Long-Term Pulmonary Infections in Heart Transplant Recipients

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Abstract

Objectives: **Pulmonary infections are life-threatening complications in heart transplant recipients. Our aim was to evaluate long-term pulmonary infections and the effect of prophylactic antimicrobial strategies on time of occurrence of pulmonary infections in heart transplant recipients.**

Materials and Methods: **Patients who underwent heart transplantation between 2003 and 2013 at Baskent University were reviewed. Demographic information and data about immunosuppression and infectious episodes were collected.**

Results: **In 82 heart transplant recipients (mean age, 33.85 y; 58 male and 24 female), 13 recipients (15.8%) developed pulmonary infections (mean age, 44.3 y; 9 male and 4 female). There were 12 patients who had dilated cardiomyopathy and 1 patient who had myocarditis before heart transplantation; 12 patients received immunosuppressive therapy in single or combination form. Pulmonary infections developed in the first month (1 patient), from first to third month (6 patients), from third to sixth month (1 patient), and > 6 months after transplantation (5 patients). Chest computed tomography showed consolidation (unilateral, 9 patients; bilateral, 4 patients). Multiple nodular consolidations were observed in 2 patients and a cavitary lesion was detected in 1 patient. Bronchoscopy was performed in 6 patients; 3 patients had *Aspergillus fumigatus* growth in bronchoalveolar lavage fluid, and 2 patients had *Acinetobacter baumannii* growth in sputum. Treatment was empiric antibiotics (6 patients), antifungal drugs (5 patients), and both antibiotics and antifungal drugs (2 patients); treatment period was 1-12 months in patients with invasive pulmonary aspergillosis.**

Conclusions: **Pulmonary infections are the most common cause of mortality in heart transplant recipients. A. fumigatus is the most common opportunistic pathogen. Heart transplant recipients with fever and cough should be evaluated for pulmonary infections, and invasive pulmonary aspergillosis should be suspected if these symptoms occur within the first 3 months. Immediately starting an empiric antibiotic is important in treating pulmonary infections in heart transplant recipients.**

Key words: Acinetobacter baumannii, Aspergillus fumigatus, *Heart transplantation, Immunosuppression*

Introduction

Pulmonary infections are commonly observed after heart transplantation. Pneumonia may occur in 30% patients. In an analysis from Mayo Clinic, the incidence decreased over three 5-year periods from 40% to 18%.[1] Risk factors for pneumonia include longstanding heart failure, subclinical multiple organ failure, potential postoperative extracorporeal assistance, and heavy immunosuppression. Post-operative lung dysfunction may result from a complicated surgical procedure, phrenic nerve and diaphragmatic dysfunction, hemorrhage, re-exploration at the surgical site, pulmonary embolism, and infections. Other factors include prolonged intubation, the effects of sternotomy on respiration, and intensive immunosuppression.[2]

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After early graft failure, infections are the second leading cause of death in heart transplant recipients, and the lungs rank first as the infection site. Pneumonia occurs within the first 4 to 6 months after transplantation and may occur from nosocomial infection, community-acquired bacteria, opportunistic microorganisms, and *cytomegalovirus*. The incidence ranges from 20% to 30% and mortality rate is 30%.[3-6] The highest fatality rate is recorded for *Aspergillus* infections (62%), despite a substantial decrease in incidence and mortality in the most recent series.[7]

We sought to evaluate long-term pulmonary infections in heart transplant recipients and to evaluate the effect of prophylactic antimicrobial strategies on time of occurrence of pulmonary infections after heart transplantation.

Materials and Methods

Study population

Patients who underwent orthotopic heart transplantation from 2003 to 2013 at Baskent University were reviewed. Demographic information, type of immunosuppression, perioperative infectious prophylaxis, follow-up clinical information, incidence of rejection, and the type of infectious episodes were collected from our transplantation database and clinical laboratory information system. Infections were listed according to the type of organism, organ involved, time of onset after transplant, and clinical outcome. Available bronchoscopy and microbiology data also were collected. The study was approved by the local ethics committee.

Diagnostic criteria

Lower respiratory tract infection was defined as *the presence of cough with purulent sputum production, temperature > 38°C, and leukocytosis with response to appropriate antimicrobial therapy*. Pneumonia was defined to include these symptoms and signs and new lung infiltrates on radiography. Although microbiologic studies were ordered, a positive result was not mandatory to confirm the diagnosis.

Cases of invasive pulmonary aspergillosis (IPA) were identified according to the Clinical Practice Guidelines of the Infectious Diseases Society of America for IPA.[8] The diagnosis was considered definite if the patient had positive histology and culture of a sample obtained from the same site or negative histology (or none done) with positive culture results of a sample obtained by protocol-specified invasive techniques (bronchoalveolar lavage [BAL], bronchial washings, brushings, or needle aspiration). The diagnosis was considered probable if;

(1) The heart transplant recipient with unexplained respiratory symptoms had abnormal chest radiographic findings and
(2) if an invasive procedure was contraindicated, the patient should have 2 positive cultures of sputum or throat samples or 1 positive culture result of a smear of a bronchoscopy specimen, or
(3) the patient should met criteria for definite invasive aspergillosis in any other organ system.[8] Positive serum galactomannan levels also suggested the diagnosis of IPA in which false positive results were excluded. Some antibiotics may cause false-positive results. The greatest problem has been in patients receiving piperacillin-tazobactam, amoxicillin, or amoxacillin-clavulate.

Statistical analyses

Data from case forms were extracted, entered into a central database, and analyzed.

Results

Patients

In a total of 82 heart transplant recipients (mean age, 33.85 y; range, 2-31 y; 58 male and 24 female), 13 patients (15.8%) developed pulmonary infections (mean age, 44.3 y; range, 20-61 y; 9 male and 4 female) (Table 1).

Indications for heart transplant

The indications for heart transplant in patients with pulmonary infections were dilated cardiomyopathy in 12 patients and myocarditis in 1 patient (Table 1).

Prophylaxis and immunosuppressive treatment

All patients received trimethoprim, sulfamethoxazole, and valganciclovir prophylaxis, and 13 patients received immunosuppressive therapy in single or combination form (Table 1).

Clinical manifestations

Pulmonary infections developed in the first month (1 patient), from first to third month (6 patients), from

third to sixth month (1 patient), and > 6 months after transplant (5 patients). Presenting symptoms were cough and/or fever (Table 1).

Radiographic manifestations

Chest computed tomography showed unilateral consolidation in 9 patients and bilateral consolidation in 4 patients. Multiple nodular consolidations were observed in 2 patients, and a cavitary lesion was detected in 1 patient (Table 2).

Microbiologic manifestations

Bronchoscopy was performed in 6 patients. There were 3 patients who had *Aspergillus fumigatus* growth in BAL fluid, and 2 patients had *Acinetobacter baumannii* growth in sputum (Table 2). Six patients developed pulmonary infections between the first to third month, 5 patients after 6 months, 1 patient in the first month, and 1 patient between the third and sixth months after heart transplantation. The other 8 patients had no growth in BAL (3 patients), sputum (3 patients), deep tracheal aspirate (1 patient), or pleural effusion (1 patient).

Treatment

Treatment was empiric antibiotics (6 patients), antifungal drugs (5 patients), and both antibiotics and antifungal drugs (2 patients); treatment period was 1 to 12 months in patients with IPA.

Prognosis

There were 4 patients who completely improved, 3 patients who remained on antifungal treatment, 3 patients who died because of rejection, and 3 patients who died because of pulmonary infection.

Discussion

Pulmonary infection is a common complication after heart transplantation. Despite improvements in the prevention of pneumonia, occurrence of pneumonia was independently predictive of mortality in this population.[9] In this study, the incidence of pulmonary infection was 15.8% in heart transplant recipients.

The risk for pulmonary infection increases due to elevated immunosuppression.[10] The immuno-

Table 1. Demographics of the Patients, Indications for Heart Transplantation, Prophylaxis, and Immunosuppressive Drug Regimen

Case	Age (y)	Sex	Indication	Perioperative Prophylaxis	Immunosuppressive Drugs
1	50	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil cyclosporine
2	50	Female	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil
3	22	Female	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone
4	32	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil tacrolimus
5	26	Female	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil tacrolimus
6	54	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole Valganciclovir	Prednisolone mycophenolate mofetil
7	61	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil tacrolimus
8	61	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Mycophenolate mofetil cyclosporine
9	43	Male	Myocarditis	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone azathioprine
10	38	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil tacrolimus
11	58	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil tacrolimus
12	20	Female	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone cyclosporine
13	61	Male	Dilated cardiomyopathy	Trimethoprim/sulfamethoxazole valganciclovir	Prednisolone mycophenolate mofetil tacrolimus

Abbreviation: MELD, model for end-stage liver disease

Table 2. Clinical and Radiographic Manifestations, Treatment Regimens, and Follow-Up of Heart Transplant Recipients With Pulmonary Infections

Case	Symptoms	Thoracic Computed Tomography	Culture Result	Treatment	Treatment Duration (mo)	Follow-up
1	Fever Cough	Unilateral consolidation	No growth	Empiric antibiotic	< 1	Died
2	Cough	Bilateral consolidation	*Acinetobacter baumannii*	Empiric antibiotic	1-3	Died
3	Cough	Unilateral consolidation	*Acinetobacter baumannii*	Empiric antibiotic + antifungal		
	< 1	Died				
4	Cough	Unilateral consolidation	No growth	Empiric antibiotic	< 1	Improved
5	Cough	Unilateral consolidation	No growth	Empiric antibiotic	< 1	Improved
6	Cough	Bilateral consolidation	*Aspergillus fumigatus*	Antifungal treatment	1-3	Still on antifungal
7	Fever	Bilateral consolidation	*Aspergillus fumigatus*	Antifungal	1-3	Still on antifungal treatment
8	Fever Cough	Bilateral consolidation	No growth	Antifungal	3-6	Died
9	Fever	Unilateral consolidation	*Aspergillus fumigatus*	Antifungal	< 1	Died
10	Fever Cough	Unilateral consolidation	No growth	Antifungal	1-3	Died
11	Cough	Unilateral consolidation	No growth	Empiric antibiotic + antifungal	1-3	Still on antifungal treatment
12	Fever	Unilateral consolidation	No growth	Empiric antibiotic	< 1	Improved
13	Cough	Unilateral consolidation	No growth	Empiric antibiotic	< 1	Improved

suppressive agents used in transplant are composed of a triple regimen of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and corticosteroids. Higher doses of each drug are administered early postoperatively when the risk of acute rejection is greatest; therefore, infection is of major concern, especially during the first 1 to 3 months after heart transplantation. Both cyclosporine and tacrolimus inhibit the activation and proliferation of T cells by inhibiting interleukin-2 production. Azathioprine is a purine analog that prevents the proliferation of activated B and T lymphocytes; therefore, both cell mediated and humoral immunity are affected. Mycophenolate mofetil often is substituted for azathioprine because it inhibits de novo purine synthesis and lymphocyte proliferation.[11] Corticosteroids are nonspecific in their effect and lead to a reduction in neutrophil chemotaxis, antigen presentation, T-cell activation and proliferation, and macrophage function.[11] Induction therapy with antilymphocyte antibodies (cytolytic agents) or interleukin 2 receptor antagonists often may be administered perioperatively to prevent acute allograft rejection. Patients at risk for *cytomegalovirus* infection are predisposed to reactivation when cytolytic agents are used.[11] Sirolimus, also known as rapamycin, inhibits the proliferative T-cell response to interleukin-2. Sirolimus is used as a substitute agent in patients intolerant or unresponsive to the calcineurin inhibitors or purine analogues.[11]

The cause of pulmonary infections in heart transplant recipients is diverse. In a previous study, pulmonary infections were caused by opportunistic microorganisms (60%), nosocomial pathogens (25%), and community-acquired bacteria and mycobacteria (15%).[12] Pulmonary infections in heart transplant recipients frequently are polymicrobial (24%-58%) in other studies.[4,13,14]

Aspergillus species were the most common cause of pulmonary infections in our population (23% isolates). The incidence of *Aspergillus* pneumonia was 3.6 cases per 100 heart transplants, similar to the incidence reported in recent studies.[3,14,15] The changes in immunosuppressive treatment and the degree of environmental exposure, which are the main risk factors for the development of pulmonary aspergillosis, could explain the occurrence of *Aspergillus* infection.

Cytomegalovirus is the microorganism that most frequently causes pneumonia after heart transplantation and accounts for 23% to 32% isolates in various studies.[4,13,14] In the present study, we did not observe *cytomegalovirus* infection in our heart transplant recipients, most probably due to our effective prophylaxis regimen.

Pneumocystis jiroveci pneumonia may be another cause of pulmonary infection in heart transplant recipients; with an incidence of 2% to 8% reported in the literature.[15-17] Prophylactic cotrimoxazole is very effective and reduces the incidence of *Pneumocystis jiroveci* pneumonia almost to 0%, as observed in the present study.

Nosocomial bacteria are the leading cause of pneumonia after heart transplantation.[12] In our study, the incidence was 2.4 episodes per 100 heart transplant recipients. *Acinetobacter baumannii* was the causative organism and resulted in death in 2 patients.

The timetable of infection in solid-organ transplantation has been useful for diagnosis. In the present study, 6 patients developed pulmonary infections between the first to third month, 5 patients after 6 months, 1 patient in the first month, and 1 patient between the third and sixth months after heart transplantation. In 50% of invasive pulmonary aspergillosis (IPA) patients, the infection occurred 3 months after heart transplant, which was consistent with data in the literature.[4,12]

Most of the clinical manifestations of pneumonia after heart transplantation are nonspecific.[12] Fever and cough were the most common symptoms in our study, and no hemoptysis was observed in any of the patients who had aspergillosis. An acute onset was observed in patients with nosocomial infection.

Some radiographic images are characteristic of specific causes of pneumonia after heart transplantation. Chest computed tomography is more sensitive than plain radiography for the diagnosis of acute pulmonary complications in immunosuppressed patients.[4] In this study, unilateral infiltrates predominated and 1 cavitary lesion was observed in a patient who had aspergillosis.

However, the diagnostic use of clinical and radiographic manifestations in pneumonia is limited after a heart transplant. Only 46% empiric treatments indicated in this study were appropriate. For this reason, quick diagnostic procedures that guide antimicrobial treatment are necessary.[18] The BAL is the main diagnostic procedure, and the diagnostic yield of BAL was 50% in our study. Other

bronchoscopic procedures are less sensitive. Examination of sputum should form part of the initial diagnostic study of pneumonia after heart transplantation, but this has limited diagnostic yield (15% in the present study).

Pulmonary infections are a leading cause of death after heart transplantation. In this study, there were 3.6 deaths due to pulmonary infections per 100 heart transplant recipients; 3.3%, 6%, and 7.6% patients died in other recent series.[3,4,14] The overall mortality in heart transplant recipients with pneumonia is from 23% to 25% (23% in our study); this rate varies widely depending on the cause.[3,4,14] *Aspergillus* pneumonia has the worst prognosis. The mortality rate associated with this pulmonary infection was 50% in a review involving 64 patients.[19]

In conclusion, pulmonary infections are the most common cause of mortality in heart transplant recipients. It is suggested that heart transplant recipients with fever and cough should be evaluated for pulmonary infection, and IPA should be suspected if these symptoms occur within the first 3 months after heart transplant. Immediate empiric antibiotic therapy is important in treating pulmonary infections in heart transplant recipients.

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