Review Article

The effect of infectious diseases on lung transplantation in Japan

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Abstract: Lung transplantation in Japan is an increasingly accessible treatment option for end-stage lung disease; however, the lack of donor organs is a persisting challenge. Five- and 10-year survival rates of lung transplant recipients in Japan are comparable, if not superior, to international standards. The outcomes of lung transplantation in Japan are likely affected by multiple factors. Infectious disease complications are a significant burden to transplant recipients and account for approximately 30% of recipient mortality in Japan, presenting a major challenge in peri-transplant management. Herein, we explore the current status of infectious disease epidemiology, available evidence surrounding infectious diseases in lung transplantation, and potentially influential factors pertinent to lung transplantation outcomes in Japan. Although infection remains the major cause of morbidity and mortality associated with lung transplantation in Japan, there is limited data and evidence. Despite some uncertainties, publicly available data suggests a low rate of antimicrobial resistance in Gram-negative bacteria and a distinct set of endemic pathogens that recipients may encounter. As a countermeasure against the burden of infectious diseases, 8 out of 10 transplant centers in Japan have a dedicated infectious diseases department. Despite these efforts, specific surveillance, prevention, and management are indispensable to improving post-transplantation infectious disease management. We accordingly lay out potential areas for improving infectious disease-related outcomes among lung transplant recipients in Japan.

Keywords: Lung transplantation; epidemiology; infectious diseases

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Introduction

Lung transplantation is a treatment option for end-stage lung disease (1,2). In 2021, 6,436 lung transplantations were performed globally (0.82 per million people), which has more than doubled since 2005 (2). Currently, deceased donor lungs comprise most of the lung transplants (2). However, there is a continuous lack of donor organs (3,4).

The survival of transplant recipients is affected by several factors, including acute cellular rejection, chronic rejection, and infectious diseases (5). The global 5-year and 10-year survival rates between 2002–2009 were approximately 56.8% and 36.1%, respectively, and the 5-year survival rate was 56.8% between 2010–2017 (6). According to the International Society for Heart and Lung Transplantation registry, mortality within the first thirty days after lung transplantation was mainly comprised of graft failure and non-cytomegalovirus (CMV) infections (7). Even

after the remainder of the first year and onwards, non-CMV infections constitute a major part of mortality, while bronchiolitis obliterans and chronic lung rejection also arise proportionally (7). Cumulatively, 21.3% of mortality from lung transplantation is caused by infection (both CMV and non-CMV infections) (7).

In contrast to global standards, lung transplantation performance in Japan has been noteworthy (6,8). For instance, the 5- and 10-year survival rates of deceased donor lung transplantation (DDLT) recipients in Japan were 73.0% and 60.7%, respectively (6,8). For living donor lung transplantation in Japan, the 5- and 10-year survival rates were also similar at 73.3% and 61.6%, respectively (6). Although survival after lung transplantation is comparable, if not superior, to international standards, morbidity and mortality among transplant recipients still have room for improvement (6). While a direct comparison is difficult given the difference in overall survival rates and lack of detailed information, infectious complications account for approximately 30% of cumulative recipient mortality in Japan, which is just as high, if not higher, than international standards (6,7). Consequently, managing infectious diseases is one of the major hurdles in further improving transplant outcomes in Japan.

Here, we describe the current situation concerning lung transplantation in Japan and the available epidemiologic data relevant to infectious diseases in lung transplantation. Although many uncertainties exist in this field, we also lay out potential future directions for improving morbidity and mortality in lung transplantation recipients.

Infectious diseases and lung transplantation in Japan

The unique aspect of lung transplantation in Japan

Japan is an island with a population of approximately 125.71 million (9). In Japan, lung transplantation was first conducted in 1998, which was after the implementation of the transplant law in 1997 (10). Until the revised organ transplant law in 2010, living-donor lobar lung transplantation (LDLLT) was the primary modality of lung transplantation due to a significant donor lung shortage (6). The revised transplant law amended the previous law by allowing the family of donation after brain death to decide on organ donation (10). In 2021, 93 lung transplants were conducted, equivalent to 0.74 transplants per million people (2). Currently, DDLT, accessible at ten institutions in Japan, is the major type of lung transplantation in Japan (6). Although lung transplantation continues to increase annually, Japan still faces an ongoing shortage of donor organs (6). For instance, 446 patients are on the waiting list in the Japan Organ Transplant Network (JOTN) as of 2020 (8). The allocation of deceased donor lungs is primarily based on the accrued time on the waiting list, favoring patients with slowly progressive diseases (10). Consequently, the average waiting time is over 900 days (including patients who have suspended their waiting status) (8). Moreover, the mortality rate of patients awaiting lung transplantation is high at approximately 37.3% (8).

Indications for DDLT are distinct among Japan and other countries (6). The major indications for lung transplantation in the United States (US) include idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (11). However, cystic fibrosis is rarely indicated in Japan due to its low incidence (6). In addition, donor shortages for DDLT have influenced the indications for lung transplantation in Japan (6,8). For instance, an age limit has been set for DDLT in which candidates should be below 55 years old for bilateral and below 60 years for single lung transplantation at the time of waitlist registration (8). Consequently, fewer patients with COPD are eligible for lung transplantation (6). As a result, the major indications for DDLT in Japan include IPF, lymphangiomatosis, interstitial pneumonia, and pulmonary hypertension (6). On the other hand, the major indications for living donor lung transplantation include post-hematopoietic stem cell transplantation lung injury, IPF, and pulmonary hypertension (6).

Infectious complications associated with lung transplantation

Infectious complications associated with solid organ transplantation (SOT) include donor and recipient-derived infectious diseases (12,13). In general, a myriad of pathogens can pose risks to lung transplant recipients (*Table 1*) (1,14-18). After transplantation, the risk of infectious disease can be divided into three phases (13). The phases can be categorized as: (I) the first month after transplantation; (II) 1–6 months after transplantation; and (III) 6 months after transplantation (13).

(I) In the first month after transplantation, the recipient is mainly subjected to nosocomial infections (13). These include hospital-acquired infections involving methicillin-resistant *Staphylococcus aureus* (*S. aureus*) and *Candida* infections at locations

Table 1 Potential pathogens to consider in infectious complications in lung transplantation according to pathogen type

Pathogens	Specific examples
A. Bacteria	
Gram-negative bacteria	*Enterobacteriaceae*†, *Pseudomonas aeruginosa*†, *Acinetobacter* spp.†, *Burkholderia cepacia*†, *Stenotrophomonas maltophilia*†
Gram-positive bacteria	*Staphylococcus aureus*†, *Enterococcus* spp.†, Coagulase-negative *Staphylococci*†, *Clostridioides difficile*†
Mycobacteria/atypical bacteria	*Mycobacterium tuberculosis*†, non-tuberculous mycobacteria†, *Nocardia* spp.†
B. Fungi	
Yeast	*Candida* spp.†, *Cryptococcus* spp.†, *Pneumocystis jirovecii*†
Mold	*Aspergillus* spp.†, Mucormycosis (*Rhizopus* spp., *Mucor* spp.)†, *Scedosporium* spp.†, *Fusarium* spp.†
Dimorphic fungi	*Histoplasma capsulatum*, *Blastomyces dermatidis*, *Coccidiodes* spp.
C. Virus	
DNA virus	HBV†, herpesviruses (HSV 1/2, VZV, CMV, EBV)†, adenovirus†
RNA virus	HCV†, influenza virus†, parainfluenza virus†, RSV†, human metapneumovirus†, SARS-CoV-2†, HIV†, HTLV-1†, West Nile virus†, Japanese encephalitis virus†, norovirus†, parvovirus†
D. Parasites	*Toxoplasma gondii*†, *Strongyloides stercoralis*†, *Leishmania* spp.†, *Trypanosoma cruzi*†, *Schistosoma* spp.†, *Taenia* spp.†, *Echinococcus* spp.†

†, potential pathogens that may be encountered in Japan. HBV, hepatitis B virus; HSV, herpes simplex virus; VZV, Varicella-zoster virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia virus type 1.

involving inserted catheters, drains, surgical sites, and anastomoses (12). Furthermore, donor-derived infections can manifest during this period (13). Recipient colonization by certain molds, the most prominent being *Aspergillus*, and drug-resistant bacteria, such as *Pseudomonas aeruginosa* (*P. aeruginosa*), can manifest as a disease post-transplantation (19-21).

(II) Once the recipient enters the 1–6-month post-transplant period, the recipient is at the highest risk for activation of latent and opportunistic infections (13). These include mycobacterial infections (*Mycobacterium tuberculosis* and non-tuberculous mycobacteria), fungal infections (including but not limited to *Cryptococcus neoformans*, *Pneumocystis jirovecii*), and viral infections, including hepatitis B and C, CMV, herpes simplex virus (HSV), Epstein-Barr Virus (EBV), and varicella-zoster virus (VZV) (13,22).

(III) Six months post-transplantation, the recipient becomes susceptible to community-acquired infections, ranging from pneumonia and urinary infections to community-acquired fungal and viral infections (*Aspergillus*, CMV, and other respiratory viruses) (13). These different at-risk periods overlap, and the list of differential diagnoses is broad, making the management of infectious diseases complicated in transplant recipients (13). Lung transplantation, in particular, is at a higher risk of infectious diseases than other SOTs due to continuous organ exposure to the environment, decreased clearance of microbes, and immunosuppression (12).

Epidemiology of infectious complications in lung transplant recipients in Japan

As mentioned above, approximately 30% of mortality in lung transplant recipients were from infectious complications in Japan (6); however, details on the mortality and morbidity of infectious complications, such as the incidence of various infections and the timing of their occurrence, are uncertain. To date, only a few reports have focused on post-transplant infectious complications in Japan. A retrospective study from Japan involving 85 lung transplant recipients revealed that the incidence of overall

survival, chronic lung allograft dysfunction-free survival, primary graft dysfunction, acute rejection, and intensive care unit stay was similar between groups with and without donor pneumonia (23). While postoperative antibiotic therapy was implemented longer in donors with pneumonia, these data suggest that perioperative antibiotic management may contribute to satisfactory outcomes in lung transplants with donor pneumonia (23). Other studies have focused on surveillance bronchoscopy post-transplantation and the prevalence of non-tuberculous mycobacterial (NTM) and *Aspergillus* infections among DDLT (24,25). However, no comprehensive data are currently available at the regional or national level. Despite some uncertainties, several inferences can be made from the publicly available infectious disease epidemiology among the general population in Japan.

Current status of bacterial infections associated with lung transplantation in Japan

Bacteria are among the most common pathogens encountered after lung transplantation (13). Along with mycobacterial infections, atypical bacteria, such as *Nocardia*, are also known to affect lung transplant recipients due to their predilection to the respiratory system (13). At-risk bacterial infections include both community and hospital-acquired infections, complicated by the increasing burden of antimicrobial resistance (AMR) (13,26). Lung transplant recipients experience a high incidence of infection with multidrug-resistant Gram-negative bacteria, mainly comprised of extended-spectrum beta-lactamase and carbapenem-resistant *Enterobacteriaceae*, ranging from 31% to 57% (27,28). On the contrary, the incidence of multidrug-resistant Gram-positive bacteria, mainly comprised of methicillin-resistant *S. aureus*, is approximately 30% (27,29). These figures likely differ depending on region/country and affect antibiotic modification in lung transplant recipients.

Since the release of the National Action Plan on Antimicrobial Resistance in 2016, Japan has implemented a one-health strategy against AMR (30-32). Several surveillance systems have been developed, including but not limited to the National Epidemiological Surveillance of Infectious Diseases (NESID) and the Japan Nosocomial Infections Surveillance (JANIS) (33,34). Recent data from 2019 suggest that the proportion of imipenem resistance remains relatively low among *Escherichia coli* (0.1%), *Klebsiella pneumoniae* (0.2%), and *P. aeruginosa* (16.2%) in 2019 (35). While the proportion of vancomycin-resistant *Enterococcus faecium* is also low, the proportion of methicillin-resistant *S. aureus* is high at approximately 48%, despite a decreasing trend (35). Consequently, the prevalence of AMR among Gram-negative bacteria is relatively low (35). However, data on AMR in lung transplant recipients in Japan need to be addressed in the future.

The incidence of NTM disease among lung transplant recipients in Japan is consistent with data from previous reports (36-38). A retrospective cohort study involving 240 consecutive lung transplant recipients revealed that five and eight patients were diagnosed with NTM disease pre-transplant and post-transplant, respectively (38). Interestingly, none of the pre-transplant recipients experienced a relapse of the NTM disease post-transplant under targeted antimicrobial therapy (38). Apart from NTM, Japan has been medium-endemic for tuberculosis (39). In recent years, however, tuberculosis cases have decreased annually, and the notification rate per 100,000 individuals has declined to 10.1 by 2020 (40). This figure is much lower than the global incidence rate of 134 per 100,000 individuals, leading to less tuberculosis exposure in lung transplant recipients in Japan (41).

Current status of fungal infections associated with lung transplantation in Japan

Fungal infections are mainly caused by yeasts or molds (13). The former mainly comprises *Candida* species and often manifests as fungemia post-transplant (13). While pneumonia caused by *Candida* species is rare, infection at the anastomotic site has been documented (1,42). Molds involve *Aspergillus* as the most common pathogen (1). Other molds include *Scedosporium* species, *Fusarium* species, *Mucor* species, and endemic fungi (1,43).

While the incidence of invasive fungal infections (IFIs) in lung transplant recipients in Japan remains uncertain, data from other countries are available. The Transplant-Associated Infection Surveillance Network (TRANSNET), a consortium of 23 US transplant centers, reported an 8.6% 1-year incidence of the first IFI for lung transplant recipients (second to small-bowel transplant recipients) (21). The most common IFIs in lung transplant recipients included aspergillosis (44%), candidiasis (23%), and other mold infections (19.8%) (21). Another study has reported that 72.7% of invasive mold infections are caused by *Aspergillus* species in lung transplant recipients (44). Within the non-*Aspergillus* infections, *Scedosporium* and *Mucor* comprised 12.8% and 7.7% (44). A retrospective

cohort study from Japan based on 240 consecutive lung transplant recipients revealed that six and seven recipients were diagnosed with aspergillosis pre-transplant and post-transplant, respectively (38). However, the burden of other fungi among lung transplant recipients in Japan is underexplored. Unlike other countries, including the US, Japan appears to have no notable endemic fungi except for sporotrichosis (45).

Along with the high incidence and direct sequelae of infection, *Aspergillus* species pose an increased risk of developing bronchiolitis obliterans (46). Moreover, infections due to *Aspergillus* species can manifest in a wide spectrum, ranging from colonization to invasive infections (46). In the early post-transplant phase, tracheobronchitis and anastomotic bronchial infection are some common presentations (47). Beyond 3 months post-transplant, the most common presentation becomes invasive pulmonary aspergillosis and systemic manifestations (47). Other clinical syndromes include allergic bronchopulmonary aspergillosis and aspergillomas (47). Mortality of invasive *Aspergillus* infections has historically been shown to exceed 50% in lung transplant patients (48,49). Invasive pulmonary infections exhibit higher mortality than tracheobronchitis, ranging from 67–82% and 23.7–29%, respectively (47-49). Single lung transplantation and late-onset disease are associated with higher mortality (47-51). Apart from the direct sequelae of *Aspergillus* infection, *Aspergillus* colonization is a known risk factor for developing bronchiolitis obliterans syndrome (BOS) (52,53). In one study, *Aspergillus* species with smaller conidia size were associated with the development of BOS, which may be due to higher dissemination into smaller airways (53). Prospective data on the burden of aspergillosis are awaited in the era of potentially better implementation of diagnostics, preventive measures, and therapeutic modalities.

Current status of viral infections surrounding lung transplantation in Japan

Post-transplant viral infections are diverse and involve herpes viruses (HSV, VZV, CMV, and EBV) as major causes (12,22). Particularly, CMV is associated with chronic allograft dysfunction and BOS, affecting long-term survival in lung transplant recipients (12). Lung transplant recipients are additionally prone to community-acquired respiratory viruses (CARVs), comprising mainly of influenza virus, parainfluenza virus, rhinovirus, metapneumovirus, adenovirus, coronavirus, and respiratory syncytial virus (15). These pathogens are associated with lower respiratory tract infections and can induce acute/chronic rejection in the recipient (15). In particular, CARVs are known to be risk factors for BOS, death from BOS, and death (54-56). Prevention based on hand hygiene and respiratory precautions is vital due to the scarcity of available vaccines against these agents, apart from influenza virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (15). Recently, however, a new vaccine has shown promise against RSV, which may have potential benefits in these vulnerable populations (15,57).

The current situation concerning viral syndromes pertinent to lung transplantation in Japan remains unclear. However, the seroprevalence of CMV in the general public has been studied and may provide insights into the risk of CMV infection in lung transplant recipients (58,59). In a systematic literature review of the global seroprevalence of CMV, 60.2% and 0.8% of women of reproductive age in Japan tested positive for CMV IgG and IgM, respectively (59). IgG seroprevalence was comparable to that in other countries, while IgM seroprevalence was slightly lower than that in Canada and the US, ranging from 2.3% to 4.5% (59). When focusing on adults aged ≥19 years, CMV IgG seroprevalence ranged from 67.2% to 70.9% (59). As a result, lung transplant recipients in Japan seem to have a comparable risk of CMV infection as in other countries (58,59).

While CARV infection in lung transplant recipients remains a topic of further investigation in Japan, data in the non-transplant population may be informative. An epidemiological study in the general population has shown that CARVs were identified in 36/131 outpatients presenting with community-acquired pneumonia, the major pathogen being either human enterovirus/human rhinovirus (60). In another study, infection due to CARV and CARV/bacterial co-infection comprised 8 and 9 cases out of 76 enrolled patients, exemplifying the significant burden of CARVs (61). The epidemiology of CARV during the coronavirus disease 2019 (COVID-19) pandemic has also been investigated and has shown that 1,215 out of 3,177 patients with community-acquired pneumonia were infected with a causative virus, the most common being human enterovirus/rhinovirus (n=655) and SARS-CoV-2 (n=264) (62). Overall, lung transplant recipients in Japan are likely exposed to CARV, similar to the general population; however, the exact burden, proportion among CARVs, and the outcomes associated with CARV infection remain to be elucidated. Since the introduction of the respiratory multiplex polymerase chain reaction panel in 2017,

more data are expected to accumulate in lung transplant recipients (63).

Other viruses endemic in Japan include human T-cell leukemia virus type 1 (HTLV-1) and Japanese encephalitis (JE) virus (17). HTLV-1 is known to be a causative agent of adult T-cell lymphoma/leukemia (ATL) and HTLV-1-associated myelopathy (HAM) (17). Several reports of HTLV-1 infection and development of HAM and ATL have been reported in heart, renal, and liver transplant recipients (64-68). Fifteen to 20 million people are estimated to be infected with HTLV-1, and relatively high HTLV-1 seroprevalence has been documented in Japan, the Caribbean area, Sub-Saharan African countries, and certain regions of Iran and Melanesia (17). The incidence rate of HTLV-1 in Japanese blood donors was estimated to be 3.8/100,000 person-years based on a nationwide study (69-71). Given the risk of prior infection, it is recommended to screen donors and recipients from endemic areas due to the potential morbidity and mortality from post-transplant HTLV infection, despite the role of immunosuppression in the development of disease being unclear (72,73). JE virus, one of the leading causes of meningoencephalitis in Southeast Asia and Western Pacific regions, is another endemic virus in Japan (74). In the general population, the case fatality rate is estimated to be approximately 14% in 2000–2018 (75). On average, 49% suffered from some form of neurological sequelae at least 1 year after discharge from the hospital (75). These figures suggest significant mortality and morbidity burden in endemic areas and stress the importance of vaccine implementation (75). To date, one case of JE has been reported in a lung transplant recipient who received a blood donation from a viremic donor (18). JE is no longer heavily prevalent in Japan, likely due to urbanization and vaccination (74,76). Between 2006–2015, JE incidence was 0.004/100,000 person-years, which approximate to 2–10 cases reported per year (76). Geographically, Western Japan is known to be more endemic (76). Given the increased opportunities for domestic/international travel, JE may be a consideration in a patient with neurological symptoms after transplantation (76).

Current status of parasitic infections associated with lung transplantation in Japan

Parasitic infections in lung transplantation are rare, although they pose a potential threat depending on the type of exposure. Post-transplant parasitosis comprises a diverse list of pathogens, including non-intestinal/intestinal protozoa/helminths (16). Some of the notable parasites noted in literature include *Toxoplasma gondii* (*T. gondii*), *Leishmania* spp., *Trypanosoma cruzi*, *Plasmodium* spp., *Cryptosporidium* spp., *Blastocystis* spp., *Microsporidia* spp., *Strongyloides stercoralis* (*S. stercoralis*), *Schistosoma* spp., and *Echinococcus* spp. (16). *T. gondii* infection has been described in non-cardiac transplant recipients, including one lung transplant recipient (77). A review of 52 toxoplasma cases after non-cardiac SOT showed that 46% were donor-transmitted, and 86% developed disease within 90 days after transplantation (78). Helminths also pose a threat to organ transplantation owing to immunosuppression and increased international travel (16). Within helminth infections, *S. stercoralis* can occur due to reactivation from latent infection, while donor-derived infections have also been reported (79). Pre-transplant recipient/donor screening for *Strongyloides* may be a potential strategy for averting post-transplant *Strongyloides* infection (79-81). *Echinococcus* spp. can cause the formation of hydatid cysts and alveolar echinococcosis (17). While *E. granulosus* is prevalent worldwide, *E. multilocularis* is frequent in the Northern Hemisphere (17). To date, there has been one case of alveolar echinococcosis arising in a lung transplant recipient (82).

Some major parasites potentially relevant to lung transplantation in Japan include *T. gondii*, *S. stercoralis*, and *Echinococcus* spp. (19). Parasitic infections in lung transplant recipients in Japan, however, have not been extensively studied to date. In general, the prevalence of *T. gondii* in Japan is low (83). For instance, a seroprevalence study in Hyogo prefecture, located in central western Japan, revealed an overall seroprevalence of 9.3% (238/2,564) (84). In pregnant women, the seroprevalence from the Western Pacific region is estimated to be 11.2%, while the global seroprevalence estimate is 32.9% (85). These data suggest that lung transplant recipients in Japan may have less exposure to *T. gondii* than in other countries. Between 2000 to 2017, 279 cases of *S. stercoralis* cases have been identified (86). The period incidence rate of the total population was 0.012 cases per 100,000 person-years (86). Most patients were reported from Okinawa and Kagoshima prefectures, located in Southern Japan, endemic for this pathogen (86). Finally, *E. multilocularis* is mainly distributed in Hokkaido, the northern island of Japan (87). Sporadic cases have also been reported on other islands of Japan, suggesting potential widespread distribution (88,89).

Table 2 Potential future steps in decreasing infectious disease complications among lung transplantation recipients

A. Evaluation of the current situation
Collection of microbiological data, including pathogens and their susceptibilities
Variability in ID management among transplant centers
B. Inter- and intra-institutional cooperation
Inter-institutional cooperation, including networking among transplant centers
Intra-institutional cooperation
Vaccination and prophylaxis protocols
Development of institution-specific ID guidelines
Transplant-specific antimicrobial stewardship programs
Defining metrics
Transplant recipient-specific antibiograms
Handshake stewardship
C. Re-evaluation and modification
Continuous & prospective collection of ID data to evaluate the effect of actions

ID, infectious diseases.

Influential background and strategies for decreasing infectious complications in Japan

The contributing factor behind favorable lung transplantation outcomes in Japan is an area of research. Undeniably, managing infectious complications plays a significant role, given its impact on transplant outcomes (90). Herein, we explore the factors that may indirectly affect the incidence of infectious complications in Japan. We discuss the unique cultural background and hygienic practices among the public and influential strategies relevant to better infectious disease management among lung transplant recipients.

Apart from immunosuppression, lung transplant recipients are particularly at risk of respiratory infections from decreased microbial clearance and continuous exposure of the donor organ to the environment (19). As a countermeasure, pharmacological preventive measures have been implemented for these recipients (19). Moreover, Japan has become accustomed to non-pharmacological preventive measures against respiratory pathogens through increased awareness of hand hygiene and mask-wearing (91). Historically, mask-wearing practices arose during the Spanish flu, which was theorized to set a barrier against pollution (91). Since the 1990s, mask-wearing has been integrated into cultural norms due to commercial, corporate, and political pressure (91). While these measures may be ritualistic among the public, the high proportion of social acceptance towards hygienic practices has promoted wider implementation (91). Recently, non-pharmacologic measures have gained attention due to the emergence of COVID-19 (92). Current evidence suggests that handwashing, mask-wearing, and social distancing are associated with a reduced incidence of COVID-19 (92). These results are likely to be related to other respiratory pathogens. Moreover, an indirect preventive effect is expected to benefit lung transplant recipients.

Management of infectious diseases in lung transplant recipients is aided by consultation with infectious diseases specialists (ID consultation) and antimicrobial stewardship programs (ASP) (90,93). Current evidence suggests that ID consultation in SOT recipients is associated with decreased mortality and rehospitalization (90). Moreover, early ID consultation seems to exert more beneficial effects by reducing healthcare resource utilization (90). Currently, 8 of 10 lung transplant centers have a dedicated department of infectious diseases (94-101). ASP also aids in optimizing antibacterial, antifungal, and antiviral interventions for infectious disease prevention (102). After implementing the national action plan on AMR in 2016, awareness of antimicrobial stewardship has increased, leading to significant reductions in the use of outpatient antibiotics (32). ASP has also become widely implemented, and 97.4% of hospitals with >500 beds have ASP (103). All hospitals offering DDLT have ASP (104-113). In summary, the accessibility to infectious disease consultation and ASP is well maintained for lung transplant recipients in Japan.

Future directions

The burden of infectious diseases among lung transplant recipients is high (6). Herein, we explore the specific challenges and potential future directions for addressing the current needs (*Table 2*) (93,114). Lung transplant recipients in Japan likely face risks of infection similar to other developed countries; however, recipients are additionally exposed to several pathogens that are endemic to Japan, including but not limited to HTLV, JE virus, *S. stercoralis*, and *Echinococcus* spp. Moreover, diagnostic modalities may be limited in some syndromes; for instance, respiratory multiplex polymerase chain reaction panel has only become available since 2017 (63,115). As a result, lung transplant

recipients in Japan may have had missed opportunities for diagnosis of CARVs (63,115). Apart from some of the obvious risks of infection in Japan, the detailed contributions of each infectious disease complication to morbidity and mortality in lung transplantation remain unclear. As a result, there is difficulty in setting priority for high-burden infections in Japan. In light of these uncertainties, the biggest challenge that Japan must overcome is to build an infrastructure capable of surveillance and collection of microbiological data, including but not limited to the syndrome, pathogen identification, and susceptibilities specific to lung transplant recipients.

In relation to surveillance, the variability in infectious disease management among transplant centers is also uncertain. Institution-specific infectious disease guidelines may exist, and comparisons can elucidate areas of uncertainty. Inter-institutional cooperation and close networking are vital in this regard (114). Specific modes of intervention include a reassessment of vaccination and prophylaxis protocols to ensure that transplant recipients receive maximal preventive effort. Institution-specific ID guidelines may also aid surgeons in taking an appropriate course of initial action against suspected episodes of infection. Another area of improvement may be strengthening transplant-specific ASP (93). Feasible actions include but are not limited to defining metrics, obtaining antibiograms specific to transplant recipients, and handshake stewardship for face-to-face discussions to optimize antimicrobial usage (93). These efforts require collaboration among multiple stakeholders within each institution, including transplant surgeons, ID consultation services, ASP, pharmacologists, and microbiologists (93). Ultimately, the prospective collection of infectious disease data is ideal for the re-evaluation and modification of applied interventions. While a major challenge in Japan, the surveillance of microbiological data, interinstitutional cooperation, and development of transplant-specific ASP are potential strategies also applicable to other nations (114,116-118).

Conclusions

The current landscape of infectious disease complications among lung transplant recipients in Japan is affected by several factors. The incidence and prevalence of major pathogens are distinct from those in other countries, particularly relevant to AMR. While several speculations can be made regarding the effectiveness of ID consultation and ASP in Japan, the true impact needs to be explored in the future. The scope for improvement of the management of infectious diseases in lung transplant recipients holds a significant prospect in Japan. Overall, our review presents the current status and future directions for improving morbidity and mortality from infectious diseases in lung transplantation recipients.

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