-lactamase producing gram-negative bacilli, were frequently involved (84 out of 127 episodes, 66.1%) in these infections. Most *Pseudomonas aeruginosa* (23 out of 31 episodes, 74.2%) and *Acinetobacter baumannii* (27 out of 29, 93.1%) infections were associated with carbapenem-resistant organisms. Among the 100 LT recipients, 24 already had respiratory colonization with carbapenem-resistant *P. aeruginosa* (8 out of 24, 33.3%) or *A. baumannii* (17 out of 24, 70.8%). The incidence of bacterial pneumonia was not different between those colonized and not colonized (6 out of 24, [25.0%] *vs.* 21 out of 76, [27.6%]; $P = 0.80$ by the χ^2 test).

Table 2. Bacterial infections after lung transplantation in the study population

Time-to-occurrence (number of episodes)	<1 month (n = 31)	1 – 6 months (n = 53)	>6 months (n = 43)	Total (n = 127)
Primary bacteremia	3 (9.7)	3 (5.7)	1 (2.3)	7 (5.5)
Staphylococcus aureus	1	-	-	1
Enterococcus faecium	-	-	1	1
Pseudomonas aeruginosa	1	-	-	1
Acinetobacter baumannii	1	2	-	3
Stenotrophomonas maltophilia	-	1	-	1
CRBSI	8 (25.8)	17 (32.1)	11 (25.6)	36 (28.3)
Staphylococcus aureus	-	-	1	1
Coagulase-negative staphylococci	2	8	5	15
Enterococcus faecium	3	-	1	4
Corynebacterium species	-	-	1	1
Klebsiella pneumoniae	1	-	2	3
Pseudomonas aeruginosa	-	2	-	2
Acinetobacter baumannii	3	6	1	10
Burkholderia cepacia	-	1	1	2
Pneumonia	8 (25.8)	12 (22.6)	23 (53.5)	44 (34.6)
Staphylococcus aureus	2	1	1	4
Streptococcus pneumoniae	-	-	1	1
Klebsiella pneumoniae	1	1	2	4
Enterobacter cloacae	-	1	-	1
Pseudomonas aeruginosa	1	9	10	20
Acinetobacter baumannii	4	2	7	13
Stenotrophomonas maltophilia	-	-	2	2
Chryseobacterium species	-	1	-	1
Burkholderia cepacia	1	-	1	2
Mycoplasma pneumoniae	-	-	2	2
Empyema	7 (22.6)	2 (3.8)	1 (2.3)	10 (7.9)
Staphylococcus aureus	2	1	-	3
Coagulase-negative Staphylococci	2	-	-	2
Enterococcus faecium	2	-	-	2
Klebsiella pneumoniae	-	1	-	1
Pseudomonas aeruginosa	-	-	1	1
Acinetobacter baumannii	1	-	-	1
Burkholderia cepacia	1	-	-	1

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Table 2. (Continued) Bacterial infections after lung transplantation in the study population

Time-to-occurrence (number of episodes)	<1 month (n = 31)	1 – 6 months (n = 53)	>6 months (n = 43)	Total (n = 127)
Bronchial mass	-	1 (1.9)	-	1 (0.8)
Actinomyces odontolyticus	-	1	-	1
Biliary infection	-	5 (9.4)	3 (7.0)	8 (6.3)
Enterococcus faecium	-	2	1	3
Corynebacterium species	-	1	-	1
Escherichia coli	-	1	-	1
Pseudomonas aeruginosa	-	2	2	4
Pancreas pseudocyst infection	-	1 (1.9)	-	1 (0.8)
Pseudomonas aeruginosa	-	1	-	1
Peritonitis, CAPD	-	1 (1.9)	-	1 (0.8)
Enterococcus faecium	-	1	-	1
Colitis, *Clostridioides difficile*	2 (6.5)	5 (9.4)	3 (7.0)	10 (7.9)
Urinary tract infection	1 (3.2)	2 (3.8)	-	3 (2.4)
Enterococcus faecium	-	1	-	1
Escherichia coli	1	-	-	1
Pseudomonas aeruginosa	-	1	-	1
Wound infection	2 (6.5)	2 (3.8)	-	4 (3.1)
Staphylococcus aureus	1	-	-	1
Coagulase-negative Staphylococci	-	1	-	1
Klebsiella pneumoniae	-	1	-	1
Stenotrophomonas maltophilia	1	-	-	1
Pressure sore, infected, grade 3	-	2 (3.8)	1 (2.3)	3 (2.4)
Escherichia coli	-	1	-	1
Pseudomonas aeruginosa	-	1	-	1
Acinetobacter baumannii	-	1	1	2
Burkholderia cepacia	-	1	-	1

Data are numbers (%) of episodes. One episode could be polymicrobial infection.
CRBSI, catheter-related bloodstream infection; CAPD, continuous ambulatory peritoneal dialysis.

2. Mycobacterial infections

Ten patients received a 3-month course of isoniazid and rifampin or a 9-month course of isoniazid for latent tuberculosis infection before LT. There was no episode of active tuberculosis after LT. In one recipient with pneumoconiosis, active pulmonary tuberculosis was revealed by the pathology and tissue culture of recipient's own lung biopsy immediately after LT. One recipient developed *Mycobacterium abscessus* lung disease at 3.5 years after LT.

3. Viral infections

Most episodes of respiratory viral infections (35 out of 40, 87.5%) occurred at 6 months after LT (**Table 3**). Seventy-four percent of these were upper respiratory tract infections in this period. Whereas four of five episodes within 6 months (one within 1 month and three between 1 and 6 month) were pneumonia resulting from respiratory syncytial virus, influenza virus or coronavirus.

Seven episodes of varicella-zoster virus infections were observed in six patients. One patient developed herpes zoster on his arm three weeks after LT while taking prophylactic valganciclovir. The six other episodes occurred at 6 months after LT (four herpes zoster, one meningitis, and one chicken pox). Epstein-Barr virus-associated posttransplant lymphoproliferative disorders occurred in two pediatric patients at 5.5 months and 18 months after LT. Epstein-Barr virus hepatitis occurred in one adult patient at 19 months after LT.

A total of 70 episodes of post-LT CMV infections were observed in the 43 patients during the study period (**Table 4**). During antiviral prophylaxis, 19 episodes of breakthrough asymptomatic CMV viremia occurred within a median of 9 days after LT (range, 1 - 60 days).

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Table 3. Respiratory viral infections after lung transplantation in the study population

Time-to-occurrence (number of episodes)	1 month (n = 1)	1 – 6 months (n = 4)	>6 months (n = 35)	Total (n = 40)
Upper respiratory infection[a]	-	1 (25.0)	26 (74.3)	27 (67.5)
Influenza virus	-	-	9	9
Parainfluenza virus	-	1	5	6
Rhinovirus	-	-	8	8
Respiratory syncytial virus	-	-	2	2
Metapneumovirus	-	-	2	2
Coronavirus	-	-	3	3
Adenovirus	-	-	1	1
Pneumonia[b]	1 (100)	3 (75.0)	9 (25.7)	13 (32.5)
Influenza virus	-	1	3	4
Parainfluenza virus	-	-	2	2
Rhinovirus	-	-	4	4
Respiratory syncytial virus	1	1	2	4
Metapneumovirus	-	-	1	1
Coronavirus	-	1	-	1

Data are numbers (%) of episodes.
[a]Four co-infected episodes, rhinovirus/influenza virus or parainfluenza virus or respiratory syncytial virus or adenovirus.
[b]Three co-infected episodes, two rhinovirus/parainfluenza virus and one influenza virus/respiratory syncytial virus.

Table 4. Cytomegalovirus infections during and after valganciclovir prophylaxis in the study population

Time-to-occurrence (number of episodes)	During prophylaxis (n = 23)	After prophylaxis (n = 47)	Total (n = 70)
Asymptomatic infection	19 (82.6)	41 (87.2)	60 (85.7)
Preemptive therapy	-	12 (25.5)	12 (17.1)
Tissue invasive disease	4 (17.4)	6 (12.8)	10 (14.3)
Gastrointestinal disease	4 (17.4)	4 (8.5)	8 (11.4)
Retinitis	-	1 (2.1)	1 (1.4)
Pneumonia	-	1 (2.1)	1 (1.4)

Data are numbers (%) of episodes.

Four gastrointestinal CMV diseases occurred during prophylaxis. These included two proven and two possible CMV diseases [16], all of which were gastrointestinal CMV disease. After the end of prophylaxis, 41 episodes of asymptomatic infection and six tissue invasive diseases occurred. Among 41 asymptomatic infections, 12 required preemptive therapy. There was no episode of CMV syndrome during the study period.

4. Fungal infections

A total of 23 episodes of post-LT fungal infections were observed in the 21 patients during the study period (**Table 5**). The most common fungal infection was candidiasis (12 out of 23. 52.2%), including catheter-related candidemia. The incidence of invasive aspergillosis was 30.4% and that of invasive mucormycosis was 17.4%. Candidiasis was mainly caused by non-albicans *Candida* species (3 out of 4, 75%) during the antifungal prophylaxis and *Candida albicans* (4 out of 8, 50%) after the antifungal prophylaxis. During antifungal prophylaxis, three episodes of invasive mucormycosis occurred at 29, 37, and 85 days after LT. No episodes of invasive aspergillosis were observed. After the end of prophylaxis, seven episodes of invasive aspergillosis occurred within a median of 11 months after LT (range, 9 - 83 months).

DISCUSSION

In this study that comprehensively covers all clinically relevant infections over a 10-year period after LT in 100 patients, we found several important implications for direct patient care: (1) one-third of bacterial infections occurred more than 6 months after LT and MDR bacteria were frequently involved; (2) the minority of respiratory viral infections occurred

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Table 5. Fungal infections during and after voriconazole prophylaxis in the study population

Time-to-occurrence (number of episodes)	During prophylaxis (n = 7)	After prophylaxis (n = 16)	Total (n = 23)
Candidiasis	4 (57.1)	8 (50.0)	12 (52.2)
Catheter-related candidemia	2 (28.6)	4 (25.0)	6 (26.1)
Oral thrush	1 (14.3)	1 (6.3)	3 (13.0)
Esophageal candidiasis	-	1 (6.3)	1 (4.3)
Pancreas pseudocyst infection	1 (14.3)	-	1 (4.3)
Wound infection	-	1 (6.3)	1 (4.3)
Aspergillosis	-	7 (43.8)	7 (30.4)
Invasive pulmonary, probable	-	5 (31.3)	5 (21.7)
Colitis	-	1 (6.3)	1 (4.3)
Sinusitis	-	1 (6.3)	1 (4.3)
Mucormycosis	3 (42.9)	1 (6.3)	4 (17.4)
Bronchus, anastomosis site	1 (14.3)	-	1 (4.3)
Pulmonary cavity	1 (14.3)	-	1 (4.3)
Ecthyma gangrenosum, nose	1 (14.3)	-	1 (4.3)
Rhinoorbitocerebral	-	1 (6.3)	1 (4.3)

Data are numbers (%) of episodes.

within 6 months, but most of them were lower respiratory tract infections; (3) several gastrointestinal CMV diseases occurred during the prophylaxis; and (4) there were no episodes of invasive aspergillosis observed during antifungal prophylaxis, but seven episodes of invasive aspergillosis occurred after the end of prophylaxis.

According to the traditional timeline, most episodes of bacterial infections were known to occur within the first month after transplantation [2], whereas we observed that two-thirds (96 out of 127) of the bacterial infections occurred after the first month of transplantation. In addition, more than half of the cases of pneumonia (23 out of 44), which was the most common bacterial infection, appeared to occur more than 6 months after transplantation. Over the past decades, most episodes of pneumonia that occurred within the first month after transplantation were generally recipient-derived, or were associated with technical complications of surgery. More tailored prophylactic antibiotic therapy has attributed to a decline in the rate of early pneumonia, and recent studies have demonstrated that more than half of the episodes occurred late after solid organ transplantation (>6 months) [17]. Our findings that 53.5% of the episodes were classified as late pneumonia were consistent with this trend.

Of the 127 post-LT bacterial infections observed, 84 (66.1%) were caused by MDR bacteria. The increased risk of early infection and colonization by MDR bacteria in LT recipients is well known [18, 19], and it is potentially due to several factors [20], including long-term hospitalization, recurrent intensive care unit admission, and requiring frequent invasive procedures, such as prolonged tracheal intubation or a central vascular catheter. We also found this high risk of MDR bacteria in LT recipients was maintained more than 6 months after the LT.

In accordance with previous studies [19], the incidence of bacterial pneumonia was not different between those colonized and not colonized with carbapenem-resistant *P. aeruginosa* or *A. baumannii* (25.0% *vs.* 27.6%; *P=0.80*). In contrast, some recent studies have reported that pretransplant airway bacterial colonization of recipients was an independent risk factor of post-LT pneumonia [21]. The effect of pretransplant colonization of MDR bacteria on the short- and long-term outcome of LT recipient is still under debate, so pretransplant colonization of MDR bacteria should not be an absolute contraindication for LT.

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Respiratory virus infection after transplantation appeared in 2 different patterns 6 months after transplantation. Most (74.3%; 26 out of 35) of the respiratory viral infections that occurred more than 6 months after LT were presented as upper respiratory tract infections. On the other hand, 80% (4 out of 5) of the respiratory viral infections within 6 months were presented as pneumonia. This difference is likely related to the high concentration of immunosuppressive agents within 6 months after LT [22].

During the study period, 10 (10.0%) of the 100 CMV seropositive LT recipients developed CMV disease. This was notably higher than the incidence of CMV disease in kidney transplant recipients (4%, 15 out of 370) or heart transplant recipients (7%, 8 out of 108) reported in our previous studies [23, 24]. In addition, there were four episodes with breakthrough CMV disease during prophylaxis. All of these cases were gastrointestinal CMV disease (two were possible and two were proven disease) [16]. Therefore, even if CMV prophylaxis was being performed in LT recipients, the invasive tests (*e.g.*, endoscopic examination) had to be performed when CMV disease was suspected.

Interestingly, all cases of invasive aspergillosis occurred after the discontinuation of antifungal prophylaxis, and more than half of them (4 out of 7, 57%) developed within 6 to 12 months after LT. The high number of cases of delayed invasive aspergillosis that occurred after completion of the prophylactic voriconazole administration indicated continued postoperative antifungal prophylaxis for 12 months, but the invasive mucormycosis could not be prevented. As an alternative, it would be possible to consider changing the prophylactic antifungal agents from voriconazole to delayed-release posaconazole. However, there was a concern about MDR invasive fungal infections in patients receiving prophylaxis with posaconazole. In fact, a cross-sectional study that surveyed the 27 active LT centers in the United States showed that posaconazole was used as a prophylactic antifungal agent in only 5% of cases [9].

The main limitation of this study was its small-scale patient cohort in a single-center and its retrospective analysis. Another limitation was that only microbiologically proven infections were included, thus difficult-to-authenticate infections or self-limiting viral infections might have been underestimated.

In summary, we analyzed the epidemiology of infectious diseases that occurred after LT in 100 patients over 10 years of long-term follow-up. Most of the cases observed corresponded to the traditional timeline of infection after organ transplantation, but infectious diseases frequently occurred at a high rate of incidence even 6 months after transplant and were characterized as distinctive features during and after discontinuation of prophylactic antibiotics. Therefore, it was necessary to continue long-term monitoring and follow-up for various infectious diseases even after transplantation, especially after the end of preventive antibiotic administration. Such efforts would be helpful to improve the long-term outcome of LT recipients.

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