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Recurring *Norovirus* & *Sapovirus* Infection in a Renal Transplant Patient

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ABSTRACT

Noroviruses and *sapoviruses* are common causes of gastroenteritis and infectious diarrhea. Although these viruses are typically of short duration in healthy individuals, immunocompromised organ transplant recipients can develop chronic, relapsing symptoms with grave outcomes. We discuss a unique case of chronic *norovirus* infection with subsequent *sapovirus* infection in a kidney transplant recipient. Relief of *norovirus* symptoms occurred after the reduction of immunosuppression and treatment with nitazoxanide. Subsequently, a superimposed *sapovirus* infection developed. Patient developed renal transplant rejection due to reduction of immunosuppression. Findings from this case study suggest that *norovirus* and *sapovirus* are associated with chronic, relapsing symptoms and significant morbidity in immunocompromised renal transplant patients and that reduction of immunosuppression in order to overcome infection risks allograft rejection. Early detection and management are essential to reduce morbidity associated with these viruses among immunocompromised transplant recipients.

Introduction

In the United States (U.S.), *norovirus* is the leading cause of gastroenteritis with diarrhea and vomiting among all ages [1]. *Norovirus* is associated with significant morbidity and mortality, especially in 3rd world countries. In low and middle income countries, *norovirus* is responsible for approximately 200,000 deaths annually among children less than 5 years of age [2,3]. More than 21 million Americans develop acute gastroenteritis yearly caused by *norovirus* infection and the virus contributes to more than 71,000 hospitalizations and 800 deaths in the U.S. every year, mainly among the elderly and young children [1]. The term *norovirus* was coined in 1968 in Norwalk, Ohio where the first case of *norovirus* was ascribed as a cause of gastroenteritis [4]. *Norovirus* is primarily spread via fecal-oral route and is highly contagious [4]. It is a non-enveloped virus with a single stranded RNA genome from the *Caliciviridae* family (Fig. 1) and can be grouped into five genogroups (GI through GV) which are further divided into at least 34 genotypes [1,2,5]. Most *norovirus* infections are caused by GI and GII *noroviruses* with the majority of outbreaks triggered by GII.4 strains [6]. In 2013, the CDC reported a new strain of *norovirus* GII.4, Sydney strain. Since the discovery of this new strain, the virus is now responsible for more than 50% of food-borne infections in the U.S.

Although *norovirus* accounts for more than 90% of viral infectious diarrhea worldwide, *sapovirus* is also a major source of enteric viral infection [5]. Like *norovirus*, *sapovirus* is from the *Caliciviridae* family. There are five genogroups of *sapovirus* (GI-G5) with nine additional genogroups proposed [7]. Clinical presentation of *sapovirus* is similar to *norovirus* and therefore cannot be differentiated from *norovirus* by symptoms alone [7]. Laboratory testing is essential to identify the pathogen.

In immunocompetent adults *norovirus/sapovirus* infections are self-limiting, lasting 24-48 hours [2]. *Norovirus* is shed in stool for prolonged periods even before and after resolution of clinical symptoms. Median viral shedding in healthy adults is around 28 days (range 20-40 days) which increases risk of secondary spread [2,5]. Immunocompromised patients are at increased risk of developing *norovirus/sapovirus* infection. The number of clinical cases of *norovirus/sapovirus* gastroenteritis among immunocompromised kidney transplant recipients is well documented in the literature and continues to rise [4]. In immunocompromised transplant recipients, these viruses can become chronic, persisting from weeks to years [2]. *Norovirus/sapovirus* are often unrecognized in clinical practice in the renal transplant population, contributing to delay in diagnosis and treatment [8]. Nearly 80% of patients who are hospitalized with these infections, experience acute kidney injury (AKI) due to severe dehydration caused by nausea, vomiting and diarrhea [9]. There is no single established treatment for *norovirus* gastroenteritis. For kidney transplant recipients, decrease in immunosuppression therapy is the mainstay of treatment for chronic *norovirus* infection [10]. This

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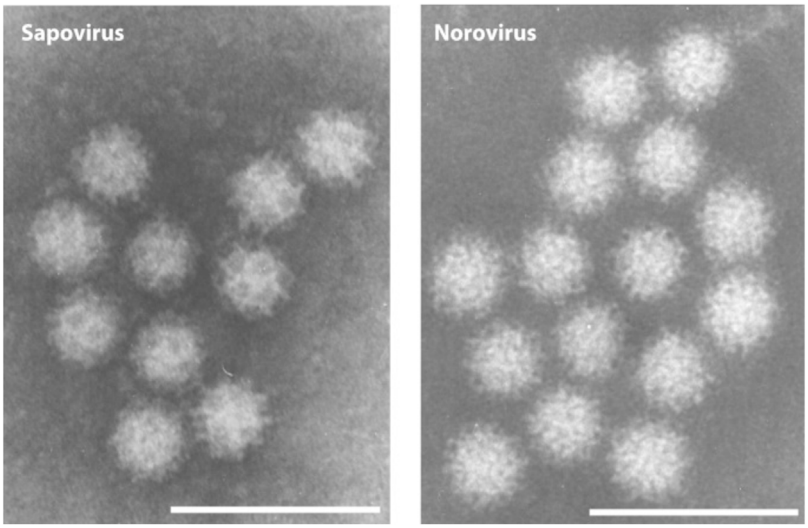

Fig. 1. Electron micro-particles of norovirus and sapovirus from clinical samples. (Reproduced with permission of American Society of Microbiology: Clinical Microbiology Reviews. 2015 Jan; 28(1): 32–53. doi: 10.1128/CMR.00011-14).

however, increases the risk of allograft rejection. We present a case of chronic relapsing and recurring *norovirus/sapovirus* infection in an elderly kidney transplant patient leading to acute kidney injury (AKI) and subsequent allograft rejection secondary to iatrogenic reduction of immunosuppression.

Case Report

The patient was a 68 year old African American male with history of deceased donor kidney transplant in 2008 for end stage renal disease secondary to hypertension. He had a history of bilateral native kidney nephrectomies for renal cell carcinoma and was on maintenance immunosuppression therapy with mycophenolate mofetil 750 mg p.o b.i.d, tacrolimus 1 mg b.i.d (with a goal level of 4-6 ng/mL), and prednisone 5 mg p.o daily. His baseline creatinine was 1.7 mg/dL.

He presented to clinic in October 2018 with complaints of fatigue, decreased appetite, chronic diarrhea (2-3 loose watery stools daily) and significant weight loss of ~ 15 kilograms over last 1 year, denying any fever, sweating, cough, hematemesis, or melena. His blood pressure was low (BP 89/59 mmhg). Laboratory work showed non-anion gap metabolic acidosis (HCO3 13 meq/L) and acute renal failure with a creatinine of 3.5 mg/dL. Tacrolimus level was found to be elevated above goal, at 14 ng/mL and this was attributed to ongoing severe diarrhea. Renal transplant ultrasound showed patent flow in transplant renal artery and vein without any significant obstruction. He was admitted to the hospital for supportive care and an extensive work up for his symptoms was undertaken. Stool *Clostridium difficile* toxins A and B were negative. Stool culture was negative for growth of any routine enteric pathogens as well as *cholera vibrio* and a qualitative fecal fat test done to rule out malabsorption was negative. Serum *Cytomegalovirus* PCR, *Epstein Barr Virus* PCR, and *cryptococcal* antigen were negative. HIV and tuberculosis T-Spot testing were negative as well. A CA 19-9 level was obtained the result of which was normal. His last colonoscopy in June 2018 did not detect any concerning lesions. There were no masses on chest x ray and on ultrasound imaging his nephrectomy beds were negative for any recurrent or remnant disease. Echocardiography showed normal ejection fraction and no valvular vegetations.

As part of malignancy work up an esophagogastroduodenoscopy was done which was unremarkable except for peptic duodenitis. Stool PCR test for *Shigatoxin* 1 and 2, *Cryptosporidium*, *Giardia, Cyclospora*, *Campylobacter, Yersinia enterocolitica, Adenovirus* and *Rotavirus* was negative but positive for *norovirus*. Patient was diagnosed with having chronic *norovirus* gastroenteritis. He received bicarbonate containing intravenous fluids during the hospitalization. Tacrolimus dose adjustments were made to target goal level. His mycophenolaate mofetil was decreased from 750 mg p.o bid to 500 mg p.o bid for immune reconstitution to increase immune response against the *norovirus*. He was also started on nitazoxanide 500 mg b.i.d for 14 days at discharge. Four days after starting nitazoxanide patient was seen in transplant clinic. Diarrhea had completely resolved. He reported better energy levels and improved appetite. Patient was advised to complete 14 days of nitazoxanide which he did. A repeat sigmoidoscopy/colonoscopy was deferred after the patient was diagnosed with norovirus gastroenteritis.

One month later patient was readmitted to hospital with complaints of feeling weak, short of breath, with loss of appetite and recurrence of diarrhea. Labs showed serum bicarbonate of 8 meq/L and creatinine of 6.7 mg/dL. The patient was also hypokalemic, hypomagnesemic and hypocalcemic. The electrolyte abnormalities were secondary to his worsening diarrhea and decreased oral intake. He received supportive care which lead to improvement in clinical and laboratory parameters. He was found to be positive for *norovirus* again on stool PCR. He was placed back on nitazoxanide for 6 weeks given relapse of symptoms after stopping nitazoxanide. Serum IgA and IgG levels were checked and were found to be adequate and hence he did not receive any oral or intravenous immunoglobulin (IVIG) infusion.

At 3 weeks follow up the patient had marked clinical improvement and had gained 6 kilograms body weight and the diarrhea had once again completely resolved. However, at this visit he was still positive for *norovirus* PCR on stool. His mycophenolate mofetil was further decreased to 250 mg p.o bid with the aim to help patient's immune system clear the virus and prevent another recurrence. Given persistently increasing weight, markedly improved general sense of well-being, no reported side effects along with continued *norovirus* shedding in stool, we extended nitazoxanide treatment beyond 6 weeks. At this point his creatinine was 1.9 mg/dL. A post nephrectomy follow up positron emission tomography (PET) scan obtained at this point showed no recurrent tumor at renal beds and no active tumor lymphadenopathy or distant metastasis.

During routine follow-up clinic visit in February 2019 while on nitazoxanide, stool PCR was negative for *norovirus* but positive for *sapovirus*. There was no diarrhea and patient was continuing to gain weight. However, patient was noted to have an increase in serum creatinine of up to 3.3 mg/dL. Ultrasound of transplanted kidney showed preserved vascular flow and mild pelvic caliectasis. There was high suspicious for renal allograft rejection due to recently lowered immunosuppression. A renal transplant biopsy was obtained which showed Banff IA acute cellular rejection (Fig. 2), acute tubular necrosis (ATN), with no arteritis, and no evidence of humoral rejection (C4d negative, no peritubular capillaritis). SV 40 stain (BK Virus) was negative. Donor specific antibodies (DSA) were negative as well. For the treatment of his acute allograft rejection he received methylprednisone 500 mg intravenously daily for 4 days, followed by a prednisone taper. Thymoglobulin was not used. His mycophenolate mofetil dose was increased back to 500 mg p.o b.i.d. The creatinine improved to a new baseline of 2.6 mg/dL after treatment of rejection. Patient was instructed to continue nitazoxanide. A repeat stool sample was again positive for *sapovirus* and negative for *norovirus.*

During follow-up visits in the outpatient clinic, patient continued to gain weight with no recurrence of diarrhea. However, repeat stool on April 2019 was again positive for *norovirus* even on nitazoxanide. In June 2019 patient stopped taking nitazoxanide as diarrhea had completely resolved. In August 2019, patient began to experience diarrhea and weight loss again. Stool PCR was positive for *norovirus*. Patient was restarted on nitazoxanide 500 mg p.o bid. See Table 1 for sequence of events. Despite initial improvement in creatinine after treatment of cellular rejection with steroids, on outpatient follow up creatinine started increasing progressively with development of uremic symptoms and patient ultimately ended up on dialysis in September 2019.

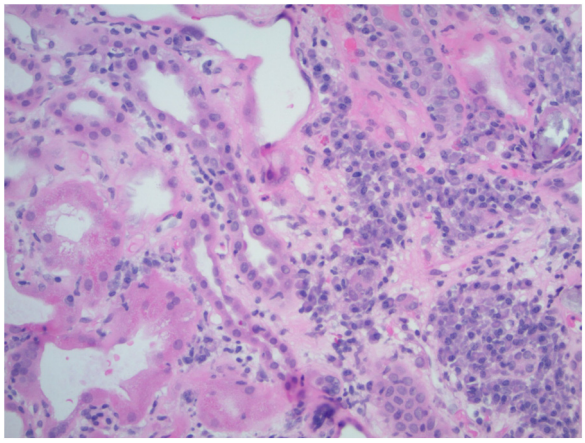

Fig. 2. Renal transplant biopsy showing significant interstitial inflammation and tubulitis along with ATN.

Discussion

Norovirus and *sapovirus* gastroenteritis is usually self-limiting in immunocompetent persons. However in immunocompromised patients, the disease is typically prolonged and recurrent with more severe symptoms. *Norovirus/sapovirus* infection has been reported to be prevalent among immunocompromised kidney transplant recipients, often associated with significant morbidity [10]. According to recent studies, norovirus is responsible for the hospitalization of more than 18% of solid organ transplant (SOT) patients with infectious diarrhea [4,9]. Noroviruses bind to antigens on enterocytes, cause edema, and severe enterocyte injury resulting in diarrhea. Clinical manifestations of *norovirus/sapovirus* gastroenteritis in immunocompromised patients include non-bloody watery diarrhea, nausea, vomiting, abdominal discomfort, bloating, weight loss and wasting [8]. Fever is unusual. Spread mainly occurs through food borne fecal-oral route but can also occur through person to person contact or from contaminated surfaces. Symptoms typically occur within 24-48 hours after exposure to the virus [8]. Both T-cell and B-cell responses are required to clear *norovirus* infection and immunosuppressive therapy is a risk factor for prolonged infection.

In kidney transplant recipients, because of iatrogenic immunosuppression, *norovirus* symptoms can be prolonged and chronic, with periods of symptom exacerbation and remission [2]. This has been attributed to evolution of virus in the immunocompromised host and genomic variation [2]. The diagnosis is usually made by reverse transcriptase polymerase chain reaction (RT-PCR) test of a stool specimen. Norovirus antigen detection assays have lower sensitivity and specificity than RT-PCR. Multiplex PCR based testing that can simultaneously detect a wide range of enteric pathogens on stool samples is increasingly being used for diagnosis of severe acute diarrhea in transplant recipients [8,11]. Literature review shows that clinical symptoms of *norovirus* can last indefinitely with protraction of viral shedding as in our case [2,4,9]. If symptoms are left untreated, kidney graft dysfunction can occur due to severe dehydration. The diarrhea can also cause disruption of P-glycoprotein efflux pump leading to supratherapeutic tacrolimus levels further worsening the acute kidney injury. Also, patients are at higher risk of rejection due to immunosuppression reduction that is done to allow host immune response to eliminate the infection. This case study documents the persistent and recurrent *norovirus/sapovirus* infection in a kidney transplant recipient and the resultant detrimental impact on patient outcome.

Table 1
Timeline of Weight, Stool PCR Results, and Nitazoxanide Treatment

Timeline	Weight (kg)	Stool PCR	Treatment
Oct 2018	59	*Norovirus* Positive	Nitazoxanide for two weeks
Nov 2018	59	*Norovirus* Positive	Nitazoxanide restarted
Dec 2019	62.1	*Norovirus* Positive	On nitazoxanide
Jan 2019	66.7	*Norovirus* Positive	On nitazoxanide
Feb 2019	69.1	*Norovirus* Negative *Sapovirus* Positive	On nitazoxanide
Mar 2019	71	*Norovirus* Negative *Sapovirus* Positive	On nitazoxanide
Apr 2019	71.8	*Norovirus* Positive *Sapovirus* Negative	On nitazoxanide
Patient stopped taking Nitazoxanide in June			
Jul 2019	63.3	Test not done	Off nitazoxanide
Aug 2019	60	*Norovirus* Positive *Sapovirus* Negative	Nitazoxanide restarted

In a retrospective study of 2182 solid organ transplant recipients in a tertiary care hospital in Netherlands, 4.6 % recipients tested positive for norovirus of which 22.7% developed chronic *norovirus* infection. Majority of the patients were renal transplant recipients. Median viral shedding period was 218 days. 56.5% of patients needed change in immunosuppression regimen due to severity of symptoms and complications [12]. Several other studies have examined the impact of infectious diarrhea among immunocompromised transplant recipients associated with *norovirus/sapovirus* infection. A recent study examined demographic, clinical and outcome variables associated with transplant recipients positive for *norovirus* [8]. Findings from this study indicated that 16% of 193 transplant recipients tested positive for *norovirus*. Of the patients who tested positive for *norovirus*, 100% experienced diarrhea, 52% abdominal pain, 58% nausea & vomiting and 35% wasting. Further findings indicate the AKI occurred in 23% of patients who tested positive for *norovirus*, which persisted after 6 months in 21% of patients. The median duration of diarrheal symptoms was 4 months and 35.4% of patients had relapse of symptoms after improvement. Longer diarrheal symptoms were associated with patients who had an incompatible kidney transplant, wasting and history of plasmapheresis. The majority of patients were treated with nitazoxanide (74%) and reduction of immunosuppression (58%). IVIG was given to 32% of patients. Another study on clinical outcomes of norovirus infection in renal transplant patients reported that 66 percent patients needed hospitalization due to severity of symptoms of which 40% developed acute kidney injury of the renal allograft. Chronic *norovirus* diarrhea developed in 15% of the patients and immunosuppression was lowered in 66% of patients. Two patients developed acute rejection within 6 months after *norovirus* diagnosis. In both patients, immunosuppression had been lowered due to severe diarrhea. Loss of eGFR over three years was significantly higher in norovirus infected patients [13].

Similar findings were reported in a retrospective study that examined the epidemiologic and clinical significance of *norovirus/sapovirus* in kidney transplant recipients hospitalized with acute and chronic diarrhea [9]. Among 41 patients hospitalized with unexplained diarrhea, almost half (n = 20) were screened for *norovirus/sapovirus* of which 16 tested positive. 94% of patients who tested positive for *norovirus/sapovirus* suffered from chronic diarrhea. Compared to other causes of diarrhea, such as parasitic or bacterial infection, patients who tested positive for *norovirus/sapovirus* experienced greater weight loss at the time of admission, longer duration of symptoms (8.7 times more) and more frequent need for immunosuppression reduction. Five patients developed rejection of allograft due to lowering of immunosuppression. Furthermore, 80% of patients hospitalized with *norovirus/sapovirus* developed AKI and exhibited prolonged viral shedding with a median time period of 289 days.

Currently, no therapy has shown to be consistently effective and there are no specific therapies for treating *norovirus/sapovirus* infection [4,14]. Symptom relief should include intravenous hydration, anti-motility agents to relieve diarrhea, and reduction in immunosuppression [2,14,15]. Immunosuppression reduction may help in reducing clinical symptoms and preventing chronic carriage and recurrent infection [15]. Reduction of immunosuppression in organ transplant recipients should be done carefully due to risk of precipitating a rejection. Limited case studies have shown nitazoxanide to be effective in treating norovirus with significant reduction in time to resolution of symptoms [10,14,15]. Nitazoxanide is a thiolide antimicrobial agent that exerts its affect against parasitic worms, protozoa, bacteria and viruses [16]. Antiviral effects of nitazoxanide are two-fold, including activation of natural antiviral defenses and inhibiting cellular pathways that lead to viral replication [16]. Niazoxanide therapy for the treatment of *norovirus/sapovirus* should be continued until stool RNA studies are negative [16]. Our patient showed a dramatic response to nitazoxanide, with complete resolution of diarrhea and gaining ~ 13 kilograms of body weight. However, our patient continued to shed and could not completely eradicate the virus unlike other reports of cure with nitazoxanide [10]. In one case report of *norovirus* gastroenteritis managed with nitazoxanide, significant clinical improvement occurred but the patient continued to shed the virus in stool for more than a month [17]. In another case series of 5 patients of *norovirus* gastroenteritis treated with nitazoxanide, 3 patients achieved complete cure with undetectable norovirus on repeat stool PCR [18]. A 2017 systematic review on activity of nitazoxanide on viral gastroenteritis concluded that nitazoxanide may be useful in reducing the disease burden in immunocompromised transplant recipients [19].

In addition to Nitazoxanide, human immunoglobulin therapy has also shown to be effective in a few isolated cases of norovirus, but with mixed results. One study describes the case of a 56 year old kidney and pancreas transplant recipient who was successfully treated with a short course of enteral human immunoglobulin via nasogastric feeding tube [4]. Subsequent stool sample for *norovirus* PCR after treatment was negative with resolution of symptoms. In another study, 12 lung transplant recipients with norovirus gastroenteritis who were treated with oral immunoglobulin for 2 days, 11 were successfully treated, whereas only 1 had reoccurrence of symptoms [20]. However, in the case of a 13 year old kidney recipient with *norovirus* gastroenteritis, administration of oral immunoglobulin and switching from tacrolimus to sirolimus was not found to be effective in producing a meaningful clinical response compared to nitazoxanide [16]. Enteral administration of immunoglobulin allows immunoglobulins to be delivered to the intestinal epithelium and thereby bind with norovirus particles potentially inhibiting further viral adherence to the intestinal endothelium and allowing viral clearance [20].

Preventive measures for *norovirus* are important given the morbidity associated with the infection. Hand hygiene is of paramount importance. Soap hand wash in more effective than alcohol based hand wash. Surfaces should be cleansed and decontaminated with detergent and chlorine bleach. Often children are source of infection to adults. Contaminated items related to children should be carefully disinfected or discarded. Persons suspected of having *norovirus* infection should avoid food handling. It is advised that fruits and vegetables be thoroughly washed and sea food be cooked properly. For healthcare setting outbreak due to *norovirus*, patient cohorting and isolation precautions are recommended. Currently there is no vaccine for prevention of *norovirus* infection but research is ongoing [21].

Conclusion

In conclusion, we present a case of recurring/relapsing *norovirus/sapovirus* infection with subsequent AKI in a 68 year old kidney transplant recipient treated who was treated with nitozoxanide and immunosuppression reduction. Norovirus/sapovirus infections are highly contagious and can be associated with detrimental outcomes in immunocompromised transplant patients. Our patient was hospitalized on 3 separate occasions over a nine month period and reduction of immunosuppression lead to renal transplant rejection. Norovirus symptoms in immunocompromised patient population are associated with periods of remission and exacerbation that can last for a long time. Currently, there is no single proven therapy to cure *norovirus/sapovirus* in the immunocompromised kidney transplant population. Treatment with medications such as nitazoxanide and immunoglobulin has proven effective in limited cases. Reduction of immunosuppression in order for patient's immune system to

clear the infection may lead to renal transplant rejection as happened in our case.

Consent: Written and informed consent was obtained from patient.

Author Contributions: SW: compiled the literature review and was involved in patient management. IG: Prepared and finalized the case report, reviewed the literature and was involved in patient management. DK: Provided the histological diagnosis of renal transplant rejection. RK: Reviewed the final draft and was involved in management of patient. SK: Provided the histopathological images.

Conflict of interest: None.

References

[1] Centers for Disease Control & Prevention (CDC). Burden of norovirus illness in the U.S.. 2019 Available at: https://www.cdc.gov/norovirus/trends-outbreaks/burden-US.html Accessed, March 9.

[2] Bok K, Green KY. Norovirus gastroenteritis in immunocompromised patients. New England Journal of Medicine. 2012;367(22):2126–32.

[3] Patel MM, Widdowson MA, Glass RI, Akazawa K, Vinjé J, Parashar UD. Systematic literature review of role of noroviruses in sporadic gastroenteritis. Emerging infectious diseases 2008;14(8):1224.

[4] Chagla Z, Quirt J, Woodward K, Neary J, Rutherford C. Chronic norovirus infection in a transplant patient successfully treated with enterally administered immune globulin. Journal of Clinical Virology 2013;58(1)306–8 Sep 1.

[5] Glass RI, Parashar UD, Estes MK. Norovirus gastroenteritis. New England Journal of Medicine. 2009;361(18)1776–85 Oct 29.

[6] Centers of Disease Control. Emergence of new norovirus strain GII.4 Sydney–United States, 2012. *Morbidity and Mortality Weekly Report* 2013;62(3)55 Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604874/. Accessed March 30, 2019.

[7] Oka T, Wang Q, Katayama K, Saif LJ. Comprehensive review of human sapoviruses. Clinical microbiology reviews. 2015;28(1)32–53 Jan 1.

[8] Avery RK, Lonze BE, Kraus ES, Marr KA, Montgomery RA. Severe chronic norovirus diarrheal disease in transplant recipients: clinical features of an under-recognized syndrome. Transplant Infectious Disease. 2017;19(2) e12674.

[9] Roos-Weil D, Ambert-Balay K, Lanternier F, Mamzer-Bruneel MF, Nochy D, Pothier P, Avettand-Fenoel V, Anglicheau D, Snanoudj R, Bererhi L, Thervet E. Impact of norovirus/sapovirus-related diarrhea in renal transplant recipients hospitalized for diarrhea. Transplantation. 2011;92(1)61–9 Jul 15.

[10] Ghusson N, Vasquez G. Successfully treated norovirus-and sapovirus-associated diarrhea in three renal transplant patients. Case reports in infectious diseases 2018;2018.

[11] Coste JF, Vuiblet V, Moustapha B, Bouin A, Lavaud S, Toupance O, de Rougemont A, Benejat L, Megraud F, Wolak-Thierry A, Villena I. Microbiological diagnosis of severe diarrhea in kidney transplant recipients by use of multiplex PCR assays. Journal of clinical microbiology 2013;51(6)1841–9 Jun 1.

[12] van Beek J, van der Eijk AA, Fraaij PL, Caliskan K, Cransberg K, Dalinghaus M, Hoek RA, Metselaar HJ, Roodnat J, Vennema H, Koopmans MP. Chronic norovirus infection among solid organ recipients in a tertiary care hospital, the Netherlands, 2006–2014. Clinical Microbiology and Infection. 2017;23(4) 265–9 Apr 1.

[13] Brakemeier S, Taxeidi SI, Dürr M, Hofmann J, Schmidt D, Bachmann F, Gaedeke J, Budde K. Clinical outcome of norovirus infection in renal transplant patients. Clinical transplantation 2016;30(10):1283–93.

[14] Lee LY, Ison MG. Diarrhea caused by viruses in transplant recipients. Transplant Infectious Disease. 2014;16(3):347–58.

[15] Angarone M, Snydman DR. AST ID Community of Practice. Diagnosis and management of diarrhea in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical transplantation. 2019;33(9)e13550.

[16] Haubrich K, Gantt S, Blydt-Hansen T. Successful treatment of chronic norovirus gastroenteritis with nitazoxanide in a pediatric kidney transplant recipient. Pediatric transplantation 2018;22(4)e13186.

[17] Siddiq DM, Koo HL, Adachi JA, Viola GM. Norovirus gastroenteritis successfully treated with nitazoxanide. Journal of Infection. 2011;63(5)394–7 Nov 1.

[18] Gorgeis J, Sizemore C, Bashey A, Holland HK, Solomon SR, Morris LE, Solh M. Nitazoxanide is effective therapy for norovirus gastroenteritis after hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2017;23(3)S197–8 Mar 1.

[19] Tan EM, Cawcutt KA, Zomok CD, Go RS, Sia IG. Activity of nitazoxanide against viral gastroenteritis: a systematic review. International Journal of Travel Medicine and Global Health. 2017;5(4)107–12 Aug 16.

[20] Gairard-Dory AC, Degot T, Hirschi S, Schuller A, Leclercq A, Renaud-Picard B, Gourieux B, Kessler R. Clinical usefulness of oral immunoglobulins in lung transplant recipients with norovirus gastroenteritis: a case series. In Transplantation proceedings 2014;46(10)3603–5 Elsevier.

[21] https://www.cdc.gov/norovirus/about/prevention.html. Site last updated November 25 2019.