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Epidemiology and clinical impact of infection in patients awaiting heart transplantation

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SUMMARY

Objectives: The aim of this study was to determine the epidemiology and clinical impact of infections in patients awaiting heart transplantation.
Methods: We evaluated all patients considered for a heart transplant in our center over a period of 18 months over a period of 18 months from 2007 to 2009. The patients were followed up for 8 months or until death, transplant, or loss to follow-up.
Results: Ninety patients were included in the study. During follow-up, 25 infections were recorded in 22 heart transplant candidates (24.4%). Respiratory infections were the most frequent infection (12 bronchitis; 48.0%), followed by skin and soft tissue infections (four infections; 16.0%), intra-abdominal infections (four infectious diarrhea; 16.0%), bacteremia (three infections; 12.0%), and urinary tract infections (two infections; 2.0%). Age, comorbidity, sex, and diabetes were not found to be risk factors for infection. Twenty-four patients (26.7%) were transplanted during follow-up. Infection before transplantation was not associated with an increased risk of mortality or a higher rate of infection in the immediate post-transplant period.
Conclusions: Infections are common in heart transplant candidates, affecting almost 25% of them. Respiratory tract infections are the most frequent type of infection. However, they are not associated with increased mortality in the immediate post-transplant period.

1. Introduction

There are few reports on the incidence and types of infection in patients with terminal heart failure, although the role of infection in hospital admissions is well known in these patients.[1] It is recognized that post-transplant infectious morbidity in heart transplant recipients is moderate,[2–5] and there are many known risk factors for infection in the early post-transplant period.[4,6] Nevertheless, there are no communications describing the epidemiology of infection in patients awaiting heart transplantation, and the impact of pre-transplant infection on the early post-transplant period is not known.

The main aim of this study was to describe the frequency, epidemiology, and risk factors for infection in patients awaiting heart transplantation. Another objective was to determine the influence of infection on waiting-list mortality and early mortality and morbidity after transplantation.

2. Materials and methods

2.1. Study population and follow-up

Our institution is a tertiary care hospital that has had a heart transplantation program since 1986. It is the reference center for heart transplantation for a population of approximately two million, and 542 heart transplants had been performed up until 2011.

Over a period of 18 months from 2007 to 2009, we prospectively included all adult patients (over the age of 14 years) who were considered for inclusion on the heart transplantation waiting list in our center. The patients were followed up for 8 months from the time they were evaluated, with clinical assessments performed at least monthly. All episodes of bacterial and fungal infection requiring either hospitalization or outpatient treatment were

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recorded, as well as the etiology of the infection when an etiological diagnosis was made.

Initial follow-up ended at transplantation, death, or loss to follow-up of the patient. Follow-up did not end if the patient was excluded from the waiting list. Patients who were transplanted were followed up for 1 month after transplantation.

2.2. Routine antibiotic prophylaxis after transplantation

Routine antibiotic prophylaxis after heart transplantation in our center is performed with cloxacillin and cefotaxime and is maintained for 5 days. Trimethoprim–sulfamethoxazole is initiated as soon as possible and maintained for the first 3–6 months.

2.3. Classification of episodes of infection

The infections were defined according to internationally accepted criteria recommended by organizations such as the American Society of Transplantation,[7] the Infectious Diseases Society of America (IDSA),[8–10] and the European Association for the Study of the Liver.[11] Infections were classified into the categories listed below.

2.3.1. Respiratory tract infection

Proven and probable cases of pneumonia and acute bronchitis were included in this category. A diagnosis of pneumonia was made in the presence of one or more of the following symptoms: cough, hemoptysis, fever, dyspnea, or pleuritic chest pain, in addition to compatible findings on a radiograph or a thoracic computerized tomography. The final diagnosis was established based on fulfillment of the above criteria as well as the presence of a positive culture in a valid respiratory sample. Cases where no organisms were isolated in respiratory samples were considered probable pneumonia. In the presence of clinical criteria for lower respiratory tract infection without radiological evidence of consolidation, a diagnosis of bronchitis was made.[8]

2.3.2. Urinary tract infection

Confirmed bacterial urinary tract infection (UTI) included cases of cystitis and pyelonephritis with positive urine culture. Cystitis was defined by the presence of a urine bacteria count of more than 10 000 colony-forming units (cfu)/ml and pyuria ($\geq$3 leukocytes per high-power field or positive leukocyte esterase), with clinical manifestations such as dysuria, high frequency and/or urinary urgency in the absence of pyelonephritis criteria.[7] Pyelonephritis was defined by the presence of a positive urine culture (>10 000 cfu/ml) and pyuria in association with tenderness at the costovertebral angle with fever and/or positive blood culture.[7] Cases of asymptomatic bacteriuria, defined as the presence of a urine bacteria count of >10 000 cfu/ml without clinical manifestations of UTI, were not included.[7]

2.3.3. Bacteremia and catheter-related bacteremia

The diagnosis of bacteremia was made in the case of isolation of a microorganism other than a skin contaminant (diphtheroids, *Bacillus spp*, or coagulase-negative staphylococci) in one culture and the presence of signs of infection (chills, fever, hypotension), or the isolation of the above contaminants in two consecutive cultures, with signs of infection.[12] When there was a focus other than catheter-related bacteremia, the episode of infection was classified as organ infection. Bacteremia was considered to be catheter-related if it met the criteria established by the IDSA.[9]

2.3.4. Intra-abdominal infection

This category included episodes of infectious diarrhea caused by bacteria, spontaneous bacterial peritonitis, and cholangitis. 'Infectious diarrhea' was defined as diarrhea due to a bacterial etiology, accompanied by symptoms of nausea, vomiting, or abdominal cramps.[10] Cholangitis was defined as cases of fever, right upper quadrant abdominal pain and cholestatic enzyme abnormalities, and/or direct hyperbilirubinemia.[7] Spontaneous bacterial peritonitis was defined as the presence of ascites and a polymorphonuclear cell count of more than 0.25×10^9/l in ascitic fluid.[11]

2.3.5. Skin and soft tissue infections

All skin and soft tissue infections (including surgical site infections) were included in this category regardless of their location and extension. Non-necrotizing infections (impetigo, erysipelas, cellulitis, or pyomyositis) and necrotizing infections (necrotizing cellulitis or fascitis and myonecrosis) were included. Infections secondary to bites, pressure ulcers, and diabetic foot ulcers were also included.[13] Surgical site infections (SSI) were included in this category. SSI was defined as infection of the skin, independently of the depth of the infection, that occurred within 30 days after the operation if no implant was left in place, or within 1 year if the implant was left in place and the infection appeared to be related to the operation.[14]

2.4. Mortality

All occurrences of death during follow-up were defined as 'crude mortality'. Deaths that could be directly attributed to an infectious episode were defined as 'death due to infection'.

2.5. Statistical analysis

The Chi-square test or Fisher's exact test was used to compare the qualitative variables, while the Student's *t*-test and Mann–Whitney *U*-test were used to compare the quantitative variables. To determine risk factors for infection and mortality based on follow-up time, we used the Cox regression analysis. Statistical significance was considered when the *p*-value was <0.05.

Table 1
Baseline characteristics of patients included in the study ($N = 90$)

Age, years, mean ± standard deviation	51.2 ± 11.8
Sex, number of males (% males)	67 (74.4%)
Charlson comorbidity index, mean ± standard deviation	2.93 ± 1.7
History of tobacco use, number of patients who use tobacco/total patients (%)	44 (48.9%)
Diabetes mellitus, number of diabetic patients/total patients (%)	24 (26.6%)
Alcohol consumption, number of patients with heavy alcohol consumption/total patients (%)	10 (11.1%)
Treatment with corticoids or other immunosuppressants at first evaluation	5 (5.6%)
Positive Toxoplasma IgG	45 (50.0%)
Positive Epstein–Barr virus IgG	78 (86.7%)
Positive cytomegalovirus IgG	75 (83.3%)
Follow-up time,[a] days, mean ± standard deviation	186.1 ± 89.8
Underlying cardiopathy	
Dilated	48 (53.3%)
Ischemic	24 (26.7%)
Congenital	10 (11.1%)
Hypertrophic	4 (4.4%)
Retransplant	1 (1.1%)
Other	3 (3.3%)

[a] Does not include post-transplant follow-up time (24.6 ± 11.0 days).

3. Results

Ninety patients were included during the study period. The baseline characteristics of patients included in the study are shown in Table 1. At the end of follow-up, 24 candidates were transplanted (26.6% of those evaluated), five (5.5%) patients died before transplantation, 14 (15.5%) patients remained on the waiting list, and 47 (52.2%) patients had been excluded from the active waiting list. No death could be directly attributed to an infectious episode.

3.1. Waiting-list follow-up

During follow-up, 25 infections were recorded in 22 heart transplant candidates (24.4%). Respiratory infections were the most frequent infection (12 bronchitis; 48.0%), followed by skin and soft tissues infections (four infections; 16.0%), intra-abdominal infections (four infectious diarrhea; 16.0%), bacteremia (three infections; 12.0%), and UTI (two infections; 2.0%).

The etiology of infection could be confirmed in seven cases (28.0%): *Escherichia coli* (two UTI and one bacteremia), *Staphylococcus aureus* (one bacteremia and one soft tissue infection), *Staphylococcus epidermidis* (one bacteremia), and *Candida albicans* (one cutaneous infection).

The association of different variables with the risk of infection in patients on the waiting list is shown in Table 2. None of the variables studied behaved as a statistically significant risk factor for infection in the patients in this study.

Patients with an infection during follow-up did not have a higher mortality while on the waiting list than those without infections (mortality in the infection group 13.9% vs. 2.9% for patients without infection; $p = 0.11$).

3.2. Immediate post-transplant follow-up

Baseline characteristics of patients who were transplanted and other aspects concerning the immediate post-transplant period are summarized in Table 3. After transplant, patients were followed up for a mean 24.6 ± 11.0 days. The proportion of transplant recipients who developed an infection in the first month after transplantation was not higher among those who had developed an infection while on the waiting list (12.5% vs. 23.7% in those without previous infection; relative risk (RR) 0.50, 95% confidence interval (CI) 0.06–4.00; $p = 0.52$). Female sex behaved as a risk factor for early infection after transplantation (RR 6.99, 95% CI 1.34–36.4; $p = 0.02$). No other factors (age, transplantation in urgency code, diabetes, or Charlson comorbidity index) were associated with a higher frequency of early infections after transplantation.

Five out of 24 patients (20.8%) died during follow-up after transplantation. Early mortality after transplantation was higher in heart transplant recipients who had developed an infection during the pre-transplant period (50.0% vs. 18.2%), although this difference was not statistically significant (RR 3.83, 95% CI 0.42–34.8; $p = 0.23$). No deaths after transplantation were attributed directly to infection. The need for dialysis after transplantation (RR 7.68, 95% CI 1.2–46.6; $p = 0.027$) and a higher Charlson comorbidity index (RR 1.71, 95% CI 1.0–2.93; $p = 0.05$) were associated with higher mortality rates after transplantation. Recipient age showed a tendency towards a higher mortality (RR 1.1, 95% CI 0.98–1.23; $p = 0.09$).

Table 2
Risk factors for infection in patients awaiting heart transplantation

	RR	95% CI	*p*-Value
Sex, male	1.56	0.32–7.59	0.57
Diabetes mellitus	1.96	0.75–5.06	0.16
Age	0.98	0.93–1.03	0.57
Charlson comorbidity index	1.31	0.99–1.73	0.053

Analysis by multivariate Cox regression. RR, relative risk; CI, confidence interval.

4. Discussion

Our results show that infection is a common complication in patients awaiting heart transplantation. This had not yet been fully established in heart transplant candidates. Our data indicate that patients with advanced heart disease awaiting transplantation are at high risk of infection, although they are generally mild infections that do not involve increased attributable mortality. In our study, respiratory infections were the most frequent type of infection. Respiratory infection is a common complication in patients with heart failure, and the cause of 60% of all hospital admissions.[1] It is therefore not surprising that respiratory infection is the most common infectious complication in patients with advanced heart disease awaiting a heart transplant.

An adequate control of infection in transplant patients must begin not at the time of transplantation but from the moment the patient is placed on the waiting list. Transplant candidates often have chronic terminal deficiencies that justify a procedure such as transplantation. They frequently have comorbidities and have extensive contact with the healthcare system. The overall clinical profile of these patients explains in itself the risk of infectious complications. This explains why it is difficult to find specific risk factors for infection in these patients, and makes it difficult to predict who will suffer from an infection.

In our study we found no evidence to suggest that patients with an infection awaiting heart transplantation are at higher risk of having another infectious complication in the first month after heart transplantation. The infections found in the immediate post-transplant period were those expected after surgery (surgical site infection) and during intensive care of the patient (respiratory tract infections, catheter-related bacteremia). These infections are related to surgery and the intensive care management post-transplantation (mechanical ventilation, central venous catheters), so previous infections may have no impact on the incidence of early infections after transplantation. The only risk factor for early infection that we found in our analysis was female sex. Although it is widely known that women are at a higher risk for some types of infections, e.g. UTI[15] and wound infection after coronary surgery,[16] we have not found female sex described as a risk factor for infection after heart transplantation in previous publications.

We were not able to demonstrate a worse survival expectancy after heart transplantation in those patients who had suffered from an infection before the transplant. Many factors are known to influence the post-transplant prognosis in patients undergoing heart transplantation, such as those recently included in the IMPACT index[17] (Index for Mortality Prediction After Cardiac Transplantation) – age, race, gender, underlying heart disease, or need for dialysis – organ ischemic time,[17] donor age,[17] transplant urgency,[18] and the recipient's weight prior to transplantation.[19] In our study, the need for dialysis after transplantation, a higher Charlson comorbidity index, and age (the latter did not reach statistical significance) behaved as risk factors for early mortality. The existence of such a large number of factors makes it difficult to determine the true impact of pre-transplant infection as an independent prognostic factor, suggesting that infection is probably less important than the factors mentioned above.

We found no other series describing the impact of infection before heart transplant on the post-transplant period. In a recent study, Sun et al.[20] also found no differences when comparing mortality at 90 and 180 days after liver transplantation in patients with and without a history of bacterial infection in the year prior to

Table 3
Characteristics of patients who were transplanted during follow-up[a]

	All transplanted patients ($n = 24$)	Early infection after transplant ($n = 7$)	No early infection ($n = 17$)	p-Value
Age, years	50.8 ± 13.8	51.8 ± 13.9	50.4 ± 14.2	NS
Sex, female	8 (33.3%)	5 (71.4%)	3 (17.6%)	0.021
Diabetes mellitus before transplant	4 (16.7%)	1 (16.7%)	3 (18.8%)	NS
Charlson comorbidity index	2.5 ± 1.4	2.3 ± 1.6	2.6 ± 1.4	NS
Need for immunosuppressants before transplant	2 (8.4%)	0	2 (13.3%)	NS
Underlying myocardiopathy				
Dilated	12 (50%)	4 (57.1%)	9 (52.9%)	
Ischemic	5 (20.8%)	2 (28.6%)	3 (17.6%)	
Hypertrophic	4 (16.7%)	1 (14.3%)	2 (11.8%)	
Congenital	1 (4.2%)	0	1 (5.9%)	
Infiltrative	1 (4.2%)	0	1 (5.9%)	
Retransplant	1 (4.2%)	0	1 (5.9%)	NS
Transplant in urgency code	5 (20.8%)	2 (28.6%)	3 (17.6%)	NS
Need for dialysis after transplant	4 (16.7%)	1 (16.7%)	3 (18.8%)	NS
Organ ischemic time, min	199 ± 47	190 ± 71	203 ± 39	NS
Immunosuppression after transplant				NS
Cyclosporine	24 (100%)	7 (100%)	17 (100%)	
Steroids	24 (100%)	7 (100%)	17 (100%)	
Mycophenolate mofetil	22 (91.6%)	6 (85.7%)	16 (94.1%)	
Everolimus	3 (12.5%)	1 (14.2%)	2 (11.7%)	
Steroids bolus	4 (16.7%)	2 (28.5%)	2 (11.7%)	
Basiliximab	1 (4.2%)	0	1 (5.8%)	

Differences were calculated by Mann–Whitney *U*-test or Fisher's test. NS, not significant.
[a] Results are mean ± standard deviation, or *n* (%).

transplantation. In another recent study, Kim et al.[21] described colonization or infection prior to liver transplantation as a predictor of death in the first 3 months after transplantation. However, in this study no deaths were attributable to infection in the group of patients presenting infection prior to transplantation.

There are several limitations to our findings, the main one being the number of patients included in the study. It is likely that a larger sample size would have permitted us to obtain significant differences in terms of the prognostic significance of infection in heart transplant candidates.

In conclusion, the frequency of infection in patients awaiting heart transplant may require collaboration between infectious disease and transplant specialists from the moment the candidate is placed on the transplant waiting list. Infections are common in heart transplant candidates, affecting almost 25% of them. The most frequent type of infection is respiratory tract infection, followed by skin and soft tissue infection and infectious diarrhea. However, infection before heart transplantation is not a risk factor for infection in the early post-transplant period, as these infections are directly related to surgery and intensive care management. Moreover, patients with an infection on the waiting list for heart transplantation do not have a worse prognosis after transplantation.

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