Received: 2 December 2016 | Accepted: 24 December 2016
DOI: 10.1111/tid.12692

Clinical presentation and outcomes of norovirus infection in intestinal allograft compared to native intestine

Diana F. Florescu[1,2] | Jessica L. Sonderup[3] | Wendy Grant[2] | Pearlie P. Chong[4] | David van Duin[4] | Andre C. Kalil[1]

[1]Transplant Infectious Diseases Program, University of Nebraska Medical Center, Omaha, NE, USA

[2]Transplant Surgery Program, University of Nebraska Medical Center, Omaha, NE, USA

[3]Internal Medicine Department, University of Nebraska Medical Center, Omaha, NE, USA

[4]Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Correspondence
Diana Florescu, MD, Transplant Infectious Diseases, Nebraska Medical Center, Omaha, NE, USA.
Email: dflorescu@unmc.edu

Abstract

Background: No data are available on clinical manifestations and course of norovirus gastroenteritis (NVE) in intestinal allograft (from intestinal and multivisceral transplant recipients, ITR) compared to native intestine (from other allograft recipients, nITR).

Methods: This was a retrospective study of solid organ transplant recipients with NVE at two centers from January 1, 2010 to April 1, 2014. Chi-square, t-test, linear and logistic regression analyses were done to compare NVE in ITR vs nITR patients.

Results: The ITR (45 patients) were compared to nITR (107 patients). ITR were younger (odds ratio [OR]=0.90; *P*<.0001), less likely to receive anti-lymphocyte induction therapy (OR=0.15; *P*<.0001), and had shorter time from transplant to NVE (OR=0.99; *P*=.008). On presentation ITR had less frequent nausea (OR=0.11; *P*<.0001) or vomiting (OR=0.36; *P*=.01), higher white blood cell count (OR=1.09; *P*=.001), and higher glomerular filtration rate (OR=1.02; *P*<.0001). ITR were less likely to receive anti-motility agents (OR=9.6; *P*<.0001). ITR were more likely to stay longer on intravenous (IV) fluids (OR=1.18; *P*<.0001); have recurrent NVE (OR=4.25; *P*<.0001); have longer hospital stay (OR=1.07; *P*<.0001); develop acute rejection (OR=5.1; *P*=.006); and have lower overall survival (OR=0.28; *P*=.006).

Conclusions: Compared to nITR, the ITR with NVE were significantly younger, had less nausea and vomiting at presentation, received less anti-motility agents, required more IV fluids, and had longer hospital stay. A trend was seen for lower survival with NVE in ITR.

KEYWORDS
enteritis, graft intestine, intestinal transplant, native intestine, norovirus

1 | INTRODUCTION

Gastrointestinal infections are commonly diagnosed after solid organ transplantation,[1] including intestinal transplantation.[2] Noroviruses (NVs) are responsible for approximately one-fifth of the acute gastroenteritis episodes worldwide.[3] Transmission of NV is facilitated by its high prevalence in the population, viral shedding even after symptoms have resolved, and its high stability in the environment. NV gastroenteritis (NVE) in transplant recipients is associated with morbidity, mortality, and graft loss mainly because of significant dehydration, changing levels of immunosuppressive drugs, and renal failure.[2,4] Furthermore, the course of NV illness in these patients can be complicated by chronic diarrhea and prolonged viral shedding.[2]

Intestinal transplantation remains an extraordinary clinical and immunological challenge owing to the high risk of complications and the need for profound immunosuppression with significant side effects.[5] The results of intestinal transplantation remain inferior to those of other transplanted allografts[5] owing to its high rate of acute, late

onset, and chronic rejection, as well as because of its higher susceptibility and lower treatment response to viral infections, compared to native intestine. Minimal human leukocyte antigen matching in intestinal transplantation, chronic host immunosuppression, local graft-versus-host reaction, and aberrant immune response within the allograft might create a favorable immunologic milieu for viral infections that are not usually seen in the intestine with other allografts.[6] Moreover, preservation of the intestinal graft, surgical procedure, and ischemia-reperfusion injury would induce heat-shock protein expression[7] and lymphocyte infiltration,[8] leading to rejection or increased susceptibility to infections. To our knowledge, no formal evaluation and comparison of clinical features and outcomes between graft and native intestines has been published to date. Our study aims to assess the clinical and outcome differences between intestinal allograft (from intestinal and multivisceral transplant recipients, ITR) and native intestine (from other allograft transplant recipients, nITR).

2 | METHODS

We retrospectively analyzed the electronic medical records of all pediatric and adult solid organ transplant recipients with a positive NV test performed at University of Nebraska Medical Center and University of North Carolina between January 1, 2010 and April 1, 2014 who had vomiting and/or diarrhea that were attributed to NV infection. Each individual patient was included only once, at the time of the first positive test. The patients included in this study were previously included in a previous analysis with a different focus—looking to identify predictor factors of persistent diarrhea in any transplant recipients with NVE.[9] Variables collected included: age; gender; allograft(s) transplanted; induction therapy; maintenance immunosuppression regimen at the time of positive test; mean tacrolimus level during the month prior to diagnosis of NV infection; rejection episodes; graft loss during the follow-up period; symptoms at the diagnosis and end of treatment (nausea, vomiting, diarrhea, fever, weight loss); frequency of bowel movements; volume of stool; mortality; laboratory values at presentation and end of therapy (white blood cells [WBCs], creatinine and creatinine clearance; serum immunoglobulin G level); standard (intravenous [IV] hydration and anti-motility agents) or experimental (nitazoxanide and IV immunoglobulin) treatment administered, dose and duration of treatment; route of immunoglobulin administration; enteral feeding; changes in immunosuppressive medications; and need for total parenteral nutrition (TPN).

2.1 | Definitions

Intestinal and liver-intestine transplant recipients were included in the ITR group, as intestinal transplantation is associated with lymphatic loss, denervation, and ischemia-reperfusion of the allograft that might have an impact on the clinical aspects of the enteric infections. Any other allograft was included in the nITR group. *Diarrhea* was defined as change in bowel habits with ≥3 unformed stools within a 24-h period or increased volume of stool by 50%. *Acute NVE* was prospectively defined as a positive NV polymerase chain reaction (PCR) in stool or gastric secretions, in the presence of corresponding clinical symptoms (vomiting and/or diarrhea or increased stool output from baseline) for less than a 2-week period. *Relapse* was defined as the recurrence of diarrhea after a 14-day symptom-free period. *Co-infection* was established when another microorganism was identified at the same time as the NV as a possible etiologic agent of diarrhea. *Rejection* was defined by the characteristic pathological findings on the allograft biopsy. NV was qualitatively detected by Norovirus ASR (Cepheid, Sunnyvale, CA, USA) real-time reverse transcriptase PCR; the assay targets the NLV RNA polymerase region/capsid junction and detects genogroups I and II.

2.2 | Protocol for diarrhea assessment

The standard protocol to evaluate a solid organ transplant recipients with diarrhea included: *Clostridium difficile* toxin assay, NV PCR, adenovirus PCR, rotavirus antigen, herpes panel DNA in the blood, stool culture, and *Giardia* and *Cryptosporidium* enzyme immunoassay. Endoscopy with intestinal allograft biopsies were routinely performed weekly for 6-8 weeks post transplantation and were taken at two locations along the small bowel with 3-5 pieces/locations; the tissue was examined by histology, immuno-histochemical stains and culture, as requested by the ordering physician. Biopsies and tissue cultures were also obtained for clinical symptoms to differentiate infection from rejection and as needed for persistent diarrheal symptoms (generally, not less than weekly until resolution of symptoms). For non-intestinal allografts, upper endoscopy or colonoscopy was performed if indicated.

The primary outcome of the study was symptom resolution 2 weeks after the start of treatment. Secondary outcomes included rejection, graft loss, all-cause mortality, need for hospitalization, length of hospital stay, and time to symptom resolution.

2.3 | Statistical analysis

Summary statistics were performed for baseline characteristics and outcomes. Student's t-test was used for continuous variables and chi-square statistics for categorical variables. Outcomes were evaluated by univariate and multivariable logistic regressions. Two multivariable logistic regression models were performed, one for factors at diagnosis of NVE and one for factors during the clinical course of NVE. Backward variable selection was used for all variables with P-value <.1. All data were analyzed using STATA procedure (version 14, Stata Corp, College Station, TX, USA).

3 | RESULTS

A total of 152 patients were included in the analysis; 45 ITR and 107 nITR: 60 (56.07%) kidney, 14 (13.08%) liver, 13 (12.15%) kidney-pancreas, 12 (11%) heart, 4 (3.74%) lung, 2 (1.87%) kidney-liver, 1 (0.93%) kidney-BMT, and 1 (0.93%) pancreas transplant

TABLE 1 Comparison of baseline characteristics between ITR and nITR

Variables	ITR (n=45)	nITR (n=107)	*P*-value
Mean age at transplant in years (SD)	7.57 (13.34)	41.76 (18.29)	<.0001
Pediatric patients (%)	40 (88.89)	12 (11.21)	<.0001
Adult patients (%)	5 (11.11)	95 (88.79)	
Induction therapy (%)	43 (95.55)	74 (69.15)	<.0001
Mean tacrolimus level 30 days prior to NVE in ng/mL (SD)	10.12 (5.13)	9.08 (4.18)	.235
CMV infection within 90 days prior to NVE (%)	3 (6.67)	8 (7.48)	.859
Gastrointestinal co-infection (%)	12 (26.67)	17 (15.89)	.131

SD, standard deviation; NVE, norovirus enteritis; CMV, cytomegalovirus; ITR, intestinal transplant recipients; nITR, non-intestinal allograft transplant recipients.

recipients. The baseline characteristics of the two groups are presented in Table 1. The mean time to diagnosis of NVE post transplantation was 762.49 days (standard deviation [SD] 1031.38) for ITR vs 1585.78 days (SD 1828.70) for nITR (*P*=.005).

3.1 | Clinical course

Hospitalization rates for NVE were 88.89% (40/45 patients) ITR vs 75.70% (81/107 patients) nITR (*P*=.089), with a mean length of hospitalization of 18.11 days (SD 21.81) vs 5.81 days (9.29) (*P*<.0001). Table 2 describes the most common symptoms, weight, WBC counts at presentation and at the end of therapy for both groups. The WBCs came back to normal range within a mean of 3.17 days (SD 8.95 days) vs 4.46 days (SD 12.63 days) (*P*=.434); renal function returned to normal after a mean of 6 days (SD 28.39 days) vs 9.04 (SD 17.39 days) (*P*=.448). Table 3 presents changes in several parameters from presentation to the end of therapy. The following parameters returned to normal range 3 months after NVE in ITR compared to nITR: WBC: 93.33% (42/45 patients) vs 87.85 (94/107 patients) (*P*=.019); glomerular filtration rate (GFR): 95.56% (43/45) ITR vs 84.11% (90/107) nITR (*P*=.001). Repeated stool testing for NV was performed in 64.44% (29/45) ITR vs 21.5% (23/107) nITR (*P*<.0001) and this test was positive in 75.86% (22/29) and 73.91% (17/23) (*P*=.872), respectively. NVE recurred in 40.91% (18/45) of ITR compared to 14.02% (15/107) of nITR recipients (*P*<.0001).

3.2 | Treatment

Treatments administered to ITR and nITR are described in Table 4.

3.3 | Comparison between ITR and nITR

In univariate analysis, factors associated with ITR include the following: younger age (OR=0.90; *P*<.0001); time from transplant to NVE diagnosis (OR=0.99; *P*=.008); more frequent induction therapy (OR=0.0000025; *P*<.0001); less frequent nausea (OR=0.14; *P*<.0001); less frequent vomiting (OR=0.36; *P*=.01); higher WBC count (OR=1.09; *P*=.001); and higher GFR (OR=1.02; *P*<.0001). Compared to nITR, the ITR group was more likely to have more frequent diarrhea resolution (OR=1.94; *P*=.15); have more days on IV fluids (OR=1.18; *P*<.0001); receive antimotility agents (OR=9.6; *P*<.0001) and TPN (OR=13.5; *P*<.0001); and have enteral formula changed (OR=7.6; *P*<.0001). The ITR group was less likely to have recurrent NVE (OR=0.24; *P*<.0001); develop acute rejection (OR=0.20; *P*=.006); or have lower survival (OR=0.28; *P*=.006).

TABLE 2 Symptoms of NVE at presentation and at the end of therapy in the ITR and nITR

Variables	IRT	nITR	*P*-value
Fever on presentation (%)	10 (22.22)	20 (18.69)	.630
Fever at the end of therapy (%)	0 (0)	3 (2.83)	.265
Nausea on presentation (%)	5 (11.11)	57 (53.27)	<.0001
Nausea at the end of therapy (%)	1 (2.22)	8 (7.48)	.390
Vomiting on presentation (%)	10 (22.22)	47 (43.93)	.010
Vomiting at the end of therapy (%)	1 (2.22)	2 91.87%)	.988
Diarrhea on presentation (%)	40 (88.89)	101 (94.39)	.249
Diarrhea at the end of therapy (%)	8 (17.78)	32 (29.91)	.199
Mean weight in kg at presentation (SD)	24.42 (20.82)	70.63 (25.42)	<.0001
Mean weight in kg at the end of therapy (SD)	22.31 (19.78)	69.93 (24.73)	<.0001
Mean WBCs at presentation (SD)	13.66 (10.46)	8.08 (6.09)	<.0001
Mean WBCs at the end of therapy (SD)	10.67 (6.39)	6.02 (2.89)	<.0001

NVE, norovirus enteritis; ITR, intestinal transplant recipients; nITR, non-intestinal allograft transplant recipients; kg, kilograms; WBCs, white blood cells; SD, standard deviation.

TABLE 3 Changes in a few parameters from presentation to the end of therapy in ITR and nITR

Variables	ITR	nITR	*P*-value
Mean weight change from presentation to the end of therapy (SD)	0.69 (0.34)	0.78 (0.34)	.873
Mean WBC change from presentation to the end of therapy (SD)	−3.56 (1.47)	−2.44 (0.57)	.397
Mean change in creatinine from presentation to the end of therapy (SD)	−0.32 (0.08)	−0.52 (0.17)	.432
Mean change in IgG level from presentation to the end of therapy (SD)	51.5 (33.5)	145.67 (180.47)	.715

ITR, intestinal transplant recipients; nITR, non-intestinal allograft transplant recipients; SD, standard deviation; WBC, white blood cell.

TABLE 4 Treatment administered to ITR compared with nITR

Variable	ITR (n=45)	nRTI (n=107)	*P*-value
IV fluid administration (%)	40 (88.89)	85 (79.44)	.149
Mean number of days of IV fluids (SD)	13.95 (19.48)	3.28 (4.31)	<.0001
Change in enteral formula to treat NVE (%)*	30 (90.91)	5 (100)	.347
Nitazoxanide administration (%)*	1 (2.22)	13 (12.15)	.030
Oral IVIG administration (%)*	2 (4.44)	7 (6.54)	.608
Nitazoxanide and oral IVIG administration (%)*	0 (0)	5 (4.67)	.058
Mean dose of oral IVIG administered in mg/kg (SD)	29.5 (6.36)	45.21 (8.58)	.050
Mean number of doses of enteral IVIG (SD)	18 (14.14)	18.42 (13.72)	.970
IVIG administered (%)*	3 (6.82)	4 (3.92)	.466
Mean dose of IVIG in mg/kg (SD)	510.57 (77.87)	349.05 (180.22)	.212
Anti-motility agent administered (%)*	4 (9.09)	52 (49.06)	<.0001
Endoscopy performed within 1 week after diagnosis of NVE (%)*	25 (55.56)	19 (17.76)	<.0001
Mean days on TPN after NVE (SD)	24.3 (21.0)	11.62 (10.57)	.118

*Did not include all patients.
ITR, intestinal transplant recipients; nITR, non-intestinal transplant recipients; IV, intravenous; SD, standard deviation; NVE, norovirus enteritis; IVIG, intravenous immunoglobulin; TPN, total parenteral nutrition.

The multivariable logistic regression for factors at diagnosis of NVE included age at transplantation; nausea, volume of stool, and GFR at presentation; and time to NVE from transplant. The only factor that remained statistically significant was age at transplantation (OR=0.98, 0.98-0.99; *P*<.001). The multivariable logistic regression for factors during the clinical course of NVE included the following: age at transplantation, administration of anti-motility agents, number of days on IV fluids, length of hospitalization, and mortality. The factors that remained statistically significant were age at transplantation (OR=0.91, 0.87-0.95; *P*<.0001); administration of anti-motility agents (OR=1274.63, 2.97-54700.4, *P*=.021); and IV fluid administration (OR=1.77, 1.02.83, *P*=.018).

3.4 | Outcomes

Rejection was diagnosed in 20% (9/45) ITR vs 4.67% (5/107) nITR (*P*=.005). Those having a functioning graft at 3 months after infection: 97.78% (44/45) ITR vs 90.65% (97/107) nITR (*P*=.210). The mean time to death after NVE was 630.69 days (SD 585.98) for ITR vs 506.18 days (SD 512.25) for nITR (*P*=.587). No deaths were attributed to NVE.

4 | DISCUSSION

Our study shows that the differences are significant in presentation and clinical course of NVE between patients with intestinal allograft (ITR) and native intestine (nITR). Compared to nITR, ITR were younger and became infected with NV earlier after transplantation, presented with more severe disease, required more frequent hospitalization, received more anti-motility agents and TPN, required prolonged IV hydration, and were more likely to develop acute rejection and to have poor overall survival. However, ITR are less likely to have nausea and vomiting at presentation compared with nITR.

There are several possible explanations for why ITR have less nausea and vomiting at presentation: (i) The gastrointestinal transit and motility in the younger ITR group (mainly pediatric patients) might be different than in the older nITR group (mainly adult patients in our

cohort). Several studies showed that with aging esophageal dysmotility increases, esophageal sphincter and peristaltic function deteriorate, and gastric emptying time is decreased;[10–12] (ii) Intestinal transplantation disrupts intestinal motility (resulting in either hypomotility or hypermotility of the intestine);[13] or (iii) Intestinal transplantation is associated with changes in the microbiome and sometimes stasis of intestinal contents leading to bacterial overgrowth, with subsequent Toll-like receptor activation inducing inflammation, rejection, and graft dysmotility.[13]

NVE roenteritis was severe at presentation in our cohort, reflected in the rate of hospitalization and dehydration (need for IV fluids). A high proportion of patients required hospitalization, a much higher rate than previously reported by Ye et al.[14] (55%). However, this may be a consequence of testing bias; patients who are admitted with diarrhea are likely to undergo a more extensive diagnostic work-up. We noticed a higher rate of admission for ITR than for nITR. Consistently, this group had higher stool output and higher WBC count corresponding to a more intense inflammatory response. ITR are more prone to dehydration and malabsorption leading to hypovolemia and severe malnutrition, which can then be complicated by sepsis and organ failure.[15] ITR recovered slower and had more prolonged hospital stays than nITR. These results are consistent with the data we previously reported, that is, ITR are not discharged quickly from the hospital, even when NVE resolved, mainly because of multiple co-morbidities.[4] In our nITR group, the length of hospital stay was slightly shorter than the one previously reported in kidney transplant recipients (mean 9.8±5.0 days),[2] probably reflecting different local practices. No nosocomial or healthcare-associated outbreaks were suspected during the study period.

Time to NVE after transplantation was shorter for ITR than nITR, possibly reflecting the profound immunosuppression and increased graft susceptibility to infections associated with ITR. Although donor-derived infections are a possibility, they could not be assessed, as we did not have testing at implantation; however, the allografts would not be taken from a donor with active intestinal pathology. In hematopoietic stem cell transplant recipients, NVE was reported at a median of 36.5 days (range, 5-517 days) post transplantation;[15] early infections might be explained by the high degree of immunosuppression combined with mucositis and graft-versus-host disease, both highly prevalent in stem cell transplant recipients. In a study published by Roos-Weil et al.[2], the mean time to infection after kidney transplantation was 37 months (SD 37 months). It is very possible that, in hematopoietic stem cell and intestinal transplantation, recipients' immunological dysfunction of the intestine plays an important role in the pathology of certain gastrointestinal infections, explaining early onset of NVE.

The ITR were more frequently retested for the persistence of NV in the stool, probably for the evaluation of abdominal symptoms and for the pre-endoscopy evaluation for rejection. However, no difference was found in the number of positive NV PCR results between the two groups. ITR were more likely to undergo endoscopy, a procedure that is necessary to assess for rejection as potential cause of diarrhea. ITR had a significantly higher number of NVE recurrences than nITR. We did not perform NV strain and variant analysis, and thus we cannot determine if the patients truly relapsed or were subsequently infected with a different NV strain. Also, we were not able to determine if genetic differences existed between the two groups regarding the susceptibility to NV infections. It has been reported that carbohydrate expression in the intestinal epithelial cells, which allows NVs to bind to the epithelium, is genetically determined and impacts the rate of NV infections.[16]

Supportive care remains the main treatment for NVE, even in transplant recipients. ITR received IV fluid for a longer period of time than nITR, and their bowel movements returned faster to baseline compared to nITR. In our cohort, nITR were more likely to receive anti-motility agents, experimental treatment with nitazoxanide alone, or nitazoxanide and oral immunoglobulin. It is possible that patients with ITR, who have intermittent diarrhea, were managed differently by the treating physicians, that is, they could be more likely to have endoscopy, and to have received less medications in view of their recurrent episodes of diarrhea. In a previous study, we reported that ITR who received induction therapy and had higher tacrolimus levels were more likely to received oral immunoglobulins, to be started on TPN, and to have immunosuppression decreased to treat NVE.[4] However, the previous study represented the University of Nebraska Medical Center experience,[4] while the new data from this study represents the combined experience from two centers. Limited evidence[4,17,18] suggests that administration of oral immunoglobulins could improve the symptoms and shorten the duration of diarrhea. Nitazoxanide experience in immunocompromised patients is even more limited;[19] most of the data come from immunocompetent patients who were treated for rotavirus and NVE in the outpatient setting with good response.[20]

Regarding outcomes, ITR had a higher rate of rejection than nITR, but it has been previously reported that rejection rates in intestinal transplantation are higher than that with other allografts.[5] We did not find a difference in the functioning graft 3 months after infection or in the time to death after NVE different between the two groups, but ITR had a lower survival rate.

Our study has the limitations inherent to any retrospective study. We had a strict definition for NVE, but the diagnosis of NVE was dependent on the documentation that could have been over-reported because of NV shedding without intestinal disease. The stool frequency and volume were well documented in the inpatient records, but not consistently documented in the outpatient records. The role of NV as an etiologic agent of diarrhea in our cases is supported by significant increased stool output not associated with rejection, immunosuppression, or change in enteral nutrition, and return of stool output to baseline at the end of treatment period. We included patients with other intestinal co-pathogens as a relatively significant proportion of recipients have co-infections; it is unclear to what extent these pathogens contributed to diarrhea and to the clinical outcomes. Because of the small number of patients who received nitazoxanide and oral immunoglobulin, we could not determine the impact of these treatments on resolution of diarrhea. Our two groups were not similar, reflecting the higher need for intestinal transplantation in the pediatric population; the ITR group predominantly

included pediatric patients, while the comparator included more adults. Although ITR were more likely to receive induction therapy, there was no difference in tacrolimus level during the 3 months prior to NVE. By comparison with ITR, nITR had higher weight at presentation and at the end of treatment, parameters most likely related to the older age of the group. On the other side, the major strengths of our study rely on the overall sample size. Also, this is the first study to our knowledge to compare epidemiology, clinical presentation, and outcome of NVE in ITR and nITR.

5 | CONCLUSIONS

Solid organ transplant recipients are susceptible to NV infections. Understanding the differences in clinical course of NVE between different allografts would help to understand who might require more aggressive intervention or might benefit from novel therapeutic agents. Our findings suggest that the intestinal allograft might be infected earlier after transplantation than the native intestine. The ITR tend to have more severe presentation reflected in more frequent hospital admissions and requirement of prolonged IV hydration, but are less likely to have nausea and vomiting at presentation compared with other allograft recipients.

ACKNOWLEDGEMENTS

The authors thank Mrs. Sandy Nelson for the preparation of this report.

REFERENCES

1. Echenique IA, Penugonda S, Stosor V, et al. Diagnostic yields in solid organ transplant recipients admitted with diarrhea. *Clin Infect Dis*. 2015;60:729-737.
2. Roos-Weil D, Ambert-Balay K, Lanternier F, et al. Impact of norovirus/sapovirus-related diarrhea in renal transplant recipients hospitalized for diarrhea. *Transplantation*. 2011;92:61-69.
3. Ahmed SM, Hall AJ, Robinson AE, et al. Global prevalence of norovirus in cases of gastroenteritis: A systematic review and meta-analysis. *Lancet Infect Dis*. 2014;14:725-730.
4. Florescu DF, Hermsen ED, Kwon JY, et al. Is there a role for oral human immunoglobulin in the treatment for norovirus enteritis in immunocompromised patients? *Pediatr Transplant*. 2011;15:718-721.
5. Pirenne J, Kawai M. Intestinal transplantation: Evolution in immunosuppression protocols. *Curr Opin Organ Transplant*. 2009;14:250-255.
6. Iwaki Y, Starzl TE, Yagihashi A, et al. Replacement of donor lymphoid tissue in small-bowel transplants. *Lancet*. 1991;337:818-819.
7. Ogita K, Hopkinson K, Nakao M, et al. Stress responses in graft and native intestine after rat heterotopic small bowel transplantation. *Transplantation*. 2000;69:2273-2277.
8. Knowlton AA, Brecher P, Apstein CS. Rapid expression of heat shock protein in the rabbit after brief cardiac ischemia. *J Clin Invest*. 1991;87:139-147.
9. Chong PP, van Duin D, Sonderup JL, et al. Predictors of persistent diarrhea in norovirus enteritis after solid organ transplantation. *Clin Transplant*. 2016;30:1488-1493.
10. Davies AE, Kidd D, Stone SP, et al. Pharyngeal sensation and gag reflex in healthy subjects. *Lancet*. 1995;345:487-488.
11. Grande L, Lacima G, Ros E, et al. Deterioration of esophageal motility with age: A manometric study of 79 healthy subjects. *Am J Gastroenterol*. 1999;94:1795-1801.
12. Grassi M, Petraccia L, Mennuni G, et al. Changes, functional disorders, and diseases in the gastrointestinal tract of elderly. *Nutr Hosp*. 2011;26:659-668.
13. von Websky MW, Kalff JC, Schafer N. Current knowledge on regulation and impairment of motility after intestinal transplantation. *Curr Opin Organ Transplant*. 2015;20:303-307.
14. Ye X, Van JN, Munoz FM, et al. Noroviruses as a cause of diarrhea in immunocompromised pediatric hematopoietic stem cell and solid organ transplant recipients. *Am J Transplant*. 2015;15:1874-1881.
15. Robles JD, Cheuk DK, Ha SY, et al. Norovirus infection in pediatric hematopoietic stem cell transplantation recipients: Incidence, risk factors, and outcome. *Biol Blood Marrow Transplant*. 2012;18:1883-1889.
16. Lindesmith L, Moe C, Marionneau S, et al. Human susceptibility and resistance to Norwalk virus infection. *Nat Med*. 2003;9:548-553.
17. Florescu DF, Hill LA, McCartan MA, et al. Two cases of Norwalk virus enteritis following small bowel transplantation treated with oral human serum immunoglobulin. *Pediatr Transplant*. 2008;12:372-375.
18. Gairard-Dory AC, Degot T, Hirschi S, et al. Clinical usefulness of oral immunoglobulins in lung transplant recipients with norovirus gastroenteritis: A case series. *Transplant Proc*. 2014;46:3603-3605.
19. Siddiq DM, Koo HL, Adachi JA, et al. Norovirus gastroenteritis successfully treated with nitazoxanide. *J Infect*. 2011;63:394-397.
20. Rossignol JF, El-Gohary YM. Nitazoxanide in the treatment of viral gastroenteritis: A randomized double-blind placebo-controlled clinical trial. *Aliment Pharmacol Ther*. 2006;24:1423-1430.

How to cite this article: Florescu DF, Sonderup JL, Grant W, Chong PP, van Duin D, Kalil AC. Clinical presentation and outcomes of norovirus infection in intestinal allograft compared to native intestine. *Transpl Infect Dis*. 2017;19:e12692. https://doi.org/10.1111/tid.12692