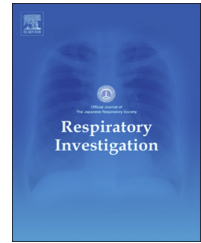




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Original article

Nontuberculous mycobacterial and *Aspergillus* infections among cadaveric lung transplant recipients in Japan



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ABSTRACT

Background: Lung transplantation is an effective treatment modality for respiratory failure. Chronic lung infections, including infections caused by nontuberculous mycobacteria (NTM) and *Aspergillus*, are difficult to control, and uncontrolled infections are relative contraindications for lung transplantation. However, few reports have documented the incidence and outcome of these infections in lung transplant recipients.

Methods: To quantify the incidence and outcomes of colonization and disease caused by NTM and aspergillosis in recipients before and after lung transplantation, we reviewed the medical records and microbiology data from 240 consecutive cadaveric lung transplant recipients between 2000 and 2014.

Results: Before lung transplantation, NTM and *Aspergillus* species were isolated from five (2.1%) and six (2.5%) patients, respectively, out of the total 240 recipients. All patients with NTM infection received treatment, resulting in culture conversion. They had no recurrence after lung transplantation. All patients with aspergillosis received treatment, one of whom

Abbreviation: NTM, nontuberculous mycobacteria; ATS/IDSA, American Thoracic Society/Infection Diseases Society America; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; EVLP, ex vivo lung perfusion; MAC, *Mycobacterium avium* complex

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had recurrence after lung transplantation. Over a median follow-up period of 3.3 years, NTM species were isolated after transplantation from eight of 240 patients (3.3%). Five of these patients met the criteria for NTM disease, and four of them received treatment. Four patients survived without a worsening of NTM disease. Over the same median follow-up period, *Aspergillus* species were isolated from seven of 240 patients (2.9%), six of whom received treatment.

Conclusions: Isolation of NTM or *Aspergillus* species from lung transplant recipients is uncommon. Adequate pre-transplant control and post-transplant management of NTM and *Aspergillus* infections allows for safe lung transplantation.

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1. Introduction

Lung transplantation is an effective treatment for respiratory failure, with a 5-year survival rate of 70% [1]. The current survival benefits and favorable outcomes mainly result from improvements in immunosuppression, anti-infective treatments, and surveillance strategies. Among a wide range of adverse effects and complications after solid organ transplantation, infections are common and potentially life threatening. Some of the most problematic infectious agents are mycobacterial and fungal pathogens [2].

Nontuberculous mycobacteria (NTM) occur in soil and water. They are increasingly being recognized as causes of pulmonary disease [3]. Structural lung disease, including interstitial pneumonias, primary pulmonary hypertension, and lymphangioleiomyomatosis are the most common indications for lung transplantation in Japan [1]. These underlying lung diseases may result in an increased risk of NTM infection during the pre- or post-transplant period. Potential risk factors for new or re-infection with NTM after lung transplantation are immunosuppression and the development of structural lung disease over time, secondary to bronchiolitis obliterans syndrome [4].

Aspergillosis is a mycotic disease caused by *Aspergillus* species, a genus of ubiquitous soil fungi. Pulmonary aspergillosis occurs almost exclusively in patients with structural lung disease and the compromised immunity that typically occurs in transplant recipients [5].

According to the International Society for Heart and Lung Transplantation's consensus document, uncontrolled NTM or *Aspergillus* infections are considered relative contraindications for lung transplantation [6]. In addition, only limited data on the incidence and conflicting data on the outcomes of these infections in the lung transplant population are available [4,7–9]. Therefore, we evaluated NTM and *Aspergillus* infections before and after lung transplantation in Japan.

2. Patients and methods

2.1. Study design

The study was a retrospective cohort study of all patients who underwent cadaveric lung transplantation between 2000 and 2014 at eight institutions in Japan: Tohoku, Dokkyo,

Chiba, Kyoto, Osaka, Okayama, Fukuoka, and Nagasaki Universities. To determine the clinical characteristics before and after transplantation, we retrospectively reviewed the patients' medical records. The data compiled included presenting features, reason for and type of transplantation, microbiology data, treatments, and post-transplant outcomes. Our retrospective review was approved by the ethics committee of Kinki-Chuo Chest Medical Center (approval number 560, October 20, 2016), Tohoku (approval number 2016-1-887, March 27, 2017), Dokkyo (approval number 28108, November 22, 2016), Chiba (approval number 2474, October 6, 2016), Kyoto (approval number R0934, November 28, 2016), Osaka (approval number 16348, May 30, 2017), Okayama (approval number 1611-013-001, November 9, 2016), Fukuoka (approval number 17-4-02, May 9, 2017), and Nagasaki Universities (approval number 17012313, January 24, 2017), and the need for informed consent was waived because of its retrospective nature. All patient data were anonymous.

2.2. Case definition

The diagnosis of pulmonary NTM disease was based on the modified criteria of the 2007 American Thoracic Society/Infection Diseases Society America (ATS/IDSA) [3]. Accordingly, a patient with a single NTM isolate from bronchoalveolar lavage or NTM isolation from two separate sputum samples, symptoms (cough, sputum, or fever), and compatible radiographic or CT imaging, if assessable, was considered to have NTM disease. NTM colonization was defined as the identification of NTM via culture of a bronchopulmonary sample in patients with no symptoms or radiologic signs of pulmonary NTM. The Guidelines for Management of Deep-Seated Mycosis were used to define *Aspergillus* infection [10]. Pulmonary *Aspergillus* infection was classified as “simple pulmonary aspergilloma”: a single cavitary disease containing a fungal mass, which is relatively stable over time and affects non-immunocompromised patients; “chronic progressive pulmonary aspergillosis”: a slowly progressive, being present for at least 1 month, and destructive disease of the lungs, usually of one or both upper lobes, with the formation of one or more fungal balls (aspergillomas); and “invasive pulmonary aspergillosis”: disseminated infection affecting the immunocompromised, which often starts in the lungs but may involve other organs and tissues through hematogenous spread [10].

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