Causes and management of postrenal transplant diarrhea: an underappreciated cause of transplant-associated morbidity

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Purpose of review
This review highlights the current literature on both infectious and noninfectious diarrhea in renal transplant recipients and provides a diagnostic algorithm for the evaluation of posttransplant diarrhea.

Recent findings
Renal transplant recipients share certain predisposing characteristics for the development of posttransplant diarrhea, including a generalized immunosuppressed state and exposure to polypharmacy, most notably broad-spectrum antimicrobial therapy. The main causes of diarrhea after transplantation are infections, immunosuppressive drugs, antibiotics and other drugs. As the cause of posttransplant diarrhea varies greatly depending on several factors, recommending a single optimal diagnostic algorithm is extremely difficult.

Summary
Physicians should be familiar with common causes that result in posttransplant diarrhea. A directed approach to diagnosis and treatment will not only help to resolve diarrhea, but also prevent potentially life-threatening consequences, such as loss of the graft. Prospective studies are needed to better assess true prevalence, risk factors and complications of diarrhea by norovirus, rotavirus and adenovirus in kidney transplant patients.

Keywords
algorithm, diarrhea, infection, kidney transplantation

INTRODUCTION

Chronic diarrhea after kidney transplantation is a common complaint, often assumed by clinicians and patients to be an inevitable part of kidney transplantation. This is neglected despite its association with fatigue, increased hospitalizations and negative impacts on recipient quality of life [1▪], graft survival and higher mortality [2▪]. Steatorrhea and malabsorption may result from severe and chronic posttransplant diarrhea and induce enteric hyperoxaluria [3,4]. Oxalate nephropathy is associated with inflammation and may have devastating effects on renal graft function [3]. Renal transplant recipients share certain predisposing characteristics for the development of posttransplant diarrhea, among the more significant of which include a generalized immunosuppressed state and exposure to polypharmacy, most notably broad-spectrum antimicrobial therapy [5]. The main causes of diarrhea after transplantation are infections, immunosuppressive drugs, antibiotics and other drugs. As the cause of posttransplant diarrhea varies greatly depending on several factors, recommending a single optimal diagnostic algorithm is extremely difficult. In this article, we review the current literature regarding both infectious and noninfectious diarrhea in renal transplant recipients and provide a diagnostic algorithm for the evaluation of posttransplant diarrhea.

EPIDEMIOLOGIC IMPACT

The cumulative incidence of diarrhea has been reported to be 11.5, 17.5 and 22.6% at 1, 2 and

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KEY POINTS

- Chronic diarrhea after kidney transplantation has negative impacts on the recipient's quality of life, graft survival and mortality.
- It is important that clinicians evaluate and attempt to diagnose the cause of diarrhea and make a distinction between noninfectious and infectious causes of diarrhea in kidney transplant recipients.
- Prospective studies are needed to better assess the true prevalence, risk factors and complications of diarrhea by norovirus, rotavirus and AdV in kidney transplant patients.

3 years after renal transplantation, respectively, based on Medicare claims in the United Network for Organ Sharing registry [2▪]. However, in a survey of 4232 Scandinavian renal transplant recipients, 53% of participants reported diarrhea, whereas the incidence estimated by their physicians was only 6.9% [1▪]. This finding emphasizes the extent to which posttransplant diarrhea is often underrecognized by practitioners.

The burden of adverse gastrointestinal symptoms inversely correlates with indicators of life quality in kidney transplant recipients [6,7]. Moreover, in one large retrospective study, posttransplant diarrhea of unknown origin (noninfectious) was associated with a two-fold increase in graft loss and risk of death [2▪].

A recent study from a single transplant center in the United States reviewed the diagnostic yield of tests for diarrhea among hospitalized transplant recipients over a period of 18 months [8▪]. The majority of the diarrheal episodes had no identifiable cause and were self-limited. The most common identifiable causes included *Clostridium difficile* infection [70 (13.1%) patients], norovirus infection [21 (3.9%) patients] and cytomegalovirus (CMV) gastrointestinal infection [19 (3.5%) patients]. About 32% of individuals taking mycophenolate mofetil (MMF) or mycofenolic acid and diagnosed with diarrhea had reductions or changes in their immune suppression.

CAUSES OF DIARRHEA: GENERAL

There are relatively little data regarding the cause of posttransplant diarrhea. A large, prospective study – the Diarrhea Diagnosis Aid and Clinical Treatment (DIDACT) study – was conducted to identify the cause of posttransplant diarrhea in renal transplant recipients [9▪]. There was a resolution of diarrhea in approximately 50% of patients either by discontinuation of diarrhea-associated nonimmunosuppressive drugs or by the treatment of concurrent infections (most frequently *Campylobacter* or CMV). In the remainder of patients, changes in immunosuppressive therapy (most commonly MMF) led to remission of diarrhea in about two-thirds of cases. Thus, considered together, the data from the DIDACT study indicate that an infectious cause of posttransplant diarrhea is present in approximately 50% of cases with CMV being the most common pathogen. The next most frequent cause is related to medication use (Table 1) [5].

CAUSE OF DIARRHEA: IMMUNOSUPPRESSIVE DRUGS

Noninfectious diarrhea is not uncommon among renal transplant recipients and has been reported to increase the risk of graft loss and mortality [2▪]. Drug-induced diarrhea is a major problem as many of the immunosuppressive agents commonly used in transplantation may cause diarrhea, with the highest incidence associated with MMF. Generally,

Table 1. Causes of posttransplant diarrhea

Infection	Noninfection
Bacteria	Immunosurpressive medications
Clostridium difficile[a]	MMF[a]
Campylobacter spp.	Tacrolimus
Salmonella spp.	Cyclosporine
Bacterial overgrowth[a]	Sirolimus
Aeromonous spp.	
Escherichia coli	
Viruses	Nonimmunosuppressive medications
CMV[a]	Antibacterial
Norovirus	Antiarrhythmic
Sapobavirus	Antidiabetic
Rotavirus	Laxatives
Adenovirus	Proton pump inhibitors
	Protease inhibitors
Parasitic	Other
Giardia	GVHD[b]
Cryptosporidium	PTLD[b]
Isosopora Cyclospora	IBD
Microsporidium	Colon cancer
Entameoba	Malabsorption
	Microscopic colitis[b]
	Malakoplakia[b]

CMV, cytomegalovirus; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; PTLD, posttransplant lymphoproliferative disease.
[a]Common causes.
[b]Rare causes.
Modified from [5].

dose reduction is followed by the decrease or the disappearance of diarrhea [10].

MMF and enteric-coated mycophenolate sodium (EC-MPS) have long been implicated in posttransplant diarrhea. A recent meta-analysis identified that the relative risk of diarrhea associated with the use of MMF is 1.57 [11]. The mechanism of MMF-induced diarrhea remains unknown. One possible mechanism is that gastrointestinal epithelial cells may be partially dependent on the de-novo pathway of purine synthesis for growth and proliferation, and are therefore vulnerable to Mycophenolic acid (MPA) inhibition leading to diarrhea [12–14]. Histologically, two different morphologic patterns can be distinguished: predominant crypt distortion, also called inflammatory bowel disease-like MPA-associated toxicity and predominant apoptosis, also called graft-versus host-like MPA-associated toxicity [13]. Whether switch of immunosuppression from MMF to EC-MPS helps reduce diarrhea symptoms is a matter of debate. A recent randomized and controlled open study suggested that patients with MMF-related diarrhea who switch to EC-MPS may have a slightly, yet significant, greater chance of returning to a target MPA doses than those maintained on MMF [7]. In most centers, the switch from MPA to azathioprine (AZA) is usually avoided because of reported reduced graft survival with AZA as compared to MMF [15], although this approach is safe in the short term [16]. The U.S. Renal Transplant Scientific Registry showed that MMF reduced the relative risk of graft loss by 27% ($P < 0.001$). Death-censored graft survival at 4 years was significantly better among MMF-treated versus AZA-treated patients [17]. The recent systemic review and meta-analysis showed that the overall summary estimate showed a significantly increased risk of skin cancer (especially squamous cell carcinoma) in relation to AZA exposure (1.56, 95% confidence interval 1.11–2.18) [18].

The use of tacrolimus may be associated with diarrhea in 29–64% of patients depending upon the dose and duration of drug usage [2▪,19]. The mechanism by which calcineurin inhibitors cause diarrhea remains unclear, although it is hypothesized that a macrolide structure may result in stimulation of the intestinal motilin receptors. Most of the tacrolimus-associated gastrointestinal side-effects have a mild course and rarely require drug discontinuation [20]. A recent study in renal transplant recipients has reported a decrease in the incidence of gastrointestinal symptoms, including diarrhea, after conversion to a daily, extended release formulation of tacrolimus [21▪▪].

Sirolimus causes self-limiting diarrhea in 14–42% of treated patients. The mechanism by which sirolimus causes diarrhea is poorly understood, although drug-induced jejunal villous atrophy [22] and a structural homology with the promotility macrolide class of drugs have been proposed as possible explanations [23].

In up to one-third of patients, antithymocyte globulin (ATG) and anti–T cell antibody (OKT3) therapies are both associated with diarrhea, which predictably lasts for 3–4 days and resolves spontaneously [24]. One mechanism by which these antibodies may cause diarrhea is by activating T cells to release tumor necrosis factor which then interferes with sodium ion absorption and also disrupts the intestinal mucosal barrier [25].

CAUSE OF DIARRHEA: INFECTIONS

Diarrhea is commonly infectious [26] and the microbes usually responsible are CMV and *C. difficile*, but the literature describes a wide range of organisms in solid organ transplant (SOT) recipients [27▪]. In the first month following transplant, patients are not yet completely immunosuppressed and infection with opportunistic pathogens is relatively uncommon. After the first few months post-transplant, opportunist pathogens become more evident as a cause of infection. It is important to remember that the individual is also being exposed to common community-associated pathogens (e.g. norovirus and enteropathogenic bacteria). *C. difficile*, CMV and norovirus are important causes of diarrhea in this population, and management should be focused on these causes [5].

Chronic norovirus infection has only recently emerged as one of the leading infectious causes (approximately 17–26% of severe posttransplant diarrhea) of posttransplant diarrhea in kidney transplant recipients [4,28]. This finding suggests that numerous cases of posttransplant diarrhea in the past may have been incorrectly solely ascribed to toxicity of immunosuppressive drugs, leading to diagnostic misconceptions and inappropriate treatments. In these patients, the course of norovirus infection tends to be more complicated, with up to 94% having chronic diarrhea and 81% having episodes of diarrhea-induced acute renal failure [4,29]. Immunocompromised patients typically have a biphasic illness in the course of norovirus. During the initial acute phase, patients will often have a more classical illness with nausea, vomiting, significant diarrhea (10–20 watery stools per day), abdominal pain and sometimes fever. This acute phase is frequently followed by a chronic phase, when patients can experience cycles of relatively normal stools followed by periods of more poorly formed stools [4].

CMV is one of the most common infectious complications affecting SOT patients and is associated with significant morbidity and occasional mortality [30]. The most common target organ is the gastrointestinal tract, causing CMV gastrointestinal disease. In a recent study of 1427 SOT patients, 7.2% developed CMV disease, of which approximately one-third had gastrointestinal involvement [31]. Risk factors for CMV disease include seronegative recipients of seropositive organs (D+/R–) and, to a lesser extent, seropositive recipients (D–/R+), lymphodepleting antibodies and more potent immunosuppressive regimens. There appears to be a direct correlation between CMV infection and the level of posttransplant immunosuppression [32,33]. The most significant risk factor for the development of CMV disease is seropositive donor/seronegative recipients gastrointestinal involvement that occurs in up to 40% of patients [30,31,34].

Data are limited on the epidemiologic and clinical features of rotavirus infection in SOT patients. However, the severe course of rotavirus infections is becoming increasingly recognized in both pediatric and adult SOT patients. In one study, rotavirus infection was diagnosed in 1.5% of SOT recipients, with most cases occurring in pediatric patients (63%) and in those who received a liver transplant [35].

In adults, adenovirus (AdV) viremia is commonly observed in the early posttransplant course (6.5–22.5%) [36], and may be associated with gastrointestinal symptoms in 10% of the cases. The epidemiology of AdV is similar in the SOT population and in the general population. A wide range of clinical syndromes associated with AdV in SOT recipients has been described, with the most clinically severe infections involving the transplanted organ or disseminated disease [37].

C. difficile is the most common cause of nosocomial diarrhea and accounts for most infectious diarrhea within the first months after transplantation [20,38]. The incidence of *C. difficile* infection (CDI) in transplanted patients has been reported to be approximately 3.5–4.5% in adult renal transplantation patients [39,40]. Risk factors that are specific to the SOT population include age above 55 years, use of ATG, retransplantation and the type of organ transplanted, with the highest rate among liver recipients [27▪,41]. The single most important risk factor for the development of CDI is recent antibiotic use. Among antibacterials, the fluoroquinolones are associated with the highest risk [42,43]. CDI has a significant effect on mortality of SOT recipients, with mortality rates between 2.3 and 8.5%, and is an independent risk for death (adjusted odds ratio 2.48, 2.22–2.76) [44].

Among parasities, the protozoan or metazoan are most common. Gastrointestinal infection due to microsporidia has been recorded in patients with SOT who experienced diarrhea and weight loss [45]. *Enterocytozoon bieneusi* is by far the most frequent strain found in kidney transplant recipients [46,47]. *Cryptosporidia* (*Cryptosporidia parvum* and *Cryptosporidia hominis*) are intracellular protozoans known to lead to severe acute diarrhea, chronic diarrheal illness and extraintestinal infection in transplanted patients [48].

DIAGNOSIS AND THERAPEUTIC STRATEGY

It is important to evaluate and attempt to diagnose the cause of diarrhea in a transplant recipient. It is imperative that the clinician makes a distinction between noninfectious and infectious causes of diarrhea. Another important factor to consider in the SOT recipient is the consequence of unnecessary reduction in immune-suppressive medications to try and manage diarrhea. However, this decision is never taken lightly as it carries the burden of potential allograft loss (Figure 1) [20,29].

The gold standard for *C. difficile* detection is the cell-based cytotoxicity assay. However, most laboratories use the easier, less expensive and more rapid fecal enzyme immunoassays or real-time PCR test. These tests have high sensitivity and specificity (90%) for the detection of CDI [49,50]. Transplanted patients can be asymptomatic carriers of *C. difficile*, but most often they develop diarrhea, intestinal obstruction, abscesses or toxic megacolon. In general, initial treatment of SOT includes fidaxomicin, metronidazole or vancomycin, with vancomycin preferred for cases of more severe infection [51▪▪,52]. Only about 70% of patients will respond to treatment with metronidazole; persistent and more severe cases will require oral vancomycin. The greatest challenge for toxigenic *Clostridium* infections remains the prevention and treatment of relapsing and refractory forms. In transplant recipients, it has been estimated that up to 20% of cases will have at least one relapse [27▪,40,41]. Fidaxomicin, ramoplanin and tigecycline are newer antibiotics that are effective for the treatment of severe or recurrent disease [53]. There have also been recent encouraging results from the use of human monoclonal antibodies against *C. difficile* toxins A and B [54]. A newer area of interest is the use of fecal microbiota transplantation (FMT) in the management of refractory CDI. FMT is a procedure that involves the instillation of donor feces, which have been processed into the colon or duodenum of the recipient. However, there are limited data on the use

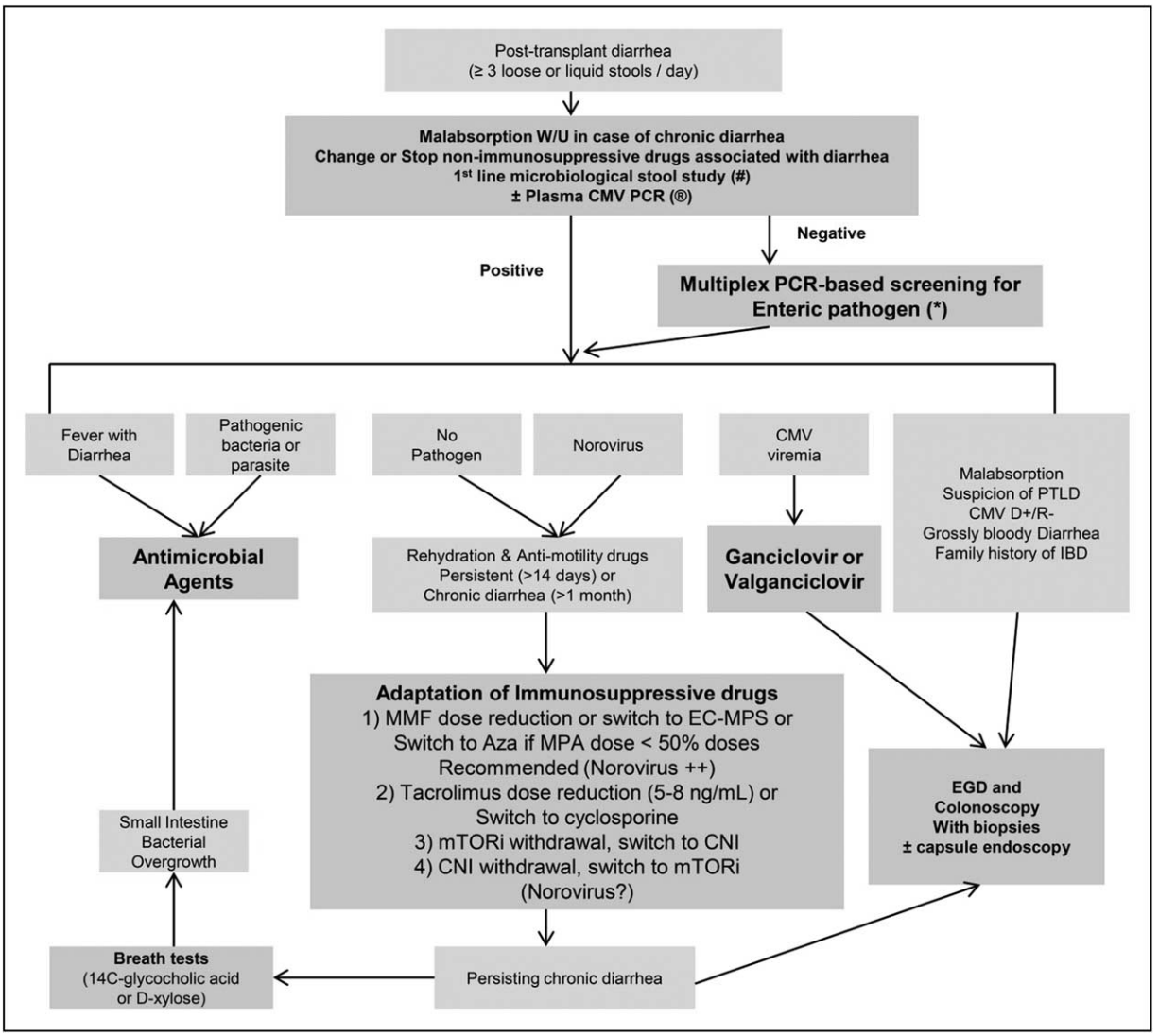

FIGURE 1. Diagnostic and therapeutic strategy for postrenal transplant diarrhea (modified from [20,29]). #The first-line microbiologic stool investigations consist of standard stool cultures for pathogenic bacteria, examinations for parasites and fungi, *C. difficile* toxin assay and quick tests for rotavirus, adenovirus and norovirus. ®In case of fever, CMV D+/Rj serologic status, cytopenia, liver enzymes studies, and plasma CMV Q-PCR should be performed. *Campylobacter* species, enteropathogenic and enterotoxigenic *Escherichia coli*, *Shigella* species, *Salmonella* species, *Yersinia*, *Clostridium difficile*, *Cryptosporidium*, *Enterocytozoon bieneusi*, Enteric viruses (rotavirus, adenovirus, norovirus and enterovirus).

of FMT in the transplant population [55▪▪,56]. The high success rate of FMT is promising; however, the high adverse effect rate is concerning and warrants further study.

The recent availability of fumagilin has been a major breakthrough in the treatment of microsporidia-related diarrhea, treatment that may lead to sustained clearance of *E. bieneusi*, with minimal reduction in immunosuppression. The use of fumagilin may, however, be limited because of drug-induced thrombocytopenia [46,47]. Cryptosporidiosis is generally diagnosed by visualization of oocysts in the stool. Immunofluorescent assays and ELISA have a sensitivity and specificity approaching 100%, which is significantly better than the traditional modified acid-fast stains [57]. Specific therapies directed toward cryptosporidium do not exist. In meta-analysis, there was no observed difference between therapy with nitazoxanide or paromomycin and placebo for immunosuppressed patients with cryptosporidiosis [58].

The diagnosis of tissue-invasive CMV disease is suggested by the presence of CMV viremia. Many patients with CMV colitis will have evidence of CMV replication in the blood via PCR, although approximately 15% will not [59]. A systematic

Table 2. Laboratory methods for cytomegalovirus colitis diagnosis

Laboratory method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Biopsy	23.2	100	100	23.2
CMV IgM and or elevation in IgG	63.7	99.5	99.5	65.3
Conventional culture	42.6	99.8	98.7	65.3
Shell Vial assay	42.8	98.4	87.6	86.9
CMV pp65 Ag	83.7	96.3	95.8	85.9
PCR	91	92.1	94.5	87.4
Real-time PCR	85.4	77.7	57.2	93.9

NPV, negative predictive value; PPV, positive predictive value.
Modified from [60▪▪].

review analyzed 18 studies to determine the most accurate means to diagnose CMV-associated colitis (Table 2) [60▪▪]. Diagnostic value of the serology may limited for the determination of an active infection in the adult population and be beneficial in the diagnosis of the new onset infections. The disadvantages of conventional culture are lower sensitivity, long incubation period, the insufficient virus quantity and the high rate of false negativity. Shell Vial Assay is a quicker method compared with the conventional culture method, but has a low sensitivity rate. CMV pp65 Antigen Test can be applied to blood and cerebrospinal fluid. The PCR method can be performed with whole blood, plasma and leukocytes. Ultimately, the definitive diagnosis of CMV gastrointestinal disease generally relies on endoscopic evidence of gastrointestinal involvement [61]. CMV is confirmed on histopathology with characteristically swollen cells containing 'owl's eye' intranuclear inclusions, or by immunohistochemical staining for pp65. Although this method is accepted as a 'gold standard' for the diagnosis of CMV active disease, viral inclusions cannot be easily seen, for they are very rare [62]. In general, patients with CMV colitis can be managed with intravenous ganciclovir (GCV) or oral valganciclovir (valGCV) [30,63▪▪]. Intravenous GCV is often used if there is concern for inadequate absorption of oral valGCV (e.g. in patients with vomiting and diarrhea) or early in the treatment of proven CMV colitis [64,65]. Optimal duration of antiviral therapy depends on the patient's clinical and virologic responses, not on a fixed period. Before antiviral therapy is stopped, the following three criteria should be met: the treatment was given for at least 2 weeks, clinical symptoms have resolved and viral load is no longer detectable, if initially detected [63▪▪]. Because recurrent CMV disease has been reported in 15–35% of SOT recipients with tissue-invasive CMV disease, many experts recommend the use of valGCV for secondary prophylaxis for 30–90 days after successful treatment (Table 3) [29,63▪▪,66].

Table 3. Major infectious causes and treatment in postkidney transplant diarrhea

Infectious causes	Recommended management
Bacteria	
Clostridium difficile	First episode: metronidazole 500 mg three times per day for 10–14 days
	Severe disease: vancomycin oral four times per day for 10–14 days
	fidaxomicin 20 mg two times per day for 10 days
	First relapse: same for first episode
	Second relapse: vancomycin taper with pulse
	≥ third relapse: consider fecal microbiota transplantation, prolonged oral vancomycin
Viruses	
Cytomegalovirus	Oral valganciclovir
	IV ganciclovir (if any concern for decreased absorption)
Norovirus	Rehydration
	Antimotility drugs
	Consider reduction in immunosuppressive drugs

Modified from [29].

Diagnosis of norovirus by PCR can be run on stool, vomitus, foods and environmental specimens [67]. A commercially available assay is the U.S. Food and Drug Administration-approved xTAG Gastrointestinal Pathogen Panel (Luminex Corp., Austin, Texas, USA), which allows for simultaneous detection of three viruses (norovirus G-I/G-II, rotavirus A and AdV 40/41), nine bacteria and three parasites. This assay has not yet been systematically tested in the immunocompromised population [68]. Supportive care is the first line of treatment with an emphasis on replenishment of fluids and electrolytes [69,70▪▪,71]. At present, the most effective strategy to manage norovirus infection is the reduction of immunosuppression [4]. It is important to know that norovirus is the key factor in the induction of posttransplant diarrhea, whereas MMF plays a critical role in the chronicity of the symptoms by preventing both the clearance of the virus and the repair of intestinal epithelium [20]. Chronic norovirus-related diarrhea remains a major concern often leading to MMF discontinuation, which has been associated with an increased risk of rejection. Several strategies have been tried in limited numbers of patients: oral or intravenous immunoglobulin, breast milk, ribavirin and nitazoxanide. A more recent cohort study failed to demonstrate improvements in total time to resolution of diarrhea, length of hospital stay or cost of hospitalization with the administration of oral human immunoglobulins [69]. At present, no vaccines are available for norovirus, although several candidate vaccines are under investigation. Because of the lack of specific treatment or vaccination, prevention plays an especially important role in norovirus infection control, especially hand hygiene and environmental sanitization [67]. Centers for disease control and prevention recommends proper hand washing with soap and water for at least 20 s, with the optional use of hand sanitizers as an adjunct but not a substitute [64].

In diagnosis of rotavirus, immune-based assays are most routinely used to rapidly detect rotavirus antigens in stool samples [72]. Other diagnostic methods such as cell culture, real time-PCR and electron microscopy remain as reference methods because of their high specificity and sensitivity [72]. Currently, no antirotaviral therapies are available, and the treatment of rotavirus infection in SOT patients is mainly supportive [73]. Contact precautions are recommended to prevent viral transmission. Contaminated surfaces should be disinfected by 95% ethanol or other alcohol-containing disinfectant, because general disinfectants (e.g. bleach) are ineffective [74]. In the United States, two live oral vaccines against rotavirus currently are licensed for use: RotaTeq (RV5) and Rotarix (RV1) [74]. Because both vaccines are live attenuated vaccines, transplant candidates should receive the vaccines before transplantation; their use posttransplant is contraindicated [75].

AdV can be diagnosed by viral culture, direct antigen detection, histopathology and PCR [9▪,37]. Although culture has traditionally been considered the gold standard for diagnosing AdV, it may take up to 28 days to develop cytopathic effects, and serotypes associated with diarrhea do not grow well in cell culture [76,77]. Direct antigen systems have been developed to detect many of the common serotypes, but their clinical utility in immunocompromised patients is unknown [77,78]. Whenever possible, detection of AdV from patient samples should be correlated with histopathology and clinical presentation to distinguish AdV disease from asymptomatic infection [77]. Limited data are available on the optimal treatment of AdV infections. Generally, diarrhea caused by AdV can be managed with supportive care and a reduced immunosuppressive regimen [77]. Diligent infectious control measures, including contact and droplet precautions, can help prevent infections in the SOT population [79].

There are limited data on a diagnostic approach, and the various epidemiologic studies have identified varying pathogens as a cause of diarrhea. The prospective Diarrhea Diagnosis Aid and Clinical Treatment study evaluated a stepwise prospective diagnostic and therapeutic flow chart that aimed to eliminate nonimmunosuppressive drug toxicity causative factors and treat infectious causes before adjusting the immunosuppressive regimen [9▪]. This study identified a specific infectious cause in 30 of 108 (28%) patients, with *Campylobacter jejuni enteritis* and CMV colitis being the most common. The most striking finding of this landmark study was that in approximately 50% of the patients, diarrhea resolved without any change in immunosuppressive therapy and only one-third of the 39 patients diagnosed with bacterial overgrowth responded to antibiotics. Initially, all patients with diarrhea should have their medications reviewed for potential causes of diarrhea, and unnecessary agents should be stopped and followed by specific testing for different causes of the diarrhea (Figure 1) [20,29]. The testing that was undertaken included bacterial culture, assessment for ova and parasites, PCR for CMV and *C. difficile* and stool lactoferrin. The next steps were breath test for bacterial overgrowth, reduction in immune suppression and colonoscopy. If these tests are negative and the diarrhea persists, empiric antidiarrheal medications, probiotics and/or lactose-free diet should be tried. There remain several

arguments definitively in support of the need to perform esophagogastroduodenoscopy and colonoscopy with biopsies to investigate persistent diarrhea after kidney transplantation. First, intestinal ulcerations because of large bowel posttransplant lymphoproliferative disorder may be accompanied by exudative enteropathy and chronic diarrhea. Second, CMV colitis with concurrent negative CMV plasma PCR has been reported [80]. Third, the presence of severe duodenal villous atrophy may prompt clinicians to change more rapidly the immunosuppressive regimen, regardless of the cause (drug-related or infectious) [81]. Finally, post transplantation de-novo inflammatory bowel disease occurs up to 10 times more frequently than in the general population [82]. Treatment of diarrhea, with hydration and focused use of antimicrobials or changes in immune suppression, is of the utmost importance. The optimization and adjustment of the immunosuppression in patients with persistent posttransplant diarrhea is an unresolved issue that warrants prospective studies. In most centers, the first change in immunosuppression consists of MMF dose reduction or switching to EC-MPS, followed ultimately by MMF-EC-MPS withdrawal [4,83] if symptoms persist.

CONCLUSION

Physicians should be familiar with common causes that result in posttransplant diarrhea. A directed approach to diagnosis and treatment will not only help to resolve diarrhea, but also prevent potentially life-threatening consequences such as loss of the graft. Prior to implicating an immunosuppressant medication as the culprit, a meticulous evaluation for other possible causes of diarrhea should always be conducted. Infectious agents and the concomitant use of other diarrhea genic medications such as proton-pump inhibitors, antibiotics and diuretics must first be excluded. Prospective studies are needed to better assess in kidney transplant patients the true prevalence, risk factors and complications of diarrhea by norovirus, rotavirus and AdV. Such studies will help guide the care of these patients and provide appropriate prevention and prompt diagnosis. Development of effective vaccines and antiviral therapies for these common viruses will likely improve patient and graft survival.

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There are no conflicts of interest.

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- ■■ of outstanding interest

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