Management of diarrhea in solid organ transplantation

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Purpose of review
Diarrhea is a common complaint in solid organ transplant recipients. We review both infectious and noninfectious causes of diarrhea and their management.

Recent findings
Diagnostics for diarrhea have now commonly incorporated multiplex gastrointestinal panels that provide rapid testing and identification of pathogens. The rate of Clostridium difficile in the transplant population has increased and fidaxomicin is now recommended as the therapy of choice for first episode and recurrences where available. Oral vancomycin remains an alternative. Norovirus is important to rule out in cases of chronic diarrhea. Nitazoxanide has shown mixed results when used as norovirus therapy. SARS-CoV-2, despite being a respiratory virus, can infect gut epithelium and present with diarrhea. Noninfectious causes especially mycophenolate-related as well as inflammatory bowel disease should be in the differential especially when no infectious cause has been identified.

Summary
A detailed history, diagnostics including molecular testing and endoscopy, and targeted therapies for infectious causes are the mainstay for management of diarrhea in the transplant recipient.

Keywords
bacterial infection, *Clostridium difficile*, cryptosporidium, multiplex gastrointestinal panel, norovirus

INTRODUCTION

Diarrhea is a common presenting feature of many illnesses in solid organ transplant (SOT) patients and can have infectious and noninfectious causes. Approximately 20% of SOT patients experience at least one episode of diarrhea within the first 3 years of transplant [1]. Diarrhea could lead to dehydration, malnutrition, weight loss, and fluctuation in levels of calcineurin-inhibitors, which can lead to significant morbidity and mortality. Diarrhea is defined as change in stool frequency (>3 loose or liquid stools per day), or change in consistency. Acute diarrhea usually lasts less than 2 weeks, while chronic diarrhea usually lasts more than 4 weeks [2]. Diarrhea lasting between 2 and 4 weeks can be termed prolonged or persistent diarrhea.

In organ transplant recipients, diarrhea can be the result of a systemic illness or a primary gastrointestinal cause. Therefore, the differential diagnosis is wide and can include infectious (viral, bacterial, parasitic) or noninfectious [drug induced, posttransplant lymphoproliferative disease (PTLD), GVHD]. Identifying the cause of diarrhea is critical for management and to avoid complications.

CLINICAL CONSIDERATIONS

In transplant recipients presenting with diarrhea, a detailed history of the patient's presenting complaint should be obtained including onset, frequency, exacerbation by foods, nocturnal symptoms, high volume or low volume diarrhea, fever and weight loss, similar presentations in the past, similar symptoms in close contacts, diet details, environmental exposure, medication history, antibiotic exposure. For example, acute onset diarrhea may represent bacterial infection, diarrhea while on antibiotics therapy suggests either antibiotic-associated diarrhea, or *Clostridioides difficile* associated diarrhea (CDAD). A history of travel can suggest various bacterial causes of traveler's diarrhea. Weight loss with chronic

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KEY POINTS

- A detailed history of the diarrheal illness can often point to clues regarding etiology.
- Multiplex gastrointestinal panels have a high sensitivity and specificity for infectious causes of diarrhea in transplant recipients.
- CDI infection has high recurrence rates in transplant recipients and fidaxomicin is the treatment of choice where available to prevent recurrences with vancomycin as an alternative therapy.
- Nitazoxanide has been used with mixed results for persistent norovirus infection.
- Diarrhea is commonly due to noninfectious causes including immunosuppressive medication.

diarrhea can suggest organic causes such as PTLD, CMV enteritis, or chronic norovirus infection.

DIAGNOSTIC CONSIDERATIONS

Diagnosis of the cause of diarrhea is important in SOT given the wide differential diagnosis and the high risk of complications. The approach usually is to start with stool culture, stool for ova and parasite, and *C. difficile*. Stool culture, however, has low yield [3]. A sample of more than 13 000 patients who had stool culture submitted as part of a diarrhea workup found only 1.47% positivity [4] whereas PCR-based testing was superior to conventional stool culture in a study of pediatric transplant patients [5]. Multiplex gastrointestinal PCR panels (e.g., BioFire Filmarray; BioFire Diagnostics, Salt Lake City, Utah, USA), which include most common viral and bacterial causes of infectious diarrhea, can increase the diagnostic yield with high sensitivity (>94%) and specificity (>97%) [6]. Interestingly, a study of stool testing with multiplex PCR (Biofire Filmarray GI Panel) in 142 asymptomatic kidney transplants showed that 30% had a pathogen detected [7]. Pathogens were primarily *C. difficile*, enteropathogenic *Escherichia coli*, and norovirus. However, the detection of these pathogens was not predictive of subsequent diarrheal illness. Another study of longitudinal stool specimen collection in 71 kidney transplant recipients showed reduced microbiota diversity in those with diarrhea compared to those with no diarrhea, suggesting a role for gut dysbiosis [8]. For diagnosis of *C. difficile*, a *C. difficile* GDH (glutamate dehydrogenase) test can be used to detect the presence of *C. difficile* in stool but does not determine whether it is toxigenic [9]. Further, an enzyme immunoassay can be done for toxins A and B or a PCR for toxin genes confirms toxin-producing *C. difficile*. If any two are positive in the appropriate clinical context, it is considered diagnostic. If the diarrhea persists and all the previous testing is negative, it is especially important in SOT to consider sending specific PCR for viruses that may not be present in common stool PCR panels, like sapovirus (if not already tested), adenovirus, norovirus, and rotavirus. Other investigations for diarrhea include blood culture which can be sent in case of fever associated with diarrhea. CT of the abdomen is useful for structural disease, lymphadenopathy, and evaluation of colitis. The last step is to perform endoscopy with biopsy (Fig. 1). Ulcerations may be seen that suggest CMV or HSV. Biopsies should be evaluated for autoimmune diseases, for example, inflammatory bowel disease, lymphoproliferative disorders, viral cytopathic effect, and immunohistochemical staining for CMV.

SYMPTOMATIC MANAGEMENT

Acute management should include intravenous (i.v.) fluids and electrolyte replacement [10]. Hypovolemic shock may require admission to the ICU and aggressive resuscitation. Definitive management depends on the underlying cause. Antimotility agents may be cautiously used but should be avoided in cases of potential inflammatory diarrhea especially when fever or blood in stool is present [2]. The use of probiotics in transplant recipients is controversial and probiotic use with undiagnosed causes of diarrhea should be avoided. A recent Cochrane review highlighted the lack of good quality evidence for the use of probiotics in transplant recipients to improve gut health [11]. Therapies directed towards specific pathogens are discussed below.

SELECTED CAUSES OF DIARRHEA

Bacterial causes of diarrhea

Bacterial diarrhea is usually acute and the diagnosis is made either by stool culture or PCR. Blood culture can be positive in severe cases. Unlike in immunocompetent individuals where bacterial diarrhea is self-limited, such a presentation in a transplant recipient usually warrants treatment. In case of severe disease, empiric therapy should be initiated to cover common bacterial pathogens, including Salmonella, Campylobacter, Shigella, and *E. coli*. Azithromycin or Ciprofloxacin could be used. Risk factors and therapies for common bacterial (excluding *C. difficile)* causes of diarrhea are summarized in Table 1. Note that bacterial overgrowth can also lead to diarrheal illness after transplant.

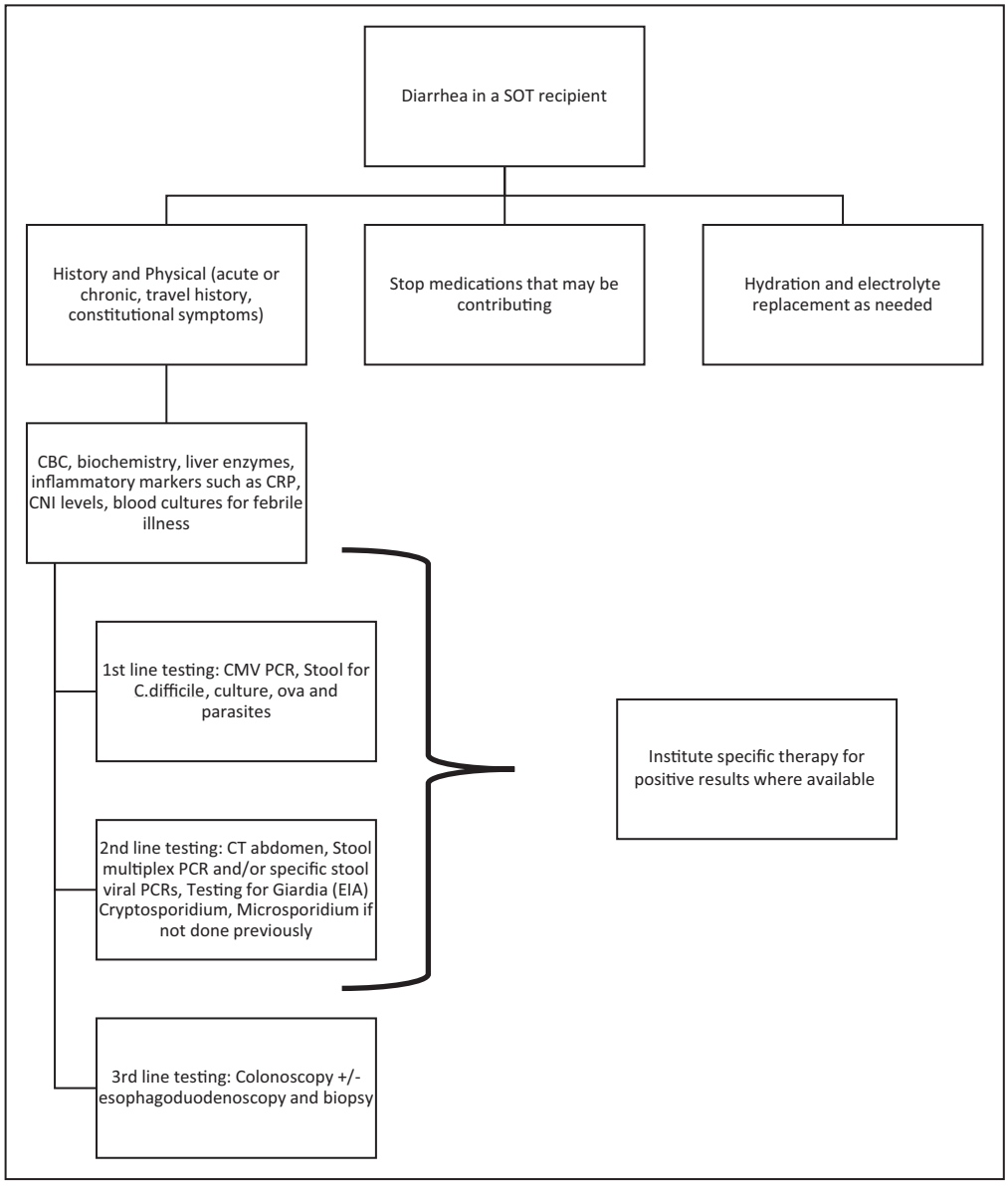

FIGURE 1. Suggested investigations for diarrhea in a transplant recipient.

Clostridioides difficile infection

C. difficile is more common in organ transplant recipients than the general population due to multiple factors including the use of immunosuppression, greater contact with healthcare systems, and increased use of antibiotics and proton-pump inhibitors. The incidence of infection ranges from 3 to 13% [12,13]. In a population-based study of more than 10 000 organ transplant patients, the incidence of CDI was 6.8% and overall 90-day mortality was 16.8% [14▪▪]. This study also showed an increasing incidence of CDI over time in the transplant population. In an international cohort of 191 organ transplant patients with CDI, the recurrence rate was approximately 12% with higher rates in lung transplant than other organ groups, and progression to severe disease occurred in 34.6% of transplant recipients [15]. Risk factors for recurrence were severe CDI during the first episode and metronidazole monotherapy. The 2021 IDSA (Infectious Diseases Society of America) guidelines recommend oral fidaxomicin as first line treatment of CDI with oral vancomycin as an acceptable alternative [16]. Multiple randomized controlled trials have shown it has a similar cure rate compared to vancomycin in treating CDI, but with better outcomes in preventing recurrence [17,18]. A retrospective study demonstrated that fidaxomicin had greater effectiveness than vancomycin in immunocompromised populations including the organ transplant population [19▪▪].

Table 1. Bacterial causes of diarrhea (excluding *Clostridioides difficile)*, with risk factors and suggested therapy

Organism	Risk factor	Treatment
Salmonella sp.	Undercooked poultry/eggs, reptiles, travel	Ciprofloxacin or ceftriaxone
Campylobacter jejuni	Undercooked poultry, unpasteurized milk, travel	Azithromycin
Shigella sp.	Contaminated food/water, travel, daycare exposure	Ciprofloxacin or azithromycin
ETEC (Enterotoxigenic *E. coli*)	Travel to endemic areas (traveler's diarrhea)	Ciprofloxacin or azithromycin
EAEC (Enteroaggregative *E. coli*)	Chronic/persistent diarrhea in immunocompromised	Ciprofloxacin
Yersinia enterocolitica	Undercooked pork, iron overload, transfusion	Doxycycline + gentamicin or ceftriaxone (if severe)
Vibrio cholerae	Contaminated water in endemic regions	Doxycycline or azithromycin
Aeromonas sp.	Contaminated water/seafood, fresh produce	Ciprofloxacin
Plesiomonas shigelloides	Freshwater or seafood exposure.	Ciprofloxacin

However, in another study in 415 high-risk patients including transplant recipients, there was no difference in CDI recurrence at 4 weeks between the two therapies [20]. Thus, if fidaxomicin is not available, vancomycin is an effective alternative. Oral metronidazole is no longer recommended as monotherapy for CDI due to higher failure rates [16,21].

For fulminant CDI, i.v. metronidazole plus high-dose oral vancomycin is recommended. Surgical consultation is warranted in this situation.

Prevention of recurrence is a major concern in SOT. Fidaxomicin is also the treatment of choice for recurrent CDI although a tapering course of oral vancomycin is also acceptable. Adjunctive i.v. bezlotoxumab (a mAb against *C. diff* toxin B) has been shown to be effective in reducing recurrence at 12-weeks [22]. However, in December 2024, bezlotuxumab was discontinued in the United States by the manufacturer.

Another option for recurrent CDI is fecal microbiota transplant (FMT) [23]. While no RCT has been conducted on the use of FMT in SOT, retrospective analyses have reported that efficacy and safety outcomes of FMT in 92 SOT recipients with recurrent CDI were comparable to those in immunocompetent individuals [24].

Viral causes of diarrhea

Cytomegalovirus

CMV infection can be a cause of acute or chronic diarrhea. A recently systematic review identified 311 cases of CMV-related gastrointestinal disease [25]. CMV enteritis may occur with or without the detection of DNAemia in peripheral blood and can present up to several years after transplant [26]. Diagnosis is generally made with endoscopy which shows classic ulcerations in the gastrointestinal tract. However, macroscopic mucosal lesions are not required to make a formal diagnosis. Instead, CMV should be documented in tissue biopsies by histopathology and immunohistochemistry to confirm the diagnosis [27]. A positive CMV PCR on biopsy is not helpful since CMV may reactivate locally secondary to damaged mucosa without being the cause of diarrhea. Treatment consists of decreasing immunosuppression and administering (val)ganciclovir. Oral antivirals can be used once diarrhea subsides. CMV enteritis should be treated until complete symptom and DNAemia resolution [26,28].

Norovirus and sapovirus

Acute norovirus infection in an immunocompetent individual can be self-resolving and generally requires supportive care including hydration. However, in transplant recipients, chronic norovirus infection is an important cause of ongoing diarrhea and weight loss. A review of 280 norovirus cases in SOT and stem cell transplant patients showed that duration of diarrhea was a median 10 days but ranged from 1 to 2100 days [29▪▪]. Diagnosis can be made with norovirus PCR or via a multiplex gastrointestinal panel that incorporates norovirus testing. Although there are no specific antivirals that target norovirus, nitazoxanide and immunoglobulin preparations have been used off-label for chronic infection [30]. Nair *et al.* [31] reviewed 79 transplant patients with norovirus diarrhea. Of these, 40% received nitazoxanide, 35% had reduction in immunosuppression, and 9% received i.v. immunoglobulin [31]. Chronic norovirus improved in 74% of patients and especially in those where immunosuppression was adjusted. Data regarding effect of

nitazoxanide are mixed, with some studies showing benefit and others showing no effect [32,33]. Patients may relapse after initial improvement and one study showed a relapse rate of 35% [33].

Sapovirus causes similar illness to norovirus, although less common, Diagnosis usually by stool PCR or multiplex gastrointestinal panel, treatment usually supportive, with hydration and reduction of immunosuppression, nitazoxanide and immunoglobulin have been used with mixed results [34,35].

Adenovirus

Adenovirus is important cause of diarrhea in SOT especially in pediatric, intestinal and liver transplant recipients [36]. Adenoviruses are classified into seven species/serotypes (A-G), each species having multiple genotypes. Gastrointestinal tract disease is primarily caused by serotype F and genotypes 40, 41 although other serotypes have also been implicated. The presentation usually varies from mild self-resolving illness to severe hemorrhagic enterocolitis that can mimic rejection in an intestinal transplant recipient. The diagnosis is usually made by blood/stool PCR; however, biopsy is necessary in a patient with intestinal transplant to rule out rejection, management is conservative and usually necessitates reduction of immunosuppression. There is no FDA approved antiviral for adenovirus; however, cidofovir has been used in multiple case series especially with disseminated adenovirus disease, the use however is limited by nephrotoxicity. Brincidofovir is an oral lipid cidofovir that has in-vitro activity against adenovirus. It's use in diarrheal disease is limited because it can also cause significant diarrhea [37].

Human astrovirus

Human astroviruses are single-stranded RNA viruses belonging to the family Astroviridae and can cause diarrhea in SOT patients [38]. Presentation ranges from self-limited to severe disseminated disease including encephalitis. Diagnosis usually made by specific RT-PCR and this pathogen is generally not included in commonly used multiple gastrointestinal panels. Management is by reduction of immunosuppression. A recent study reported successfully treating Astrovirus in a liver transplant patient by stopping mycophenolate [39].

SARS-CoV-2

Diarrhea may be a prominent feature of SARS-CoV-2 infection and can occur in more than 50% of transplant patients with clinical illness [40]. Infection of the intestinal epithelium can occur and viral RNA has been detected in gastrointestinal tissue with subsequent activation of intraepithelial $CD8^+$ T-cells leading to an inflammatory process [41]. Therapy is directed towards stopping viral replication with antivirals such as remdesivir and nirmatrelvir/ritonavir.

Other viruses

Rotaviruses can cause diarrhea worldwide and can be detected using immune-based assays. Other uncommon viral causes of diarrhea that have been described in transplantation include human bocavirus, torovirus, and cosaviruses. Bocavirus was described in fecal samples from 10 kidney transplant patients in Brazil as well as a symptomatic diarrheal illness in a pediatric liver transplant recipient that had spontaneous resolution [42,43]. A Canadian outbreak of viral gastroenteritis including in immunocompromised found torovirus to be a causative agent [44]. Cosavirus is also described as a persistent cause of diarrhea in a lung transplant recipient [45]. There are numerous other viruses associated with gastroenteritis including picronabirnavirus, salivirus, bufavirus, Aichivirus, Saffold virus [46]. However, diagnosis for these viruses is based on specific viral PCRs and there are no specific therapies.

Parasitic causes of diarrhea

Cryptosporidiosis

Cryptosporidium is a protozoan transmitted through water or food exposure. It is increasingly recognized as a cause of persistent or chronic diarrhea in SOT, leading to significant morbidity. In a study of 47 SOT patients, mainly kidney transplant recipients, cryptosporidiosis was associated with a high rate of AKI, and three patients died [47]. The diagnosis is usually delayed and made by stool PCR. Historically, diagnosis was often missed because standard stool O&P has low sensitivity unless special stains were used. Management is challenging and consists of nitazoxanide which is an antiparasitic approved for use in immunocompetent patients for Cryptosporidiosis; however, in SOT recipients it is associated with high failure and relapse rates. There is no consensus on appropriate treatment. A combination of nitazoxanide with other therapies including azithromycin, rifaximin or paromomycin has been used [48]. Other off-label therapies attempted include spiramycin and quinolones.

Intestinal microsporidiosis

Microsporidia are spore-forming intracellular parasites (related to fungi). Of these, *Enterocytozoon bieneusi* is the most common cause of intestinal microsporidiosis in SOT recipients. While it causes acute self-resolving diarrhea in immunocompetent patients, in SOT patients it can cause chronic watery diarrhea, malnutrition, and weight loss. Diagnosis of

microsporidiosis can be made by stool microscopic examination and staining specimens with a modified trichrome stain; however, stool PCR is more sensitive and specific. Management of *E. bieneusi* includes decreasing immunosuppression and using antimicrosporidia treatment regimens. However, the only effective antimicrosporidia agent, fumagillin, is not commercially available. Nitazoxanide has been tried but has a high failure rate. In a recent study of 154 SOT patients with *E. bieneusi*, the authors compared three strategies: decreased immunosuppression, nitazoxanide, and fumagillin [49▪▪]. Although all treatment approaches had comparable clinical remission, the fumagillin group achieved the highest stool clearance and lowest relapse rate. The availability of oral fumagillin remains a challenge in many parts of the world. A less common cause of intestinal microsporidiosis is *Encephalitozoon intestinalis*. Albendazole has been used to treat this species with some success.

Noninfectious causes

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is the most common malignancy after solid organ transplantation. It can involve the gastrointestinal tract and present with chronic diarrhea [50]. PTLD usually arises from EBV-infected B cells that persist and proliferate due to immunosuppression but can also be unrelated to EBV especially if the patient is several years posttransplant. Risk factors include type of transplant (with intestinal transplant having the highest risk) and an EBV seronegative recipient receiving an organ from a seropositive donor [51]. Diagnosis is often suspected with rising EBV viral load in the blood, although there is no clear cutoff value. The diagnosis usually made by colonoscopy with biopsy [52]. Management usually starts with reducing or stopping immunosuppression. However, this is not always effective. Rituximab anti-CD20 mAb has shown about 35% response rate. In more severe or refractory cases, chemotherapy may be needed [53].

Drug-induced diarrhea

A careful medication review should be made whenever evaluating a patient with unexplained diarrhea in SOT. A common medication that can usually cause diarrhea is mycophenolate. Management of mycophenolate-induced diarrhea is usually done either by decreasing the dose of mycophenolate, changing the preparation, or switching to azathioprine [54]. However, diarrhea is also described with tacrolimus, cyclosporine, and sirolimus. Antibiotics can also induce diarrhea that is unrelated to *C. difficile* infection.

Other noninfectious causes

New onset inflammatory bowel disease (IBD) can also present with chronic unexplained bloody diarrhea. A negative workup for infectious causes should raise the suspicion of IBD, especially in patients with liver transplant [55]. The diagnosis usually made by colonoscopy with biopsy. In addition, microscopic colitis should also be considered in the differential and referral to a specialist in primary inflammatory gastrointestinal disorders is warranted. Graft-vs-host disease is extremely rare in SOT with one study showing an incidence of 1.2% in liver transplantation [56▪▪]. However, it can present with skin rash, fever, diarrhea, and cytopenias [57]. Diagnosis is usually made by clinical presentation and histological finding of recipient target tissue invasion by donor lymphoid cells. Unfortunately, the prognosis is extremely poor with a very high mortality rate [56▪▪]. Management usually starts with increasing the immunosuppression.

CONCLUSION

In summary, diarrhea in a transplant patient represents a common symptom and should be thoroughly investigated. Definitive management depends on the causative infectious agent. However, noninfectious causes continue to feature prominently and should be considered once infectious workup is complete. Future research is especially needed to determine effective therapies for viral and parasitic diarrheal illness.

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Conflicts of interest

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