Epidemiology, Risk Factors, and Effect of Antifungal Prophylaxis on Early Invasive Fungal Infection in Heart Transplant Recipients

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Abstract

Background: Invasive fungal infection (IFI) in heart transplant recipients is associated with increased mortality and poor outcomes. Estimated the risk of 1-year IFI in heart transplant recipients is about 3.4-8.6% with renal replacement therapy, delayed chest closure, and reoperation suggested as risk factors. The role of antifungal prophylaxis is unclear. The transplant program in Mayo provides 6 months of universal azole prophylaxis for those heart transplant recipients residing in areas where *Coccidioides* is endemic, in addition to clinician directed prophylaxis for those deemed at increased risk where *Coccidioides* is not endemic. We sought to define epidemiology and risk factors for 1-year IFI and determine the effect of antifungal prophylaxis.

Methods: We conducted a retrospective cohort study of patients undergoing single-organ heart transplantation at Mayo Rochester, Florida, or Arizona from January 2000 to March 2019. We identified baseline characteristics, details of transplant hospitalization such as need for renal replacement therapy, open chest, reoperation, and operative time, receipt of antifungal prophylaxis, and diagnosis of IFI. Multivariable Cox analysis was performed to identify risk factors of time to 1-year IFI.

Results: A total of 966 heart transplant recipients were identified with a median age of 56 years (IQR 47, 62) and 72% male. 444 patients received antifungal prophylaxis which included 34% itraconazole, 32% fluconazole, 18% voriconazole, 15% echinocandin, and < 1% amphotericin or posaconazole. Over 1-year follow-up, 62 patients developed IFI with a cumulative incidence of 6.4%. The most common organisms were *Aspergillus* (50%) and *Candida* (27%). In a multivariable model, factors associated with 1-year IFI were post-transplant renal replacement therapy (HR 3.34, 95% CI 1.69-6.60; P < 0.001) and antifungal prophylaxis (HR 0.32, 95% CI 0.11-0.96; P=0.042). Operative time, recent hospitalization, open chest, and post-transplant mechanical circulatory device were not associated with 1-year IFI.

Conclusions: Renal replacement therapy after transplantation is associated with 1-year IFI. Antifungal prophylaxis appears to be protective and should be considered in high-risk patients.

Table 1: Patient Characteristics

Age at transplant, (IQR)		56 (47, 62)
Gender, male (%)		697 (72.2%)
Transplant indication, n (%)	Non-ischemic cardiomyopathy	493 (51.0%)
	Ischemic cardiomyopathy	349 (36.1%)
	Amyloidosis	29 (3.0%)
	Other	95 (9.8%)
Re-transplantation, n (%)		19 (2.0%)
Pre-transplant MCD, n (%)	Total	372 (38.5%)
	LVAD	310 (32.1%)
	RVAD	26 (2.7%)
	ECMO	10 (1.0%)
	Total artificial heart	26 (2.7%)
30-day pre-transplant hospitalization, n (%)		501 (51.9%)
Operative time, minutes (IQR)		364 (306, 440)
Induction immunosuppression, n (%)[1]	Anti-thymocyte globulin	648 (69.9%)
	OKT3	173 (18.7%)
	Basiliximab	44 (4.7%)
	Alemtuzumab	1 (0.1%)
	None	61 (6.6%)
Post-transplant RRT, n (%)		82 (8.5%)
Post-transplant LVAD		10 (1.0%)
Post-transplant RVAD		32 (3.3%)
Post-transplant ECMO		26 (2.7%)
30-day post-transplant reoperation, n (%)		156 (16.1%)
Open chest, n (%)		82 (8.5%)
Antifungal prophylaxis, n (%)	Total	444 (46%)
	Itraconazole	151 (34%)
	Fluconazole	144 (32.4%)
	Voriconazole	79 (17.8%)
	Echinocandin	68 (15.3%)
	Posaconazole	1 (0.2%)
	Amphotericin B	1 (0.2%)
12-month CMV, n (%)		215 (22.3%)
12-month ACR, n (%)		239 (24.8%)
12-month AMR, n (%)		45 (4.7%)

IQR, interquartile range; MCD, mechanical circulatory device; LVAD, left ventricular assist device; RVAD, right ventricular assist device; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; CMV, cytomegalovirus; ACR, acute cellular rejection; AMR, antibody-mediated rejection

Objectives

Epidemiology:
Provide updated epidemiology and microbiology of invasive fungal infection (IFI) in heart transplant recipients

Risk Factors:
Analyze which factors are associated with IFI, yeast infection, and mold infection in heart transplant recipients.

Prophylaxis:
Determine the effect of antifungal prophylaxis in our population, where prophylaxis is largely determined by residence in areas endemic with *Coccidioides*.

Methods

- Retrospective cohort study from January 2000 through March 2019
- Site: Mayo Clinic in Arizona, Florida, and Rochester
- Inclusion: Age ≥ 18 years, single-organ heart transplantation performed at a Mayo Clinic site.
- Exclusion: Age < 18 years, transplant performed elsewhere, multiple organ transplantation, inadequate available transplantation data.
- Multivariable Cox analysis for identifying risk factors, identified a priori.

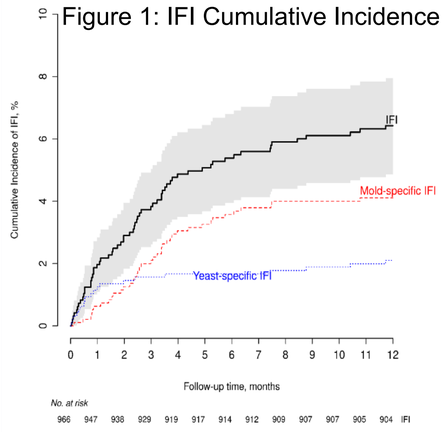
Results

- 12-month cumulative incidence of IFI **6.4%** (median 2.4 months).
- Multivariable analysis of risk for IFI:
  - Fungal prophylaxis **HR 0.32 (0.11 – 0.96), p = 0.042**
  - Post-transplant RRT **HR 3.34 (1.69 – 6.60), p < 0.001**
  - Open chest, operative time, post-transplant MCD, and recent hospitalization **non-significant**
- Multivariable analysis of risk for invasive mold:
  - Fungal prophylaxis **HR 0.34 (0.10 – 1.14), p = 0.080**
  - Post-transplant RRT **HR 3.00 (1.29 – 6.97), p = 0.010**
  - Open chest **non-significant**
- Univariate analysis of risk for invasive yeast:
  - Post-transplant RRT **HR 4.38 (1.68 – 11.43), p = 0.003**
  - Open chest **HR 4.19 (1.55 – 11.35), p = 0.005**
  - Operative time **HR 1.50 (0.83 – 2.72), p = 0.019.**
- 12-month IFI HR for mortality: **2.92 (1.93 – 4.40), p < 0.001**.

Table 2: IFI Microbiology (n = 62)

Mold Organisms, n (%)	Aspergillus	31 (50%)
	Mucormycosis	5 (8.1%)
	Alternaria	1 (1.6%)
	Ochroconis	1 (1.6%)
	Trichophyton	1 (1.6%)
Yeast Organisms, n (%)	Candida	17 (27.4%)
	Cryptococcus	3 (4.8%)
Dimorphic Fungus, n (%)	Coccidioides	3 (4.8%)
Location, n (%)	Pulmonary	33 (53.2%)
	Disseminated	13 (21.0%)
	Mediastinitis	9 (14.5%)
	Skin	4 (6.5%)
	Other	3 (4.8%)

Figure 1: IFI Cumulative Incidence



Discussion

- Renal replacement therapy was identified as a significant risk factor for IFI overall, as well as mold and yeast infections specifically.
- Yeast risk factors appear related to nosocomial and surgical factors.
- Mold risk factors seem less driven by surgical factors and may be related more to cumulative immunosuppression and medical complexities as previously identified.
- Antifungal prophylaxis was protective in IFI overall with a similar effect in mold infection, though non-significant in this smaller population.
- Patients who were diagnosed with IFI within 12 months of transplantation were at a much higher risk for mortality.

Conclusions

- High incidence of IFI after heart transplantation.
- Most yeast infections occur in first month, while mold infections occur over the first 6 months.
- Patients requiring post-transplant RRT are at highest risk for IFI.
- IFI associated with nearly 3-times mortality.
- Antifungal prophylaxis should be considered in patients at high risk.

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