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Incidence and risk factors for herpes zoster following heart transplantation

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Abstract

Background—Data on the incidence, timing, and risk factors for herpes zoster (HZ) in heart transplant (HT) recipients are limited.

Methods—We determined HZ incidence rates and actuarial estimates of time to first HZ episode in 314 HT recipients at our institution from 1995 to 2010. We developed Cox models to assess potential risk factors for HZ in HT.

Results—Median age at HT was 54 (range, 17–71) years; 237 (76%) were male. There were 60 episodes of HZ in 51 patients, with an overall incidence rate of 31.6 cases (95% confidence interval [CI], 23.5–41.6)/1000 person-years. Although most cases occurred during the first post-HT year, cumulative HZ incidence was 0.078 at 1, 0.15 at 5, and 0.20 at 10 years. Many patients had substantial HZ morbidity, including 14% with herpes zoster ophthalmicus and 45% with PHN. Adjusting for age, gender, and acute cellular rejection episodes, exposure to mycophenolate mofetil (MMF) was an independent risk factor for HZ (adjusted hazard ratio [HR] 2.18; 95% CI, 1.20–3.96; $P=0.01$), while ganciclovir-based cytomegalovirus prophylaxis reduced HZ risk (adjusted HR 0.09; 95% CI, 0.01–0.71; $P=0.02$). Although age and female gender increased HZ risk, the magnitude of their effect was not statistically significant in Cox models.

Conclusions—HZ is common and morbid after HT, particularly with MMF exposure. Ganciclovir prophylaxis is effective in reducing the short-term risk of HZ, but the steady incidence of cases for years post HT makes long-term HZ prevention challenging. Augmenting varicella zoster virus immunity post HT with vaccines warrants further exploration.

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Keywords

herpes zoster; varicella zoster virus; mycophenolate mofetil; heart transplantation

Data on the incidence and timing of varicella zoster virus (VZV) reactivation after heart transplantation (HT) are limited. Herpes zoster (HZ) is common in solid organ transplant (SOT) recipients, with a reported incidence 2- to 10-fold higher than the general population (1–3). Reactivation is often highly morbid in the post-transplant setting, with dissemination and visceral involvement in up to 33% of patients and local scarring, bacterial superinfection, and debilitating post-herpetic neuralgia (PHN) in approximately 20–40% of patients with cutaneous HZ (2, 4, 5).

Prior studies examining the incidence of HZ reactivation post transplant have suggested higher rates in HT recipients compared with liver, kidney, or lung transplant recipients, although the number of HT patients has been limited in these analyses (1, 5). We sought to investigate the incidence patterns of HZ in a large, single-center HT cohort to determine whether antiviral prophylaxis or vaccination strategies might be useful in preventing this morbid infectious complication and to determine specific risk factors for HZ in HT recipients.

Patients and methods

Study population

We reviewed the records of all patients who underwent HT at our institution from January 1, 1995 through March 1, 2010 and recorded patient demographics, pretransplant VZV and cytomegalovirus (CMV) serostatus, details of immunosuppressive and herpesvirus prophylaxis regimens, episodes of allograft acute cellular rejection (ACR) treated with an increase in immunosuppressive agents, and all HZ episodes. Patients who received concurrent renal transplantation were excluded from all analyses.

Routine care

Immunosuppression—All patients received methylprednisolone 1000 mg by intravenous (IV) infusion in the operating room, followed by 125 mg IV every 8 h for 3 doses, then a tapering dose of corticosteroids. Patients with substantial renal dysfunction at the time of HT, defined as preoperative renal dysfunction, perioperative renal injury, or postoperative anuria, as adjudicated jointly by a staff transplant surgeon and transplant cardiologist within 24–48 h of HT, received OKT3 (1995 to May 2001) or daclizumab (May 2001 to the end of the study period) 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.

Herpesvirus prophylaxis—From 1996 to 2001, donor CMV seropositive/recipient seronegative (D+/R–) patients generally received IV ganciclovir, then oral ganciclovir, for 4

months post HT. From 2001 to 2002, CMV D+/R– patients received IV ganciclovir or oral valganciclovir for 4 months. From November 2002 to the end of the study period, HT recipients received oral valganciclovir prophylaxis for 4–6 months post HT, if either the donor or recipient were CMV seropositive. CMV D–/R– patients did not routinely receive acyclovir prophylaxis over this period.

ACR—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 ACR by standard International Society for Heart and Lung Transplantation criteria.⁽⁶⁾ Patients who received an increased dose of oral corticosteroids, high-dose IV corticosteroids, OKT3, anti-thymocyte globulin (ATG), or daclizumab for treatment of ACR on biopsy were considered to have ‘treated ACR’ for these analyses. Patients did not resume herpesvirus prophylaxis during these ACR episodes.

HZ episodes

Incident HZ cases post HT were verified by review of electronic and paper medical records. Details of the clinical manifestations of HZ, including the appearance and anatomic distribution of the characteristic rash, date of symptom onset, results of confirmatory viral cultures, VZV direct fluorescence antigen testing or VZV polymerase chain reaction testing if available, antiviral agents used for HZ treatment, and analgesic agents used to treat PHN were recorded.

Statistical methods

We determined HZ incidence rates and crude incidence rate ratios in the overall cohort and in strata of age, gender, race, post-HT year, and the chronologic period when the HT was performed. We calculated actuarial estimates of time to the first VZV episode using the Kaplan–Meier method, and developed Cox proportional hazards models to evaluate risk factors we thought *a priori* might affect the hazard of HZ, including age (1, 7), gender (8, 9), MMF exposure (7, 10), ACR (5), CMV disease (11), and ganciclovir or valganciclovir prophylaxis (8, 12). ACR and exposure to herpesvirus prophylaxis were modeled as time-varying covariates. We assumed an effect duration of 90 days for each ACR 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 assessed for a non-log-linear (quadratic, cubic, spline-shaped) relationship between age and the hazard of HZ, and examined whether acute rejection, mycophenolate exposure, or herpesvirus prophylaxis had differential effects on the hazard of HZ by gender and age. 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 11 (Stata Corp, College Station, Texas USA), and a *P*-value < 0.05 was considered statistically significant. This study was approved by the Partners Human Research Committee.

Results

During the study period, there were 314 HT recipients (Table 1). Median age at the time of HT was 54 years, and the cohort was predominantly male (75.5%) and white (87.6%). Most patients received steroids alone for induction; 85 (27.1%) patients with impaired renal function on the day of HT also received OKT3 or daclizumab to delay initiation of calcineurin inhibitors. Overall, 134 (42.7%) patients received ganciclovir or valganciclovir prophylaxis for a median of 143 days post HT. A total of 137 (43.6%) patients had at least 1 episode of ACR treated with an increased dose of oral steroids, high-dose corticosteroids, OKT3, ATG, or daclizumab. Median follow-up time was 4.1 (interquartile range [IQR], 1.0–8.1) years.

A total of 60 HZ episodes occurred in 51 patients over the study period; 1 patient had 3 discrete HZ episodes, and 3 patients had 2 discrete episodes. The median time to first HZ episode was 2.1 years (IQR 0.5–6.1 years; range 2 days–14.2 years). Of 51 initial HZ episodes, 40 (78%) were uncomplicated cutaneous zoster involving a single dermatome, 7 (14%) were herpes zoster ophthalmicus, 3 (6%) were cutaneous zoster involving multiple non-contiguous dermatomes, and 1 (2%) was a disseminated VZV infection with meningoencephalitis. No patients developed bacterial superinfection of their cutaneous HZ lesions. Of these 51 patients with HZ, 23 (45%) had PHN requiring analgesic therapy and 8 (16%) had sustained symptoms requiring analgesic therapy for >3 months.

The overall incidence rate of HZ over the study period was 31.6 cases/1000 person-years (95% CI, 23.5–41.6; Table 2). The incidence rate of HZ generally rose with age at transplantation, although HZ incidence was highest at 45.1 cases/1000 person-years in 51–60 year olds and declined to 26.4/1000 person-years in patients >60 years of age, despite comparable daclizumab or OKT3 exposure and a higher proportion of patients receiving MMF in our oldest cohort (50/79 patients >60 years at HT versus 118/235 patients ≤60 years at HT; Fisher's exact $P = 0.05$). Women had a higher incidence of HZ than men, with an incidence rate ratio of 1.60 (95% CI, 0.89–2.89). The rate of HZ was comparable between CMV serostatus groups. The incidence of HZ cases was most dense in the first post-HT year at 83.3 cases/1000 person-years and declined significantly thereafter. The incidence rate of HZ was similar in patients who received methylprednisolone with OKT3 or daclizumab for induction immunosuppression and in those who received methylprednisolone alone. The incidence rate of HZ was slightly higher in patients with at least 1 episode of ACR compared with patients without any rejection episodes. Although most HZ cases occurred during the first year following HT, the incidence of HZ was fairly steady over the remainder of the study period, with a cumulative incidence of 0.08, 0.15 and 0.20 at 1, 5, and 10 years post transplant, respectively (Fig. 1, Table 3).

On univariable analysis, mycophenolate exposure increased the hazard of HZ starting 9–10 months post HT and lasting throughout the follow-up period (Fig. 2), while exposure to herpesvirus prophylaxis reduced the hazard of HZ. The hazard of HZ was greater with each decade of age, female gender, and ACR, and lower with CMV disease, but these factors were not statistically significant in univariable Cox models (Table 4).

In the multivariable model, mycophenolate exposure increased the risk of HZ, with a HR of 2.18 (95% CI, 1.20–3.96; $P = 0.01$), while ganciclovir or valganciclovir prophylaxis reduced the risk of HZ, with a HR of 0.09 (95% CI, 0.01–0.71; $P = 0.02$), adjusting for age, ACR, and gender (Table 3). Age and female gender conferred an increased hazard of HZ, but the magnitude of their effect was not statistically significant. CMV disease was omitted from the final multivariable model, because of its strong collinearity with ACR and the use of herpesvirus prophylaxis.

Effect estimates in our final multivariable model were not affected by adjustment for chronologic period of HT. We found no evidence of a differential effect of ACR, MMF exposure, or herpesvirus prophylaxis on the hazard of HZ by strata of gender or age.

Discussion

We found a high incidence of HZ in our large HT cohort, with age-stratified incidence rates 3–10 times higher than reported in large community health plan databases (8, 12). Although the incidence rate of HZ was highest during the first year post transplant, cases occurred steadily thereafter over the entire follow-up period. The hazard of HZ increased with mycophenolate-containing immunosuppressive regimens and decreased with ganciclovir or valganciclovir antiviral prophylaxis. Many patients had considerable morbidity from HZ infection, including zoster ophthalmicus, systemic VZV dissemination, and PHN.

Most prior studies of HZ incidence in HT recipients have been highly heterogeneous in their immunosuppressive and antiviral prophylaxis protocols and follow-up time (13–15). In general, these cross-sectional studies have reported the overall fraction of patients developing HZ (4.4–25.1%) without accounting for person-time at risk. Thus, a direct comparison with our study findings is challenging, although the global cumulative incidence of patients with HZ in our cohort (16.2%) falls in the higher end of this range (1, 5). Our HZ incidence estimates are higher than the rate of 22.2–27.2/1000 person-years reported in 2 large mixed cohorts of SOT recipients, although both studies described a higher incidence of HZ in their HT subgroups, with an incidence rate as high as 40.0/1000 person-years in one study (3, 16). The incidence of HZ was highest during the first post-HT year, as expected with the well-defined acute impairment in VZV-specific cellular immunity over first several months following HT (1, 7, 17–19), but cases occurred at a steady rate over the entire follow-up period, which is in agreement with prior studies in HT and other SOT cohorts (20).

We identified exposure to MMF as an important, independent risk factor for HZ in HT patients. Long-term follow-up of a randomized controlled trial of MMF versus azathioprine-containing immunosuppressive regimens in HT patients previously suggested an association between mycophenolate and an increased risk of HZ: 14.5% of patients receiving mycophenolate and 9.7% of patients receiving azathioprine developed HZ at 3 years (5, 21–24). A potential link between mycophenolate exposure and HZ has also been described in the setting of kidney and liver transplantation (25, 26), bullous dermatoses (27), psoriasis (28), and atopic dermatitis (29, 30). The mechanism behind the increased risk of HZ with mycophenolate is unclear. Substantial inter- and intra-individual variability exists in

mycophenolic acid exposure with fixed-dose mycophenolate regimens (30, 31), and anecdotal reports have noted severe and recurrent herpesvirus infections, including HZ, in transplant recipients with high serum trough mycophenolic acid concentrations (31).

Age at transplant increased the risk of HZ, with a HR of 1.24 per decade, consistent with effect estimates in other large studies of HZ in SOT patients (4, 16). However, as noted in some of these other studies, the magnitude of this effect was not statistically significant in our univariable or multivariable models. Interestingly, HZ incidence increased in our cohort across age strata to a maximum of 45.1 cases/1000 person-years, or 8–9-fold higher than the community incidence in patients of comparable age (12) in patients who were 51–60 years old at the time of HT. Incidence then declined to 26.4 cases/1000 person-years in patients 60 years at HT, or 2–3-fold higher than immunocompetent hosts of similar age, despite similar induction immunosuppression regimens, comparable duration of post-HT follow-up time, and a higher proportion of patients receiving MMF-containing regimens in patients in this age strata, compared with younger patients. The substantial impairment in VZV-specific cellular immunity induced by exogenous immunosuppression in SOT may modify the relationship between natural senescence of VZV immune containment and HZ seen in immunocompetent populations, and shift the incidence curve to younger patients (4, 5).

Strengths of our study include a large cohort with a long median duration of follow-up, which allowed a detailed examination of HZ incidence patterns and determination of HZ risk factors specific to the HT population. Patients were followed closely post HT, with high-quality documentation of incident HZ cases, so our incidence rate estimates are likely to reflect the true incidence in this cohort. As with any single-center retrospective study, our findings should be interpreted in the context of our institutional transplantation practices over the study period.

Although HZ rates were evenly distributed between CMV serostatus groups over the first post-HT year, we implemented acyclovir prophylaxis post HT in all CMV D–/R– patients at our institution, in response to the very high early HZ incidence rates in this study, so that all patients now receive 4–6 months of herpesvirus prophylaxis following HT. Although acyclovir has been shown to be safe and effective in preventing herpesvirus infections for up to a year following hematopoietic stem cell transplantation (SCT) (32, 33), limited evidence supports longer term herpesvirus prophylaxis in HT or other SOT recipients (10).

The prevention of HZ is challenging beyond the initial post-transplant period. Currently available live attenuated varicella vaccines (Varivax® and Zostavax®) are not recommended in SOT recipients because of the risk of disseminated disease in immunocompromised hosts (10). Although isolated reports note safe administration of these vaccines in pediatric renal transplant (34) and in selected hematopoietic SCT recipients (35), no safety data are available in the HT setting. A heat-inactivated, live attenuated varicella vaccine was shown to reduce HZ episodes and increase VZV CD4+ proliferative responses in patients who received autologous SCT for lymphoma (36). Similarly, a novel adjuvanted VZV glycoprotein E vaccine was reported to augment anti-glycoprotein E antibody concentrations and glycoprotein E-activated CD4+ cells in adults receiving autologous SCT for hematologic malignancy in a recent randomized phase I/II study (37). Given the high

incidence of HZ that persists for years post HT and the substantial morbidity of HZ in this population, augmenting VZV immunity post HT with vaccines clearly warrants further study.

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Fig. 1.
Cumulative incidence of herpes zoster following heart transplantation.

Fig. 2.
Cumulative incidence of herpes zoster by mycophenolate exposure.

Table 1
Baseline characteristics of the heart transplant cohort (*n* = 314)

Median age, years (IQR; range)	54 (44, 60; 17, 71)
Male, <i>n</i> (%)	237 (75.5)
Race or ethnicity	
White	275 (87.6)
Black	18 (5.7)
Hispanic	13 (4.1)
Asian	8 (2.5)
Indication for heart transplant, <i>n</i> (%)	
Ischemic cardiomyopathy	125 (39.8)
Dilated cardiomyopathy	120 (38.2)
Valvular cardiomyopathy	19 (6.1)
Hypertrophic cardiomyopathy	19 (6.1)
Congenital heart disease	7 (2.2)
Other ¹	24 (7.6)
CMV serostatus, <i>n</i> (%)	
D+/R–	78 (24.8)
D+/R+	88 (28.0)
D–/R+	60 (19.1)
D–/R–	88 (28.0)
CMV disease, <i>n</i> (%)	11 (3.5)
Recipient VZV seropositive (<i>n</i> = 286); <i>n</i> (%)	283 (99.0)
Induction immunosuppression, <i>n</i> (%)	
Methylprednisolone alone	229 (72.9)
Methylprednisolone + OKT3 or daclizumab	85 (27.1)
Ganciclovir or valganciclovir prophylaxis, <i>n</i> (%)	134 (42.7)
Median duration of ganciclovir or valganciclovir prophylaxis, days (IQR; range)	143 (113, 173; 1, 485)
1 episode of treated acute cellular rejection, <i>n</i> (%)	137 (43.6)

IQR, interquartile range; CMV, cytomegalovirus; D, donor; R, recipient; VZV, varicella zoster virus.

¹ Other: 13 adriamycin-induced cardiomyopathy, 3 radiation-induced cardiomyopathy, 3 acute viral myocarditis, 2 arrhythmogenic right ventricular cardiomyopathy, 2 giant cell myocarditis, 1 amyloidosis.

Table 2

Herpes zoster (HZ) incidence rates

Variable	N	HZ cases	Person-years at risk	HZ incidence rate (95% CI) ^I	IRR (95% CI)
Whole cohort	314	51	1612.8	31.6(23.5,41.6)	
Age at transplant, years					
40	52	4	278.5	14.4 (3.9, 36.8)	-
41–50	60	9	333.7	27.0(12.3,51.2)	1.88 (0.58, 6.10)
51–60	123	28	621.5	45.1 (29.9, 65.1)	3.14(1.10,8.94)
>60	79	10	379.2	26.4(12.7, 48.5)	1.84 (0.58, 5.86)
Gender					
Male	237	35	1254.8	27.9 (19.4, 38.8)	-
Female	77	16	358.0	44.7 (25.6, 72.6)	1.60 (0.89,2.89)
Race or Ethnicity					
White	275	46	1403.4	32.8 (24.0, 43.7)	-
Black	18	3	88.7	33.8 (7.0, 98.8)	1.03 (0.32,3.32)
Other ²	21	2	120.8	16.6 (2.0, 59.8)	0.51 (0.12, 2.08)
CMV serostatus					
D+/R–	78	12	405.2	29.6(15.3,51.7)	-
D+/R+	88	13	453.8	28.7(15.2, 49.0)	0.97 (0.44, 2.12)
D–/R+	60	12	276.2	43.5 (22.4, 75.9)	1.47 (0.66,3.27)
D–/R–	88	14	477.7	29.3 (16.0, 49.2)	0.99 (0.46, 2.14)
CMV disease					
No	303	50	1545.4	32.4 (24.0, 42.7)	-
Yes	11	1	67.5	14.8 (1.9, 82.4)	0.46 (0.06, 3.31)
HT period, by changes in standard immunosuppression regimens					
1995–2002	170	32	1187.6	27.0 (18.4, 38.0)	-
2002–2008	98	16	379.5	42.2 (24.1, 68.5)	1.57 (0.86,2.85)
	46	3	45.8	65.9 (13.3,192.6)	2.43 (0.74, 7.94)

Variable	N	HZ cases	Person-years at risk	HZ incidence rate (95% CI) ¹	IRR (95% CI)
2008–2010					
HT period, by changes in standard CMV prophylaxis regimens	154	31	1102.6	28.1 (19.1,39.9)	-
1995–2001	33	4	186.0	21.5 (5.8,55.1)	0.76 (0.27, 2.17)
2001–2002	127	16	324.3	49.3 (28.2, 80.1)	1.76 (0.96,3.21)
2002–2010					
Post-HT year					
Year 1	314	22	264.2	83.3 (52.2,126.1)	-
Year 2	236	3	218.1	13.8 (2.8,40.2)	0.17 (0.05, 0.55)
Year 3	206	3	194.4	15.4 (3.2,45.1)	0.19 (0.06, 0.62)
Year 4	185	4	176.6	22.7 (6.2, 58.0)	0.27 (0.09, 0.79)
Year 5	159	5	146.1	34.2 (11.1,79.9)	0.44 (0.16, 1.09)
Year 6+	134	14	617.4	22.7 (12.4, 38.1)	0.27 (0.14, 0.53)
Induction regimen					
Methylprednisolone	229	41	1278.0	32.1 (23.0, 43.5)	-
Methylprednisolone + OKT3 or daclizumab	85	10	334.8	29.9 (14.3, 54.9)	0.93 (0.47, 1.86)
Acute cellular rejection					
No	177	24	825.0	29.1 (18.6, 43.3)	-
Yes	137	27	787.8	34.3 (22.6, 49.9)	1.18 (0.68,2.04)
Mycophenolate exposure					
No	146	22	976.6	22.5 (14.1,34.1)	-
Yes	168	29	636.3	45.5 (30.5, 65.5)	2.02 (1.16,3.52)

CI, confidence interval; IRR, incidence rate ratio; CMV, cytomegalovirus; D, donor; R, recipient; HT, heart transplantation.

¹ Cases per 1000 person-years.

² Hispanic, Asian.

Table 3
Actuarial cumulative incidence of herpes zoster (HZ) following heart transplantation

Post-transplant year	<i>N</i> ¹	HZ events ²	Actuarial cumulative incidence of HZ (95% CI)
1	237	22	0.078 (0.052, 0.12)
2	207	3	0.095 (0.062, 0.13)
3	186	3	0.10 (0.073, 0.15)
4	160	4	0.13 (0.090, 0.17)
5	135	5	0.15 (0.11, 0.21)
6	121	1	0.16 (0.12, 0.22)
7	101	4	0.19 (0.14, 0.25)
8	81	0	0.19 (0.14, 0.25)
9	76	0	0.19 (0.14, 0.25)
10	68	1	0.20 (0.15, 0.27)
11	48	4	0.25 (0.19, 0.33)
12	38	1	0.27 (0.20, 0.36)
13	21	2	0.33 (0.24, 0.45)
14	12	0	0.33 (0.24, 0.45)
15	1	1	0.40 (0.26, 0.59)

CI, confidence interval.

¹ Number of patients remaining at the end of each post-transplant year.

² Number of herpes zoster events during each post-transplant year.

Table 4
Risk factors for herpes zoster in heart transplantation

Variable	Univariable	Multivariable
Age, per decade	1.26 (0.97, 1.62); $P = 0.08$	1.24 (0.95, 1.61); $P = 0.11$
Female gender	1.57 (0.87, 2.84); $P = 0.14$	1.54 (0.85, 2.79); $P = 0.16$
Acute cellular rejection ¹	1.52 (0.57, 4.08); $P = 0.41$	1.32 (0.49, 3.55); $P = 0.58$
Mycophenolate mofetil	2.01 (1.11, 3.66); $P = 0.02$	2.18 (1.20, 3.96); $P = 0.01$
Herpesvirus prophylaxis ¹	0.12 (0.02, 0.96); $P = 0.04$	0.09 (0.01, 0.71); $P = 0.02$
CMV disease	0.75 (0.10, 5.64); $P = 0.78$	— ²

Risks displayed as hazard ratio (95% confidence interval).

¹ Modeled as a time-varying covariate.

² Cytomegalovirus (CMV) disease was omitted from the final multivariable model because of strong collinearity with acute cellular rejection and the use of herpesvirus prophylaxis.