Traveler's Diarrhea Recommendations for Solid Organ Transplant Recipients and Donors

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Diarrhea is the most common illness in people traveling from resource-rich to resource-limited regions of the world.[1] Most episodes of traveler's diarrhea (TD) are benign and self-limited, but may require extra care in immunosuppressed patients.[2,3] The major associated problem is dehydration, which can be exacerbated by immunosuppressive agents.

TD refers to diarrhea that develops during or within 10 days of returning from travel to resource-limited countries or regions. For epidemiological purposes, it is traditionally categorized into 3 forms: severe, moderate, and mild.[4] Severe TD refers to the passage of 6 or more unformed stools in a 24-hour period irrespective of the presence of at least 1 of these other symptoms: nausea, vomiting, abdominal pain or cramps, fever, or blood in stools. Moderate TD is defined as the passage of 1 or 2 unformed stools in 24 hours, plus at least 1 of the above symptoms or 3 to 5 unformed stools in 24 hours without other symptoms. Passage of 1 or 2 unformed stools in 24 hours without other symptoms is considered mild. Recently, a more functional classification has been proposed, taking into account the tolerability of the diarrheal illness and functional impairment of the patient that it causes.[5,6]

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EPIDEMIOLOGY

The incidence of TD is approximately 10% to 40%, depending on the travel destination. There have been few systematic studies in transplant recipients, so much of the discussion below is extrapolated from studies in all travelers. In immunosuppressed travelers, rates of infection are not necessarily higher, but the severity of illness can be increased.[3,7] The viral, bacterial, and parasitic organisms that cause TD are usually transmitted by food and water, and the risk of TD is the highest in regions where sanitation and hygienic practices are poor. South and Southeast Asia, Africa (except South Africa), South and Central America, and Mexico are considered high risk (incidence greater than 20%). Regions that are moderate risk (10-20%) include Caribbean Islands, South Africa, Central and East Asia, Eastern Europe, and the Middle East, including Israel. Northern and Western Europe, Australia and New Zealand, the United States, Canada, Singapore, and Japan are classified as low-risk areas (less than 10%).[4] Two decades ago, the incidence of TD was about 60%[8,9] but it has decreased in countries with increasing economies and in some previously high-risk destinations with improved tourism infrastructure. South Asia, India, Nepal, and West/Central Africa remain the destinations with the highest risk.

The largest experience in travelers returning with disease acquired during travel to developing countries comes from GeoSentinel, the global surveillance network of the International Society of Travel Medicine and the United States Centers for Disease Control and Prevention[10,11] Since GeoSentinel's inception in 1995, it has grown to include more than 50 reporting sites in 24 countries on 6 continents, with over 200 000 patient records collected. Retrospective observational studies from the GeoSentinel network showed that rates of gastrointestinal infection reported in travelers returning to high-income settings, such as Western and Northern Europe, were inversely related to the income level of the country they had visited.[3,12,13] These studies are particularly valuable for providing insight into the etiology and risk factors for the development of prolonged diarrhea in returned travelers. These differ from the bacterial and viral causes of the more common short-lived diarrhea typically experienced by travelers earlier during their travel.

Risk Groups

Environmental Factors

The risk of having diarrhea is highest during the first 7 days of travel and then progressively decreases. As well as destination, style of travel and available budget are important as they often determine where a traveler purchases meals. Backpackers often favor street vendors, which are known to have a high-risk of contaminated food.[14] Buffet-style foods exposed to warm environmental conditions, even those served in a 5-star hotel, are also associated with a high incidence of TD.[15] The risk of TD varies depending on the season, with a higher risk during warmer and wetter seasons.[16]

Host Factors

Genetic factors associated with an increased risk of TD are being increasingly recognized and are also being linked with susceptibility to postdiarrheal irritable bowel syndrome.[17] For example, polymorphisms in genes controlling production of the proinflamatory cytokine interleukin 8 and lactoferrin correlate with greater intestinal inflammation and symptoms in US travelers to Mexico.[18,19] Osteoprotegerin, an immunoregulatory member of the tumor necrosis factor receptor superfamily, may function as an antiinflammatory modulator that increases susceptibility to TD and CD14, a receptor for bacterial lipopolysaccharide binding, is associated with the innate immune response to enteric infection and inflammation. Single-nucleotide polymorphisms of these may increase susceptibility to TD.[20,21] Possession of different blood group ABO (H) histocompatibility antigens has long been associated with susceptibility to bacterial enteropathogens, such as *Vibrio cholerae*, and more recently absence mutations in the related FUT2 gene, which provides ligands for virus binding, have been shown to reduce susceptibility to Norovirus infection.[22,23]

Younger travelers tend to have a greater risk of acquiring TD, probably because they eat more food, resulting in the ingestion of a larger quantity of pathogens.[24] Also, younger travelers are more adventurous.[24] Anything that reduces the gastric acid barrier to pathogens increases the risk of a wide variety of gastrointestinal infections from cholera to *Clostridium difficile*. This includes gastric sugery for peptic ulcer disease, antacids, H2 receptor antagonists and protein pump inhibitors. Many transplant recipients will be taking these medications.[25,26]

ETIOLOGY

Because there are few studies of travel-related diarrhea in transplant patients, the following discussion extrapolates from more general studies in travelers, highlighting areas of known or potential differences in the immunosuppressed. Although causes of diarrhea in solid-organ transplant recipients are similar to those in the general population, there are some differences, such as a higher incidence of drug-induced diarrhea and opportunistic infections in transplant patients.[25] In a study of 52 diarrheal episodes among 43 solid-organ transplant recipients, the cause was determined in 43 (83%) recipients. Infectious etiologies accounted for 77% of cases, whereas drug-related diarrhea occurred in 23%.[26]

The relative importance of different pathogens in traveler's diarrhea greatly varies per the region visited and the season of travel.[1] As in the general population, bacterial agents are the most frequent cause of TD in transplant patients.[27] The most common causes are enterotoxigenic *Escherichia coli* (ETEC) and enteroaggregative *E. coli*, followed by *Shigella*, *Salmonella*, *Campylobacter*, *Aeromonas*, *noncholeric vibrios*, and *Plesiomonas* spp.[1] In Asia, *Campylobacter jejuni* is a particularly frequent cause of traveler's diarrhea.[28]

Although viruses are rarely identified as the cause of traveler's diarrhea, their true importance is probably underappreciated because specific diagnostic tests (such as polymerase chain reaction) are not often performed in routine clinical practice.[29] Noroviruses are recognized to be a leading cause of acute viral gastroenteritis worldwide and have been implicated in TD in visitors to Mexico, especially during the winter.[30] Although noroviruses are increasingly being recognized as a significant cause of both acute and chronic diarrhea in solid-organ transplant recipients, their role as a cause of TD has not been specifically analyzed.[31,32] Rotaviruses are known not only as a cause of TD but also of severe gastroenteritis in immunocompromised hosts, including transplant patients.[33]

Certain parasitic infections (*Cryptosporidium* spp, *Cystoisospora belli*, *Cyclospora* spp, *Microsporidia*, *Giardia intestinalis*) are highly prevalent in developing regions, and may be a significant cause of gastroenteritis in solid-organ recipients.[34] However, most of the available information on diarrhea due to intestinal protozoa in transplant patients is derived from case reports or small series from single institutions.[35,36]

Cryptosporidium and *Giardia* the most common parasites infecting transplant recipients, especially in travelers to endemic regions.[34] Cryptosporidial infection is a common cause of infective diarrhea in transplant recipients in endemic areas, such as India, the Middle East, and South America. In India, its prevalence was estimated to be over 20% in a study conducted by Udgiri et al.[36] The microsporidia most often linked to gastrointestinal illnesses are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. However, *Entameba histolytica* is rarely identified in transplant recipients.[34]

Strongyloides stercoralis is a gut nematode that causes chronic gastrointestinal and skin manifestations due to its autoinfective lifecycle. Transplant recipients are at risk for developing *Strongyloides* hyperinfection syndrome secondary to chronic intestinal infection, acquisition of primary *Strongyloides* infection in tropical and subtropical areas, or allograft transmission.[37]

Coinfection is a common feature of parasitic infection in the setting of transplantation, and invasive disease may be associated with disseminated viral or bacterial infections.[34]

CLINICAL MANIFESTATIONS

TD is characterized by an increase in frequency of bowel movements and a change in consistency of the stool (soft to liquid) that usually begins within 2 to 3 days of arrival. More than 90% of illnesses start within the first 2 weeks.[1,6,28]

Three overlapping syndromes may be discerned. The first is short-lived watery diarrhea with little or no fever. This may be triggered by invasive pathogens, and be associated with secretory diarrhea. The second syndrome is a more prolonged disease, which may be accompanied by bloody diarrhea (dysentery) and fever. The third is chronic diarrhea lasting for more than 1 month, which affects 1% to 3% of patients with diarrhea. This syndrome is often associated with parasitic infections, but also can be due to invasive bacterial pathogens, such as *Shigella*, *Salmonella*, and *Campylobacter*.[11,12] Giardiasis and amebiasis can be linked with chronic diarrhea in solid-organ transplant recipients. *Giardia* usually causes enteritis with watery diarrhea, malabsorption, bloating and flatulence,

whereas amebiasis produces more often colitis with bloody stools.[25] Intestinal microsporidiosis is also a well-known cause of chronic diarrhea and wasting in immunocompromised hosts.[38]

Diarrhea in organ transplant recipients is a potentially debilitating condition that can lead to severe dehydration, which compromises renal function, a marked increase in toxicity of immunosuppressants, and organ rejection, producing a negative impact on the recipient's quality of life.[26,39] Long-term complications of TD can occur, such as postinfectious irritable bowel syndrome, reactive arthritis often associated with HLA-B27, and Guillain-Barré syndrome.[3] It is not clear whether long-term sequelae such as irritable bowel syndrome are more common or severe in solid-organ transplant recipients compared with other travelers.

DIAGNOSIS APPROACH

Most self-limited episodes of diarrhea while traveling will not require investigation, but a different approach is needed for diarrhea that persists. This approach is sometimes limited to investigation of those that continue to have diarrhea after empiric treatment for common pathogens, such as *Giardia*.[40] Discriminating between immunosuppression-related and infection-related gastrointestinal complications after transplantation can be difficult and is often based on the patient's net state immunosuppression, the presence of anatomic abnormalities and the patient's epidemiologic exposures.[41] For this reason, we advocate a low threshold for laboratory workup of transplant patients with travel-related diarrhea, to include both travel and other causes. Diagnosis and management of posttransplant diarrhea should include stool culture, stool *C. difficile* assessment, and blood *Cytomegalovirus* (CMV) quantitative viral load. A stepwise approach to the general diagnosis of diarrhea in solid organ recipients has been described elsewhere.[41]

Importantly, transplant recipients suffering from diarrhea refractory to standard treatment, especially those at risk for additional waterborne diseases, should undergo a full evaluation for intestinal parasitic infection.[42] This includes fecal testing for leukocytes, ova, and parasites; appropriate stains for *Cryptosporidium* spp, *Cystoisospora belli* and *Cyclospora cayetanensis*; *Giardia* and *Cryptosporidium* antigen screen or enzyme immunoassay; and *Norovirus* detection by polymerase chain reaction. Although new multipathogen molecular tests are very promising, they need further validation and standardization before becoming widely implemented.[1,6,42]

TREATMENT

The majority of food-borne illnesses, including TD, are self-limited, and require mainly supportive management and fluid replacement. Fluids and electrolytes should be replaced aggressively because diarrhea-induced dehydration can result in renal insufficiency and enhance the potential toxicities of antirejection medications. Antimotility agents, such as loperamide, are also recommended with good evidence for added efficacy when used in combination with antibacterial therapy.[43] Bismuth subsalicylate has been used to treat TD, but should be used with caution in solid-organ transplant patients because it is converted to salicylic acid and bismuth salts, and these can result in toxicity among transplant patients with diminished renal function.

Solid-organ transplant recipients may be at increased risk of complications, including bloodstream infection (with potential seeding at distant sites). Dehydration can potentiate the nephrotoxic effects of calcineurin inhibitors. More aggressive treatment of TD is therefore recommended for solid-organ transplant recipients.[44] Although randomized controlled clinical trials have not been performed specifically in transplant recipients, the clinical benefit of treating TD has been demonstrated in numerous studies performed in the non-transplant population.[45,46] In a meta-analysis of controlled trials, antibiotic treatment was significantly associated with shorter duration of diarrhea, although it also led to higher incidence of side effects.[46] Data from these studies in non-transplant population serve as evidence to support these recommendations for the management of transplant patients with TD.

Empiric antibiotic therapy is recommended for those with moderate to severe frequency of TD (3 or more stools per day), and for all those with invasive symptoms (eg, bloody stools) and systemic illness (eg, fever).[1,6,47] However, short lived mild diarrhea (1-2 stools per day) without systemic symptoms, that is tolerated by the patient, rarely requires antimicrobial therapy. Antibiotic regimens are chosen to target the most common bacterial pathogens, including ETEC and enteroaggregative *E. coli*, followed by *Salmonella, Shigella* and *Campylobacter jejuni*. These usually cover the less commonly encountered causes, such as *Aeromonas* spp, *Plesiomonas* spp, and *Vibrio* spp.[27,48,49]

The first-line empiric drug regimens against these bacterial pathogens are ciprofloxacin, levofloxacin, and azithromycin (Table 1). In general, ciprofloxacin is the standard empiric drug for self-treatment of TD except for travelers to South and Southeast Asia, where azithromycin is the preferred drug.[1,6] In separate studies, single doses of ciprofloxacin (500 mg orally), levofloxacin (500 mg orally), and azithromycin (1000 mg orally) were effective in reducing the severity and duration of diarrhea in most travelers.[50-52] Multiple doses taken over a course of 3 to 7 days have also been recommended[44] (Table 1). In some studies, however, single-dose azithromycin had better efficacy than a 3-day regimen and had less side effects.[53]

The choice of empiric regimen should take into consideration the resistance patterns in a specific geographic location.[54] For example, the widespread use of fluoroquinolones for empiric treatment of TD and other bacterial infections has led to the selection and emergence of ciprofloxacin resistance, especially among *Campylobacter* isolates.[55,56] There is increasing resistance to fluoroquinolones among *Campylobacter* isolates in Thailand, and azithromycin is now recommended as first-line empiric treatment of diarrhea among travelers in Thailand and Southeast Asia.[53] In a randomized study, azithromycin treatment resulted in a better outcome than levofloxacin treatment of TD in Thailand, where the predominant pathogen was *Campylobacter* species.[53] There have also been increasing reports of quinolone-resistant *Shigella*[57] and *Salmonella*[58] isolates among travelers returning from India. The potential for drug-drug interactions should be considered in the treatment of TD among transplant recipients. Although rifaximin has been approved for the treatment of traveler's diarrhea caused by noninvasive bacterial pathogens, some caution against its use among solid-organ transplant recipients due to its potential for interaction with cyclosporine.[59] However, rifaximin is a nonabsorbable rifamycin that is not expected to inhibit the cytochrome p450

TABLE 1.

Recommendations for empiric and targeted antimicrobial treatment of TD

Empiric and targeted antibacterial therapy for TD	
Ciprofloxacin	500 mg PO BID for 1-3 d 500 mg PO single dose
Levofloxacin	500 mg PO QD for 1-3 d 500 mg PO single dose
Azithromycin	500 mg PO QD for 1-3 d 1000 mg PO single dose
Antiparasitic regimens for TD	
Metronidazole	500-750 mg PO TID for 5-10 d (amebiasis) or 250 mg PO TID for 5-7 d (giardiasis)
Tinidazole	2 g PO single dose (giardiasis) or once daily for 3 d (amebiasis)
Nitazoxanide	500-1000 mg PO BID for 14 d or until diarrhea resolves (amebiasis, cryptosporidiosis, giardiasis)
Paromomycin	25-35 mg/kg/day PO TID for 5-10 d (amebiasis)
Trimethoprim-sulfamethoxazole	1 double-strength tablet PO BID for 7-10 d (cyclosporiasis, cystoisosporiasis)

isoenzymes. The role of rifaximin as self-administered empiric therapy is debated because patients are often unable to distinguish noninvasive from the invasive forms of diarrhea, so a second (systemically active) antimicrobial would need to be given concurrently. Azithromycin, a macrolide antibiotic, may inhibit cytochrome p450 and reduce tacrolimus metabolism, leading to higher systemic tacrolimus levels that can manifest as nephrotoxicity and neurotoxicity. Nephrotoxicity may be further enhanced by diarrhea-induced dehydration. These interactions do not contraindicate the use of azithromycin, but do highlight the role of hydration, and monitoring and adjustment of immunosuppressive drug levels in solid-organ transplant patients with TD.

If TD does not improve after empiric antibacterial therapy, solid-organ transplant patients should seek medical consultation and have their stools examined for resistant bacterial pathogens and/or other potential nonbacterial causes (see diagnosis).[60] Antimicrobial susceptibility testing should be performed for bacterial enteropathogens to guide antibiotic therapy (Table 1).

Parasitic infections account for 1% to 20% of all cases of TD, including *G. intestinalis*, *Cryptosporidium spp*, *Cyclospora cayetanensis*, *Cystoisospora belli* and *Entameba histolytica*.[61,62] In contrast to the sudden onset symptoms for bacterial and viral diarrhea, the onset is more gradual for parasitic infections. First-line treatments for *G. intestinalis*, the most common parasitic cause of TD, include metronidazole, tinidazole or nitazoxanide (Table 1).[63] Drug-resistant parasites have been reported with increasing frequency in certain parts of the world, particularly nitroimidazole resistance in *G. intestinalis* infections acquired in India.[64] These may require treatment with second-line agents such as albendazole, paromomycin or mepacrine (quinacrine).[63] Entameba infections are also treated with metronidazole or tinidazole, usually combined with a lumicidal agent such as paromomycin (Table 1). Cryptosporidium infections are often self-limited, but nitazoxanide may be considered for severe cases. *Cyclospora* and *Cystoisospora* infections are generally treated with trimethoprim-sulfamethoxazole (Table 1).

Viral causes of TD are often self-limited, but if severe and persistent, one should consider reducing the dose of pharmacologic immunosuppression. CMV may also reactivate to cause gastrointestinal disease that most often presents as diarrhea, coincident with travel. CMV is treated with intravenous ganciclovir (5 mg/kg every 12 hours) or oral valganciclovir (900 mg PO BID)[65] for at least 14 days. Other pathogens that may present with diarrhea during travel include *C. difficile*,[66] especially among solid-organ transplant recipients who are at risk due to use of antibiotic prophylaxis. Treatment of *C. difficile* consists of oral vancomycin (125-250 mg PO QID), metronidazole (500 mg PO or IV TID) or fidaxomicin (200 mg BID) depending on local licencing and availability. Noninfectious causes of diarrhea may be observed among solid-organ transplant recipients, sometimes as an adverse effect of mycophenolate mofetil. Treatment of drug-associated diarrhea entails reduction in the dose, or substitution of the culprit drug with another alternative immunosuppressive therapy.

PREVENTION

Individualized risk assessments should be made about potential hazards for all travelers, particularly those with immunosuppression. Transplant patients who already have gastrointestinal problems and/or whose hydration status is in fine balance, may need special counseling about the wisdom of travel to high-risk settings.[67,68]

Advice should be provided about personal hygiene and dietary precautions. There is good evidence that hand washing before handling food reduces the risk of diarrheal disease and travelers should consider carrying antiseptic wipes or alcohol hand rubs for situations where water may not be available for hand washing.[69] Protection of the water supply or sterilizing water at the point of delivery reduces the incidence of diarrheal disease in resource-poor settings, and travelers to areas with poor sanitation may need to carry sterilization tablets, water filters, or both (a wide variety are available).[70] Travelers should be reminded to examine drinks purchased in bottles and cans to ensure that the original seal is present (to ensure they are tamper free), and to use a drinking straw if drinking directly from the container, to avoid imbibing pathogens present on the surface of the bottle or can. Ice in cooled drinks may be of uncertain origin and sterility and should be avoided, and bottled water should be used to clean teeth. Alcoholic drinks may potentiate diarrhea and dehydration.

The conventional advice is to avoid all foodstuff that have not been freshly prepared or properly cooked. High-risk foods are salads, foods that have been reheated, food left uncovered and therefore visited by flies, and any food cooked in unhygienic circumstances. Food that is freshly cooked by a street vendor and served immediately on sterile plates may be safer than food left out in a hotel buffet. The old adage "cook it, boil it, peel it or forget it" emphasizes the need to avoid contamination of fruit and other uncooked foods by fingers of uncertain cleanliness. However, much food is not cooked to a high enough temperature to kill all enteropathogens. Repeated anecdotal experience and many surveys have shown poor compliance by travelers with advice about

safe food and water and little impact of such advice on the incidence of TD.[1,6,28,71]

Other preventive measures should be considered for this high-risk group. The evidence base for effectiveness of prebiotics and probiotics is poor and they are not widely recommended. Loperamide or similar antimotility agents have been recommended by some in the past, but there is no evidence to support their use in prevention (as opposed to treatment).[72] Bismuth salicylate has moderate efficacy in preventing travelers diarrhea but has to be taken frequently, has associated problems such as staining the tongue and teeth, and should be avoided by people with salicylate allergy. Toxicity has been reported in patients with renal insufficiency; as this is common in solid-organ transplant recipients, bismuth salicylate is a less attractive option for this group of travelers.

Short-term chemoprophylaxis with systemically absorbed antibiotics is highly effective in preventing traveler's diarrhea, provided that enteropathogens at the destination are susceptible. Current opinion favours avoiding the use of such agents for trips lasting more than 14 days, after which most but not all risk of TD has reduced, and limiting such use to essential trips for business or leisure reasons.[6] As solid-organ transplant patients are at increased risk of complications of TD, there may be more reason to prescribe prophylaxis, but this still has to be balanced against the risk of side-effects of medication and drug-drug interactions. The acquisition of multidrug resistant enteropathogens is an increasingly important hazard of travel. There is increasing evidence that even short-term travel to the Indian subcontinent carries a high risk of acquiring MDR pathogens and that this risk is increased in those that use prophylactic antibiotics.[73,74] Although this is not harmful for the individual *per se*, it could pose problems for solid-organ transplant patients who become carriers and may become sources of MDR pathogens in their local and hospital environments.

The systemic agents usually recommended are quinolones such as ciprofloxacin taken in standard doses for short periods. In Asian countries, such as Thailand and India, where quinolone resistance is common, azithromycin might be preferred for prophylaxis but drug-drug interactions (eg with tacrolimus) must be considered. The nonabsorbed antimicrobial rifaximin is increasingly recommended for prophylaxis, but its potential for use in treatment is very limited in solid-organ transplant patients as invasive pathogens would not be covered.

Finally, what about a role for immunization? Cholera vaccine is only indicated for the small number of travelers who will be working in settings where cholera is a risk, for example, in humanitarian outbreak relief. It does not provide adequate protection against other causes of TD and should not be recommended for that purpose.[75,76] Despite intense interest and research on vaccines against other bacteria causing TD, results have been disappointing to date even when vaccines induce good immunity.[77] As effective vaccines against *Norovirus* infection become available, travelers will be a very good group in which to test efficacy, particularly in known high-risk settings such as cruise ships. However, these are not yet available.

In summary, most evidence about prevention and treatment of TD in solid-organ transplant patients is extrapolated from other groups of nonimmunosuppressed travelers. The higher risk of illness in transplant patients justifies more aggressive preventive and therapeutic approaches than in other travelers but this should be tempered by careful consideration of drug-drug interactions. Each patient should have an individualized risk assessment for each trip, and on occasions it may be necessary to recommend changes to the itinerary.

ORGAN DONORS WITH DIARRHEA

Living donors originating from resource-poor countries have potential risk for transmission of enteropathogenic strains of *Salmonella*, *Shigella*, ETEC (or any, bacterial enteric pathogens), but the actual risk of transmission from such donors remains undetermined. Therefore, they should be screened out for intestinal parasites and enteropathogenic bacteria before donation.

Donors with unexplained persistent diarrhea should be investigated and deferred until the diagnosis and appropriate treatment.

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