Predictors of persistent diarrhea in norovirus enteritis after solid organ transplantation

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Abstract

Solid organ transplant (SOT) recipients may develop protracted diarrheal illness from norovirus. We performed a retrospective chart review between January 2010 and April 2014 to identify predictors of persistent diarrhea in transplant recipients with norovirus enteritis. A total of 152 SOT recipients with mean age of 31.5 years (SD 23.1) were included: 43.4% male, 34.2% pediatric patients. Allograft types were abdominal 136 (89.5%) (kidney [39.5%], liver-small bowel [23%], other [27%]) and thoracic 16 (10.5%). The median time to diagnosis of first norovirus enteritis episode from date of transplantation was 1.7 (0.3-5.3) years. At time of presentation, diarrhea was present in 141 (93%). Thirty percent had persistent diarrhea at 2 weeks. Hospitalization was required for treatment in 121 (80%) of episodes with the mean length of stay of 10±15.2 days. Most (91%) infections were due to norovirus genogroup II, and gastrointestinal coinfections were seen in 23 (19%) norovirus enteritis episodes. Nausea at time of diagnosis (P=.002) and cytomegalovirus (CMV) infection in the preceding 90 days (P=.036) were identified as independent risk factors for persistent diarrhea using univariate and multivariable logistic regression. Our study shows that nausea on presentation and prior CMV infection were associated with persistent diarrhea in patients with norovirus enteritis.

KEYWORDS

diarrhea, gastroenteritis, norovirus, transplant, viral infections

1 | INTRODUCTION

Noroviruses (NV) are the most common cause of acute nonbacterial gastroenteritis in the United States and worldwide.[1,2] Disease due to NV is usually mild and self-limiting in immunocompetent individuals. In SOT recipients, NV is the second most common cause of diarrhea after *Clostridium difficile*.[3] In this population, NV is increasingly recognized as an etiology of prolonged diarrhea and wasting syndrome.[4-8] Chronic NV infection is associated with significant morbidity ranging from dehydration, allograft dysfunction, recurrent hospitalizations, malnutrition, and dysfunctional intestinal mucosal barrier leading to impaired absorption of medications.[4-8]

Treatment of chronic NV infection in SOT recipients is challenging due to lack of effective specific antiviral therapy. Experimental therapies such as nitazoxanide, intravenous (IV), or enteral immunoglobulins (Ig) have been tried alone or in combination with variable efficacy.[9-13] In addition, intensity of immunosuppression may be reduced in an attempt to clear NV, but this carries the risk of allograft rejection.[4] Immunocompromised individuals often shed NV for prolonged periods of time, with significant infection control implications.

While efforts are underway to develop NV vaccines and identify effective antiviral therapies, the clinical course and natural history of NV gastroenteritis in SOT recipients remain incompletely defined. It is unclear how many of the SOT recipients infected with NV develop

persistent infection and chronic symptoms. Risk factors for persistent diarrhea in this patient population have not been identified. In this study, we aimed to characterize the course of NV infection in SOT recipients, as well as the predictors of persistent NV-associated diarrhea.

2 | PATIENTS AND METHODS

2.1 | Subject identification

This was a retrospective study performed at two major solid organ transplantation centers: the University of Nebraska Medical Center and the University of North Carolina at Chapel Hill. Adult and pediatric SOT recipients with at least one positive NV PCR from stool or other gastrointestinal (GI) specimens between 1/1/2010 and 4/1/2014 were identified using electronic medical records and microbiology databases at respective institutions. Each individual patient was included only once, at the time of the first positive test for NV. The Institutional Review Boards at both institutions approved this study (IRB Approval Numbers: 14-1273 and 307-14-EP).

2.2 | Definitions

Norovirus gastroenteritis (NVE) was defined as positive NV PCR in stool or gastric secretions in the presence of GI symptoms such as nausea, vomiting, and/or diarrhea. Diarrhea was defined as change in bowel habits with ≥3 unformed stools within a 24-hour period or medical documentation of diarrhea by the treating healthcare provider. Relapse was defined as recurrence of upper and/or lower GI symptoms with a positive NV PCR, after either symptom improvement or resolution was documented. Documented presence and severity of symptoms was assessed at 2 weeks from end of treatment; patients who continued to have diarrhea at 2 weeks are considered to have persistent diarrhea. SOT recipients were categorized ad hoc into one of four treatment groups: nitazoxanide only (those who received at least one dose of nitazoxanide), enteral Ig only (those who received at least one dose of enteral Ig), combination therapy (those who received at least one dose of enteral Ig and nitazoxanide), and supportive treatment only (those who did not receive any nitazoxanide or enteral Ig). Patients in the treatment and supportive treatment group may have received one or more of the following: antimotility agents, intravenous (IV) fluid resuscitation, total parenteral nutrition (TPN) support, changes in immunosuppressive regimen, and/or dietary manipulations.

2.3 | Data abstraction

Data abstracted from electronic medical records included: baseline characteristics (age, gender, race, organ transplanted); induction immunosuppression; immunosuppressive regimen at time of NV diagnosis; mean tacrolimus and cyclosporine levels, mean daily corticosteroid dose during the month prior to diagnosis of norovirus infection; rejection episodes in the 3 months preceding diagnosis and during the follow-up period; allograft dysfunction during the follow-up period;

symptoms and laboratory values at time of diagnosis and follow-up (nausea, vomiting, diarrhea frequency and volume of bowel movements, fevers, white blood cell [WBC] count, serum creatinine and creatinine clearance as determined by Cockcroft-Gault for adult patients or Schwartz for pediatric patients, serum immunoglobulin G [Ig] level); norovirus genotype; relapse of the norovirus enteritis; results of repeat norovirus testing if available; type of GI coinfections; treatment (nitazoxanide, enteral Ig, IVIg, decrease or change in immunosuppression, IV fluids, TPN support, administration of antimotility agents); treatment dose and duration; need for hospitalization and length of hospital stay; overall mortality. The follow-up period extends from the first positive test until the last documented encounter in the electronic medical record.

2.4 | Statistical analysis

Primary outcome was resolution of diarrhea at 2 weeks from end of treatment or supportive therapy. Secondary outcomes included need for hospitalization, length of hospital stay, time to symptom resolution, relapse rates, and allograft dysfunction at 3 months. T test and chi-square test were performed for continuous and categorical variables, respectively. Risk factors for persistent diarrhea at 2 weeks (primary outcome) were evaluated using univariate and multivariable logistic regressions. Backward stepwise variable selection was used for all variables with P-value <.1. Propensity score analyses were performed to evaluate the effect of different therapies on the primary outcome. All tests were considered statistically significant at a P-value of <.05. All statistical analyses in this study were performed using Stata statistical software (version 14, StataCorp, College Station, TX, USA.).

3 | RESULTS

During the study period, 152 SOT recipients with NVE, 52 (34%) pediatric patients were identified (Table 1). The mean age (±SD) was 31.5±23.1 years, and 60 (39%) were kidney transplant recipients. Eighteen patients (12%) received enteral therapy (nitazoxanide only, enteral Ig only, or combination therapy) in addition to supportive therapy; 134 patients (88%) received supportive treatment only.

3.1 | Characteristics of NVE episodes

The median time to diagnosis of first NVE episode from date of transplantation was 1.7 years (IQR: 0.3-5.3 years), with mean of 3.7±4.6 years. At time of presentation, diarrhea was present in 141 (93%), nausea in 62 (41%), and fever in 30 (20%) NVE episodes (Table 2). Most (91%) of these episodes were due to norovirus genogroup II, and the rest (9%) were due to genogroup I. GI coinfections were seen in 23 (19%) NVE episodes: *Clostridium difficile* (n=9, 6%), adenovirus (n=8, 5%), cytomegalovirus (CMV) (n=5, 3%), rotavirus (n=3, 2%), CMV and adenovirus (n=1, 0.6%), *Campylobacter* spp. (n=1, 0.6%), and *Escherichia coli* (n=1, 0.6%). All GI CMV coinfections were biopsy proven by colonoscopies.

TABLE 1 Characteristics of solid organ transplant recipients with norovirus infection

Characteristics	Supportive treatment n=134 (88%)	Enteral treatment[a] n=18 (12%)	All patients with NV infection N=152
Age at time of transplant[b]	29.7 (22.8)	42.7 (22.3)	31.5 (23.1)
Caucasian	88 (66)	13 (72)	101 (67)
Male gender	75 (56)	11 (61)	86 (57)
Transplant type			
Kidney	53 (40)	7 (39)	60 (39)
Liver	13 (10)	1 (5.5)	14 (9)
Heart	8 (6)	4 (22)	12 (8)
Small bowel	8 (6)	1 (5.5)	9 (6)
Lung	1 (1)	3 (17)	4 (3)
Pancreas	1 (1)	0 (0)	1 (1)
Simultaneous[c]	50 (36)	2 (11)	52 (34)
Induction IS			
Basiliximab	66 (49)	8 (44)	74 (49)
Thymoglobulin	38 (28)	1 (6)	39 (26)
Alemtuzumab	4 (3)	1 (6)	5 (3)
None	26 (20)	8 (44)	34 (22)
Maintenance IS[b,d]			
Tacrolimus level	9.3 (0.4)	10.2 (1.3)	9.4 (4.5)
Cyclosporine level	300 (76)	N/A	300 (76)
Prednisone dose[e]	6 (0.5)	4.6 (0.7)	6 (4.2)
Rejection 90 days prior	11 (8)	0 (0)	11 (7)

IS, immunosuppression; NV, norovirus; N/A, not applicable.
[a]Includes patients who received nitazoxanide only (n=9 [5%]), enteral Ig only (n=4 [3%]), or both nitazoxanide and enteral Ig (n=5 [3%]).
[b]Indicates values in mean (SD).
[c]Simultaneous includes pancreas and kidney (n=13), liver and kidney (n=2), liver and small bowel (n=33), kidney, liver and small bowel (n=1) and kidney and BMT (n=1).
[d]Within 30 days of NV diagnosis.
[e]Dose in mg per day.

3.2 | Outcomes

Persistent diarrhea (2 weeks from initiation of enteral or supportive treatment) occurred in 30% of NVE episodes. The median time to resolution of diarrhea was 6 days (IQR: 2-11 days), with a mean of 10±13 days. Hospitalization was required for treatment in 121 (80%) of episodes; the mean length of stay was 10±15.2 days. During the follow-up period, NVE relapse was diagnosed in 33 (22%) patients. Data on repeat NV test results were available in 52 patients, of which 39 (75%) remained positive. At 3 months from time of NVE diagnosis, 141 (93%) continued to have functional allografts. At 1 year from NVE diagnosis, 12 of 152 patients had died (1-year mortality rate 8%), with the mean time to death of 574±545.2 days.

3.3 | Treatment of NVE

In the enteral treatment group, nine (6%) patients received nitazoxanide monotherapy, four (3%) received enteral Ig monotherapy, and five (3%) were treated with both nitazoxanide and enteral Ig in addition to supportive therapy (Table 2). The mean number of nitazoxanide doses received per patient was 22±10.6, with a mean dose of 7.3±1.7 mg/kg. The mean enteral Ig dose administered was 42±10.4 mg/kg per dose, with a mean of 18±12.9 dose per patient. Supportive management of NVE included IV fluid administration (125 of 152 [82%], mean of 6.5±12.3 days), TPN (26 of 152 [17%], mean of 21±3.65 days), and antimotility agent(s) (56 of 152 [37%]). In addition, the immunosuppression was decreased in 78 (52%) patients, changed in five (3.3%) patients, and IVIg administered to three (3%) patients. The mean IVIG dose was 418±160.4 mg/kg. In patients receiving enteral feeding, the formula was changed in 10 (6.6%) patients prior to and 35 (23%) after NVE diagnosis.

3.4 | Risk factors for persistent diarrhea

Risk factors for persistent diarrhea at 2 weeks were evaluated using univariate and multivariable logistic regression, with results demonstrated in Tables 3 and 4, respectively. Age at transplantation, nausea at presentation, recent CMV infection, and use of antimotility agents were included in the multivariable logistic regression model. Factors that remained statistically significant in the multivariable model were nausea at presentation (OR=4.41, 95% CI: 1.75-11.15), and CMV infection in the 90 days preceding NVE diagnosis (OR=5.56, 95% CI: 1.12-27.62) (Table 4). Four propensity score regression models were performed to evaluate the potential efficacy of different therapies. In none of these models was any treatment found to be associated with a decreased risk for persistent diarrhea. The first two models included all significant variables from the univariate analyses and compared (i) nitazoxanide vs no nitazoxanide (OR=0.85, 95% CI: 0.58-1.26) and (ii) any enteral treatment vs no enteral treatment (OR=0.86, 95% CI: 0.68-1.10); the second two models included supportive treatments (ie, intravenous fluids, TPN, and immunosuppression reduction) and compared (i) nitazoxanide vs no nitazoxanide (OR=0.86, 95% CI: 0.40-1.87) and (ii) any enteral treatment vs no enteral treatment (OR=0.94, 95% CI: 0.52-1.68).

4 | DISCUSSION

Our study is the largest cohort of NV-infected SOT recipients reported to date. Previous studies have mostly been limited to case reports or series, or combined SOT with hematopoietic stem cell transplant recipients,[4,5,7,8,14,15] all of which limited the ability to make meaningful conclusions regarding NVE in organ transplant recipients. We focused on the clinical course of NVE in SOT recipients using multi-institutional data, and we also identified predictors of persistent NVE diarrhea.

Nausea at time of presentation and CMV infection in the 90 days prior to diagnosis were identified as significant and independent risk

TABLE 2 Clinical characteristics and treatment of norovirus enteritis

Characteristics	Supportive treatment n=134 (88%)	Enteral treatment[a] n=18 (12%)	All patients with NV infection n=152
Days from transplant[a]	1257 (127)	1973 (641)	1342 (135)
Symptoms at presentation			
Diarrhea	124 (93)	17 (94)	141 (93)
Nausea	53 (40)	9 (50)	62 (41)
Vomiting	49 (37)	7 (39)	56 (37)
Fever	29 (22)	1 (6)	30 (20)
Laboratory values at presentation[a]			
WBC	10 (0.7)	7.8 (1.4)	9.7 (8)
Serum creatinine	1.7 (0.2)	2.4 (0.3)	1.8 (1.8)
Total serum IgG	663 (113)	792 (181)	692 (404)
CMV infection 90 days prior	7 (5)	4 (22)	11 (7)
NV genogroup II	121 (90)	18 (100)	139 (91)
GI coinfections	24 (18)	4 (22)	28 (18)
Treatment			
Hospitalized	103 (78)	18 (100)	121 (80)
Length of hospital stay in days[a]	8.7	15.6	9.5 (15.2)
Enteral treatment			
Nitazoxanide	N/A	9 (6)	N/A
Enteral IG	N/A	4 (3)	N/A
Nitazoxanide & enteral IG	N/A	5 (3)	N/A
Supportive treatment			
TPN	22 (16)	4 (22)	26 (17)
IVIG	6 (5)	1 (6)	7 (5)
Antimotility agent	43 (33)	13 (72)	56 (37)
Symptoms at 2 weeks from end of treatment			
Diarrhea	32 (24)	8 (44)	40 (26)
Nausea	7 (5)	2 (11)	9 (6)
Vomiting	2 (2)	1 (6)	3 (2)
Fever	3 (2)	0 (0)	3 (2)
Laboratory values at 2 weeks from end of treatment[a]			
WBC	7.6 (0.5)	6.6 (0.9)	7.5 (4.8)
Serum creatinine	1.3 (0.2)	1.9 (0.3)	1.4 (1.6)
Total serum IgG	655 (98.8)	1002 (39)	829 (222.8)
Functioning allograft at 3 months	126 (94)	15 (83)	141 (93)
Relapse of NV Infection	26 (19)	7 (39)	33 (22)

CMV, cytomegalovirus; GI, gastrointestinal; IVIG, intravenous immunoglobulin; NV, norovirus; TPN, total parenteral nutrition; WBC, white blood cell count.
[a]Values are in mean (SD).

factors for persistent diarrhea from NVE in our cohort. Nausea at time of presentation may be a surrogate marker of high norovirus viral load, thus increasing the likelihood of developing prolonged diarrhea. Previously, high NV fecal load has been reported to significantly correlate with prolonged diarrhea.[15] Alternatively, persistent diarrhea could be a manifestation of functional GI disorders such as postinfectious irritable bowel syndrome (PI-IBS) or lactose intolerance. A previous study showed that attendees at a medical conference who developed acute gastroenteritis due to NV had seven times the odds of developing PI-IBS at 3 months compared to those who did not have NVE.[16] In the same study, those who had vomiting at time of presentation had 10 times the odds of subsequent development of PI-IBS compared to those who did not.[17] While the association of PI-IBS has been described for enteric bacterial pathogens such as *Campylobacter*, *Salmonella*, *Shigella*, and *E. coli*,[18] its association with NVE and other viral gastroenteritis deserves further exploration and needs to be confirmed by more studies.

TABLE 3 Risk factors for persistent diarrhea at 2 weeks from start of therapy using univariate logistic regression

Variable	OR	95% CI	*P*-value
At time of transplant			
Age	1.02	1.00-1.04	.019
SBT vs other allografts	1.94	0.79-4.73	.146
T-cell depleting agents administered	1.10	0.49-2.59	.829
At time of NV diagnosis			
Fever	1.74	0.74-4.09	.204
Nausea	4.12	1.83-9.27	.001
Vomiting	2.11	0.99-4.53	.054
NV genogroup II	0.86	0.24-3.06	.821
Coinfection (other GI pathogens)	0.90	0.35-2.31	.830
CMV infection	5.27	1.25-22.3	.024
Rejection requiring treatment	2.58	0.54-12.21	.233
Treatment variables			
Nitazoxanide	0.54	0.17-1.67	.282
No. of nitazoxanide doses	0.85	0.72-1.00	.049
Enteral Ig & nitazoxanide	1.77	0.19-16.34	.616
IVIg	2.31	0.26-20.5	.451
Antimotility agent	0.40	0.19-0.88	.022
Reduction in immunosuppression	0.95	0.44-2.02	.887

CI, confidence intervals; CMV, cytomegalovirus; GI, gastrointestinal; Ig, immunoglobulin; IS, immunosuppression; IV, intravenous; NV, norovirus; OR, odds ratio; SBT, small bowel transplants.

TABLE 4 Risk factors for persistent diarrhea at 2 weeks from start of therapy using multivariable logistic regression

Variable	OR	95% CI	*P*-value
Age at time of transplant	1.00	0.98-1.03	.781
CMV infection 90 days prior to NV diagnosis	5.75	1.12-27.62	.036
Nausea at time of NV diagnosis	4.41	1.75-11.15	.002
Administration of antimotility agent	0.55	0.22-1.37	.197

CI, confidence intervals; CMV, cytomegalovirus; NV, norovirus; OR, odds ratio.

Patients with CMV infection in the 90 days prior to NV diagnosis had almost six times the odds of persistent NV-associated diarrhea at 2 weeks compared to those without CMV infection. While this association has not been described for NV, the increased incidence of various bacterial, fungal, and viral infections is well documented in SOT recipients with CMV infection.[16,19-21] This could be a result of direct effect from CMV infection causing tissue-invasive disease, or the ability of CMV to modulate the immune system resulting in numerous indirect effects such as immune exhaustion[22] that in turn results in persistence of NV infection. Additionally, CMV infection could also be a marker of over immunosuppression reflecting an overall increased susceptibility to infections.

Previous studies have identified organ transplantation and immunosuppression as independent risk factors for prolonged shedding of NV.[24,25] This phenomenon not only has infection control implications, but NV-infected immunocompromised patients with prolonged shedding can also serve as reservoirs for emergence of novel NV variants.[23] However, its exact role in disease pathogenesis is not entirely clear, as chronic viral shedders may be asymptomatic.[15,24,25] As NV can be detected in stool of asymptomatic and healthy individuals using RT-qPCR,[26] this further complicates the interpretation of diagnostic results.

The proportion of NV-infected organ transplant recipients who developed persistent diarrhea was 30% in our study compared to 50% in the study by Ye et al.[15] persistent diarrhea was defined as lasting ≥14 days in both studies. We found similar GI coinfection rates (19%), NVE relapse rates (22%), and NV genogroup II infection rates (91%) in comparison with the study results by Ye et al. (20%, 30%, and 100%, respectively).[15] On the other hand, a higher proportion of our patients required hospitalization (80% vs 55%) and NVE occurred later in the post-transplant course for our patients (mean time to diagnosis of first episode of 1342 days vs median time of 136.5 days).

In contrast to the acute and self-limiting nature of NVE in immunocompetent hosts, organ transplant recipients who develop persistent symptoms from NVE present unique challenges from the management standpoint due to the lack of effective antiviral treatment. In a randomized placebo-controlled trial of outpatients with viral enteritis, the subset of NV-infected patients treated with nitazoxanide had significantly shorter time from first dose to resolution of symptoms compared to patients who received placebo. The median time to symptom resolution was 1.5 days (IQR: 0.5-2.5) for the nitazoxanide group compared with 2.5 days (IQR: 1.5-4.5) for the placebo group (*P*<.001).[11] However, the number of patients who received enteral treatment in our study was too small to make any meaningful conclusions regarding efficacy of nitazoxanide and/or enteral Ig in SOT recipients. A multicenter randomized placebo-controlled trial is needed to evaluate the safety and efficacy of enteral treatments in transplant patients.

In a small study, administration of oral immunoglobulins for NVE leads to resolution of diarrhea and decrease stool output, without any impact on the length of hospital stay and the hospital cost.[13] The rationale for this route of administration of immunoglobulins would be to inhibit the viral replication in the intestinal lumen and to block the adhesion of the virus to the intestinal epithelium.

Our study has several limitations. As test of cure was not routinely performed for NV at both institutions, information on follow-up stool test results was limited. Therefore, duration of viral shedding and viral evolution by way of sequence analysis could not be ascertained. Quantitative NV viral loads were not performed from gastric secretions or stool for correlation and information regarding specific NV genotypes is not available. The number of patients who received some form of enteral treatment for NVE was small, thus limiting our ability

to draw any conclusions regarding treatment efficacy of these agents. Adequately powered randomized clinical trials are needed to determine whether nitazoxanide and/or enteral Ig may be of use in selected SOT recipients with NVE.

In conclusion, we showed that nausea and recent CMV infection are independent predictors of persistent diarrhea in NV-infected SOT recipients. Norovirus enteritis is associated with high rates of persistent diarrhea and relapse.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

D.v.D, P.P.C, and D.F.F. contributed to the conception and design of the study. P.P.C, J.L.S, and D.F.F. contributed to acquisition of data for the study. A.C.K. performed data analysis. A.C.K, D.F.F., P.P.C., J.L.S, W.J.G, and D.v.D contributed to interpretation of data for the study. P.P.C drafted the manuscript. All authors critically revised and approved of the final version of the manuscript to be published.

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