Infectious Complications After Heart Transplantation in Chinese Recipients

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Several factors appear to influence the incidence and type of infectious complications among different populations of transplant recipients. This study sought to assess the incidence and type of infection after transplantation in Chinese heart allograft recipients. A total of 130 infectious episodes occurred in 192 consecutive heart transplantation patients between June 1993 and May 2004. The median length of follow-up was 46.7 ± 38.4 months. The 1-, 5- and 10-year survival rates were $81.8 \pm 2.8\%$, $63.0 \pm 3.8\%$ and $45.7 \pm 7.7\%$. Infection was the leading cause of early and late deaths. Of the infectious episodes, 66 (51%) were caused by bacteria, 35 (27%) by viruses, 10 (8%) by fungi, 7 (5%) by *Mycobacterium tuberculosis* and 12 (9%) by other pathogens. The most common bacterial infectious episodes were caused by methicillin-resistant *Staphylococcus aureus* (20 of 66). The most common viral infections were varicella zoster virus infection in 12 (34%), cytomegalovirus infection in 9 (26%) and hepatitis B virus infection in 8 (23%). There was only one episode of clinical syndrome compatible to *Pneumocystis jiroveci* pneumonia. In conclusion, there was low incidence of *Pneumocystis jiroveci* pneumonia and cytomegalovirus infection, and high incidence of *Mycobacterium tuberculosis* infection in Chinese heart allograft recipients.

Key words: Chinese, heart transplantation, infection

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Introduction

Infection is a common cause of morbidity and mortality in patients with heart transplantation (1–4). Early infections within the first month after transplantation are usually caused by nosocomial pathogens, such as *Pseudomonas*

aeruginosa, *Staphylococcus aureus* and some *Enterobacteriaceae*. The sites of infection include blood, respiratory tract, urinary tract and surgical wounds. Late infections, occurring after the first month and within the first year of transplantation, are commonly caused by cytomegalovirus, *Pneumocystis jiroveci*, *Legionella* and fungi (1,5).

Several factors appear to influence the incidence and type of infectious complications among different populations of transplant recipients. They included the type, duration and intensity of the immunosuppressive drugs, geographic differences in the exposure to community and hospital-acquired pathogens and the introduction of prophylactic antimicrobial strategies after transplantation (1,6). The purpose of this study was to assess the incidence of infectious complications in heart transplantation recipients at our hospital and to evaluate the difference between western and Chinese population.

Patients and Methods

Patient population

A total of 192 consecutive patients who underwent heart transplantation from June 1993 through May 2004 at National Taiwan University Hospital were included. Pre-transplantation clinical and demographic information on the transplant recipients and donors, type of immunosuppression, type of perioperative infectious prophylaxis, follow-up clinical information, and incidence and type of infectious episodes were collected and recorded. The infections were listed according to type of organism (bacterium, virus, fungus, parasite), location of infection, time of onset of infection after transplantation and clinical outcome. Serological screening for cytomegalovirus, *Toxoplasma gondii*, hepatitis B antigens and antibodies, human immunodeficiency virus antibody and hepatitis C antibody was performed for donors and recipients. Tuberculin skin test was not routinely performed. Patients with previous history of tuberculosis or imaging evidence of pulmonary tuberculosis were excluded for transplantation.

Immunosuppression

All patients received triple-drug immunosuppressive therapy according to our heart transplantation protocol previously described (7). Since 1995, we started to use rabbit antithymocyte globulins for induction therapy. Azathioprine (4 mg/kg) was given 1 h before the operation. Solumedrol (1000 mg) was infused while release of the aortic cross-clamp. Rabbit antithymocyte globulin (1.5–2.5 mg/kg/day) was given after transplantation for 5 days. Cyclosporine was started orally within 5 days after transplantation or after the recovery of renal function. Cyclosporine dose was adjusted according to renal function and serum cyclosporine level, which was maintained at the trough level of 300–500 ng/mL during the first 3 months after transplantation and 200–300 ng/mL 1 year after transplantation. Azathioprine was given

at 1–2 mg/kg/day after transplantation, with the dose adjusted to maintain a white blood cell count 4000–6000/mm³. Prednisone (0.5 mg/kg/day) was started on the second postoperative day and tapered to 0.2 mg/kg/day by the first month after transplantation. Tacrolimus (FK-506) and mycophenolate mofetil (Cellcept) were used for recurrent rejection or severe adverse reactions to cyclosporine and azathioprine. Since 2004, we started to use mycophenolate mofetil for primary immunosuppression instead of azathioprine. To prevent nephrotoxicity, cyclosporine dose was decreased to maintain serum trough level of 250–350 ng/mL during the first 3 months after transplantation and 150–250 ng/mL 1 year after transplantation.

All patients were followed monthly at special cardiac transplantation clinic. Standard chest roentgenogram, blood tests, electrocardiogram and physical examinations were routinely performed at regular intervals. The mean follow-up duration was 46.7 ± 38.4 months. None of them was lost to follow-up.

Prophylactic regimen

Perioperative prophylactic antibiotics included 1 g of cefazolin given intravenously to recipients every 8 h until removal of endotracheal tube and drain tubes. In an attempt to prevent oropharyngeal candidiasis, mycostatin suspension (5 cc, 'swish and swallow') was given orally four times a day for 1 month after transplantation. Acyclovir 200 mg every 6 h was used for prophylaxis against herpes simplex virus and varicella zoster virus for 1 month after transplantation. No prophylactic agents were used for prevention of *Pneumocystis jiroveci* infection and *Mycobacterium tuberculosis* infection. Trimethoprim–sulfamethoxazole prophylaxis (one double-strength tablet twice a day) was given for 6 months after transplantation in those patients who were seropositive for *Toxoplasma gondii* or received donors seropositive for *Toxoplasma gondii*. If the recipients had positive cytomegalovirus antibody preoperatively, no specific prophylaxis was given. Intravenous ganciclovir has been administered after transplantation for 1 month only in those cases in which the donor is positive and the recipient is negative for cytomegalovirus antibodies. These patients also received intravenous human cytomegalovirus immunoglobulin for 6 weeks.

Post-transplantation outcome

Major post-transplant events were categorized as 'acute rejection', 'infection' and 'transplant coronary artery disease'. Blood, urine and sputum culture specimens were taken when indicated by the presence of fever or suspected infection. Chest radiographs were obtained daily until the transplant recipient's cardiopulmonary status stabilized and 2–3 times weekly thereafter, until discharge from the hospital.

Bacterial infections were diagnosed by routine methods. The diagnosis of bacterial pulmonary infection required the presence of new or worsening pulmonary infiltrates and growth of organisms in cultures of sputum samples. The diagnosis of urinary tract infection was diagnosed on the basis of the finding of associated symptoms, pyuria and a positive urine culture. The diagnosis of fungal infection required histologic evidence of tissue invasion or isolation from blood or an otherwise sterile site. Diagnosis of viral infection required a significant rise in serological test titer (a four-fold rise in serial serum samples) and/or one of the following: a newly positive IgM antibody titer associated with clinical evidence of disease requiring antiviral therapy; seroconversion; virus isolation or histopathologic evidence of the virus. The isolated finding of a rise in serological test titer without signs or symptoms and not requiring antiviral therapy was not used as a criterion of active viral infection. Cytomegalovirus disease was defined as patients who had clinical or pathological manifestations of infection and cytomegalovirus infection as patients who have only serological or virological evidence of infection with or without disease. Cytomegalovirus antigen was not routinely used for diagnosis of cytomegalovirus disease. Infections caused by *Pneu-*

mocystis jiroveci or *Toxoplasma gondii* were diagnosed by characteristic cytological and/or histologic findings. All consecutive infectious episodes in each transplant recipient were included. Mild infections treated in the outpatient setting were not included in the present series.

Statistical analysis

The results are expressed as median with a range or as frequencies for the categorical variables. The survival curve was plotted by the Kaplan-Meier method. Statistical differences between groups were calculated using Fisher exact test. Differences were considered significant at $p < 0.05$.

Results

Patients

From 1993 to 2004, 192 consecutive patients underwent cardiac transplantation for end-stage heart disease. The median age of the recipients was 48.45 years (range: 0.1–70.8). Of the 192 patients, 155 (81%) were males and 37 (19%) were females; 5 patients (3%) underwent retransplantation because of acute allograft rejection in two patients and transplant coronary artery disease in three patients. Three patients underwent heterotopic heart transplantation because of poor donor heart in two patients and high pulmonary vascular resistance in one patient. Five patients underwent simultaneous heart and kidney transplantation.

Diagnosed underlying heart diseases among the recipients included idiopathic dilated cardiomyopathy in 97 (51%), coronary artery disease in 60 (31%), valvular heart disease in 13 (7%), congenital heart disease in 10 (5%), postpartum cardiomyopathy in 3 (2%), transplant coronary artery disease in 3 (2%), restrictive cardiomyopathy in 2 (1%), acute allograft rejection in 2 (1%) and primary amyloidosis and primary cardiac tumor each in 1 patient. No patients had radiological evidence of pulmonary tuberculosis and serological evidence of human immunodeficiency virus infection. No patients ever received antituberculous therapy before transplantation.

The causes of early death (<30 days after transplantation) were infection in seven patients, surgical bleeding in five patients, acute rejection in three patients and major stroke in one patient. The causes of late death (>30 days after transplantation) were infection in 16 patients, transplant coronary artery disease in 10 patients, acute rejection in 8 patients, malignancy in 3 patients and others in 10 patients. Infection was the leading cause of early death and late death. The 1-, 5- and 10-year survival rates by Kaplan-Meier method were 81.8 ± 2.8%, 63.0 ± 3.8% and 45.7 ± 7.7%.

Infectious episodes

During the study period, 130 infectious episodes occurred in the 192 patients and the average episode per patient was 0.68. A total of 66 (51%) of the infectious episodes were bacterial, 35 (27%) were viral, 10 (8%) were fungal, 7 (5%)

were *Mycobacterium tuberculosis* and 12 (9%) by other pathogens. The sites of infectious episodes were blood in 38 (29%), lung in 27 (21%), skin in 23 (18%), superficial or deep sternal wound in 12 (9%), urine in 11 (8%), liver in 9 (7%), eye in 2 (1%), joint in 2 (1%), lymph nodes in 2 (1%), central nervous system in 2 (1%) and stool and paranasal sinus each in 1 patient.

The most common bacterial infectious episodes were caused by methicillin-resistant *Staphylococcus aureus* (20 of 66). Gram-positive bacteria, particularly *Staphylococcus* species, accounted for 45% of 66 bacterial infections. Gram-negative bacteria, most commonly *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, accounted for 39% of 66 bacterial infections.

The most common viral infections were varicella zoster virus infection in 12 (34%), cytomegalovirus infection in 9 (26%) and hepatitis B virus infection in 8 (23%). There was only one case of primary varicella zoster virus infection (chickenpox) in a 10-year-old girl. She underwent emergency heart transplantation without varicella prophylaxis because of decompensated heart failure. Among the 11 herpes zoster infections, all were localized disease and occurred ranging from 6 to 95 months (median, 33) after transplantation. Among the nine cytomegalovirus infections, focal cytomegalovirus disease occurred in five patients as retinitis in two, pneumonia in one, hepatitis in one and skin in one patient. The onset time of cytomegalovirus infections ranged from 2 days to 28 months (median: 10 months) after transplantation. A total of 14 patients had trimethoprim-sulfamethoxazole prophylaxis for *Toxoplasma gondii* after transplantation. There was no infection caused by *Toxoplasma gondii*.

Cytomegalovirus serological test results were available for 183 donors; 171 (93%) of them were positive for cytomegalovirus-specific IgG antibodies. Results of cytomegalovirus serological tests were available for 163 recipients; 121 (74%) were positive preoperatively. Cytomegalovirus serological test results were available for 160 donor/recipient (D/R) pairs; of these, 3 (2%) were D-/R-, 8 (5%) D-/R+, 37 (23%) D+/R- and 112 (70%) D+/R+. Intravenous ganciclovir has been administered after transplantation in only 10 patients in which the donor is positive and the recipient is negative for cytomegalovirus antibodies. The other 27 D+/R- patients did not have intravenous ganciclovir because of patient factors or economic problems. Cytomegalovirus infection developed in one D-/R- patients (33%), 0 D-/R+ patients (0%), five D+/R+ patients (4%) and one D+/R- patients (3%). The serologic data were unclear in two patients with post-transplant cytomegalovirus infection.

Hepatitis B virus serological test results were available for 190 donors; 31 (16%) of them were positive for hepatitis B virus surface antigen. Results of hepatitis B virus serologic tests were available for 191 recipients; 13 (7%) were

positive for hepatitis B virus surface antigen and 26 (14%) were negative for both hepatitis B virus antigen and antibodies preoperatively. Eight patients with hepatitis virus infection were successfully controlled with lamivudine therapy. Among the 31 hearts from donors positive for hepatitis B virus surface antigen, 28 were given to recipients either positive for hepatitis B virus surface antigen or positive for hepatitis B virus antibody. Three recipients who were negative for hepatitis B virus received hearts from donors positive for hepatitis B virus surface antigen and one patient developed hepatitis B virus infection 9 months after transplantation.

***Pneumocystis jiroveci* pneumonia**

There was only one episode of clinical syndrome compatible to *Pneumocystis jiroveci* pneumonia. This patient was a 45-year-old diabetic male. He underwent orthotopic heart transplantation because of end-stage coronary artery disease. The postoperative course was smooth and there was no acute rejection. Maintenance immunosuppression included cyclosporine, mycophenolate mofetil and prednisolone. However, he had fever, severe dyspnea and rapidly progressive pneumonia 5 months after transplantation. High-resolution computed tomography of the chest showed ground-glass pattern of bilateral pulmonary infiltration. Bronchoalveolar lavage and lung biopsy were not performed because of severe hypoxemia. He was treated as *Pneumocystis jiroveci* pneumonia and received trimethoprim-sulfamethoxazole. Intravenous ganciclovir was also given because of concurrent cytomegalovirus infection during treatment. He recovered slowly and was followed at out patient clinic for 2 months after treatment.

Mycobacterium tuberculosis

Of the 130 infectious episodes, 7 cases were caused by *Mycobacterium tuberculosis*. Patient data were listed in Table 1. The median onset of time was 38 months (range: 3–85). Three patients had extrapulmonary infection. No patient died of severe infection.

Comparison with western series

The comparison of patient characteristics and incidence of infectious episodes after transplantation was listed on Table 2. Only those series published after 1990 was listed for comparison (1,4,8–10). The incidences of common pathogens were compared between our Hsu's series, Stanford's series (1) and Miller's series of multicenter registry (4). In our patients, there was a significantly low incidence of *Pneumocystis jiroveci* pneumonia ($p < 0.001$ between Hsu and Stanford; $p = 0.223$ between Hsu and Miller by Fisher exact test) and cytomegalovirus infection ($p < 0.001$ between Hsu and Stanford; $p < 0.001$ between Hsu and Miller by Fisher exact test), but high incidence of *Mycobacterium tuberculosis* infection ($p = 0.002$ between Hsu and Stanford; $p < 0.001$ between Hsu and Miller by Fisher exact test).

Table 1: Patient data in seven patients with *Mycobacterium tuberculosis* infection

No.	Age (years)	Sex	Medical comorbidities before and after transplant	Months after transplant	Immunosuppression	Site of infection	Outcome after infection
1	66	M	Diabetes mellitus, prostate carcinoma	85	C, M	Lung	Died 7 months carcinoma
2	62	M	None	62	C, M, P	Lung, joint	Alive 24 months
3	68	F	Anemia	67	C, M, P	Lung	Alive 15 months
4	64	M	Diabetes mellitus, uremia, hypertension	37	T, P	Lung, intestine	Alive 11 months
5	66	M	Hypertension	18	T, M	Lung	Alive 22 months
6	56	M	Diabetes mellitus	38	C, M, P	Lung, joint	Alive 2 months
7	44	M	None	3	T, P	Lung	Alive 93 months

Table 2: Comparison of post-transplant infections between Taiwan and western patients

Author	Hsu	Montoya	Cisneros	Grossi	Waser	Miller
Year of publication	2005	2001	1998	1992	1994	1994
Country	Taiwan	USA	Spain	Italy	Switzerland	USA
Patient number	192	620	307	662	100	814
Age in years (mean)	45.1 ± 16.8	40.4	NA	NA	44.8 ± 11.6	48.1 ± 14.4
Male	81%	78%	NA	NA	92%	80%
Dilated cardiomyopathy	51%	39%	NA	NA	46%	38%
Follow-up in months (median)	43.8	NA	NA	NA	21.7 ± 15.5	8.2
Crude incidence						
Cytomegalovirus*	9 (4.7%)	141 (22.7%)	20 (6.5%)	58 (8.8%)	16 (16%)	108 (13.3%)
<i>Mycobacterium tuberculosis</i> *	7 (3.6%)	3 (0.5%)	3 (1%)	4 (0.6%)	NA	1 (0.1%)
<i>Pneumocystis jiroveci</i> **	1 (0.5%)	43 (6.9%)	11 (3.6%)	7 (1.0%)	4 (4%)	17 (2.1%)
<i>Toxoplasma gondii</i>	0	4 (0.6%)	NA	8 (1.2%)	4 (4%)	3 (0.4%)
<i>Salmonella</i> sp.	3 (1.6%)	2 (0.3%)	NA	NA	NA	NA
<i>Nocardia</i> sp.	2 (1.0%)	23 (3.7%)	4 (1.3%)	2 (0.3%)	NA	2 (0.2%)
<i>Cryptococcus</i>	2 (1.0%)	4 (0.6%)	NA	1 (0.2%)	NA	1 (0.1%)

NA = not available.

*p < 0.002 between Hsu and Montoya and between Hsu and Miller by Fisher exact test.

**p < 0.001 between Hsu and Montoya by Fisher exact test.

Discussion

Mycobacterium tuberculosis

The incidence of active tuberculosis infection in transplant recipients worldwide ranged from 0.18% to 15% (11–19). The diagnosis and effective management of tuberculosis after transplantation warrant recognition of the unique epidemiological and clinical characteristics of tuberculosis in transplant recipients. In Spain, the overall incidence of tuberculosis was 0.8% in all transplant recipients. The site of infection was pulmonary in 63% of the cases, disseminated in 25% and extrapulmonary in 12%. Tuberculosis developed from 15 days to 13 years after transplantation (13). However, the prevalence of post-transplant tuberculosis is increasing globally and is high in Asia (15–19). Post-transplant tuberculosis occurs in 12–20% of renal transplant patients in India and results in the death of 20–25% of those patients. Cyclosporine therapy, diabetes mellitus and chronic liver disease are risk factors for post-transplant tuberculosis (15,16). The incidence of *Mycobacterium tuberculosis* infection in heart transplant recipients was low (<1%) in western countries (1,4,8,10,20). In our patients, the incidence of *Mycobacterium tuberculosis* infection was

3.6%, which is much higher than that reported in western countries. Tuberculosis is an endemic infectious disease in Taiwan (21).

Cytomegalovirus

Cytomegalovirus infection is a major cause of mortality and morbidity after heart transplantation (1–6). Data obtained from the Cardiac Transplant Research Database Group showed that the primary location of cytomegalovirus infection was blood in 43%, lung in 30%, gastrointestinal tract in 23% and other sites in 3%. Risk factors for cytomegalovirus infection included pre-transplantation cytomegalovirus serology and use of cytolytic induction therapy (22). In our patients, although we used induction therapy in every patient, the incidence of post-transplant cytomegalovirus infection was less than 5%. In addition, the most common manifestation of cytomegalovirus infection was the focal disease (5 of 9), not the most commonly disseminated form. Involvement of the retina occurred in 2 of 9 infected patients. In our study, donor cytomegalovirus seropositive rate was 93% and the recipient cytomegalovirus seropositive rate was 74%. The high cytomegalovirus seropositive rate in Taiwan

population contributes to low incidence of post-transplant cytomegalovirus disease and the predominance of focal disease. It also reduces the incidence of transplant coronary artery disease in Chinese heart recipients (7). However, the case recognition of post-transplant cytomegalovirus infection might be suboptimal because of the lack of the use of more sensitive virologic tests. Further study is needed to prove our point.

***Pneumocystis jiroveci* pneumonia**

Pneumocystis jiroveci remains an important pathogen in patients who undergo solid organ and hematopoietic transplantation (1,23–27). The risk is greatest after lung transplants, in individuals with invasive cytomegalovirus disease, during intensive immunosuppression for acute rejection and during periods of neutropenia (23–27). The incidence of *Pneumocystis jiroveci* pneumonia during the first year following transplantation was higher than that during subsequent years (27). The incidence of *Pneumocystis jiroveci* pneumonia after heart transplantation varies according to the literature between 1% and 5% (1,4,5,8–10,23–25,28). Prophylaxis with trimethoprim-sulfamethoxazole prevents many opportunistic infections, including infection with *Pneumocystis jiroveci*, *Toxoplasma gondii* and some community-acquired pathogens (1,23–25). *Pneumocystis jiroveci* infection occurred in patients who did not take or could not tolerate trimethoprim-sulfamethoxazole as a prophylactic agent. Continued prophylaxis is recommended in high-risk recipients or in countries where *Pneumocystis jiroveci* infection is prevalent (27,28). However, administration of trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis jiroveci* infection during the first year following transplantation has not been universally adopted. Waser et al. (9) reported a 4% incidence of *Pneumocystis jiroveci* pneumonia among their heart transplant recipients despite the lack of routine use of trimethoprim-sulfamethoxazole. They suggest that this low incidence is related to a low prevalence of *Pneumocystis jiroveci* in the Swiss population and does not justify the routine use of trimethoprim-sulfamethoxazole prophylaxis.

In our study, only 14 patients (7%) had trimethoprim-sulfamethoxazole prophylaxis for *Toxoplasma gondii* infection after transplantation, and the incidence of *Pneumocystis jiroveci* pneumonia was extremely low (<1%). Whether the prevalence of *Pneumocystis jiroveci* in the Chinese population is low or not is unknown. However, in Taiwan, *Pneumocystis jiroveci* pneumonia was a dominant cause of opportunistic infection in patients with human immunodeficiency virus infection (29) and in patients with bone marrow transplantation (19). In a case-control study performed in renal transplant recipients (30), the risk of *Pneumocystis jiroveci* pneumonia is related to the number and type of rejection treatments, to the occurrence of cytomegalovirus infection, to other infections such as tuberculosis and hepatitis C and to more potent immunosuppressive agents.

Patients who developed *Pneumocystis jiroveci* pneumonia while receiving trimethoprim-sulfamethoxazole prophylaxis were frequently coinfecting with cytomegalovirus (31,32), tuberculosis and bacterial pneumonia (30). Arend et al. (33) also reported that the risk of *Pneumocystis jiroveci* pneumonia in renal transplant recipients was positively related to rejection and cytomegalovirus infection. In our patients, the incidence of cytomegalovirus infection was low (4.7%), and the incidence of *Mycobacterium tuberculosis* infection was high (3.6%).

In summary, our heart transplant patients did not receive trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis. There was a significantly low incidence of *Pneumocystis jiroveci* pneumonia and cytomegalovirus infection, and high incidence of *Mycobacterium tuberculosis* infection in Taiwan.

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