MEDICO RESEARCH CHRONICLES
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2019.6.1.481
OPEN ACCESS
Contents available at: www.medrech.com

DIARRHEA IN RENAL TRANSPLANT RECIPIENTS – A CROSS SECTIONAL STUDY

G. Gowthaman[1*], N. D. Srinivasaprasad[2], K. Thirumalvalavan[2], S. Sujith[2], M. Edwin Fernando[3], R. Selvi[4]

1. Senior Resident, Department of Nephrology
2. Assistant Professor, Department of Nephrology
3. Prof & Head, Department of Nephrology, Gout. Stanley Hospital, Chennai
4. Prof & Head, Department of Microbiology, Gout. Stanley Hospital, Chennai
Government. Stanley Medical College, Tamilnadu Dr. M. G. R. Medical University, Chennai, Tamilnadu, India

ARTICLE INFO **ABSTRACT** **ORIGINAL RESEARCH ARTICLE**

Article History
Received: Feb' 2019
Accepted: Feb' 2019
Keywords: Post-transplant diarrhea, immune-suppression, infection

Background and Objectives:
Post-transplant diarrhea is a frequent complication of renal transplantation. Post-transplant diarrhea is associated with reduced quality of life[1], hastened decline of graft function and higher mortality[2]. Diarrhea is often neglected by patients and clinicians and considered as a side effect of immunosuppressive regimens. The aim of this study is to identify the etiology, clinical profile, and outcome of diarrhea in renal transplant recipients.

Patients and Methods:
Over 1-year period renal transplant recipients with diarrhea were analyzed. Diarrhea was defined as three or more semisolid or liquid stools per day for minimum of 3 days duration. After obtaining detailed history, patients were subjected to clinical examination. Blood samples were collected for biochemical investigations and stool samples for microbiological examination. We adopted DIDACT protocol for investigating the diarrheal episode in recipients[3].

Results:
A total of 46 patients were enrolled in this study. Males were predominant in number
36 (78.2%). This included 33 live related renal transplant recipients (LRRTR) and 13 deceased donor renal transplant recipients (DDRTR). The mean age of the patients was 33.2±9.12 years.
A majority of them had diarrhea after 1 year of transplantation (n= 29, 63.1%). Infective causes were identified in 6 patients and optimization of immunosuppression's was done in 11 patients.

Conclusion:
In our study, most of the recipients (63.1%) had diarrhea after one year of renal transplantation. The cause of Diarrhea was unclear in a significant number (n=22) of the study population.

Corresponding author*

INTRODUCTION

Gastro-intestinal (GI) adverse events (infections [bacterial, viral, fungal], abdomen pain, nausea/vomiting, dyspepsia and diarrhea)[4,5] are common in transplant recipients, diarrhea being the most common. Severe and chronic post-transplant diarrhea may lead to hypovolemia, malabsorption, rehospitalization, noncompliance and greater risk of graft loss and death. In addition, decreased intestinal P-glycoprotein (or multidrug resistant protein 1) enzymatic activity leads to elevated tacrolimus trough levels[6] and subsequent renal toxicity. Mycophenolate Mofetil (MMF) dose adjustment or poor adherence to MMF treatment after GI complications is associated with significantly increased risk of graft loss.[7-9] Though diarrhea in post-transplant recipients is generally attributed to immunosuppressive drugs, they may also occur secondary to other causes like Post transplant Diabetes Mellitus (PTDM), concurrent infections[10-12] or other non-immunosuppressive medications.[4] It is therefore recommended to investigate the cause for diarrhea in any patient on immune suppression. Furthermore, the relationship of GI complications to all relevant non immunosuppressive treatments should be tested before any changes to immunosuppressive therapy are made.

OBJECTIVES

To identify the etiology, clinical profile and outcome of diarrhea in renal transplant recipients.

PATIENTS & METHODS

Renal allograft recipients who were admitted at our center with diarrhea (defined as three or more semisolid or liquid stools per day for duration of ≥ 3 days) during the study period (November 2017 to October 2018) were included in the study.

Patients with features of acute abdomen (acute pancreatitis, appendicitis, cholecystitis, peptic ulcer &complications, intestinal ischemia, diverticulitis, bowel perforation) that required surgical intervention within 48 hours of admission were excluded. All patients were included in this study after obtaining informed written consent. Institutional Ethical committee clearance was obtained. A detailed history was obtained regarding the nature of renal transplant surgery (Living related/ deceased donor), medications, duration after transplant, dietary habits, nature of stool and its frequency/ associated symptoms. Patients were examined to look for signs of volume loss and malnutrition. Blood samples were collected for complete blood count, erythrocyte sedimentation rate, renal function tests, liver function tests and viral markers. Stool samples were collected from all recipients in a universal sterile container. The stool samples were subjected to concentration techniques to yield ova and cyst. All samples were subjected to a set of infectious and noninfectious panel of tests. The panel of tests which were done to exclude infectious etiology were - stool culture, stool WBC, antigen test for rotavirus, ova and parasite examination, gram staining and modified AFB staining. The panel of tests which were done to exclude noninfectious cause for diarrhea include trypsin/ chymotrypsin, fecal fat, calprotectin test, fecal occult blood test. Serum quantitative CMV PCR assay was done in selected patients[13]. Patients who had persistent diarrhea were subjected to Colonoscopy.

STASTISTICAL ANALYSIS:

Data was entered in MS Excel and analyzed using SPSS 18 version. Mean ±Standard deviation and proportion was calculated according to data types. Chi square test was used for descriptive variables. P value < 0.05 was considered statistically significant.

RESULTS:

Total number of patients who were admitted for various post-transplant

complications during the study period was 251. Patients with diarrhea constituted about 46(18.32%) of total admissions. Males 36(78.2%) outnumbered females 10(21.7%). LRRTR n=33(71.7%) was significantly more than DDRTR 13(28.2%). Most of them were in the age group of 21 to 40 years amounting to 34(73.9%). Less than 20 years was 5(10.8%) and more than 40 years was 7(15.2%)

Diarrhea was more common 1 year following transplant (n= 29, 63.1%) with significant p value (p=0.008). Within 1st post-transplant year, the diarrheal episode was more common during 6 to 12-month period (n=9). In less than 1-month period, only 2 patients had diarrhea, and only 6 patients had diarrhea from 1 to 6 months post-transplant.

Table 1. Demographics and baseline characteristics

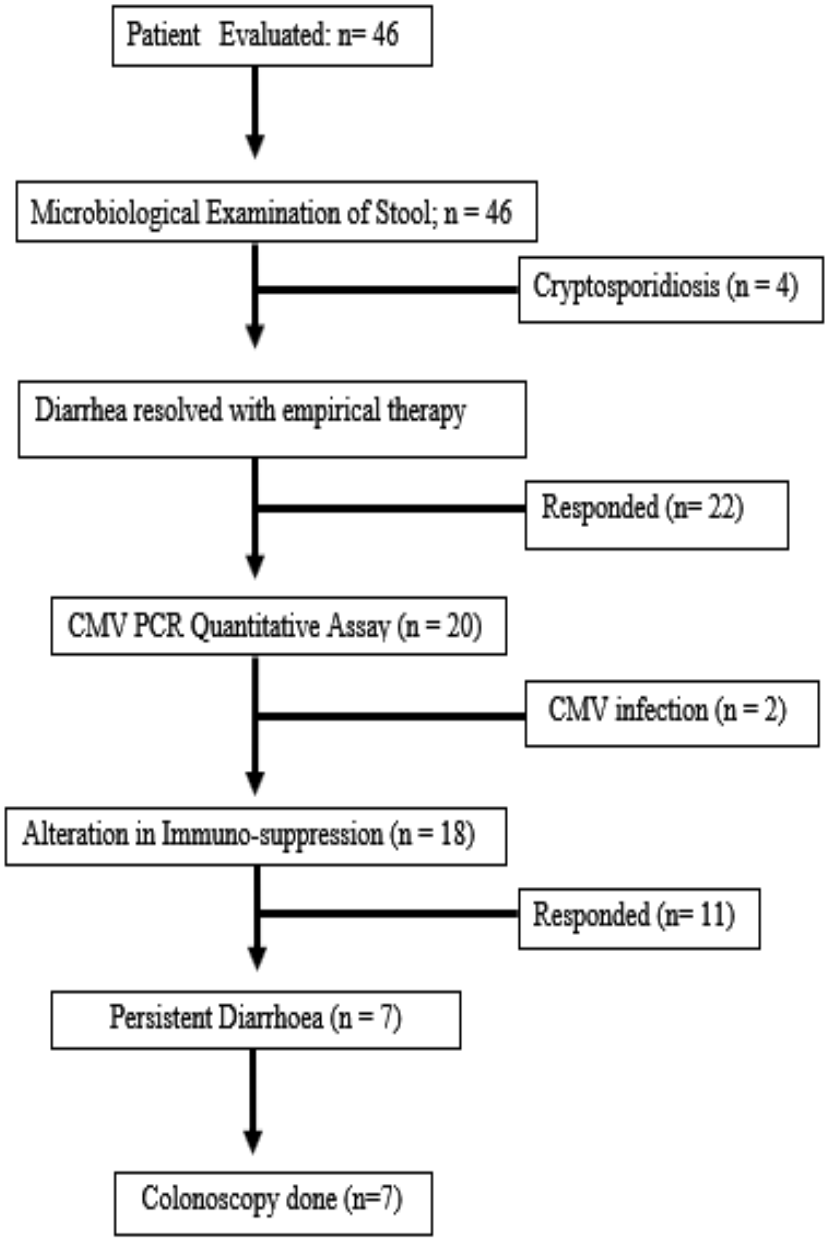
Parameter	**N=46**
Age (years) Mean (SD) Range	 33.02 (9.12) 16 – 58
Clinical features, n (%) Blood or mucous stool Abdominal Pain Oral ulcer Fever	46 (100.0) 26 (56.52) 4 (8.70) 1 (2.17) 0
Serum urea (mg/dl), mean (SD)	41.5 (12.96)
Serum creatinine (mg/dl), mean (SD)	1.74 (0.77)

Microbiological examination of stools gave positive diagnosis in 4 patients. All positive diagnosis of infections were parasites mainly cryptosporidium, which was diagnosed by the presence of oocysts in a modified acid-fast staining of stool. 2 patients were diagnosed with CMV infection by quantitative RT -PCR assay[13] (blood). Colonoscopy was done in 7 patients with persistent diarrhea, out of which 5 patients had nonspecific colitis (biopsy proven).

Of 46 recipients included in this study, 43 recipients (93.4%) were on Mycophenolate mofetil. MMF was temporarily stopped in 6(13.1%) patients; dose was reduced in 2(4.3%) patients. MMF was switched over to Azathioprine in 3(6.5%) patients.

In the remaining 22 patients, cause could not be identified and were treated empirically. Complications observed during this study were graft dysfunction (n=12), hypotension (n=2) and hypokalemia (n=1). All of the above recovered after appropriate management.

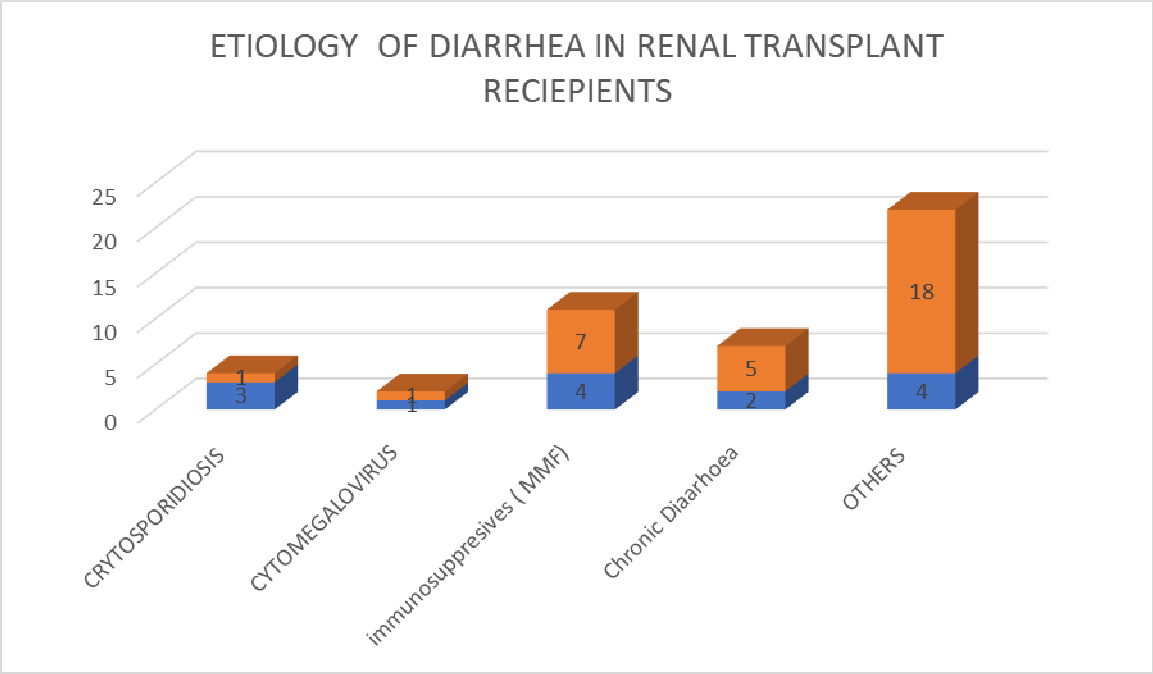
Flowchart for Evaluation of Diarrhea in Renal Transplant Recipients



DISCUSSION:

The present study was done to identify the incidence, clinical profile and outcome of diarrhea in renal allograft recipients. This study showed that diarrhea was more common 1 year after transplantation and most of them improved with symptomatic management and empirical antibiotics. The exact reason for the high incidence of diarrhea in recipients after 1-year post transplant period is not known. However, the possible reason may be that, despite progressive decrease in net immune-suppression over time, the microbial load to which the patient is exposed remains the same in both early and late post-transplant period. The other possible reasons for the late occurrence of diarrhea may be due to the presence of other risk factors like low socio-economic status, poor hygiene and post-transplant diabetes mellitus.

This result is consistent with early studies including the DIDACT study in 2006[3].



Though immunosuppression is usually considered as a cause for diarrhea, other drugs and infection should be considered first, as any inadvertent change in immunosuppression may result in rejection. Hence post-transplant diarrhea should be fully investigated before changing the immunosuppressive regimen.

About 50% study population improved with symptomatic management and empirical antibiotics. Infective causes were identified in only 6 patients (cryptosporidiosis-4 and CMV PCR positive in 2 patients).Cryptosporidium infection diagnosis was made primarily by the presence of oocysts in a modified stool acid fast staining, Enzyme- linked immunosorbent assay and immunofluorescent assay can significantly increase diagnostic sensitivity to as high as 100%.Clinical course of cryptosporidium was frequently relapsing in nature[14].Cytomegalovirus infection generally associated with increased risk of additional infections like EBV-associated PTLD and other viruses. Cryptosporidiosis was treated effectively by Nitazoxanide and Azithromycin[15] and CMV by oral Valgancyclovir[16,17]. Patients who had no identified cause were empirically treated with antibacterial agents (metronidazole and ciprofloxacin).

Colonoscopy was done in 7 patients with persistent diarrhea more than 2 weeks duration; showed features of nonspecific colitis in 5 and remaining 2 were normal study.

LIMITATION:

Our study was a single center cross sectional study of 1year duration with small sample size. Estimation of serum level of MMF was not done in our study to identify MMF induced Diarrhea.

CONCLUSION:

In our study of diarrhea in renal transplant recipients, diarrhea was common in more than 1 year of post-transplant period; statically significant. Cryptosporidiosis was the commonest infective agent. The cause of diarrhea was unclear in a significant number of patients.

ACKNOWLEDGEMENTS:

We would like to acknowledge the Dept. of Medical Gastroenterology for their support in performing colonoscopy for our recipients.

Disclosures: None

Conflicts of interest: None

REFERENCES:

1. Ekberg H, Kyllonen L, Madsen S, et al. Clinicians underestimate gastrointestinal symptoms and overestimate quality of life in renal transplant recipients: a

multinational survey of nephrologists. Transplantation 2007;84:1052.
2. Bunnapradist S, Neri L, Wong W, et al. Incidence and risk factors for diarrhea following kidney transplantation and association with graft loss and mortality. Am J Kidney Dis. 2008;51:478.
3. Severe Diarrhea in Renal Transplant Patients: Results of DIDACT Study, Amer. Journal of Transplantation 2006;6: 1466-1472
4. Pescovitz MD, Navarro MT. Immuno-supressive therapy and post-transplantation diarrhea. Clin transplant 2001;15(Suppl 4): 23-28.
5. Helderman JH, Goral S. Gastrointestinal complications of transplant immunosuppression. J AM Soc Nephrol 2002; 13:277-287
6. Lemahieu W,Maes B, Verbeke K, et al.Cytochrome P450 3A4 and P glycoprotein activity and assimilation of tacrolimus in transplant patients with persistent diarrhea. Am J Transplant 2005;5: 1383
7. Bunnapradist S, Lentine KL, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. Transplantation 2006; 82:102
8. Takemoto SK, Pinsky BW, Schnitzler MA et al. A retrospective analysis of immuno-supperssion compliance, dose reduction and discontinuation in kidney transplant recipients. Am J Transplant 2007;7:2704
9. Knoll GA, Mac Donald I, Khan A, et al. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. J Am Soc Nephrol 2003;14:2381-2386.
10. Altiparmak MR, Trablus S, Pamuk ON et al. Diarrhoea following renal transplantation. Clin Transplant 2002; 16: 212-216.
11. Fishman JA, Rubin RH. Infection in organ-transplant recipients, N Engl J Med 1998;338:1741-1751
12. Rubin RH. Gastrointestinal infections disease complications following transplantation and their differentiation from immunosuppressant- induced gastrointestinal toxicities. Clin Transplant 2001;15(Suppl 4):11-22
13. Durand CM,Marr KA,Arnold CA,et al.Detection of cytomegalovirus DNA in plasma as an adjunct diagnostic for gastrointestinal tract disease in kidney and liver transplant recipients.Clin Infect Dis 2013;57:1550.
14. Diarrhea After Kidney Transplantation: A New look at a Frequent symptom, Transplantation, volume 98,Number8
15. Minz M,Udgiri NK,Heer MK,et al.Cryptosporidiasis in live related renal tranaplant recipients:a single center experience. Transplantation 2004;77:1916.
16. Luan FL, Chopra P, Park J, Norman S, Cibrik D, Ojo A, Efficacy of valganciclovir in the treatment of cytomegalovirus disease in kidney and pancreas transplant recipients. Transplant Proc 2006;38:3673-5.
17. Humar A, Siegal D, Moussa G, Kumar D,A prospective assessment of valganciclovir for the treatment of cytomegalovirus infection and disease in transplant recipients. J Infect Dis 2005;192:1154-7.