Original Research Paper

Volume-8 | Issue-8 | August-2018 | PRINT ISSN No 2249-555X

Medicine

PROFILE OF INFECTIONS IN RENAL TRANSPLANT RECIPIENTS

Brig K Satyanand	Consultant & HoD Medicine, CHSC
Maj Rajat Govind*	MD Medicine, Gd Spl CHSC, Pune *Corresponding Author
Maj Sreevatsa T	MD Medicine

ABSTRACT Commonest morbidity following transplant surgery is due to increasing incidence of infection due to factors like, preexisting illness in recipeint and donor, reactivation of latent infection and invasion by opportunistic infections due to immunosppressive status of transplant recipients. This study was concieved to profile pattern of infections, their timing from transplant surgery and its outcome in cases of RTR. It was found that 76 episodes of infection happened amongst 110 patients of RTR requiring hospitalisation; there were total four deaths of which three were due to infections. The number of infections in the first four weeks was 7, 37 were within 6 months & 32 in the period 6 months and beyond. Bacterial infections were 48 viral 16, fungal infections, Tuberculosis 4 with protozoa & parasitic infections 1 each. The number of HCV positive cases was 10 and that of HBV was 2. HIV positivity was nil. The results are better than the findings in developed countries; however large study is needed to confirm this hypothesis.

KEYWORDS : RTR (RENAL TRANSPLANT RECIPEINT), NODAT (NEW ONSET DIABETES AFTER TRANSPLANTATION), VAP (VENTILATOR ACQUIRED PNEUMONIA), ATG (ANTI LYMPHOCYTIC GLOBULIN), MMF (MYCOPHENOLATE MOFETIL)

INTRODUCTION

115,000 solid-organs are transplanted every year are performed with 70% kidney, 20% liver and heart, lungs, pancreas being the rest[1]

The infection in recipients is due to immunosuppressive drugs, blunted inflammatory response, neutropenia (2), diabetes, viral infections and environmental exposure.

The infection risk for recipient is determined by the epidemiologic exposure, status of immunosuppression and protection offered by the vaccination and chemoprophylaxis drugs

The epidemiology of infections is different from western literature. This study was conceived to describe the infections that occur in RTR (renal transplant recipients), in the Indian scenario, to analyze pattern of infections, their timing from transplant and outcome over a period of 18 months in a tertiary care hospital.

AIMS & OBJECTIVES

The Study was conceived to profile, pattern of infections, their timing from transplant and outcome in case of RTR.

MATERIAL AND METHODS

It was a cross sectional & prospective study with study population of RTR who were transplanted before or after October 2014 and till Apr 16 and on OPD follow up thereafter.

110 were new RTR and 240 were on follow up in post-transplant OPD of a tertiary care center. RTR who had infection warranting admission were included and similar patients who were not available and unwilling for the study were excluded, after obtaining clearance from institutional ethical and scientific committee.

Statistical analysis:-

(a) Using Pearson chi-square/fisher exact test, comparison of nominal or ordinal data.
(b) Categorical data are described as number of patient (n) percentages. Numerical data is presented in Mean + SD.
(c) To analyze the data SPSS version 16.0 was used.

OBSERVATIONS AND RESULTS

A total of 67 patients presented with 76 infectious episodes.

Demographics: The mean age of the RTR was 38 +/- 10 years. 30(45%) were female and 37 (55%) were male.

Immunosuppressive agent usage:-

(a) 31 cases (46 %) were induced with Basiliximab, 5 cases (7%) with ATG, 4 cases (6%) with Dacilizumab and 27 cases (40%) received no induction.
(b) 57 patients were on MMF (85%), 10 cases (15%) were on Azathioprine. Prednisolone was given to 65 cases (97%). Tacrolimus used in 57 cases (85%) and cyclosporine in 5 cases (7%). Everolimus (mTOR inhibitor) use was in 18 cases (27%).(Ref Table no. 1)

Type of donor: Sibling 17 cases (25%), spouse 14 cases (21%), relative 12 cases (18%), mother 8 cases (13%), cadaver 07 cases (10%), father 5 cases (7 %) and unrelated donor, 4 cases (6%).

Symptomatology: -

i. Fever in 70 (92%) of all admissions.
ii. Respiratory symptoms in 43 patients (56%).
iii. 15 patients of UTI, increased frequency (50%) in 22 patients and dysuria (34%), Graft tenderness of the transplant kidney was in 15%.
iv. Gastro intestinal symptoms were evident in 17 (22.3%),
v. CNS symptoms in 18, with headache in (72%), altered sensorium and neck rigidity in (11% each).

Timeline of infections:-

The number of infections in the first four weeks was 7 (9 %), 37 cases (48%) in the 0- 6 months & 32 (42%) in the 6 months and beyond.

System wise infections:-

In the 0-1 month period, of 7 infectious episodes, two were perinephric abscesses, two were URTI, two were enteritis, and one skin abscess. In the first six month period, 37 episodes of infections, pneumonia in (29%) and UTI in (21%). In 6 months and beyond, 32 infections were documented, UTI was (50%), pneumonia was (34%).

Type of organism (Ref picture1):-

First month was bacterial (85.7%). viral infections in 56% in the 1- 6 months. In the post 6 months period, 50% were bacterial, followed by 33% viral infections.

System wise infections: - UTI (n=26, 34%). Pneumonias at 32% (n=24). The multisystem was involved in 4 patients (5%). Gastro intestinal infections constituted 13% and CNS infections 3%.

Microbiology data: -bacterial infections were 48 (63%) viral 16 (21%), fungal infections 6 (8%). Out of theses Tuberculosis was seen in 4 (5%) with protozoal & parasitic infections 1 each. The number of HCV positive cases was 10 (13.2%) and that of HBV was 2 (2.6%). HIV positivity was nil.

Microbiological diagnosis:-

Microbiologically confirmed diagnosis was 55.26% (42 infections).

Out of theses 23 were culture positive UTI, 01 was cryptococcal meningitis, 01 Dengue patient, 08 had respiratory tract infections with gram+cocci. 02 patients had tuberculosis 01 patient was diagnosed as Vivax malaria, 01 patient had CMV IgM positivity with value < 10 CU and 01 had CMV IgG positivity with value > 462 CU, 02 patients had PCP (on BAL), 02 patients had tuberculosis based on Gene Xpert from BAL.

Recurrent infections: -The number of re admissions was 6 (9%).

Complete hemogram: -
33 (48.7%) patients had low Hb%, 4 (5.3%) required blood transfusion (Hb <7g/dL). 31 (40.8%) had leucocytosis, PBS normal in 69 (90.8%), left shift and toxic granules was seen in 5 (6.6%). Lymphocytosis was observed in 2 (2.6%) of all the patients.

Graft Dysfunction : -1/3rd patients had evidence of graft dysfunction with creatinine values of(> 1.2 mg/dl) in 24 (35.5%).

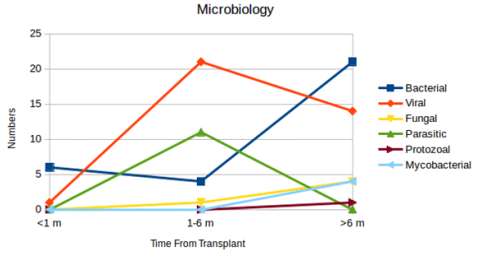
NODAT: - The number of patients with NODAT was 8 (10.5%).

Mortality :- There were 4 fatalities (4 %) and due to infection 3(3%). Cryptococcus meningitis developed respiratory failure &developed VAP on the day 4 of intubation. 01 patient with Pneumocystis pneumonia developed respiratory failure and septic shock. Invasive mucor pneumonia succumbed to septic shock. DKA which was managed in the ICU with intensive insulin therapy. The mortality in our case series was less and comparable with international data.

Table 1: Demographic Profile of the patients with infection:-

Mean Age	38	Male	Female	Total
SD Age	10	37	30	67
Induction	ATG	2	3	5
	Basiliximab	17	14	31
	Dacilizumab	2	2	4
	No Induction	16	11	27
	Total	37	30	67
CNI	Cyclosporine	3	2	5
	Tacrolimus	32	25	57
	No CNI	2	3	5
	Total	37	30	67
Anti Proliferative agents	MMF	34	23	57
	Azathioprine	3	7	10
	Total	37	30	67
m TOR Inh	Everolimus	12	6	18
	No Everolimus	25	24	49
	Total	37	30	67
Steroids	Prednisolone	37	28	65
	No Steroids	0	2	02
	Total	37	30	67

Picture 2: Microbiology of various infections:-



DISCUSSION:-
Infection in RTR were analysed prospectively in our center with an objective of studying the timeline, the influence of various factors on their occurence and the outcome.

76 infectious episodes were found with 41 male and 35 female. The number of RTR on follow up was 240. RTR during the study period was 110 Fever in a RTR may indicate an infectious or noninfectious cause. Infection is responsible for 75% of fevers. Viruses are the most frequent cause, (55%). The noninfectious causes of fever are allograft rejection (13%), malignancy, drug fever, and pulmonary emboli account In our study, 70 /76 presented with fever.

Among all the infections, 48 (63%) were bacterial, 16 (21%) viral, 6 (8%) fungal, 4 (5%) mycobacterial infections, and parasitic and protozoal infections were 1 (1 %) each. This is comparable with data from international studies [3- 4].

According to Rubin's time table of post renal transplant infections, bacterial, catheter site, surgical site and aspiration are common in the first month. In the 1- 6 months period, with prophylaxis against HBV and PCP, the common infections are respiratory like tuberculosis, cryptococcal infections, hcv infection and bk virus nephropathy. The post 6 months period has mostly opportunistic viral and fungal infections.

We observed a similar pattern in the 0-1 and 1-6 month periods, with predominantly perinephric abscesses, enteritis, cutaneous abscesses and upper respiratory infections, mostly all bacterial in the first month.

In the 1-6 month period, we observed one viral hbv hepatitis flare. The patient was not vaccinated. Most common infections were urinary tract infections and pneumonias. We had 4 undiagnosed fevers that had presented with myalgia, arhtralgia and headache in this period which we presume were viral, as they were self remitting and investigations were negative.In the later than 6 months period, we saw predominantly urinary infections and pneumonias. This deviation from the traditional paradigm can be explained as follows.

Firstly, the 'time table' is only a guideline to keep a watch for specific infections at specific times and variation is expected.

Secondly, the study was based in a tropical country. Ours is the second most populous country in the world. Tuberculosis is common with nearly two to three million affected in the community. The risk of spread is high. Bacterial infections at all times in post-transplant patients in our study suggest abundance of bacteria in the environment. This could be because of poor hygiene or lack of facilities at remote villages and difficult field areas. Compliance of the community at large in getting treatment for infections is poor. Poverty and cheaply available CAM use in infections are obstacles to proper care in the dependent population and to some extent, the veterans. The man made maladie of drug resistance, which we dreaded but didn't encounter in our study is undoubtedly the final nail in the coffin of a transplant recipient.

Thirdly, our patients are not all domicile of Delhi. Our center is a referral center and patients come from far and wide. Places, some of which are endemic for infections like malaria (the North Eastern states), visceral leishmaniasis (Bihar), and actinomycosis (Madurai) are the very places to which some of our patients belong.

According to studies, urinary tract infection (UTI) is the most common bacterial infection encountered in 30-60% of RTR [5-6]. We had similar experience with urinary tract infection (36 %) being the commonest infection.

Most (71%) were lower urinary tract infections in our study. 29% patients had acute graft pyelonephritis in our study as evidenced by graft tenderness. 70% of the AGPN happened later than 6 months from transplant. And 29% were seen less than 6 months. In other studies, AGPN has been seen to be associated with graft dysfunction. IN a study observed, that in all patients who had graft dysfunction, renal biopsy demonstrated acute grafts pyelonephritis in 23%. The median time to AGPN after transplantation was 10.9 months (range: 0.3-56.2 months). Nine patients had early AGPN (within 6 months) and the other 17 had late AGPN. [7].

Our data on AGPN is similar to the data from other studies discuss the incidence of TB in renal allograft recipients is 12.3% [8].

According to data, about 45-60% of TB occurs in the first year after transplantation. A global review on TB estimated the median time for onset at 9 months post transplantation. Latt as per clinical records of adult kidney recipients transplanted between 1 January 1986 and 31 December 1995 TB was diagnosed in 14 of 384 with an incidence of 3.64%. [9]

In our study, 4 out of 76 infections were tuberculosis. Out of them, 25%

had NODAT. We observed that 100% of all the TB occurred in the later than 6 months period. 50% infections occurred at one year from transplant and 25% at 2 years and 25% at 4 years. There was no MDR TB in our study.

As 50% of Tuberculosis in our study occurred at 12 months, this matched the median time in other studies mentioned above.

We couldn't relate the delayed occurrence of TB with any drug usage as all our patients received uniform standard triple drug immunosuppression.

There were, 4 cases of TB, study with longer duration of observation may show different incidence Genitourinary TB in allograft is rare which is cryptic with constitutional symptoms and graft dysfunction due to rejections [10] graft being involved with TB in this study was not found.

Four proven cases (BAL and sputum) of PJP were detected.In absence of trimethoprim-sulfamethoxazole (TMP-SMX) chemoprophylaxis for pneumocystis jirovecii (PCP), the incidence of infection was 0.6 to 11.5% in RTR. Asymptomatic PCP was the cause of 16% (6/27) of infections in lung transplant recipients. [11] The total no of 6 fungal infections were detected, PJP formed 66% of these infections One case of Cryptococcus meningitis was detected by positive antigen test on the CSF. The patient had a stormy course and succumbed to the illness in hospital.

Fungal infections in RTR are due to opportunistic variety. systemic fungal infections was found in 23 of 51 autopsy reports, Concurrent bacterial, viral, or parasitic infections were present 87% of the time. Death, however, can be the result of isolated fungal infections. [12]

Relationship between drugs and infections:- As the majority of the patients were on Tacrolimus, Prednisolone and MMF, it was difficult to find a pattern correlating a specific immunosuppressive drug with a specific infection. The decreased requirement of ICU care & decreased mortality (4 deaths 3.04%) in this study was because of prompt recognition & treatment of the infections with 7 (10.52%) requiring ICU care.

There is a requirement for a larger study with more patients enrolled and observed for a longer duration to establish the relationship between various variables and the pattern of infection and the role of dose modification.

CONCLUSION: -

The overall number of infection was 76.

1. The most common infection was UTI (36%), followed by pneumonia.
2. 63% of all infections were bacterial
3. 5% of all infections were tubercular in origin.
4. Timeline of infections :-
   (a) Earliest infection (0-1 month) was UTI and skin infection.
   (b) Predominant infection in 1-6 month period was pneumonia then UTI, Gastro-enteritiits, meningitis.
   (c) Late infections (> 6 months) were predominantly urinary and respiratory. Tuberculosis was seen in 5%, PJP was seen in 5% .
5. No statistically significant relationship could be established between specific immunosuppressive drug and a particular infection and a larger and longer study would be needed for studying the same.

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