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Risk factors for invasive fungal disease in heart transplant recipients

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BACKGROUND: Heart transplant (HT) recipients are at risk for invasive fungal disease (IFD), a morbid and potentially fatal complication.

METHODS: We performed a retrospective cohort study to evaluate the incidence and risk factors for IFD in HT recipients from 1995 to 2012 at a single center. IFD cases were classified as proven or probable IFD according to current consensus definitions of the European Organization for Research and Treatment of Cancer/Mycoses Study Group. We calculated IFD incidence rates and used Cox proportional hazards models to determine IFD risk factors.

RESULTS: Three hundred sixty patients underwent HT during the study period. The most common indications were dilated (39%) and ischemic (37%) cardiomyopathy. There were 23 (6.4%) cases of proven (21) or probable (2) IFD, for a cumulative incidence rate of 1.23 per 100 person-years (95% CI 0.78 to 1.84). *Candida* (11) and *Aspergillus* (5) were the most common etiologic fungi. Thirteen cases (56%) occurred within 3 months of HT, with a 3-month incidence of 3.8% (95% CI 2.2 to 6.4). Delayed chest closure (HR 3.3, 95% CI 1.4 to 7.6, $p = 0.01$) and the addition of OKT3, anti-thymocyte globulin or daclizumab to standard corticosteroid induction therapy (HR 2.7, 95% CI 1.1 to 6.2, $p = 0.02$) were independently associated with an increased risk of IFD.

CONCLUSIONS: IFD incidence was greatest within the first 3 months post-HT, largely reflecting early surgical-site and nosocomial *Candida* and *Aspergillus* infections. Patients receiving additional induction immunosuppression or delayed chest closure were at increased risk for IFD. Peri-transplant anti-fungal prophylaxis should be considered in this subset of HT recipients.

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Heart transplant (HT) recipients are at risk for invasive fungal disease (IFD), a morbid and potentially fatal complication of transplantation. Surveillance studies of heart and other solid-organ transplant (SOT) recipients have suggested an overall IFD incidence of 1% to 12% with an attributable mortality of between 35% and 75%.[1–7] Some studies have explored empirical anti-fungal prophylaxis after HT,[6,8] but data regarding IFD incidence, timing and risk factors in the HT population are very limited. In this study, we sought to estimate IFD incidence and identify IFD risk factors in a cohort of HT patients to identify patients who may benefit from anti-fungal prophylaxis.

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Methods

Study population

All patients receiving a first HT at Brigham and Women's Hospital (Boston, MA) between January 1, 1995 and December 31, 2012 were included in the study cohort and follow-up events were censored on March 1, 2013. We recorded the following data: patients' demographics; donor and recipient cytomegalovirus (CMV) serostatus; induction and maintenance immunosuppressive regimens; episodes of acute cellular allograft rejection treated with increased immunosuppressive therapy; and details of all IFD episodes. The study was approved by the Partners Human Research Committee.

Immunosuppression

All patients received methylprednisolone 1,000 mg by intravenous (IV) infusion in the operating room, followed by 125 mg IV every 8 hours for three doses, then a tapering dose of corticosteroids. Patients with substantial renal dysfunction at the time of HT, defined as pre-operative renal dysfunction, peri-operative renal injury or post-operative anuria, as adjudicated jointly by a staff transplant surgeon and transplant cardiologist within 24 to 48 hours of HT, received additional induction immunosuppression with OKT3 (1995 to 2001), daclizumab (2001 to 2010) or anti-thymocyte globulin (ATG) (2010 to 2012) to delay initiation of potentially nephrotoxic calcineurin inhibitors. Standard maintenance immunosuppression consisted of prednisone, cyclosporine and azathioprine from 1995 to 2002; prednisone, cyclosporine and mycophenolate mofetil (MMF) from 2002 to 2008; and prednisone, tacrolimus and MMF from 2008 to the end of the study period.

Acute cellular rejection

Routine endomyocardial biopsies were performed at 1, 2, 3, 4 and 6 weeks, and 2, 3, 4, 5, 6, 8, 10, 12, 15 and 18 months post-HT, and annually thereafter, with more frequent biopsies in patients with recurrent rejection episodes. Biopsy specimens were assessed for evidence of acute cellular rejection by standard criteria of the International Society for Heart and Lung Transplantation.[9] Patients who received an increased dose of oral corticosteroids, high-dose IV corticosteroids, OKT3, ATG or daclizumab for treatment of acute cellular rejection on biopsy were considered to have "treated acute cellular rejection."

Anti-fungal prophylaxis

No patients received systemic or inhaled anti-fungal prophylaxis over the study period, other than standard trimethoprim-sulfamethoxazole *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis for 6 months post-HT.

HEPA filtering

The air in all operating rooms and in all intensive-care unit and ward rooms was HEPA filtered over the study period.

IFD cases

IFD cases were identified via a systematic review of the electronic and paper longitudinal medical records of every HT recipient in our cohort, consisting of all provider notes, including all infectious diseases specialist consultation notes (at our hospital, all cases of suspected fungal infection are referred for transplant infectious diseases consultation), and results of all relevant radiology, pathology studies and clinical mycology data (cultures, serum fungal antigen testing). Using data on relevant host factors, imaging studies and mycology, we classified proven or probable IFD cases according to current consensus definitions of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG).[10]

Statistical methods

We determined incidence rates of IFD in the HT cohort and calculated actuarial estimates of time to first IFD episode and death using the Kaplan–Meier method. We developed Cox proportional hazards models to evaluate risk factors that we believed "a priori" could affect the risk of IFD, such as: age; gender; additional induction immunosuppression (which, by indication, was perfectly collinear with renal dysfunction at the time of HT); acute cellular rejection; ventricular assist device (VAD) pre-transplant; peri-transplant VAD placement due to allograft failure within 1 week of HT; reoperation within 10 days of initial HT; and delayed chest closure, defined as patients whose chest incision was not immediately closed after the HT procedure. Based on a review of the limited existing literature on risk factors for IFD in HT,[8,11] we also assessed the risk of IFD after developing CMV disease. Acute cellular rejection was modeled as a time-varying covariate—we assumed an effect duration of 90 days for each acute cellular rejection episode treated with a transient increase in the dose of oral prednisone and a duration of 180 days for each episode treated with high-dose corticosteroids, OKT3, ATG or daclizumab. We verified the appropriateness of the proportional hazards assumption for each variable in our final multivariable model by plotting Schoenfeld residuals and by testing for an interaction between each of these variables and follow-up time. All analyses were performed using STATA version 11 (StataCorp, College Station, TX).

Results

Demographic and transplant characteristics of the 360 HT recipients are presented in Table 1. One hundred six patients (29.4%) underwent reoperation within 10 days of HT, most for delayed chest closure (Table 1). Although most patients received corticosteroids alone for induction immunosuppression, 88 patients (24.4%) with renal dysfunction received additional induction immunosuppression with OKT3, daclizumab or ATG, to delay initiation of calcineurin inhibitors post-HT. Median follow-up time for the cohort was 4.1 years (interquartile range [IQR] 1.3 to 15.2 years) after HT.

There were 23 cases of proven (21) or probable (2) IFD over the study period (Table 2). *Candida* (11) and *Aspergillus* (5) were the most common etiologic fungi. Of the *Candida* infections, there were 7 cases of *Candida fungemia* and 4 cases involving fungemia and surgical-site infections. Of the *Aspergillus* infections, there were 2 surgical-site infections, 2 cases of pneumonia and 1 case of disseminated aspergillosis.

The overall IFD incidence rate was 1.23 per 100 person-years (95% confidence interval [CI] 0.78 to 1.84). Most IFD