

The Incidence, Clinical Characteristics and Risk Factors of Tuberculosis Among Renal Allograft Recipients at National Kidney and Transplant Institute

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Abstract

Objective: Renal allograft recipients are at higher risk of developing tuberculosis (TB) as compared to the general population. The infection also carries with it a significant morbidity and mortality. However, data is limited regarding its incidence and risk factor analysis in our setting. This study determined the incidence, characteristics and risk factors of post-transplant TB in National Kidney and Transplant Institute (NKTi).

Methods: This is a retrospective study involving chart review of 1,621 renal allograft recipients from 2003-2009. We recorded demographic information, transplant characteristics, median time to diagnosis of TB and forms of TB.

Results: The incidence of TB in renal allograft recipients is 2.6%. Median time to diagnosis of TB after transplant is 21 months (one to 105 months). Risk factors identified in this study were previous history of TB (OR 4.15, 95% CI 1.4-12.2), one episode of rejection (OR 2.33, 95% CI 1.2-4.6) and subsequent use of methylprednisolone as anti-

rejection therapy (OR 2.36, 95% CI 1.3-4.4). Patients given a tacrolimus based regimen (OR 0.5, 95% CI 0.24-1.03) and those without episode of rejection (OR 0.43, 95% CI 0.22-0.84) had less tendency to develop post-transplant TB. There were no sufficient evidence to prove association between onset of TB and use of isoniazid prophylaxis, use of induction immunosuppression and type of immunosuppression. Eighty one percent (81%) had pulmonary and 19% had extrapulmonary forms of TB.

Conclusion: Incidence of TB among renal allograft recipients is lower as compared to other high TB burden countries but is still higher as compared to the general Filipino population. The study identified multiple risk factors for post-transplant TB. Prevention of these diseases and identification of patients at risk are as important as early diagnosis and treatment of post-transplant TB.

Keywords: renal transplant, TB, risk factors, immunosuppression, rejection

Introduction

Tuberculosis (TB) remains to be a major health problem in the Philippines. The latter is considered a high-TB burden country where TB ranks sixth amongst the leading cause of morbidity and mortality.^{1,2}

Renal transplantation is the treatment of choice in end stage renal disease patients. With the recent advancement in immune modulation and development of newer and more potent immunosuppressant drugs, long term outcome has become more favorable and significantly improved. However, chronic exposure to immunosuppressive medications places the recipient at higher risk to develop opportunistic infections, including TB.

As compared to the general population, risk of acquiring TB is significantly higher among kidney transplant (KT) patients (50-100 fold).³ The incidence of TB varies according to geographic locations. In countries where TB is endemic, the reported incidence in renal transplant patients is 12.4-15.2% in Pakistan⁴, 11.8% in India⁵, 11% in South Africa.⁶ In non-endemic regions, i.e. North America and Europe, incidence is significantly lower as it approaches only 0.5-1% and 0.7-5%, respectively. In our institution, a study done by Celestial in 2001 reported a one year incidence rate of 4.9%.⁷

Due to the higher dosages of immunosuppressive drugs during the first year after transplantation, infection with TB is highest during this time.^{7,8,10} In a local prospective study done by Mendoza in 1997, TB occurred more commonly in the six months or later in the first post-transplant year.¹⁰ Celestial reported a median time to diagnosis of TB after transplantation to be 12 months (Range: one to 160 months).⁷ Other countries reported a longer time to diagnosis of TB after transplantation. In Thailand¹⁰ and Turkey,¹¹ it occurred at 36 months (four to 115 months) and 44 months

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(three to 111 months), respectively. Majority of the cases was secondary to activation of latent TB in the transplant recipient. Other mechanisms of infection include 1) Latent TB infection in a living or deceased donor 2) de novo exposure post-transplantation and 3) when a patient with active TB urgently requires a transplant.

Multiple risk factors have also been associated with the development of TB in transplant patients. In a case-control study done by Basiri in 2006, it has shown that longer duration of hemodialysis prior to transplantation and increasing number of rejection episodes with subsequent use of methylprednisolone pulsing as anti-rejection treatment (OR 2.7, 95% CI, 1.3-5.6) increases the risk of post-transplant TB significantly.¹³ In a prospective cohort study done by John in 2001, higher risk was seen in patients with diabetes mellitus (2.2 times), chronic liver disease (1.7 times) and those with coexisting infections (2.4 times) (including deep mycoses, cytomegalovirus (CMV), *Pneumocystis carinii* pneumonia (PCP), *Nocardia*).¹⁴ In a study done in Taiwan in 2012, patients with chronic obstructive pulmonary disease were also mentioned as an independent risk factor for post-transplant TB with an OR 1.50.¹⁵

The type of immunosuppression therapy also influences the risk for acquiring TB after transplant. In a prospective cohort study among Indian renal allograft recipients in 2001, it was found out that the risk of post-transplant TB when on cyclosporine (CsA) therapy was 2.5 and 1.9 times at more or less six months and ≤ 12 months, respectively, compared with patients on prednisolone plus azathioprine therapy as immunosuppressive therapy.¹⁴ However, with the emergence of new and more potent immunosuppressive drugs like mycophenolate and tacrolimus, susceptibility to TB seems to be higher. In the more recent study done in Thailand in 2008, it has been shown that patients given mycophenolate or tacrolimus were at higher risk for the development of TB after transplantation as compared to those who were given conventional therapy with cyclosporine and prednisone (OR 9.682, 95% CI 2.133-43.942).¹⁰

Use of lymphocyte depleting agents such as anti-thymocyte globulin (ATG) and alemtuzumab may also facilitate the development of post-transplant TB by impairing cell-mediated immunity.¹⁶

Prophylaxis with isoniazid (INH) after transplantation has conflicting results in both observational and randomized control trials. However, in the meta-analysis done by Currie in 2010, they found that risk of TB infection was significantly reduced with INH prophylaxis (RR 0.31, 95% CI 0.19-0.51).¹⁷ Only one local data regarding this matter was found after extensive review of literature. This was done by Celestial in 2001 wherein TB infection rates were correlated with the duration

of isoniazid prophylaxis. A trend towards benefit was observed with a six-month isoniazid prophylaxis (RR 0.21 95% CI 0.03-1.70) as compared with less than three months (RR 1.07 95% CI 0.47-2.45) and three to six months (RR 0.63 95% CI 0.47-1.87).⁷

Tuberculosis among kidney transplant patients presents as a special challenge to clinicians due to its atypical presentation and greater frequency of extrapulmonary manifestations.^{18,19} Response to treatment with the standard anti-tuberculous therapy is the same as in immunocompetent individuals. Treatment of active TB in renal transplant recipients is the same as in the general population, i.e. two months of quadruple therapy combining rifampicin, isoniazid, pyrazinamide and ethambutol followed by a four-month maintenance phase using rifampicin and isoniazid.²⁰

However, treatment is complicated due to the interaction of the antituberculous medications, particularly rifampicin, with the immunosuppressants increasing risk for graft rejection.^{21,22} Although the mechanism still remains unclear, graft dysfunction can also be caused by direct effects of the TB itself.²¹

In addition, the severity of active TB disease is much higher in transplant recipients, with mortality rates between 20-30%.^{22,23} This represents a 10-fold higher mortality as compared to immunocompetent individuals. Most fatality (57-83%) in these patients is directly attributable to TB.²⁴ Additional features contributing to an increased morbidity and mortality include the difficulty in early diagnosis resulting in delay in initiation of therapy, and increased incidence of disseminated disease at the time of diagnosis.

Significance

National Kidney and Transplant Institute (NKTI) already performed over 2500 renal transplantation since its initiation of the program in 1983. Truly, we are considered the leading renal transplant center in the Philippines. With the increasing number of renal transplant recipients, the incidence of TB is expected to increase as well. Reducing this risk is an important priority in organ transplantation.

However, there is only limited local data regarding the incidence of TB in kidney allograft recipients in the Philippines. To our knowledge, there is still no data regarding risk factor identification among this special population of patients in our setting. This study is to be undertaken to report the experience with TB in renal allograft recipients in our institution for the past seven years.

Objectives

General:

To determine the incidence, clinical characteristics and risk factors of TB among kidney allograft recipients admitted at NKTl from 2003 to 2009

Specific:

1. To determine the median time to diagnosis of TB from the time of transplantation
2. To determine the incidence of TB among renal allograft recipients from 2003-2009 at NKTl
3. To identify the clinical risk factors associated with development of TB in renal allograft recipients
4. To determine the forms of TB among renal allograft recipients

Methodology

Study Design and Population

This is a retrospective study that utilized chart review of kidney allograft recipients at the NKTl from January 2003 to December 2009.

Study population

The study population included 1) patients 18 years old and above 2) those with available in-patient chart for review (during the time of transplantation, acute rejection episodes (if any), during the time of diagnosis of TB, follow-up period) 3) diagnostic work-up for TB was done at NKTl. To avoid confounding effects, the following patients were excluded: 1) foreign recipients 2) those undergoing anti-TB treatment at the time of transplantation 3) those with history of previous transplantation 4) those who had less than one year of follow-up after diagnosis of TB post-kidney transplant (graft loss or underwent allograft nephrectomy, died from causes other than TB).

Materials and Methods

a. Sample Size estimation

A total of 1540 KT patients was the computed sample size. This sample size was required to detect a 2.0% difference between the Cyclosporine (CsA) and non-CsA group that the proportion of TB among kidney transplants on cyclosporine is 3.0% and 1.0% among those on other immunosuppressant (mycophenolate or tacrolimus). Level of confidence is set at 95% and power at 80%.

b. Data Collection procedure

There were a total of 2,109 renal transplant procedures performed in NKTl from January 2003 to December 2009. Selection of study population was based on the inclusion and exclusion criteria. A database of these subjects which includes baseline demographic, pre- and post-transplant variables was provided by

DOH/NKTl Renal Disease Control Program – Philippine Society of Nephrology based on their Kidney Transplant Registry. Medical records of the subjects were searched for any episode of bacteriologically confirmed or clinically diagnosed TB (pulmonary or extrapulmonary) that developed in the post-transplant period (See Definition of Terms). Records were also reviewed if the patient developed rejection episode after transplantation. All in-patient records from time of transplant up to time of diagnosis of TB, time of death or up to June 2013, whichever comes first, were reviewed.

c. Definition of Terms

Diagnosis of Tuberculosis (adapted from WHO)²⁵

- i. Bacteriologically confirmed TB case - One from whom a biological specimen is positive by smear microscopy, culture or WHO approved rapid diagnostics (WRD).
- ii. Clinically diagnosed TB case - One who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who decided to give the patient a full course of TB treatment - includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation

Anatomical Site of TB Disease (adapted from WHO)²⁵

i. Pulmonary

Pulmonary TB (PTB) refers to a case of TB involving the lung parenchyma. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

ii. Extrapulmonary (EPTB)

EPTB refers to a case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed M. or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of TB chemotherapy. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease.

Statistical Analysis

SPSS version 18 was used in tabulating and computing the statistics. Discrete variables were presented as counts and percentages, while continuous variables were represented by their means and

Table I: Demographic characteristics, pre- and post-transplant variables in the TB and non-TB groups

	Post-transplant TB		No Post-transplant TB		p-value
	n = 42		n = 1578		
Age (Mean $\pm$ SD)	43 $\pm$ 13.5		41 $\pm$ 12.6		0.162
Length of dialysis prior to transplant (Mean $\pm$ SD)	11.0 $\pm$ 11.3		12.4 $\pm$ 43.0		0.797
	No.	%	No.	%	
Gender					0.964
Male	27	64.3	1004	63.9	0.482
Female	15	35.7	566	36.1	0.482
Type of Renal Allograft					0.226
LRD	16	38.1	788	49.9	0.060
LNRD	18	42.9	643	40.8	0.383
Cadaveric	8	19.0	144	9.1	0.052
Primary Renal Disease					0.457
Glomerulonephritis	19	45.2	934	59.2	0.036
Diabetic Nephropathy	11	26.2	274	17.4	0.099
Hypertensive Nephrosclerosis	9	21.4	210	13.3	0.102
Autosomal Dominant Polycystic Kidney Disease	1	2.4	48	3.0	0.391
Chronic Pyelonephritis	1	2.4	39	2.5	0.485
Unknown	0	.0	4	.3	0.023
Others	1	2.4	69	4.4	0.204
Co-morbidities					0.000
Hypertension	35	83.3	986	62.5	0.006
Diabetes Mellitus	6	14.3	310	19.7	0.387
Ischemic Heart Disease	0	.0	49	3.1	0.246
PTB	4	9.5	39	2.5	0.005
Collagen Disease	1	2.4	11	.7	0.209
Gout	1	2.4	10	.6	0.174
Congestive Heart Failure	1	2.4	9	.6	0.139
Stroke	2	4.8	7	.4	0.000
COPD	0	.0	6	.4	0.689
Malignancy	1	2.4	1	.1	0.000
Others	0	.0	29	1.8	0.375
None	0	.0	443	28.1	0.000
INH Prophylaxis Post KT					0.882
Yes	36	85.7	1405	89.3	0.438
No	6	14.3	169	10.7	0.438
Induction Immunosuppression					0.525
Interleukin-2 receptor blockers	11	26.2	292	18.5	0.131
Lymphocyte depleting agents	6	14.3	193	12.2	0.353
Others	0	.0	12	.8	0.000
None	25	59.5	1081	68.5	0.121
Maintenance Immunosuppression					0.011
Cyclosporine based	28	66.7	929	58.9	0.145
Tacrolimus based	10	23.8	605	38.3	0.015
Others	4	9.5	44	2.8	0.069
Number of Rejection Episodes prior to TB Diagnosis					0.014
None	21	55.3	1165	74.5	0.006
One	15	39.5	357	22.8	0.014

Two	1	2.6	35	2.2	0.438
Three	1	2.6	6	.4	0.182
Treatment for Rejection Episodes					0.000
Steroids	18	90.0	381	96.2	0.005
Alemtuzumab	0	.0	8	2.0	0.644
Others	0	.0	8	2.0	0.315

Legend: TB: tuberculosis, LRD: living-related donor, LNRD: living non-related donor, COPD: chronic obstructive pulmonary disease; ATG: anti-thymocyte globulin, INH prophylaxis 300mg/ tablet OD x one to three months

standard deviation. For univariate analysis, Chi-square test and independent sample t-test were used to identify variables which were significant in determining the incidence of developing TB. P-value less than 0.05 was considered significant. For multivariate analysis, multivariate logistic regression was run to compute for the odds ratio and coefficient of the significant variables.

Results

A total of 2109 renal allograft recipients from 2003-2009 were screened. Of these, 1,620 patients met the inclusion criteria and were analyzed. Among the excluded subjects, 174 were foreign recipients, 92 had missing medical records, 66 had missing transplant records, 51 were less than 18 years old during time of transplant, 44 had graft loss or graft nephrectomy or expired immediately (less than six months) after transplantation due to causes other than TB, 31 were ongoing anti-TB treatment on time of transplant, the rest either had history of previous transplantation or the TB was not diagnosed at NKTI.

Among the 1,620 patients analyzed, TB was identified in 42 patients with an incidence of 2.6%. Table I shows the details of the demographic characteristics, pre and post-transplant variables analyzed in this study. Mean age among those with post-transplant TB was 43 yrs. $\pm$ 13.5 years, slightly older than those without TB whose mean age was 41 yrs. $\pm$ 12.6 years. There is slight male predominance in patients with TB as compared to those without. Gender ratio for both groups was 64% male and 36% female. Glomerulonephritis was the most common primary renal disease among the patients studied. Among those who developed post-transplant TB, previous history of PTB and hypertension were more common as co morbid diseases. More of those who did not develop post-transplant TB received tacrolimus-based immunosuppression.

Table II shows the multinomial logistic regression of the factors associated with post-transplant TB. The risk of developing post-transplant TB is associated with hypertension (OR 3.0, 95% CI 1.3-6.8), history of previous TB (OR 4.15, 95% CI 1.41-12.21), and one rejection episode

(OR 2.33, 95% CI 1.2-4.57) and treatment with steroid pulsing for rejection episodes (OR 2.36, 95% CI 1.265-4.389). On the other hand, patients given a tacrolimus based regimen as maintenance immunosuppression (OR 0.50, 95% CI 0.2453-1.030) were less likely to develop TB as compared to patients given a cyclosporine based regimen. Similarly, patients with no rejection episode had less tendency to develop post-transplant TB (OR 0.43, 95% CI 0.22-0.84).

The median duration of time between transplantation and TB was 21 months (range: 1-105 months). Twelve of the 42 patients who developed TB (28.57%) were diagnosed within the first six months of transplant.

The use of isoniazid prophylaxis was not found to be statistically significant in terms of decreasing risk of developing post-transplant TB. Among those who were given isoniazid prophylaxis, 2.5% of patients developed TB. This is smaller compared to the 3.4% who were not given prophylaxis and developed TB.

The data were further analyzed by grouping the subjects with post-transplant TB into two: early TB (diagnosed with TB within six months after transplant) and late TB (diagnosed with TB beyond six months after transplant) (Table III). Among those who were given isoniazid prophylaxis, more patients were observed to develop late onset TB rather than early onset TB. There were no sufficient evidence to prove association between onset of TB, use of induction immunosuppression and type of immunosuppression.

Among the 42 patients diagnosed with TB after transplantation, 81% (n=34) had pulmonary site involvement while 19% (n=8) had extrapulmonary TB (Table IV). Among the 34 patients with primary pulmonary site involvement, four patients (11.7%) also had other sites of organ involvement (disseminated) which includes involvement of other organ system like lymph nodes (n=1), meninges (n=1), genitourinary (n=1) and lymph nodes and bone (n=1). Gastrointestinal TB was the most common form of extrapulmonary TB observed in this study (n=3, 7.1%).

Table II: Multinomial logistic regression of factors associated with post-transplant TB

Variable	Odds Ratio	95% Confidence Interval	
		Lower Bound	Upper Bound
Hypertension	3.00	1.33	6.80
PTB	4.15	1.41	12.21
Stroke	11.21	2.26	55.72
Malignancy	38.46	2.36	625.69
Tacrolimus as maintenance immunosuppression	0.50	0.25	1.03
No rejection episode	0.43	0.22	0.84
One rejection episode	2.33	1.2	4.57
Steroids as anti-rejection Treatment	2.36	1.27	4.39

Table III: Factors associated with onset of TB

Variables	Early TB		Late TB		p-value
	n = 12		n = 30		
	No.	%	No.	%	
Use of INH Prophylaxis					0.288
Yes	9	75	27	90	0.136
No	3	25	3	10	0.136
Induction Immunosuppression					0.752
Lymphocyte depleting agents	3	25.0	8	26.7	0.455
Interleukin-2 receptor blockers	1	8.3	5	16.7	0.213
None	8	66.7	17	56.7	0.270
Maintenance Immunosuppression					0.334
CsA/MMF/Steroids	8	66.7	18	60.0	0.341
Tacrolimus/MMF/Steroids	3	25.0	7	23.3	0.455
CsA/Sirolimus/Steroids	0	0.0	1	3.3	0.155
CsA/Everolimus/Steroids	1	8.3	0	0.0	0.148
Others	0	0.0	4	13.3	0.016

Table IV: Anatomical site of TB disease

Site	Number of patients (%) n=42
Pulmonary	34 (81%)
Lung alone	30
Lung + lymph node	1
Lung + meninges	1
Lung + bone	1
Lung + lymph node + bone	1
Extrapulmonary	8 (19%)
Pleura	0
Lymph nodes	2
Abdomen	3
Genito-urinary	1
Skin	1
Joint and Bones	1
Meninges	1

Discussion

Incidence

Renal allograft recipients have a higher risk of developing post-transplant TB as compared to the general population. Incidence in the post-transplant period is largely associated to the endemic nature of TB in a particular area. The Philippines is considered to be one of the high-burden TB countries in the world with an incidence of 275 in every 100,000 as of 2010. In our series of 1620 renal allograft recipients from 2003-2009, 42 patients or 2.6% developed post-transplant TB. This is lower than that of other endemic areas like Pakistan or India which reported an incidence of 12.4-15.2%⁴ and 11.8%,⁵ respectively. A decreasing trend in incidence was observed based on previous studies in our center where incidence was found to be 6.5% in 1988,²⁷ 6.0% in 1997⁹ and 4.9% in 2001.⁷ This may reflect a decreasing incidence of TB among transplant patients probably due in part because of improving renal transplant care and TB prevention. However, it should be emphasized that this study only analyzed renal allograft recipients diagnosed with TB in the inpatient setting, disregarding patients diagnosed in an outpatient setting which may also be considerable in number. These patients may represent the cases of severe forms of TB, serious enough to require confinement. Caution should also be made in interpreting this result since the previous studies used a different study design and a different transplant treatment protocol that might affect the results.

Median Time to Diagnosis of TB

The median duration of time between transplantation and TB was 21 months (one to 105 months), longer as compared to a study done by Celestial⁷ in 2001 where he reported a median time to diagnosis of TB to be 12 months (one to 160 months). But comparison is difficult to be made since the immunosuppression regimen used during the period of study of Celestial was different in this present study.

Risk factors for Post-Transplant TB

An interesting information identified in this study was that hypertension (OR 3.00, 95% CI 1.32-6.80) was also found to be associated with the development of TB after transplant. Hypertension in combination with chronic kidney disease may increase the risk of developing TB post-transplant. A history of TB was found to be a significant factor in the development of TB after transplant (OR 4.15, 95% CI 1.41-12.21). This may be due to reactivation of latent TB present prior to transplant due to depressed cellular immunity while on immunosuppression medications. In this series, diabetes mellitus and COPD were not significantly associated with TB, contrary to previous reports. Diabetes was found to increase the risk 2.2 times in a series done

by John¹⁴ in 2001 while COPD has an OR of 1.5 by a study done by Ou¹⁵ in 2012.

In our retrospective study, isoniazid prophylaxis did not show any statistically significant benefit in minimizing the risk of having TB post-transplant. However, there was a trend toward delaying onset of TB among those who were given isoniazid prophylaxis probably by delaying reactivation of latent TB. This data may be clinically significant since delaying onset of TB into a period when immunosuppressant dosages are at its lowest and when immune system is less impaired may translate to a less complicated course and treatment of TB. There is still a need for a large multicenter trial to support the evidence of benefit of isoniazid prophylaxis in transplant patients in our setting.

Due to the immunosuppressive effects of dialysis and end stage renal disease, longer duration of dialysis prior to transplant was said to be a risk factor for TB in a study done by Basiri.¹³ However, our study was not able to confirm this finding possibly because majority of our patients were transplanted within one year after initiation of dialysis (11.0 ± 11.3 months versus Basiri's 12.4 ± 43.0).

Use of interleukin-2 receptor antagonists (basiliximab and daclizumab) and lymphocyte-depleting agents (Anti-thymocyte globulin and alemtuzumab) impairs lymphocyte function and depress cellular mediated immunity, therefore, creating an ideal environment for reactivation or new infection with TB. However, in our study, we were not able to provide evidence of association between use of these agents and risk of TB.

Contrary to a recent study in Thailand¹⁰ in 2008 where they concluded that tacrolimus and mycophenolate increased the risk of TB as compared to cyclosporine based regimen, we found that patients on a tacrolimus based regimen had less tendency to develop post-transplant TB as compared to those given a cyclosporine based regimen (OR 0.50, 95% CI 0.25-1.03). A prospective study with a bigger sample size or a randomized controlled trial might be needed to further support this. Despite higher dosages of immunosuppressive medications on the first six months post-transplant, only 28.57% of patients who developed post-transplant TB were diagnosed during this period. No particular regimen was also found to be associated with earlier onset of TB. Hence, it might not only be the degree or type of immunosuppression, but also, the duration of immunosuppression that play a role in the development of TB in the post-transplant period. Difficulty in the diagnosis and atypical presentation of TB among transplant patients may also be a factor relating to a delay in diagnosis.

Rejection episode exposes the patient to higher dosages or addition of other immunosuppressive drugs which places the patient at higher risk for developing

TB. In our study, having one episode of rejection (OR 2.3, 95% CI 1.2-4.6) with subsequent use of steroid pulsing as anti-rejection treatment (OR 2.36, 95% CI 1.2-4.4) were found to be associated with an increased risk of having post-transplant TB. But increasing the number of rejection episode did not place the patient at higher risk which is contrary to a previous study done by Basiri¹³ in 2006 where in he reported increasing risk of TB as the number of rejection episodes increases.

Form of TB

Pulmonary TB (81%) is more common than extrapulmonary TB (19%) in our studied population. This observation is consistent with several other studies.^{10,11,14} Our study also gave additional evidence that extrapulmonary and disseminated forms of TB are frequent among transplant recipients. These findings emphasized the effects of immunosuppression to increase the risk of reactivation and unusual presentation of TB.

Conclusion and Recommendations

Our present study showed that the incidence of TB in Filipino transplant recipients at our institution is 2.6%, lower as compared to other high TB burden countries and with an apparent decrease in trend as compared to previous local studies. Pulmonary tuberculosis is the predominant type of TB but increased frequency of extrapulmonary forms was observed. Hence, a high index of clinical suspicion with early diagnosis is required. Other comorbidities that were not analyzed in this study such as liver cirrhosis, hepatitis B and C infections and new-onset diabetes mellitus after transplant (NODAT) may also be interesting factors to be investigated in future studies. We also recommend that patients with history of rejection and subsequent use of methylprednisolone pulsing receive isoniazid prophylaxis. There should also be vigilant monitoring and high index of suspicion for tuberculous infections after being given such therapy.

The commonly used regimen of tacrolimus/mycophenolate/prednisone seems to have decreased risk for post-transplant TB as compared to the cyclosporine based regimen. A larger and more sophisticated study design is recommended to support this observation.

Limitations of the Study

It is important to emphasize that our study has several limitations. First, being a retrospective study utilizing chart review only, we are restricted to informations that were available on the medical records. We were only able to verify the demographic data

and some pre-transplant variables on the database provided by the REDCOP registry. Second, only renal allograft recipients diagnosed while confined in the hospital were analyzed, disregarding a considerable number of patients at risk for developing TB in the outpatient setting. The patients with TB that were included in our study may be those that present with severe forms of TB requiring hospital admission. Third, given the above the limitations and the fact that there is no accurate way of determining follow-up rate, we might also missed some patients that may have met the exclusion criteria (graft loss or immediate death within one year of transplant, transfer to another institution, etc).

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