Very Late Onset Infections Among Long Term Survivors of Kidney Transplantation

Harry Cheung[1], Marwan M. Azar[2], Geliang Gan[3], Yanhong Deng[3], Elizabeth Cohen[4], Sanjay Kulkarni[5], Maricar Malinis[2]

[1] Yale School of Medicine, [2] Section of Infectious Diseases, Yale School of Medicine [3] Yale Center for Analytical Sciences, Yale School of Public Health,
[4] Yale New Haven Transplant Center, [5] Section of Transplant Surgery, Yale School of Medicine

Presenting Author Contact: harry.cheung@yale.edu

Introduction

- The highest risk for post-transplant infection is within the first year of kidney transplant due to significant immunosuppression.
- In the absence of acute rejection, immune reconstitution can occur beyond 1 year after kidney transplantation with decreasing risk for infection.
- Post-transplant infections are well characterized in the immediate post kidney transplant period. [1]
- However, there is lack of data surrounding the epidemiology of infections beyond 10 years of kidney transplant among long term survivors.

Objectives

- To determine the incidence of very late-onset infections (VLIs) in long term survivors of KT (≥10 years).
- To determine risk factors associated with VLIs in long term survivors of KT.

Methods

- A retrospective review of medical charts of KT recipients who survived more than 10 years after transplantation was conducted.
- Subjects included were: KT recipients who underwent transplantation as an adult (age ≥18) between 2003-2009 and survived 10 years or more after KT.
- Data collected included: demographics, comorbidities, CMV donor /recipient serologies, induction and maintenance immunosuppression.
- Pertinent data to describe VLIs (defined as any infection ≥10 years status-post transplant) was collected including date of infection, microbiological data, and absolute lymphocyte count (ALC).
- For patients with no VLI, the most recent ALC value documented was utilized.
- Infections were categorized per consensus definitions of the Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN) and the American Society of Transplantation. [2,3]
- Simple logistic regression was performed to determine characteristics associated with risk for VLIs.

Results

Table 1: **Demographics, comorbidities, immunosuppression, and clinical data for all patients**

Variable	All Patients (n = 332)	No Very-Late Onset Infections (n = 229)	All Very-Late Onset Infections (n = 103)
Median Age at Time of Transplant (range)	46 (18-76)	46 (18-76)	47 (20-73)
Age at Time of Transplant			
18-29	36 (10.8%)	30 (13.1%)	6 (5.8%)
30-39	72 (21.7%)	48 (21%)	24 (23.3%)
40-49	83 (25%)	58 (25.3%)	25 (24.3)
50-59	94 (28.3%)	64 (28%)	30 (29.1%)
60-69	39 (11.8%)	24 (10.4%)	15 (14.6%)
70-79	8 (2.4%)	5 (2.2%)	3 (2.9%)
Alive At Time of Study	294 (88.6%)	211 (92.1%)	83 (80.6%)
Living Donor	146 (44%)	109 (47.6%)	37 (35.9%)
Retransplantation	28 (8.4%)	16 (7.0%)	12 (11.6%)
Median Years From Transplant to Last Follow Up (range)	12.1 (10-37)	11.9 (10-16)	13.1 (10-37)
Mean Charlson Comorbidity Index (SD)	4.7 (2.0)	4.4 (1.8)	6.3 (2.2)
Male	207 (62%)	146 (63.8%)	60 (58.3%)
Race/Ethnicity			
Asian	16 (4.8%)	10 (4.4%)	6 (5.8%)
Black	78 (23.5%)	52 (22.7%)	26 (25.2%)
Hispanic	39 (11.7%)	23 (10%)	16 (15.5%)
White	198 (59.6%)	143 (62.4%)	55 (53.4%)
Native American	1 (0.3%)	1 (0.4%)	0
Induction Regimens			
Basiliximab	81 (24.4%)	51 (22.3%)	30 (29.1%)
Daclizumab	21 (6.3%)	16 (7.0%)	5 (4.9%)
Methylprednisolone	116 (34.9%)	74 (32.3%)	42 (40.8%)
Thymoglobulin	57 (17.2%)	38 (16.7%)	19 (18.4%)
Unknown/Unspecified	59 (17.8%)	52 (22.7%)	7 (6.8%)
Maintenance Regimens			
Belatacept and prednisone	13 (3.9%)	6 (2.6%)	7 (6.8%)
Belatacept, mycophenolate, and prednisone	16 (4.8%)	8 (3.5%)	8 (7.8%)
Cycosporine, mycophenolate, and prednisone	17 (5.1%)	10 (4.4%)	7 (6.8%)
Tacrolimus and azathioprine	20 (6.0%)	18 (7.8%)	2 (1.9%)
Tacrolimus and mycophenolate	22 (6.6%)	14 (6.1%)	8 (7.8%)
Tacrolimus and prednisone	43 (13%)	27 (11.8%)	16 (15.5%)
Tacrolimus, mycophenolate, and prednisone	161 (48.5%)	120 (52.4%)	41 (39.8%)
Unknown	9 (2.7%)	8 (3.5%)	1 (0.97%)
Other	31 (9.3%)	18 (7.8%)	13 (12.6%)
Comorbidities			
Hepatitis C	14 (4.2%)	10 (4.4%)	4 (3.9%)
Diabetes	140 (42.2%)	85 (37.1%)	55 (53.4%)
Renal Disease Requiring Renal Replacement Therapy	56 (16.9%)	29 (12.7%)	27 (26.2%)
Cardiovascular Disease	114 (34.3%)	67 (29.3%)	47 (45.6%)
Lung Disease	6 (1.8%)	3 (1.3%)	3 (2.9%)
Chronic Liver Disease	17 (5.1%)	12 (5.2%)	5 (4.9%)
Cerebrovascular Injury	26 (7.8%)	13 (5.7%)	13 (12.6%)
Malignancy	54 (16.3%)	34 (14.8%)	20 (19.4%)
Number of Total Very Late-Onset Infections			
1	62 (18.7%)	0	62 (60.2%)
2	24 (7.2%)	0	24 (23.3%)
3	9 (2.7%)	0	9 (8.7%)
4+	8 (2.4%)	0	8 (7.8%)
Serologic Data			
CMV D+/R-	27 (8.1%)	21 (9.2%)	6 (5.8%)
CMV D-/R-	26 (7.8%)	21 (9.2%)	5 (4.9%)
CMV D?/R-	126 (38%)	88 (38.4%)	38 (36.9%)
CMV R+	153 (46.1%)	99 (43.2%	54 (52.4%)
Mean Absolute Lymphocyte Count (10^3/μL)	1.37	1.48	1.11

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Results

- Of the 332 KT recipients that met inclusion criteria, the majority were male (62.0%), White (59.6%).
- The largest proportion underwent KT transplantation between the ages of 50-59 (28.3%).
- The mean Charlson Comorbidity Index (CCI) was 4.7 (S.D. 2.0).
- 103 KT recipients (31%) experienced ≥ 1 VLI amounting to a total of 187 infection episodes.
- Compared to those without VLI, KT recipients with VLI were more likely to have diabetes (p=0.005), cardiovascular disease (p = 0.004), low absolute lymphocyte count (p<0.001) and on dialysis (p=0.002).
- Of the 103 KTR with VLI, 16 (15.5%) developed an opportunistic infection.
- The most common episodes of non-opportunistic infections were urinary tract infections (n=85, 45.5%), pneumonia (n=35, 18.7%), and gastrointestinal (n=18, 9.6%).
- The most commonly isolated pathogens were *E. coli* (n=30, 16%), *K. pneumoniae* (n=16, 8.6%), MSSA (n=7, 3.7%) and *P. aeruginosa* (n=7, 3.7%).
- Diabetes, dialysis, cerebrovascular disease, cardiovascular disease, lower ALC, and a higher CCI were associated with increased risk of VLI (p < 0.05) while living donor transplantation was protective (p=0.04).
- Every additional 1 year after transplant was associated with an increased risk of VLI (OR=1.31, p <0.001).

Discussion/Conclusions

- Overall, VLIs occurred in one-third of long-term survivors of KT.
- VLIs included both conventional (community-acquired and nosocomial) and opportunistic pathogens.
- Diabetes, dialysis, cerebrovascular disease, cardiovascular disease, lower ALC, and a higher CCI were associated with increased risk of VLI.
- The risk for infection in this group could be compounded by immunosenescence as well as chronic, cumulative immunosuppression and the burden of co-morbidities.
- This is the first study to begin the process of characterizing infections in the "very late" post-transplant period, defined as ≥10 years post-transplant.
- Awareness of risk factors for VLIs can guide preventative strategies to reduce infection risk which may include antimicrobial prophylaxis, immunization strategies and glycemic control.

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