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**Diagnosis and Management of Diarrhea in Solid Organ Transplant Recipients:
Guidelines from the American Society of Transplantation Infectious Diseases
Community of Practice**



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Abstract:

These guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention and management of diarrhea in the pre- and post-transplant period. Diarrhea in an organ transplant recipient may result in significant morbidity including dehydration, increased toxicity of medications and rejection. Transplant recipients are affected by a wide range of etiologies of diarrhea with the most common causes being *Clostridioides* (formerly *Clostridium*) *difficile* infection, cytomegalovirus (CMV) and norovirus. Other bacterial, viral and parasitic causes can result in diarrhea but are far less common. Further, non-infectious causes including medication toxicity, inflammatory bowel disease, post-transplant lymphoproliferative disease (PTLD) and

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malignancy can also result in diarrhea in the transplant population. Management of diarrhea in this population is directed at the cause of the diarrhea, instituting therapy where appropriate and maintaining proper hydration. Identification of the cause to the diarrhea needs to be timely and focused.

Introduction:

In the United States it is estimated that over 150 million outpatient visits, 500,000 hospitalizations and 5000 deaths result from acute gastroenteritis.[1] The prevalence of diarrhea in solid organ transplant (SOT) recipients has been estimated to vary from 20-50%.[4-6] Diarrhea in this population is a potentially debilitating condition that can lead to dehydration, potentiation of medication toxicity, organ rejection and death.[7] Other effects of diarrhea include the impact on the recipient's quality of life, repeated hospitalization, and weight loss.[8] While many of the etiologies for diarrhea are similar between the transplant and non-transplant populations, there are some major differences between these populations, namely a higher incidence of opportunistic pathogens (e.g. *Cryptosporidium* or cytomegalovirus), higher likelihood to develop chronic diarrhea (e.g. norovirus), medication-induced diarrhea (e.g. mycophenolate) and the development of graft-versus-host disease.[9]

For those providing care for transplant recipients, it is important to diagnose the specific cause of diarrhea in the SOT recipient in order to provide appropriate and targeted therapy to prevent the complications diarrhea causes in this population. This guideline will provide the transplant provider with information on the presentation, etiology, diagnosis and treatment of diarrhea in the transplant recipient.

Presentation of Diarrhea in SOT Recipients

The clinical presentation of diarrhea in the transplant recipient is similar to the non-transplant recipient. The Infectious Diseases Society of America and the World Health organization define diarrhea as an increased frequency of bowel movements (≥ 3 per day) and change in consistency of the stool (soft to liquid).[9] Diarrhea is also classified based on the duration of symptoms: “acute” diarrhea <14 days, “persistent” 14-29 days and “chronic” diarrhea >30 days.[9] Specific characteristics of the diarrhea may help point toward an etiology. Fever associated with diarrhea may indicate a viral cause (e.g. norovirus, cytomegalovirus [CMV]), invasive bacterial cause (e.g. *Campylobacter*) or rarely a parasitic infection (*Entamoeba histolytica*). Visible blood in the stool and abdominal pain may be associated with invasive bacteria (e.g. *Yersinia*, *Shigella*, *Salmonella*), CMV or *Entamoeba*. Non-bloody, watery diarrhea with or without vomiting typically signifies viral infection or medication induced diarrhea.[10, 11] See Table 1 for common etiologies of diarrhea in SOT recipients.

Epidemiology and Etiology of Diarrhea in SOT Recipients

General gastrointestinal (GI) symptoms including diarrhea occur frequently in transplant recipients.[2, 5] Among transplant recipients, the prevalence of diarrhea is between 20-50%.[2, 5, 8] A multi-year database review of renal transplant recipients in the United States estimated the three-year cumulative incidence of diarrhea to be about 22%.[12] The etiologic spectrum of diarrhea in SOT recipients is wide and includes infectious and non-infectious causes.[12-16] The most commonly identified etiology of diarrhea is infectious with medication-induced diarrhea a very common cause as well.[13-15] Diarrhea in SOT recipients results in higher rates of morbidity

related to graft dysfunction and elevations in immune suppressant drug levels with potential toxicity of these agents and hospitalization, especially the development of renal toxicity caused by calcineurin inhibitors in the setting of dehydration caused by diarrhea.[15]

A few studies have focused on defining the etiology of post-transplant diarrhea in SOT recipients. Large population and database studies have identified female gender, the use of tacrolimus and the combination of tacrolimus and mycophenolate to be significantly associated with the development of diarrhea in the transplant recipient.[2, 8, 12] The Diarrhea Diagnosis Aid and Clinical Treatment (DIDACT) study from Belgium attempted to identify the etiology of post-transplant diarrhea in renal transplant recipients.[16] One-hundred and eight patients presenting with diarrhea over a two-year period were evaluated using a stepwise diagnostic approach. The most common cause of the diarrhea was medications (73%) with 60% of these cases identified as immunosuppression-mediated diarrhea.[16] An infectious cause was identified in 64% of patients with bacterial overgrowth occurring in 36%, bacterial infection in 20% and CMV infection in 7%.[16] A single center report in the United States reviewed the diagnosis of diarrhea among hospitalized transplant recipients over the course of an 18-month period.[14] A majority of the diarrheal episodes had no identifiable etiology and were self-limited. Of the identifiable causes of diarrhea, the most common etiologic agent was *C. difficile* infection (13.1%) followed by norovirus infection (3.9%) and CMV gastrointestinal infection (3.5%). Bacterial enterocolitis and parasitic causes of diarrhea were rare (<1% of cases). Approximately one-third of patients taking mycophenolate mofetil (MMF) or mycophenolic acid (MPA) required dosage reductions after being

diagnosed with diarrhea. Another interesting finding is the simultaneous presentation of pyelonephritis and the development of diarrhea, which may account for up to 10% of causes of diarrhea.[14, 16]

A study from Turkey compared the etiology of diarrhea in SOT recipients versus immune competent individuals.[13] An infectious cause was identified in 77% of the diarrheal episodes in transplant recipients with the most common pathogens being parasites, *Giardia* (17%) and *Cryptosporidium* (13%). CMV, *C. difficile* and pathogenic bacterial infections were also identified as causes of the diarrhea. The predominant non-infectious cause for the diarrhea was related to medication use and included MMF, antibiotics, colchicine and laxatives. CMV infection and *Cryptosporidium* were more frequently identified in the transplant population versus the immune competent controls.[13] Clinicians should be aware of regional differences in the etiology of diarrhea in SOT recipients, and diagnostic and treatment strategies should be individualized for the specific practice region.

Non-infectious causes of diarrhea are very common among solid organ transplantation and must be considered as an etiology. However, this ascribed cause is a diagnosis of exclusion after other causes are ruled out. All of the commonly used immune suppressant agents may cause diarrhea with the highest incidence associated with mycophenolate mofetil (MMF).[10, 11, 17] The diarrhea induced by both MMF and MPA is dose dependent and is secondary to direct enterocyte damage.[10, 18] The calcineurin inhibitors (cyclosporine and tacrolimus) can also cause diarrhea. The diarrhea caused by tacrolimus and cyclosporine may be related to the macrolide effects of tacrolimus, which result in increased gastrointestinal

motility.[19] Diarrhea is an infrequent adverse effect of sirolimus and everolimus as well.[20]

Other non-infectious causes of diarrhea include graft-versus-host disease (GVHD) and post-transplant lymphoproliferative disorder (PTLD). GVHD is seen as a cause of diarrhea primarily in small bowel transplant recipients but is a very rare cause of diarrhea in other organ transplants.[21, 22] Symptoms of GVHD include chronic diarrhea, abdominal pain and bleeding along with fever, rash and pancytopenia. PTLD is a heterogeneous group of lymphoproliferative disorders ranging from benign to malignant lymphoid disease and is most commonly associated with Epstein-Barr virus (EBV) infection of B-lymphocytes.[23] The gastrointestinal tract is the most frequent extranodal site for PTLD and any portion of the GI tract can be involved.[24, 25] Symptoms of PTLD of the GI tract include chronic diarrhea, weight loss, protein losing enteropathy, anorexia and abdominal pain.[25]

Recommendations:

1. A detailed clinical history should be obtained on all SOT recipients presenting with diarrhea **(strong, moderate)**
2. Clinicians must have heightened suspicion for infection as a cause of diarrhea in SOT recipients **(strong, moderate)**.
3. Clinicians should be aware of regional differences in the etiology of diarrhea in SOT recipients, and diagnostic and treatment strategies should be individualized for the specific practice region **(strong, high)**.

Infectious Etiologies of Diarrhea in Solid Organ Transplant Recipients

The infectious etiology of post-transplant diarrhea is similar to that found in the immune competent individual, but there are some distinct differences related to immune suppression, the net state of immune suppression and chronic antibiotic use.[13] Transplant recipients are at risk of infection with common community associated pathogens as well (norovirus, enteropathogenic bacteria) but may be more susceptible to symptomatic infection than immunocompetent individuals. After the first few months post-transplant, opportunistic pathogens become more evident as a cause of infection. A list of potential causes of diarrhea, diagnosis and treatment in this patient population is in Table 2. The following sections will focus on a review of the more common causes of diarrhea in transplant recipients.

***Clostridioides difficile* (see *C. difficile* section of 4th edition of the AST ID Guidelines)**

Clostridioides difficile is a spore-forming anaerobic bacterium that causes diarrhea by the production of 2 exotoxins, toxin A and toxin B. These toxins trigger a cytotoxic response on the colonic mucosa, which results in neutrophil infiltrate and cytokine production resulting in diarrhea. The incidence rates for *C. difficile* infection (CDI) in transplant recipients vary from <1% to 23% and varies based on the organ transplanted with the lowest incidence in kidney transplant recipients and the highest incidence in liver and lung transplant recipients. [14, 26-33] A 2009 registry study found an incidence of 2.7% for recipients of SOT admitted to hospitals within the United States.[31] There has been an increase in the incidence and severity of CDI that has been seen in both the general population and the SOT population, which may be secondary to the emergence of the North American pulse field gel electrophoresis type 1/restriction enzyme analysis type B1/ PCR-ribotype 027

(NAP1/BI/027) strain.[34] A longitudinal study at a single transplant center in Austria evaluated the CDI rates from 1996 to 2005.[32] The cumulative incidence for CDI during this time period was 1.74%. The rates of CDI increased over time from 3 episodes/year (1996-2001) to 7.5 episodes/year (2002-2004) to 15 episodes/year in 2005.[32] A second longitudinal study reviewed the incidence of CDI in SOT recipients in Quebec over a 10 year period.[27] The overall incidence of CDI increased from 4.5% in 1999 to a peak of 21.1% in 2005 with a subsequent reduction to 9.5% in 2010. The increased incidence in 2005 was likely related to an outbreak of *C. difficile* in Quebec. The peak frequency of CDI was six to ten days post-transplant and liver recipients had the highest risk of infection.[27]

The most important risk factor for the development of CDI is antibacterial exposure. Risk factors that are specific to SOT population include age >55 years, use of antithymocyte globulin, re-transplantation and the type of organ transplanted. The highest rate of CDI is among liver recipients.[27, 28] .

CDI in transplant recipients has also been associated with increased rates of transplant organ dysfunction, higher rates of other infections (CMV, pneumonia), longer hospital stay and higher costs.[27, 29, 31] *C. difficile* infection in SOT recipients has been associated with CMV co-infection. A case series of nine cases of co-infection identified a delay in the diagnosis of CMV infection and a high mortality rate (33%).[35] CDI has a significant effect on mortality of SOT recipients, with mortality rates between 2.3-8.5% and is an independent risk for death (aOR 2.48; 2.22-2.76).[27, 29, 31, 32]

Norovirus

Noroviruses are non-enveloped, single-stranded RNA viruses belonging to the family *Caliciviridae*. [36] There are five major genogroups, GI through GV, with genogroups GI, GII, and GIV being associated with human disease and a majority of recent outbreaks being caused by the GII.4 genotype. [37, 38] Noroviruses are one of the leading causes of diarrhea, accounting for >90% of non-bacterial infectious diarrhea and an estimated 19-21 million cases in the United States annually. [39, 40]

Norovirus infection can occur year round, but outbreaks frequently occur during the winter months. [41, 42] Transmission of norovirus occurs via the fecal-oral route, via inhalation of aerosols from vomitus or contact with contaminated environmental surfaces. [42, 43] The risk of transmission from SOT recipients with chronic disease has not been studied extensively.

Norovirus has increasingly been recognized to be a common cause of both acute and chronic diarrhea among SOT recipients. Patients will have a typical acute norovirus infection, associated with nausea, vomiting and diarrhea, but SOT recipients frequently develop chronic shedding associated with prolonged, sometimes intermittent, diarrhea that may be debilitating and associated with development of renal insufficiency, morbidity and rarely fatal complications. [36, 44-50] Viral shedding may be very prolonged in transplant recipients, with a median of 289 days (97-898 days). [51, 52]

There are few studies evaluating the incidence and course of norovirus infection in the transplant recipient. [51-53] One of the largest studies evaluating norovirus in particular found an incidence of 18.4%. Of the individuals with norovirus, 94% had

chronic diarrhea and, when compared with other causes of diarrhea, were more likely to have weight loss and require a more frequent reduction in immunosuppressive agents. A majority of these patients developed acute renal failure secondary to the diarrhea.[51] Case series have demonstrated prolonged episodes of shedding and intermittent diarrhea.[52, 53] Chronic shedding in the immunocompromised individual leads to genetic mutation and viral evolution, which may increase antigenicity and promote viral persistence.[52]

Cytomegalovirus (see CMV section of 4th edition of AST ID Guidelines)

Human CMV is a dsDNA virus, which is a member of the herpes virus family and is one of the most significant pathogens affecting transplant recipients. CMV infection results in a multitude of direct (CMV syndrome and tissue-invasive disease) and indirect effects including allograft dysfunction and rejection, increased susceptibility to other opportunistic infections and death. The most significant risk factor for the development of CMV disease is the donor and recipient serostatus prior to transplantation with the highest risk of infection seen in those that are CMV negative recipients of a CMV seropositive donor organ. Other risk factors include the net level of immune suppression, acute rejection, advanced age and poor allograft function in renal recipients.[54, 55]

The spectrum of events that is caused by CMV is diverse and includes asymptomatic DNAemia, CMV syndrome (fevers, fatigue and DNAemia) and tissue-invasive disease. Gastrointestinal infection is the most common tissue-invasive disease in SOT recipients and includes colitis, esophagitis, gastritis, and enteritis.[54] Often the signs might be subtle, with epigastric distress manifested by some degree of

dyspepsia or discomfort. More typical symptoms of CMV colitis are abdominal pain, diarrhea and fever.[56] CMV infection of the GI tract has also been associated with other causes of colitis including *C. difficile* infection and inflammatory bowel disease.[57-59] CMV can also cause hepatitis, cholangitis, cholangioathy and pancreatitis [37, 60, 61] which may or may not be accompanied by diarrhea.

Diagnostic Evaluation

It is important to evaluate and attempt to diagnose the cause of diarrhea in a transplant recipient. Identification of a specific pathogen or cause for the diarrhea allows for focused treatment and monitoring for improvement. Traditionally stool testing for a microbial pathogen has been of low yield in both immunocompetent and immunocompromised patients. Surveillance data of all persons presenting with acute diarrhea to emergency departments in the United States identified an enteric bacterial pathogen in 17% of those tested.[9] In the immunocompromised population a few studies have demonstrated the low yield of broad testing for bacterial pathogens. A single center study in the United States found an identifiable pathogen in 27% of SOT recipients evaluated for diarrhea.[14] A study at a large cancer center with broad testing of stool in hematopoietic stem cell recipients with diarrhea found similar results with a positive result in 28%.[62] A targeted approach that focuses on the clinical presentation of diarrhea and epidemiologic factors can increase the likelihood of identifying a causative pathogen.[9] For the transplant recipient, this focused approach may miss serious infections and lead to complications related to untreated infection or may lead to unnecessary reductions in immune suppression that may result in rejection or damage to the allograft. While a rapid evaluation of

the cause of diarrhea is essential for SOT recipients, existing data suggest that a more informed, staged approach may be appropriate.

There is limited data on a specific diagnostic approach best suited for the transplant recipient with diarrhea. The DIDACT study attempted to define a stepwise approach to the diagnosis of diarrhea.[16] Using this stepwise approach, a diagnosis for the diarrhea was found in a majority of the individuals in the study. The approach started with the cessation of any non-immune suppressive medications that could cause diarrhea followed by specific testing for different causes of the diarrhea. 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 a breath test for bacterial overgrowth, reduction in immune suppression, colonoscopy and finally empiric antidiarrheals and/or probiotics. It is interesting to note that even in patients diagnosed with a bacterial diarrhea or bacterial overgrowth, not all responded to treatment and a second diagnosis was made.[16] Use of colonoscopy to identify abnormal mucosa has been utilized in transplant recipients with chronic diarrhea. Retrospective reviews have identified colonoscopic or histopathologic abnormalities in 20% to 45% of patients.[63, 64] Colonic inflammation was the most common finding with many of the cases being related to CMV colitis, drug toxicity or *de novo* inflammatory bowel disease.[63, 64] A cost analysis of diagnostic tests performed on SOT recipients with diarrhea identified that a step-wise approach to testing can reduce costs without compromising diagnostic yields. First stage evaluation included testing stool for *C. difficile* PCR and food-borne pathogens and serum or whole blood testing for CMV by PCR. Second stage evaluation included stool testing for norovirus PCR, evaluation for parasites and possible endoscopy.[65]

Newer, and potentially more accurate, culture independent diagnostic testing methods such as enzyme immunoassays and nucleic acid amplification tests (NAAT) may increase the yield of stool testing. A recent study evaluated seven multiplex polymerase chain reaction (PCR) platforms for the detection of enteric pathogens. These tests were performed on patients with severe diarrhea suspected to be of infectious etiology and compared the results with traditional microbiologic methods.[66] Assessment of the stool using the PCR techniques was three times more likely to identify a pathogen versus traditional techniques (72% vs. 26%). Norovirus and *Campylobacter* were the most frequently identified pathogens by molecular testing. The control arm consisting of asymptomatic transplant and non-transplant patients identified asymptomatic carriage of *E. coli*, *Campylobacter* and norovirus.[66] It should be noted that the sensitivity for each pathogen varied across the various PCR assays and was often inferior to single probe assays. Further validation and assessment of the cost effectiveness of these culture independent diagnostic tests need to be performed prior to implementing these tests into everyday clinical practice. However, most clinical labs are implementing these assays and results from studies of transplant patients should be forthcoming.

A reasonable approach to the diagnosis of diarrhea in transplant recipients is a stepwise approach focusing on drug effects, common and worrisome pathogens, bacterial overgrowth and colonic pathology (PTLD, GVHD, IBD, etc.) (Figure 1). All patients with diarrhea should have their medications reviewed for potential causes of diarrhea and unnecessary agents should be stopped. Patients should then have stool sent for testing for *C. difficile* and bacterial pathogens, and whole blood or serum CMV viral load assessed. Tissue invasive disease caused by CMV can be

presumed by the presence of diarrhea and an elevated serum CMV plasma or whole blood viral load; however, definitive diagnosis of tissue invasive CMV is made by performing upper and lower endoscopy and examining tissue specimens for histopathologic changes and immunohistochemical staining for the presence of CMV.[55] Sometimes CMV viral load can be negative by blood test, but gastrointestinal exam positive, more often in those who are CMV seropositive.[67] If these tests are negative, testing for norovirus (and other viral pathogens) by PCR and common parasitic infections (Cryptosporidium and Giardia EIA) should be performed as well as testing for bacterial overgrowth with a ¹⁴C-glycocholic acid or D-xylose breath test should be considered. It is reasonable to reserve ova and parasite examination for those patients with refractory diarrhea or clear exposure to high risk regions for less common parasites. If no diagnosis is made and the diarrhea persists, modification in immune suppressive agents should be undertaken and studies for more unusual pathogens such as *Microsporidia*, *Cystoisospora*, *Cyclospora*, and other ova and parasites should be performed. Depending on the degree and persistence of diarrhea, colonoscopy should be considered if initial diagnostic tests are negative; upper endoscopy should be restricted to patients with symptoms of the upper GI tract. These procedures may help in diagnosis of inflammatory conditions, medication effects on the bowel mucosa and unusual causes of diarrhea (e.g. *Mycobacterium avium* infection).[68] If all tests are negative and the diarrhea persists, empiric antidiarrheal medications, probiotics and/or lactose free diet should be tried. Prospective studies validating such an approach will optimize this proposed algorithm. For regions outside of the United States where different pathogens may be present more frequently, a different diagnostic approach should be considered.

Recommendation

1. Initial testing for SOT recipients with diarrhea should include testing for *C. difficile* and bacterial pathogens in the stool and CMV PCR testing in the serum (**strong, moderate**)
2. All patients with diarrhea should have their medications reviewed for potential causes of diarrhea and unnecessary agents should be stopped (**Strong, moderate**)
3. SOT recipients with fever and bloody diarrhea should be evaluated for invasive enteropathogens and CMV (**strong, moderate**)
4. Persistent diarrhea should prompt testing for norovirus and parasitic causes for diarrhea. (**strong, moderate**)
5. Colonoscopy with or without biopsy should be performed on SOT recipients with chronic diarrhea that have had a negative infectious evaluation *or* for those not responding to targeted therapy (**strong, moderate**)
6. If available, multiplex PCR testing for stool pathogens should be performed on all SOT recipients presenting with diarrhea (**weak, moderate**)

Treatment

General considerations for treatment

In most immune competent individuals the diarrheal illness is self-limited and treatment is generally not required or recommended.[9] In general, SOT recipients with diarrhea and an identifiable pathogen require treatment. Treatment of the causative pathogen can hasten recovery, decrease potential damage to the allograft and prevent recurrences of disease. Treatment should be targeted against the pathogen that is identified (Table 2, Figure 1). On occasion empiric therapy is

warranted secondary to severity of illness, signs of inflammatory diarrhea, persistent diarrhea and when a bacterial pathogen is the most likely cause of the diarrhea (Table 3).[9] The mainstay of therapy for a diarrheal illness, no matter the cause, is fluid replacement.[9, 69, 70] Oral rehydration is the preferred method for rehydration. For severe dehydration or hypovolemic shock, intravenous rehydration should be used with either normal saline or lactated Ringer's solution (Table 3).[71] Antimicrobial treatment should focus on the suspected or identified causative agent. When symptoms suggest an inflammatory cause of the diarrhea or the symptoms are severe, empiric therapy should be initiated. Empiric therapy typically targets the common bacterial pathogens known to cause diarrhea. In North America, these include *Salmonella*, *Campylobacter*, *C. difficile*, *Shigella* and Shiga-toxin *E. coli*. [9] A fluoroquinolone (e.g. ciprofloxacin) or a macrolide (e.g. azithromycin) can be used empirically to treat suspected bacterial diarrhea.[9, 72] (Table 3) For parasitic causes of diarrhea, treatment is individualized to the pathogen that has been identified along with reduction of immune suppression. (Table 2) We will detail the management of *C. difficile*, CMV and norovirus here. For pathogen specific management see Table 2 or refer to the IDSA/SHEA Diarrhea Guidelines 2017 [9] and specific organism guidelines presented by the AST-IDCOP (**see *C. difficile* and CMV sections of the 4th edition of AST ID Guidelines**).

Clostridioides difficile

The evaluation and treatment of CDI has been extensively reviewed elsewhere [73-75] as well as the AST-IDCOP guideline on the management of *C. difficile* infection in SOT recipients. Initial treatment of the SOT recipient with CDI is the same as non-transplant patients. The recommended therapies for mild to severe CDI are oral vancomycin 125 mg every 6 hours or fidaxomicin 200 mg twice per day for 10 days

(oral metronidazole is no longer recommended for the treatment of CDI per the 2018 IDSA/SHEA guidelines).[74] Fulminant CDI (presence of hypotension, ileus or megacolon) is treated with high dose oral vancomycin (500 mg every 6 hours) plus intravenous metronidazole 500 mg every 8 hours. For patients with an ileus, rectal vancomycin may be added. One of the challenges with *C. difficile* infection is the management of recurrent or relapsing infection. Treatment options for persons that develop recurrent or relapsing CDI can be found in the *C difficile* section of the 4th edition of the AST ID Guidelines.

Norovirus

At this time, there are no specific therapies for norovirus infection. Treatment should be focused on symptomatic relief of the diarrhea with anti-motility agents, rehydration and reduction in immune suppression.[41] Reduction of immunosuppression may assist in the reduction of symptoms of norovirus and may prevent persistent carriage and recurrent disease from norovirus. [45, 52, 53, 76] Several strategies to control viral replication have been tried in limited numbers of patients: oral or intravenous immunoglobulin, breast milk, ribavirin, and nitazoxanide. Several case series have demonstrated varying effects of oral human immunoglobulin on the diarrheal symptoms of norovirus; however, a cohort study failed to demonstrate improvements in total time to resolution of diarrhea, length of hospital stay or cost with administration of oral human immunoglobulin.[36, 46, 77, 78] Systemic administration of immunoglobulin has also provided conflicting evidence on clinical impact.[36] Nitazoxanide has demonstrated effectiveness in treating norovirus with significant reductions in time to resolution of symptoms.[79] Data from an on-going Phase 2 study (NCT033395405) evaluating the safety and efficacy of nitazoxanide in

the treatment of norovirus in SOT and Bone Marrow Transplant recipients will help define the role of this agent in the treatment of norovirus infection in this vulnerable population. These compounds may help in the prevention and treatment of norovirus infection and data from ongoing trials will help determine the most effective strategy to treat and control norovirus infection.

CMV (see also CMV section of the 4th edition of AST ID Guidelines).

The approach to evaluation and treatment of CMV disease in SOT recipients has been extensively reviewed elsewhere [55] For detailed management of CMV disease see the **see CMV section of the 4th edition of AST ID Guidelines.**

Management of CMV relies on antiviral medications with activity against CMV; these agents include valganciclovir (VGCV), ganciclovir (GCV), cidofovir and foscarnet.

Initial treatment of CMV disease is with either oral VGCV or intravenous GCV. Oral VGCV can be used for tissue invasive disease if there are mild symptoms. In persons with more severe diarrhea, intravenous GCV is recommended. It is important to monitor renal function and adjust dosing for level of renal function.

When there is concern for GCV resistance, foscarnet should be used for initial treatment, and CMV resistance testing should be performed. Treatment should be continued for a minimum of two weeks with associated resolution of symptoms and eradication of CMV DNAemia. Current guidelines do not recommend continued secondary prophylaxis, given lack of efficacy; however, some transplant centers will utilize a period of secondary prophylaxis for higher risk SOT recipients who develop CMV disease.[55]

Recommendations

1. Empiric anti-motility therapy should be considered in SOT recipients with diarrhea that is negative for *C. difficile*, and where there is no evidence of megacolon or inflammatory diarrhea **(weak, moderate)**
2. SOT recipients with diarrhea and mild to moderate dehydration should be given reduced osmolarity rehydration fluids. **(strong, moderate)**
3. Isotonic intravenous fluids should be administered for those with severe dehydration, shock, altered mental status or ileus **(strong, high)**
4. Antimicrobial therapy should be modified to target any identified pathogen suspected to be the cause of the diarrhea. **(strong, high)**

Conclusion

Diarrhea is a common complication of SOT and poses significant morbidity to the individual. Multiple infectious and non-infectious etiologies have been demonstrated to cause diarrhea in these patients. Immunosuppressive medications are common non-infectious causes of diarrhea while *C. difficile*, norovirus and CMV are the most common infectious causes of diarrhea in the SOT population. A standard, stepwise approach needs to be validated in order to optimally diagnose a case and optimize test utilization. New multi-pathogen molecular testing is promising, but these tests need further validation and standardization before becoming widely used. Variations in the local epidemiology of diarrhea should inform tailored diagnostic approaches at individual centers. Treatment of the diarrhea, with hydration and focused use of antimicrobials or changes in immune suppression, is of the utmost importance.

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Table 1. Common Causes of Post-Transplant Diarrhea.

IS-immunosuppressive, PTLD-Post-Transplant Lymphoproliferative Disorder, GVHD- Graft Versus Host Disease, IBD- Inflammatory Bowel Disease, spp.- species

Table 2. Infectious Causes of Post-Transplant Diarrhea and Management.

*Selection of agent should be based on local antibiogram and susceptibility of the organism

**Fumagillin is not available in the US

BID- twice a day, TID- three times per day, QID- four times per day, IS- immune suppressive, CMV- cytomegalovirus, VAN- vancomycin, FDX- fidaxomicin, TMP-SMX trimethoprim-sulfamethoxazole

Table 3. Empiric Therapy for Diarrhea in Solid Organ Transplant recipients

a- antibacterial is given orally; b- first line choice when there is a high concern for fluoroquinolone resistance; c- preferred for febrile diarrhea; ORS- Oral rehydration Solution

Figure 1. A Stepwise Algorithm for the Diagnosis of Post-Transplant Diarrhea.

CMV-cytomegalovirus, EGD- esophagogastroduodenoscopy, FDX- fidaxomicin, GVHD- graft versus host disease, IBD- inflammatory bowel disease, IS- immune suppressive, NAT- Nucleic Acid Test, PCR- polymerase chain reaction, PTLD- post-transplant lymphoproliferative disease, qPCR- quantitative polymerase chain reaction, VAN- vancomycin.

Table 1. Common Causes of Post-Transplant Diarrhea	
Infectious	
Bacterial	Viruses
<ul style="list-style-type: none"> • <i>C. difficile</i> • <i>Campylobacter</i> spp. • <i>Salmonella</i> spp. • Bacterial overgrowth • <i>Aeromonas</i> spp. • <i>E. coli</i> 	<ul style="list-style-type: none"> • CMV • Norovirus • Sapovirus • Rotavirus • Adenovirus • Enterovirus
Parasite	
<ul style="list-style-type: none"> • <i>Giardia</i> • <i>Cryptosporidium</i> • <i>Cystoisospora</i> • <i>Cyclospora</i> • <i>Microsporidium</i> • <i>Entamoeba</i> 	
Non-Infectious	
IS Medications	Other
<ul style="list-style-type: none"> • Mycophenolate • Tacrolimus • Cyclosporine • Sirolimus 	<ul style="list-style-type: none"> • GVHD • PTLD • IBD • Colon cancer • Malabsorption
Non-IS medications	
<ul style="list-style-type: none"> • Antibacterial • Anti-arrhythmic • Anti-diabetic • Laxatives • Proton Pump Inhibitors • Protease inhibitors 	

Table 2. Infectious Causes of Post-Transplant Diarrhea and Management

Etiologic Agent	Recommended Treatment
Bacterial	
<ul style="list-style-type: none">• <i>C. difficile</i>	First episode: <ul style="list-style-type: none">• VAN oral 125 mg QID for 10 days• FDX 200 mg BID for 10 days First episode, fulminant: <ul style="list-style-type: none">• VAN 500 mg 4 times per day oral or rectal plus IV metronidazole 500 mg every 8 hours For management of relapsed or recurrent <i>C. difficile</i> infection see the <i>C. difficile</i> section of 4th edition of the AST-ID Guidelines
<ul style="list-style-type: none">• <i>Campylobacter</i> spp.*	Azithromycin Ciprofloxacin
<ul style="list-style-type: none">• <i>Salmonella</i> spp.* (non-typhi)	Ceftriaxone TMP-SMX Ciprofloxacin Amoxicillin
<ul style="list-style-type: none">• <i>Shigella</i> spp.*	Azithromycin Ciprofloxacin Ceftriaxone
<ul style="list-style-type: none">• <i>Non-Vibrio cholera</i>*	For invasive disease: Ceftriaxone plus doxycycline TMP-SMX plus aminoglycoside
<ul style="list-style-type: none">• <i>Yersinia enterocolitica</i>*	TMP-SMX Cefotaxime Ciprofloxacin
<ul style="list-style-type: none">• <i>E. coli</i> (enterophogenic)*	Fluoroquinolone Cephalosporin
<ul style="list-style-type: none">• <i>E.coli</i> (enterohemorrhagic)	Avoid anti-motility agents Role of antibacterials unclear and should be avoided
<ul style="list-style-type: none">• Bacterial Overgrowth	Fluoroquinolone, Amoxicillin-clavulanate

Parasites	
• <i>Cryptosporidium</i>	Nitazoxanide Paromomycin
• <i>Giardia</i>	Tindazole Metronidazole Nitazoxanide
• <i>Cyclospora</i>	TMP-SMX Nitazoxanide
• <i>Cystoisospora</i>	TMP-SMX Pyrimethamine
Fungus	
Microsporidia	
• <i>Enterocytozoan bieneusi</i>	Fumagillin 20mg TID for 14 days**
• <i>Encephalitozoan</i> spp.	Albendazole 400mg BID for 1-3 weeks
Viruses	
• CMV	Oral VGCV IV GCV (If any concern for decreased absorption, IV therapy is favored)
• Norovirus	Rehydration Anti-motility agents Consider reduction in IS medications Nitazoxanide

Table 3. Empiric Therapy for Diarrhea in Solid Organ Transplant recipients

Rehydration	Dose	
ORS	2-4 liter/day	Replace until vomiting and diarrhea has resolved
Normal Saline Lactated Ringer's	20 ml/kg body weight	Reserved for severe dehydration Continue until pulse, perfusion and mental status returns to normal
Antibacterial	Dose	Duration
Levofloxacin ^a	Adult: 500 mg Pediatric: 10 mg/kg, max 500 mg	Single dose or 3-day course
Ciprofloxacin ^a	Adult: 750 mg Pediatric: 15 mg/kg, max 500 mg	Single dose
	Adult: 500 mg Pediatric: 15 mg/kg, max 500 mg	3-day course
Azithromycin ^{a, b, c}	Adult: 1000 mg Pediatric: 10 mg/kg, max 500 mg	Single dose
	Adult: 500 mg Pediatric: 10 mg/kg, max 500 mg	3-day course

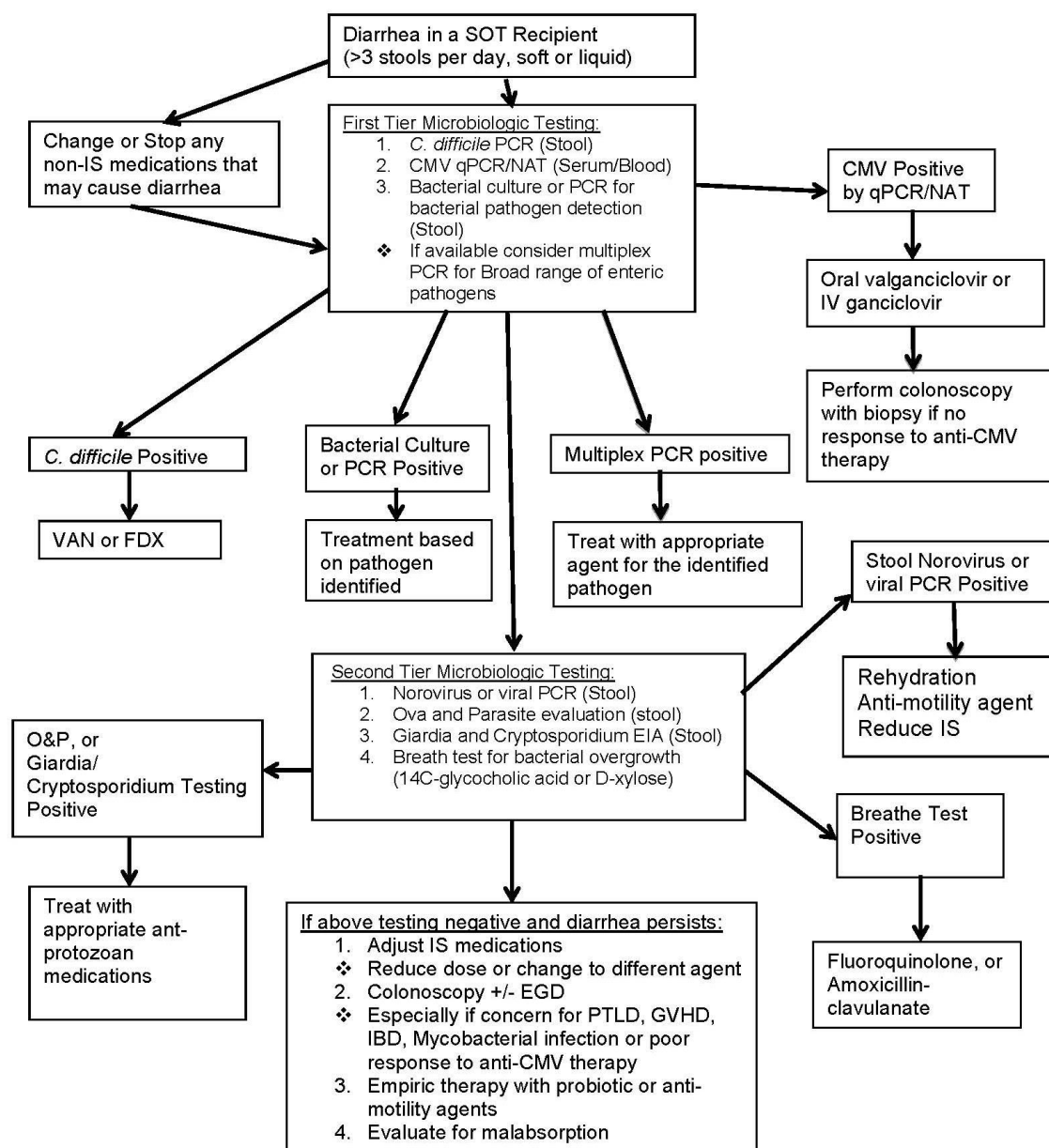


Figure 1. A Stepwise Algorithm for the Diagnosis of Post-Transplant Diarrhea.