



Diarrhea in a Patient With Combined Kidney-Pancreas Transplant

Krunal Amin, Vinay Choksi, Samira S. Farouk, and Matthew A. Sparks

Clinical Presentation

A 47-year-old man with acute worsening of chronic diarrhea was admitted to the hospital with a serum creatinine of 2.2 mg/dL from a baseline of 1.6 mg/dL. Medical history was remarkable for type 1 diabetes mellitus (diagnosed 8 years prior) complicated by kidney failure requiring kidney-pancreas transplant (cytomegalovirus [CMV] IgG-positive donor; CMV IgG-negative recipient) 3 years before presentation. The patient reported having long-standing diarrhea with 5 to 8 bowel movements per day for 25 years. Prior workup for his chronic diarrhea, including colonoscopy and testing for celiac disease, was unremarkable. In the previous 3 months, the frequency of his bowel movements increased to 10 to 12 loose stools per day.

On admission, the patient's vital signs were a temperature of 36.4 °C, blood pressure 146/89 mm Hg, and heart rate 84 beats per minute. He had lost 15 kg (from 87 kg to 72 kg) over 6 months. Physical examination revealed a nontender kidney allograft in the right lower abdominal quadrant and an arteriovenous fistula in the right upper extremity with a thrill. Medications at the time of admission included tacrolimus 2 mg AM 1 mg PM, enteric-coated mycophenolate sodium 720 mg twice a day, and prednisone 5 mg daily. Results of initial laboratory evaluation are summarized in Table 1. Complete blood count and liver function tests were within normal limits. Kidney ultrasound showed patent transplant vasculature without hydronephrosis.

- What is the differential diagnosis of diarrhea following solid organ transplantation?
- What should be included in the diagnostic evaluation of posttransplant diarrhea?
- What is the most likely explanation for this patient's diarrhea?
- How should this patient be managed?

Discussion

What is the differential diagnosis of diarrhea following solid organ transplantation?

Diarrhea is a frequent complication after transplantation, with 3-year posttransplant cumulative incidence reported to be around 22%. It has been associated with worse clinical outcomes, including acute kidney injury (AKI), supratherapeutic tacrolimus

and mycophenolate levels, and decreased graft and patient survival.¹ Causes of diarrhea in a patient with a solid organ transplant are outlined in Box 1. The most common causes of diarrhea in patients after transplantation include infections, immunosuppressive medications, and antibiotics.^{2,3}

Noninfectious diarrhea in patients after transplantation is commonly due to immunosuppressive drugs, with the highest incidence associated with mycophenolic acid.¹ Notably, patients with combined kidney-pancreas transplants are at a greater risk for rejection and thus have higher exposure to immunosuppression compared to those with other solid organ transplants. Infectious diarrhea following kidney transplantation is frequently attributed to *Clostridium difficile*, CMV, and norovirus.

What should be included in the diagnostic evaluation of diarrhea in patients after transplantation?

It is critical to evaluate the cause of diarrhea in a kidney transplant recipient, as identification of a specific etiology may allow for a focused treatment.⁴ Current guidelines for evaluation of diarrhea in solid-organ transplant recipients from the Infectious Disease Community of Practice of the American Society of Transplantation start with stopping any nonimmunosuppressive medications that may cause diarrhea—such as proton pump inhibitors, H₂ agonists, and oral hypoglycemics—and first-line microbiological testing including *Clostridium difficile* polymerase chain reaction (PCR), CMV PCR, and multiplex PCR if available (Fig 1). If these tests return negative results, second-tier microbiological testing should include stool PCR for viral pathogen, ova, and parasite evaluation; giardia and cryptosporidium enzyme immunoassay; and breath test for bacterial overgrowth.⁵ Figure 1 outlines a stepwise diagnostic algorithm with additional considerations if this further testing also gives negative results.

In this patient, tacrolimus level was found to be within desired therapeutic limits (7 ng/mL) and first-line microbiological testing was negative. Stool ova and parasite and stool culture were also negative. Fecal multiplex PCR was positive for sapovirus.

What is the most likely explanation for this patient's diarrhea?

Given the positive stool PCR, the most likely diagnosis is sapovirus infection resulting in acute worsening of chronic diarrhea.

Several recent case reports have described sapovirus infections leading to chronic, severe diarrhea in patients after kidney transplant.^{6,7} The prevalence of posttransplant

Table 1. Pertinent Laboratory Parameters

Parameter	Result	Reference Range
Chemistry studies		
Sodium, mEq/L	141	135-145
Potassium, mEq/L	3.5	3.5-5.1
Chloride, mEq/L	114	98-108
Carbon dioxide, mEq/L	19	20-31
SUN, mg/dL	41	8-20
Creatinine, mg/dL	2.2	0.5-0.9
Glucose, mg/dL	121	65-100
Calcium, mg/dL	9	8.5-10.4
Phosphorus, mg/dL	2.3	2.5-4.5
Magnesium, mg/dL	2.1	1.6-2.6
Infectious		
CMV DNA, IU/mL	<200	
BK virus DNA, copies/mL	<500	

Abbreviations: CMV, cytomegalovirus; SUN, serum urea nitrogen.

sapovirus is unknown. Sapoviruses are nonenveloped, single-stranded positive-sense RNA viruses that belong to the *Caliciviridae* family along with norovirus. Diagnosis is typically made via real-time PCR or multiplex PCR testing of a stool sample.⁸ For example, one multiplex PCR assay tests for a variety of stool pathogens including parasites (*Cryptosporidium*, *Cyclospora cayetanensis*, *Entamoeba histolytica*, *Giardia lamblia*), bacteria (*Campylobacter*, *Shigelloides* species, *Salmonella*, *Vibrio* species, and *Yersinia enterocolitica*, among others), and viruses (eg, adenovirus, astrovirus, norovirus, rotavirus, and sapovirus).⁹

How should this patient be managed?

To date there have been no therapies shown to be effective in treating sapovirus infections. Previous reports have demonstrated symptom relief with intravenous fluids, antimotility agents such as loperamide, and reduction of immunosuppression to promote the immune system to clear the viral infection. In addition, tacrolimus levels should be closely monitored, as enterocyte damage can disrupt the P-glycoprotein efflux pump, leading to increased serum tacrolimus levels. Limited case studies have also suggested nitazoxanide as a potential therapeutic agent. Nitazoxanide is an antimicrobial agent that exerts its effect on viruses by activating natural antiviral defenses and inhibiting cellular pathways leading to viral replication. Currently, evidence for its efficacy is limited to case reports.^{6,7}

Reducing mycophenolate dosage in response to post-transplant diarrhea is a common practice and has been shown to have some efficacy in patients with persistent diarrhea regardless of cause. However, caution should be used when opting for this treatment strategy, as reductions in mycophenolate dose have also been shown to be associated with rejection and decreased allograft survival.¹⁰ Other possible treatment options include switching mycophenolic acid to an enteric-coated mycophenolate or azathioprine, both of which have been associated with a lower risk of developing posttransplant diarrhea.

Box 1. Etiologies of Diarrhea in Patients Posttransplantation

Infectious

- Bacteria
 - *Clostridium difficile*
 - *Campylobacter* spp.
 - *Salmonella* spp.
 - *Bacterial overgrowth*
 - *Aeromonas* spp.
 - *Escherichia coli*
- Viruses
 - CMV
 - Norovirus
 - Sapovirus
 - Rotavirus
 - Adenovirus
 - Enterovirus
- Parasitic
 - *Giardia*
 - *Cryptosporidium*
 - *Isospora*, *Cyclospora*
 - *Microsporidium*
 - *Entamoeba*

Noninfectious

- Immunosuppressive medications
 - Mycophenolate
 - Tacrolimus
 - Cyclosporine
 - Sirolimus
- Nonimmunosuppressive medications
 - Antibacterial
 - Antiarrhythmic
 - Antidiabetic
 - Laxatives
 - Proton pump inhibitors
 - Protease inhibitors
- Other
 - GVHD
 - PTLD
 - IBD
 - Colon cancer
 - Malabsorption

Adapted from Shin and Chandraker² (Wolter Kluwer Health, Inc) with permission of the copyright holder, and based also in part on Pant et al.⁹ Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; PTLD, posttransplant lymphoproliferative disease.

This patient was managed with intravenous fluids and reduction of his mycophenolate dosage from 720 mg twice a day to 360 mg twice a day. By hospital day 3, his serum creatinine had returned to baseline with interval improvement of acute diarrhea. At 3 weeks follow-up, the patient showed marked clinical improvement, with 2 to 3 kg of weight gain and complete resolution of his acute-on-chronic diarrhea.

Final Diagnosis

Sapovirus infection presenting with diarrhea and AKI in the setting of volume depletion.

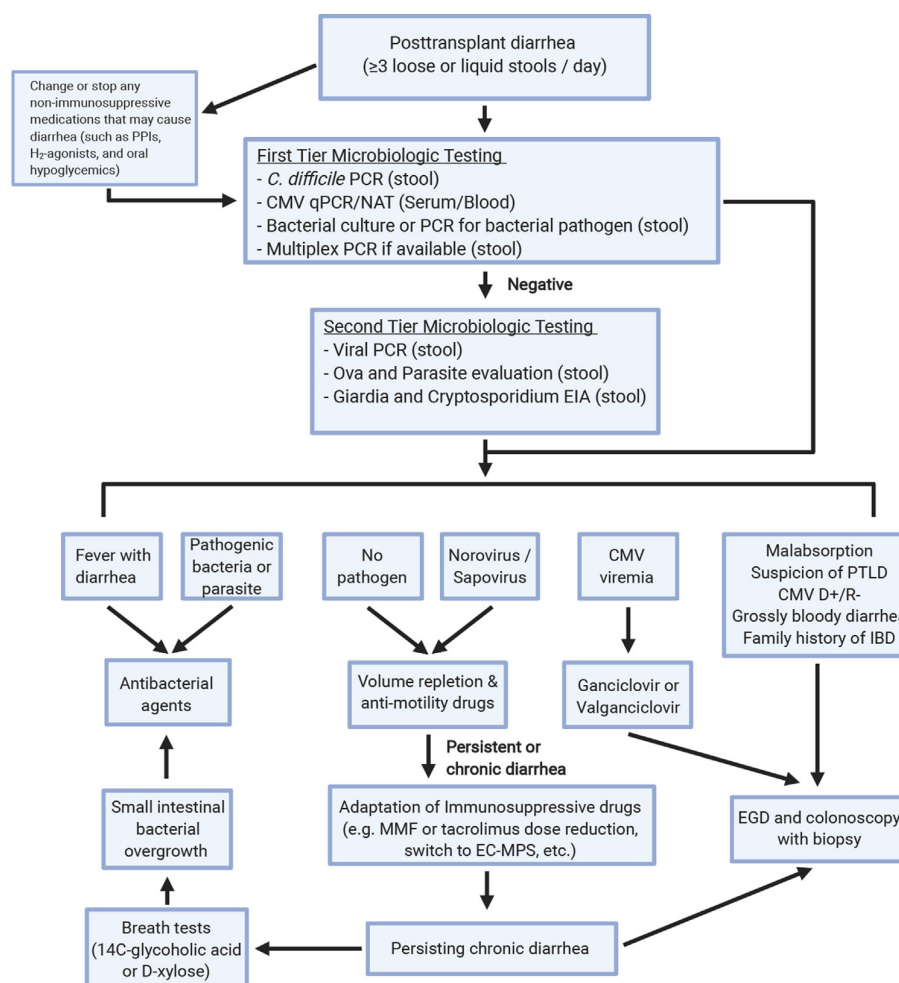


Figure 1. Diagnostic strategy for post-kidney transplant diarrhea. First-tier testing includes testing for *C. difficile*, CMV qPCR/NAT (quantitative PCR/nucleic acid testing), stool bacterial culture or PCR, and multiplex PCR if available. Multiplex PCR includes testing for *Campylobacter*, *Shigelloides* species, *Salmonella*, *Vibrio* species, *Yersinia enterocolitica*, *Escherichia coli* including enteropathogenic and enterotoxigenic species, *Cryptosporidium*, *Cyclospora cayetansis*, *Entamoeba histolytica*, *Giardia lamblia*, and enteric viruses (adenovirus, astrovirus, norovirus, rotavirus, and sapovirus). Figure created with Bio-Render.com based on information in Angarone et al.⁵

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