Evaluation of Noro virus infection in Kidney transplant recipients presenting with persistent or chronic diarrheoa

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INTRODUCTION

- Diarrhoea is one of the most common gastrointestinal disorders leading to significant impairment in quality of life in kidney transplant recipients.[1] The prevalence of diarrhoea in solid organ transplant recipients has been estimated to vary from 20% to 50%.[2,3,4]
- In kidney transplant recipients, there is higher frequency of opportunistic pathogens infections (e.g., Cryptosporidium or cytomegalovirus), higher likelihood to develop chronic diarrhoea (e.g., Norovirus), medication induced diarrhoea (e.g., mycophenolate, tacrolimus) and impact of diarrhoea on kidney allograft function.
- Norovirus infection has emerged as one of the important causes of persistent and chronic diarrhoea in kidney transplant recipients.[6-13] The incidence of Norovirus infection in kidney transplant recipients has been reported ranging from 7.3% to 35% in various studies.[10] It is associated with significant weight loss, graft dysfunction, morbidity and chronic viral shedding.[6-13]
- In absence of any specific treatment for Norovirus infection[14], mainstay of treatment is supportive care and reduction of immunosuppression. It is necessary to reduce immunosuppression to achieve relief of symptoms and clearance of viral shedding.[6-13]

AIMS AND OBJECTIVES

- To evaluate the clinical significance of Norovirus infection in kidney transplant recipients presenting with persistent or chronic diarrhoea.

MATERIALS AND METHODS

- **Study design:** Single centre, prospective observational study
- **Study Population**
- **Inclusion criteria:** Between December 2019 to November 2020, all kidney transplant recipients presenting with persistent (≥3 stools/day for ≥14 consecutive days) or chronic (≥28 days) diarrhoea.
- **Exclusion criteria:** Patients with prior history of inflammatory bowel disease.
- Patients were evaluated in stepwise manner to determine cause of diarrhoea. Stool samples were evaluated for Norovirus infection by RTPCR assay.

- Specimen:
- Stool specimen were collected in container (Cary-Blair Transport Media) ~5 gm. For low volume samples, a Fecal Swab Cary-Blair transport were used. Cary-Blair specimens were frozen at -94°F (-70°C).
- Methodology:
- Tests were performed using TaqMan real-time reverse transcription-PCR assay (Fast-track diagnostic: FTD 45–64 Kit). The detection and typing of Norovirus were done by conserved nucleotide sequences of the ORF1-ORF2 junction region of the Norovirus genome.
- Patients were followed for 12 months after enrolment. Response to treatment in terms of clinical and laboratory parameters were noted.

RESULTS

Study Layout

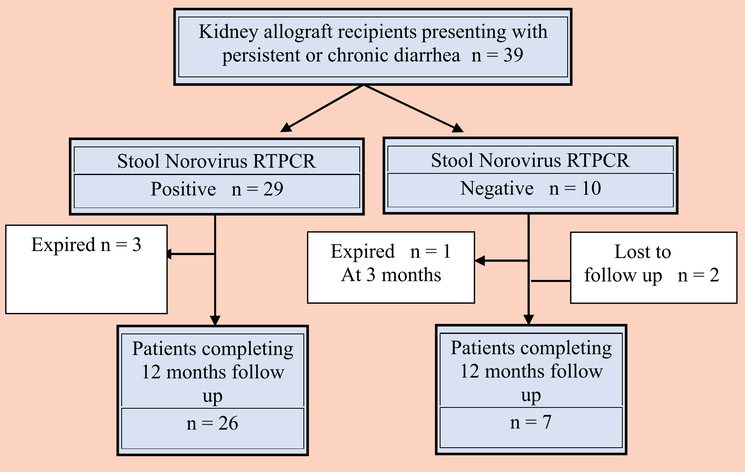


Figure 1: Study Layout

RESULTS

Demographic and Patients Characteristics	Norovirus Positive n = 29
• Age (Mean ± SD, Years)	46 ± 12.8
• Sex (Male/Female)	24 / 05
• Cause of Kidney Failure	
Diabetic Kidney Disease	03
ADPKD	03
Obstructive Uropathy	04
Chronic Glomerulonephritis	03
Undetermined	13
Other	03
• Donor	
Parents	14
Siblings	03
Other than related / Spouse	12
• HLA mismatch (HLA A, B, DR)	
>3/6	12
3 or less	17
• Presence of Donor Specific Antibodies	0

Demographic and Patients Characteristics	Norovirus Positive n = 29
• Induction Agent	
Nil	11
ATG	11
Il 2 receptor Antagonist	07
Rituximab + PLEX	0
• Immunosuppression before transplant	2
2nd Transplant	1
• Rejection Episode before diarrhoea onset	4
Rejection Treatment:	
Methylprednisolone (MPS)	1
ATG and MPS	3
• Immunosuppression at onset of diarrhoea	
Prednisolone + Tacrolimus + MMF	**23** (79%)
Prednisolone + Tacrolimus + Azathioprine	**05** (17%)
Prednisolone + Tacrolimus	**01** (04%)

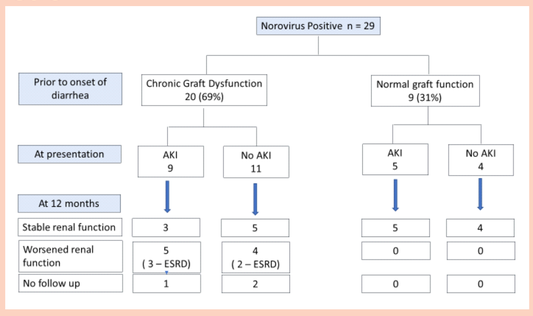
Clinical and Laboratory Parameters

Clinical Parameters	Positive n = 29
• Median time from Transplant to diarrhoea (Months)	63.5 (Range 12.4 to 143.4)
• Median Duration of Symptoms (Days)	60 (Range 14 to 365)
• Hypotension	1
• Weight loss	
Number of patients	29 (100%)
Weight loss, mean ± SD (kg)	6.3±3.3
• Hospitalization n (%)	25 (86%)
Mean Days of Hospitalization	5±2.79
• Treatment with anti-diarrhoeal medications prior to enrolment	29 (100%)

Laboratory parameters	Positive (29)
Creatinine 3 months before onset of diarrhoea Mean ± SD (mg/dl)	1.63 ± 0.5
Creatinine at time of enrolment Mean ± SD (mg/dL)	2.26 ± 0.76
AKI – Acute Kidney Injury (=25% rise in creatinine after onset of diarrhoea); n (%))	14 (48%)
Hb (mean ±SD; g/dl)	10.5 ± 2
Total leucocytes count (mean ±SD; cells/mm³)	8006.9 ± 3051.2
Absolute Lymphocytes Count (mean ±SD; cells/mm³)	1151.7 ± 701
Platelets (mean± SD, Lakh/mm³)	2.5 ± 1.1
Total Protein (mean± SD; g/dl)	6.7 ± 0.76
Albumin (mean ±SD; g/dl)	3.5 ± 0.37

OUTCOMES ON FOLLOW UP

Renal functio



Over all

- 14 patients (48%) had AKI at enrolment
- 09 patients (31%) had worsening of renal function at 12 months, 5 (17%) were initiated on maintenance dialysis.

*Chronic allograft dysfunction defined as presence of proteinuria or >25% rise in creatinine from best post-transplant creatinine or on basis of chronic changes on graft biopsy.
**AKI defined as >25% rise in creatinine at enrolment compared to value 3 months before onset of diarrhoea
*** Worsening of renal function at 12 months defined as >25% rise in creatinine, compared to value at enrolment

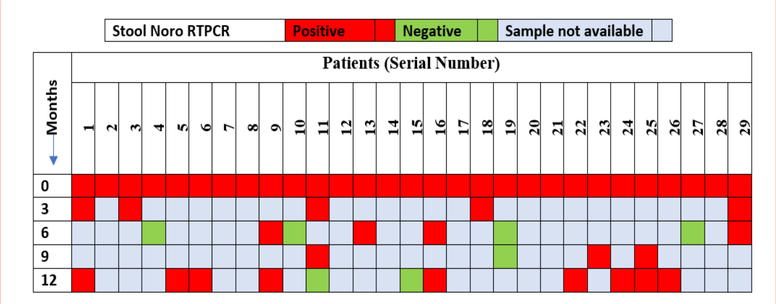
OUTCOMES ON FOLLOW UP

Weight

Noro RTPCR	Positive n = 29
Weight before onset of diarrhoea (mean ±SD; kg)	63.1 ± 11.3
Weight at enrolment;(mean ± SD; kg)	56.7 ± 11.1
Weight loss; (mean ± SD; kg)	6.3 ± 3.3
Completion of 12 months follow up (total)	n = 26
Patients with persistent weight loss	7 (24%)
Patients with weight gain	16 (58.6%)
Patients with steady weight	3 (10.3%)

OUTCOMES ON FOLLOW UP

Chronic Viral Shedding



Norovirus was detected in 9 out of 11 samples evaluated at 12 months of follow up.

COMPARISON WITH OTHER STUDIES

Characteristics	Our Study	Westhoff et al,[6] 2009	Schorn et al,[7] 2010	Roos-Weil et al,[8] 2011	Coste et al[9] 2013	Grass et al[10] 2021
Number of Norovirus Positive patients	29 out of 39	2	9	15	14/49	72
Median duration from transplant-to-diarrhoea onset (Months)	59 (12 - 143)	-	42, (1.3–125)	37±37 Mean value		46.5 (17.8 - 81.5)
Median Duration of diarrhoea (Days)	60 (14 - 365)	Up to 7 months in 1 case	150 (24–898)	261 (24 - 1008)		40 (15 - 66)
Weight loss (Kg)	6.4 (1.7-7.3) Median	1		8.6% ± 4.3% Mean	3.8 ± 2.7 mean	66% cases
AKI	48%	-	-	81%		60%
Immune suppression drugs Modification	86%	100%	-	100%	-	93%
Viral Shedding (Days)	90 to 365 days	-	230 (97 to 898)	289 (107 to 581	-	-

LIMITATIONS

- It was a single centre study.
- Follow up stool samples were not available at periodic interval in all cases.
- We had short duration of follow up.
- No control group (Kidney transplant recipient without diarrhoea, non-transplant population) were included in our study.
- Stool samples were not evaluated for all possible gastrointestinal viral / bacterial / parasitic pathogens using molecular techniques.

CONCLUSION

- Norovirus is common cause of persistent and chronic diarrhoea in renal transplant recipients.
- It is seen late after transplant and is associated with significant weight loss and graft dysfunction.
- Immunosuppression reduction is associated with improvement in diarrhoea and weight gain in majority of patients. However, renal function may not improve.
- Viral shedding may continue despite improvements in symptoms.

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