Fungal infection in lung transplant recipients in perioperative period from one lung transplant center

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Background: This study aimed to analyze the distribution and prophylaxis strategy of pathogens causing fungal infection in lung transplant recipients from cardiac-brain dead donors in the perioperative period to provide evidence for antifungal prophylaxis and treatment in lung transplant recipients.

Methods: This retrospective study evaluated 194 lung transplant recipients from January 2015 to December 2016. Fungal pathogens were isolated and identified from respiratory tract cultures before and after transplantation in the perioperative period. The galactomannan (GM) testing of bronchoalveolar lavage fluid (BALF) might facilitate the diagnosis of *Aspergillus* infection. Data were statistically analyzed using SPSS 19.0.

Results: A total of 31 cases of fungal strains isolated from the 194 recipients were identified prior to lung transplantation, and the positive rate was 16.0% (31/194). A total of 27 cases of isolated fungal strains in the 194 recipients were identified, and the positive rate after lung transplantation was 13.9% (27/194) in the perioperative period. A total of 54 cases with positive fungal infection (27.8%) were detected before and after lung transplantation. Overall, 10.3% (20/194) of the lung transplant recipients developed fungal infection in the observation period. The most common fungal pathogens were filamentous fungi and *Candida albicans*.

Conclusions: Our data suggested that fungi were frequently isolated before and after transplantation from respiratory samples. However, the incidence of invasive fungal infection in lung transplant recipients in the perioperative period was relatively low. Targeted antifungal prophylaxis and treatment should be applied on the basis of the fungal distribution status of different individuals.

Keywords: Lung transplantation; fungal; infection; perioperative period

Introduction

The risk of fungal infection after lung transplantation is high. Fungal infection directly induces the occurrence of relevant complications after surgery and is closely correlated with the mortality of recipients in the perioperative period after lung transplantation (1,2). According to a study (3), the occurrence rate of fungal infection among patients with lung transplantation is approximately at 15–35%, and more than 80% of them are mainly induced by *Candida* and *Aspergillus*. Other fungi, such as *Trichosporon asahii* and *Fusarium*, are also involved in pathogenic processes. Invasive *Candida* infection has presented a decreasing occurrence rate among patients, but *Aspergillus* infection has posed a major risk of poor prognosis among individuals (4).

Table 1 Characteristics of the 194 recipients

Characteristics	Number
Sex, (%)	
Male	152 (78.4)
Female	42 (21.6)
Median age [range], years	54 [13–75]; IQR 45–63
Average days of hospitalization	49
Type of transplantation, (%)	
SL	93 (47.9)
BL	100 (51.5)
BL after SL	1 (0.5)
Underlying disease, (%)	
Cystic fibrosis	105 (54.1)
Chronic obstructive pulmonary disease	31 (16.0)
Silicosis	16 (8.2)
Bronchiectasis, (%)	14 (7.2)
Pulmonary infection	9 (4.6)
Pulmonary lymphangioleiomyomatosis	6 (3.1)
Bronchiolitis obliterans	4 (2.1)
Primary pulmonary hypertension	2 (1.0)
Others	7 (3.6)
Total number of transplants	194

BL, bilateral lung; SL, single lung.

Therefore, fungal distribution after lung transplantation should be investigated to select antibiotics and decrease fungal infection. In this study, we investigated the incidence of fungal infection in 194 patients with lung transplantation in the perioperative period and the fungal distribution among these patients.

Methods

Patients

This study involved a retrospective single-center analysis. Specimens were collected from patients with allogeneic single or bilateral lung transplants in Wuxi People's Hospital affiliated to Nanjing Medical University from January 2015 to December 2016. A total of 194 individuals received the transplant, and all of the donors came from citizen's voluntary donations. These donors were declared dead because of cardio-cerebrovascular diseases. The detailed information is shown in *Table 1*. The recipients and the donors shared the same blood type, presented negative lymphocyte cross matching, and exhibited a panel-reactive antibody <10%. The recipients were provided with regular extracorporeal circulation support and extracorporeal membrane oxygenation for lung transplantation. This study summarized the results of the fungal culture assays for *Candida* and *Aspergillus* from the sputum and bronchoalveolar lavage fluid (BALF) of the patients in the perioperative period. *Aspergillus* infection was diagnosed by detecting galactomannan (GM), which is an antigen of *Aspergillus*, from the serum of patients. The study was approved by the Research Ethics Board of Wuxi People's Hospital.

Definition and categories of fungal infections

In this study, fungal infections were defined and categorized based on fungal classification guidelines according to ISHLT and EORTC criteria (5). Fungal colonization was defined as isolation of fungi in the absence of clinical or radiographic evidence of invasive disease. Pulmonary fungal infection (PFI) based on symptoms, radiology, and histopathology and were categorized into proven, probable, or possible cases. Proven PFI had positive culture, symptoms suggestive of PFI, radiological findings or locally visualized purulent sputum without competing etiology, and positive histopathology or cultured organism from sterile tissue. Probable PFI were defined as those with clinical evidence of infection and positive culture and/or GM antigen assay, and absent or negative histopathology. Possible PFI meet a clinical standard, but there is no microbiological evidence.

Detection of fungal infection

Fungal infection was diagnosed on the basis of the clinical symbols of patients, tomography results, bronchoscopy, microbial detection, pathologic study, and GM detection. The sputum and BALF of patients with potential fungal infection were collected for fungal culture assays. The fungal strains were identified on the basis of morphological characteristics and through microscopic analysis by using standard taxonomic keys. In GM detection, if the result

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Table 2 Spectrum of fungal in 194 lung transplant patients during perioperative period

Fungal	Pretransplant		Post-transplant	
	Frequency	Incidence rate, %	Frequency	Incidence rate, %
Candida spp.	24	12.4	21	10.8
Candida albicans	19	9.8	16	8.2
Torulopsis glabrata	4	2.1	5	2.6
Candida Krusei	1	0.5	0	0
Filamentous fungi	8	4.1	7	3.6
Aspergillus species	5	2.6	5	2.6
Non-*Aspergillus* filamentous fungi	3	1.5	2	1.0
Total	32	16.5	28	14.4

from the sample [sample optical density (OD) value/average OD value of the critical control] was ≥0.5, it was considered positive.

Immunosuppression for the recipients

Cyclosporin A or tacrolimus was orally administered. A large dose of methylprednisolone was injected into the vein, and basiliximab treatment was conducted during the operation and 4 days after the operation to avoid the occurrence of reperfusion of the transplanted lung during operation. After transplantation was completed, tacrolimus or cyclosporin A, mycophenolate mofetil, and prednisone combination treatment was administered to maintain immunosuppression.

Statistical analysis

Descriptive statistics was used to characterize the study population. Chi-square analysis was performed to compare categorical variants based on the statistically analyzed data. Data were examined in SPSS 19.0, and $P<0.05$ was considered statistically significant.

Results

Fungal distribution before lung transplantation

At least one kind of fungal infection (16.0%) was detected in 31 recipients as observed in the specimens collected from the respiratory system of the 194 recipients. One of the recipients was detected with two kinds of fungi, namely, filamentous fungi and *Candida albicans*. The detected fungi

were mainly *Candida* (*C. albicans*, *T. glabrata*, and *C. krusei*) and filamentous fungi (*Table 2*).

Fungal distribution in the perioperative period after lung transplantation

After lung transplantation, 27 recipients were detected with at least one kind of fungi (13.9%) among the specimens collected from the respiratory system of the 194 recipients. One of the recipients had filamentous fungi and *C. albicans*. The detected fungi were mainly *Candida* (*C. albicans*, *T. glabrata*, and *C. krusei*) and filamentous fungi (*Table 2*). Of the 31 fungal infection-positive cases detected before transplantation, 4 had the same kind of fungi (2.1%). Of these 4 cases, 2 had *C. albicans*, and 2 had *T. glabrata* and *C. krusei* in the perioperative period after transplantation. A total of 54 cases were positive for fungal infection (27.8%) as shown by the summary of the cases before and after transplantation. The most common pathogens causing invasive fungal infections after lung transplantation were *Aspergillus* spp. and *Candida* spp. (most commonly *C. albicans*). *Aspergillus* infections remain among the most significant opportunistic infections after lung transplantation. The clinical manifestations of filamentous fungal infections were ulcerative tracheobronchitis, invasive pulmonary parenchymal diseases, disseminated multiple organ diseases and/or mycelia. *Candida* spp. infections often caused fungemia, mediastinitis and pleural space infection.

Detection of Aspergillus antigen (GM)
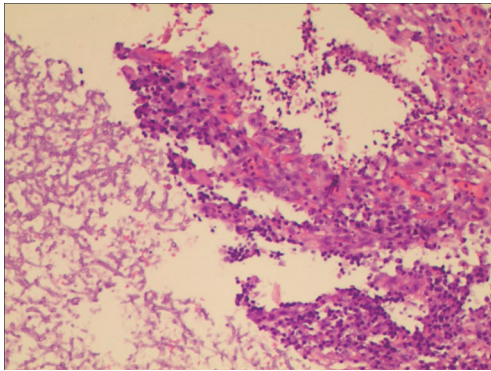
GM positive was determined in 6 recipients before

Figure 1 Microscopic appearance of lung tissue showed the fungal hyphae of *Aspergillus* (HE staining, ×400 magnification).

Figure 2 Microscopic examination of the culture sample showing annellidic and ampulliform conidiogenous cells along with large, globose, conidial heads (cotton-blue staining, ×1,000 magnification).

lung transplantation. The results ranged from 0.503 to 0.833 with an average of 0.603 before transplantation. After transplantation, GM positive was determined in 8 recipients, and the results ranged from 0.504 to 4.311 with an average of 1.423. Of these GM-positive recipients, 4 were detected with filamentous fungal infection before or after transplantation.

Fungal infection in the perioperative period after transplantation

The fungal detection assays of respiratory secretions and the analysis of the clinical symbols revealed that 20 cases of the 194 recipients were detected with fungal infection, including anastomosis infection and bronchial inflammation (10.3%), during the perioperative period

after transplantation. Of the 20 cases, 12 and 9 had fungal infection before and after transplantation, respectively, 6 were GM positive, 13 had filamentous fungal infection before or after transplantation, and 9 had confirmed *Aspergillus* infection (*Figures 1,2* and *Table 3*). There were 3 patients presenting with a post-transplant event by the same class as a pre-transplant event, and they were all colonized with the same species (*Aspergillus*). Among the 20 patients with post-transplant fungal infection, the 8 patients did not present pre-transplant fungal infection. Although pre-transplant fungal colonization or infection was significantly associated with pre-transplant fungal infection, however, not all patients colonized with fungal would develop subsequent fungal infection. The infection ratio between single- and double-lung transplantation did not significantly differ (χ^2=0.0907, P=0.7632). The effects of the basic diseases on the recipients with fungal infection did not also significantly differ (χ^2=3.6060, P=0.0576). Among lung transplant recipients with fungal infection, 60% (12/20) of infections were re-infection and 40% (8/20) of infections were *de novo* infection, respectively. The common pathogen species isolates that we see in lung transplant recipients were *Aspergillus* and *Candida*. Compared with the infection ratio between single- and double-lung, the difference was not statistically significant (χ^2=0.0907, P=0.7632). Compared with the impact of the basic diseases within the recipients to fungal infection, the difference was not statistically significant (χ^2=3.6060, P=0.0576).

Discussion

Fungal infection is a common complication among the recipients of lung transplantation. The most common fungi causing infection include *Candida* and *Aspergillus* (5). *Candida* constitutes the majority of the infected fungi (43–80%) in the perioperative period after lung transplantation (3). In our study, 75% of the cases were attributed to *Candida*. Although *Candida* is commonly observed in fungal infection, it is usually found in the pharynx oralis. As such, whether the detected *Candida* is colonized or obtained from external invasion is difficult to determine. *Candida* infection frequently occurs 1 month after transplantation and is a common cause of invasive fungal infection. *Candida* infection is usually correlated with ICU duration and *Candida* colonization before transplantation and surgery. However, *Candida* rarely causes pulmonary parenchyma infection in the lungs (6).

Aspergillus, which is commonly distributed in the

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Table 3 Baseline characteristics of 20 patients with fungal infection (20 cases) in perioperative period

No.	Sex	Age	Underlying lung disease	Pre-transplant fungal culture	Post-transplant fungal culture	GM index
1	Male	40	Cystic fibrosis	*Aspergillus*	–	–
2	Male	53	Cystic fibrosis	Non-*Aspergillus* Filamentous fungi	–	–
3	Male	33	Bronchiectasis	*Candida albicans*	–	–
4	Male	59	Cystic fibrosis	Non-*Aspergillus* Filamentous fungi	–	–
5	Male	45	Cystic fibrosis	Non-*Aspergillus* Filamentous fungi	–	–
6	Male	62	Cystic fibrosis	*Candida albicans*	–	–
7	Male	39	Cystic fibrosis	*Aspergillus*	–	1.681
8	Male	65	Cystic fibrosis	*Aspergillus*	*Aspergillus*	–
9	Male	49	Silicosis	*Candida albicans*	–	–
10	Female	63	Cystic fibrosis	*Candida albicans*	–	–
11	Male	59	Cystic fibrosis	*Candida albicans*	–	–
12	Male	52	Cystic fibrosis	–	Non-*Aspergillus* Filamentous fungi, *Candida albicans*	–
13	Male	63	Cystic fibrosis	–	*Aspergillus*	4.311
14	Male	60	Cystic fibrosis	–	*Aspergillus*	–
15	Male	37	Cystic fibrosis	–	*Candida albicans*	–
16	Female	42	Bronchiectasis	–	*Candida albicans*	–
17	Male	48	Bronchiectasis	–	*Aspergillus*	0.513
18	Male	65	Chronic obstructive pulmonary disease	–	*Aspergillus*	1.37
19	Male	33	Silicosis	–	*Aspergillus*	0.658
20	Male	60	Cystic fibrosis	*Aspergillus*	–	0.546

The hyphens (–) indicate undetected or negative results. GM, galactomannan.

environment, is a common cause of invasive fungal infection. For individuals with a normal immune system, *Aspergillus* does not cause any invasive *Aspergillus*-related diseases. However, *Aspergillus* causes a high risk of disease occurrence for recipients of lung transplantation with a compromised immune system. Luong *et al.* (7) reported that approximately 40% of lung transplant recipients have *Aspergillus* colonization in the respiratory system, and 6–16% of them develop invasive *Aspergillus*-related diseases. Colonization is usually transient, however, it increases the risk of invasive disease. Invasive aspergillosis

is considered a major problem in lung transplantation. Patients with lung fibrosis have a high risk of *Aspergillus* infection. Luong *et al.* (8) indicated that 70% of patients with pulmonary cystic fibrosis have *Aspergillus* colonization before lung transplantation, and 22.5% of them develop invasive *Aspergillus*-related diseases. The average period of the infection is 42 days after transplantation. The occurrence rate of the disease is four times higher than that of the recipients with non-*Aspergillus* colonization in the respiratory system. The clinical center managing lung transplantation diagnosed a total of 194 recipients

before and after lung transplantation. A total of 13 cases (6.7%) with non-repeated filamentous fungal infection were reported. Nine cases of *Aspergillus* infection, which accounted for 4.6%, were detected. On the basis of the results of a prognosis study on 328 cases of lung transplantation, Hosseini-Moghaddam *et al.* (4) found that the fungal infection rate within 1 year is 21.6%, and 8.8% of cases are diagnosed as *Aspergillus* infection. Solé and Salavert (3) retrospectively studied 251 cases of lung transplantation and found that 86 cases (approximately 34%) have *Aspergillus* infection. Data from different transplantation centers remarkably differ, indicating that the clinical criteria of *Aspergillus* infection, *Aspergillus* culture assay, data collection timing, and fungal prophylaxis methods may vary across different centers. In addition, a sensitive biomarker is not established in the diagnosis of invasive *Aspergillus* infection. Thus, an insufficient frequency of patients for fungal culture assay and *Aspergillus* antigen detection affects the calculation of the occurrence of *Aspergillus* infection. The infection rate summarized from our center was comparatively low because of the limited detection on the recently diagnosed patients after transplantation. By contrast, the prophylaxis and treatment of fungi efficiently decreased the occurrence rate of fungal infection. *Aspergillus* infection in the perioperative period after lung transplantation involves colonization, bronchitis, anastomosis infection, invasive pulmonary aspergillosis (IPA), and disseminated *Aspergillus* diseases. Although *Aspergillus* colonization of the respiratory system presents irrelevant symbol at the early stage, the later stage after transplantation usually induces bronchiolitis obliterans syndrome (BOS). Multivariate regression analysis has shown that *Aspergillus* colonization is an individual risk factor of BOS (9). The death rates between the patients with *Aspergillus* anastomosis infection in the perioperative period and the patients without an obvious infection symptom were not significantly different. However, a retrospective study showed that *Aspergillus* colonization decreased the long-term survival rate (4). The occurrence rate of IPA is approximately 5–10% and usually observed in patients with severe immunodeficiency, but the death rate of these patients can reach 80% (6). In the study, one of 20 fungal infection patients died after transplantation was detected with IPA-related during in the perioperative period. *Aspergillus* fumigatus, the most pathogenic *Aspergillus* species, produces the most infections, however, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger* have been increasingly reported in invasive pulmonary

infection. *Aspergillus* spp. is by far the most common fungal disease caused by fungi, although non-*Aspergillus* fungi have become an important and increasingly more common pathogens. However, in lung transplant recipients, the scope and overall impact of these emerging fungal pathogens have not been fully determined (3).

The prophylaxis and treatment of fungal infection at the early stage are important because fungal infection after lung transplantation rapidly develops and causes severe outcomes. Anti-fungal drugs are widely used among patients with lung transplantation, including the universal prophylaxis for all recipients after transplantation and preemptive treatment for patients with fungal colonization (4). However, no unified criteria for the prophylaxis and treatment of fungal infection have been presented (10-12). In our center, all patients received intravenous administration of antifungal prophylaxis drugs included by echinococcin or triazole combined with inhaled amphotericin B or liposomal immediately after lung transplant. Because most of the recipients in our center were older and weaker, echinococcins were generally chosen as the initial regimen for systemic drug medication for the comprehensive consideration of the efficacy and safety of drugs. Among the 20 recipients in this group, 17 recipients were given caspofungin or micafungin, however, in the other 3 recipients with *Aspergillus* colonization or infection before operation, voriconazole was as the first choice. The target prophylaxis strategy should be based on the results of regular bronchoscopy and fungal culture assay. We normally apply fluconazole for *C. albicans* infection. For *Aspergillus* colonization, 85% of transplantation centers applied one or two kinds of anti-fungal medicines. The frequently used medicines included oral voriconazole (80.0%). Voriconazole has an anti-fungal capacity for a wide profile of fungal species and low minimum inhibitory concentration (MIC) values. However, its long-term usage is limited by strong liver toxicity and interactions among different immunosuppression medicines. The inhaled amphotericin B treatment has limited toxicity to individuals, can directly target fungal infected tissues, has a high utilization of individuals, and cannot induce drug resistance. For the target prophylaxis strategy, 55% of transplantation centers can proceed from 3 months to 1 year (12). A universal prophylaxis strategy is applied within 3 months after transplantation, and personalized prophylaxis strategies are performed on the basis of different individuals. For patients with *Aspergillus* colonization before or after lung transplantation, anti-fungal prophylaxis and treatment can last 3 months, thereby efficiently decreasing the occurrence

rate of IPA (4,12,13).

For the treatment of IPA, most of the transplantation centers selected 3 to 5 anti-fungal drugs with a course of treatment of more than 1 year. The frequently used drug was voriconazole followed by amphotericin B and echinocandins (e.g., micafungin and caspofungin). Interactions with immunosuppression agents should be considered when recipients take voriconazole (14,15). According to a recent study, some of the cases with *Aspergillus fumigatus* are resistant to voriconazole and itraconazole (16). The occurrence of voriconazole and itraconazole-resistant molds, or the emergence of secondary resistance to amphotericin B, challenges the choice of antifungal drugs applied as first-line treatment. In our center, the therapeutic strategies included intravenous caspofungin, micafungin, voriconazole, posaconazole, amphotericin B, nebulized amphotericin B or amphotericin B liposome, gargled mycostatin, combined with interventional bronchoscopy. For the treatment of *Candida* infection after lung transplantation, fluconazole can be applied to treat patients with decreased non-polymorphonuclear leukocytes and patients at a low risk of *C. glabrata* and *C. krusei* infections. For patients with severe *Candida* infection, echinocandins and amphotericin B liposome are the first-line empiric treatment. Empiric treatment should be adjusted on the basis of the results of fungal culture assay and drug sensitivity test. The course of treatment is different based on the infection level and severity of patients (17). *Candida* treatment normally lasts 2 weeks, and invasive fungal infection persists longer for treatment (18).

In conclusion, our data showed the high risk of fungal infection in the perioperative period after lung transplantation. The main fungal genus was *Candida*, especially *C. albicans*. The fungal infection induced by *Aspergillus* frequently occurred and had a poor prognosis. Bronchoscopy, fungal culture assay, and GM detection should be conducted for patients with a suspected fungal infection in the perioperative period after lung transplantation. GM detection may facilitate the diagnosis of IPA after lung transplantation. But the value of GM is limited, negative results do not exclude invasive fungal infections. The gold standard of diagnosis includes fungal culture and microscopic examination of the infected tissue. It suggested that routine pre-transplant fungal sputum culture, and most importantly, intraoperative BALF culture from the native lung, is useful for identifying higher-risk patients with IPA. It is important for developing efficient targeted preventative strategies to reduce IPA-related the morbidity and mortality. Targeted prophylaxis and treatment should be performed to treat fungal infection on the basis of the results of fungal distribution. However, these processes vary among centers because different transplantation centers have various prophylaxis and treatment strategies against fungal infection. Therefore, relevant strategies from different centers should be summarized to establish the criteria in the selection of anti-fungal drugs and the preparation of dosage and course of treatment.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This project was approved by the Research Ethics Board of the Affiliated Wuxi People's Hospital of Nanjing Medical University (approval No. HS2019011).

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