5 Late Posttransplant Period: Posttransplant Vaccination, Travel Advice, Foodborne Infections

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5.1 Foodborne Diseases

5.1.1 Definitions and Epidemiology

Foodborne diseases are diseases caused by ingestion of food contaminated with microorganisms or chemicals at any stage in the process from food production to consumption.

Immunosuppressed patients are more susceptible to foodborne diseases and have a greater risk of severe illness [1, 2]. Besides immunosuppression, SOT recipients have other predisposing factors such as liver or kidney dysfunction, use of antacids and antimicrobials, and nutrition deficiencies. The inoculum of organisms needed to cause symptomatic disease is likely lower in this population [3].

The causes of foodborne diseases can be classified mainly in two categories: Chemical hazards, including chemical contaminants as well as natural toxins and infectious agents, the most frequent cause of foodborne diseases. Pathogens can cause different types of foodborne illness: (a) foodborne infections, when the pathogen causes disease directly when ingested; (b) foodborne intoxication, when the illness is caused by toxins produced in the food by pathogens; and (c) foodborne toxin-mediated infection, when the pathogens produce toxins in the body after being ingested.

The top five infections that cause foodborne illness in Western countries are norovirus, *Salmonella* spp., *Clostridium perfringens*, *Campylobacter* spp., and *Staphylococcus aureus*. Other microorganisms, such as *Clostridium botulinum*,

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Listeria, and Shiga toxin-producing *Escherichia coli* O157, seldom cause illnesses, although they usually are life-threatening.

Noroviruses are highly resistant to harsh environmental conditions, with an infectious oral dose <20 viral particles. Infected food workers are frequently the source of the outbreaks. Other sources of infection are foods (oysters, fruits, and vegetables) or touching the mouth after contact with contaminated objects or persons infected with norovirus [4].

Campylobacter spp. is the most common bacterial cause of human gastroenteritis in the world. It is generally associated with the consumption and handling of chicken and, less commonly, with the consumption of raw milk, red meat, contaminated water, or transmission from household pets or farm animals.

Salmonella spp. are a major cause of foodborne illness throughout the world. The bacteria are generally transmitted to humans through consumption of contaminated food of animal origin, mainly meat, poultry, eggs, and milk. Person-to-person transmission can also occur through the fecal-oral route.

Although *C. perfringens* may be normal intestinal flora, illness is caused by ingestion of food contaminated with large numbers of bacteria that produce enough toxins in the intestines to cause illness. Beef, poultry, and dried or precooked foods are common sources of *C. perfringens* infections [5].

Escherichia coli infection is usually transmitted through the consumption of contaminated water or food, such as undercooked meat products, raw milk, and fecal contamination of vegetables. Some strains such as the Shiga toxin-producing *E. coli* (STEC) can cause severe foodborne disease. *E. coli* STEC is heat-sensitive; therefore cooking food thoroughly can avoid transmission.

Staphylococcal food poisoning occurs when eating uncooked foods contaminated with toxins produced by *Staphylococcus aureus*.

The main source of hepatitis E virus transmission is the consumption of raw or undercooked, infected meat or direct contact with infected animals. For SOT patients exposed to HEV, infection can become chronic, with rapidly progressing liver disease.

5.1.2 Diagnosis

History is very important when evaluating a patient with a suspicion of foodborne disease. The clinician must consider the history, epidemiologic features, the symptoms, and signs. The most common clinical presentation of foodborne disease is diarrhea. However, such diseases can have other serious consequences such as kidney and liver failure, neural disorders, reactive arthritis, and death. None of the symptoms of foodborne illness are specific, although they may vary depending on the etiology (Table 5.1).

Contrary to immunocompetent adults, norovirus gastroenteritis in SOT recipients frequently results in chronic symptoms that persist weeks to months [6, 7]. In these patients, norovirus infection is accompanied by weight loss, dehydration, and renal insufficiency; symptoms last considerably longer than most other etiologies [8].

Table 5.1 Foodborne diseases

Etiology	Incubation period	Symptoms	Food sources
Bacillus cereus	10–16 h	Nausea, abdominal pain watery diarrhea, vomiting	Cereal products, rice, vanilla sauces, eat
Campylobacter jejuni	2–5 days	Diarrhea (bloody sometimes), severe abdominal pain, fever, bacteremia	Poultry, beef lever, raw seafood, contaminated water, raw milk
Clostridium botulinum	12–72 h	Bulbar palsy, descending paralysis, lack of fever	Home-canned low-acid food, fermented fish
Clostridium perfringens	8–16 h	Abdominal pain, watery diarrhea	Undercooked foods, meat, poultry, gravy sauces, soups
E. coli O157:h7	24–72 h	Severe abdominal pain, diarrhea (bloody), nausea, vomiting, HUS	Soft unpasteurized cheese, contaminated water, undercooked foods
E. coli (traveler's diarrhea)	1–3 days	Abdominal cramps, vomiting, watery diarrhea	Food or water contaminated with human feces
Listeria monocytogenes	9–48 h for gastrointestinal symptoms, 2–6 weeks for invasive disease	Nausea, vomiting, stomach cramps, diarrhea, bacteremia, meningitis constipation, fever	Raw milk or milk products, undercooked poultry, unwashed raw vegetables
Salmonella spp.	12–36 h (up to 72 h)	Abdominal pain, diarrhea, chills, fever, nausea, vomiting, bacteremia	Poultry, meat products, eggs and eggs products, fecal-contaminated food
Shigella spp.	4–7 days	Abdominal pain, diarrhea (sometimes bloody), chills, fever	Moist prepared foods, salads, raw fruits and vegetables, raw milk, poultry
Staphylococcus aureus	2–4 h	Nausea, vomiting, abdominal pain, diarrhea	Ham, meat, poultry, cream-filled pastry, food mixtures, leftover foods
Vibrio parahaemolyticus	4–96 h	Abdominal cramps, fever, nausea, vomiting, watery diarrhea	Undercooked or raw seafood
Vibrio vulnificus	1–7 days	Abdominal pain, bleeding, diarrhea, ulcers, vomiting, death	Undercooked or raw seafood
Yersinia spp.	24–48 h	Watery diarrhea, vomiting, abdominal pain, fever, sore throat	Meats, oysters, tofu, fish, unpasteurized milk, soy products

(continued)

Table 5.1 (continued)

Etiology	Incubation period	Symptoms	Food sources
Hepatitis A	15–50 days	Abdominal pain, diarrhea, fever, headache, jaundice, nausea	Shellfish, fecal-contaminated water or food
Norovirus	12–48 h	Abdominal cramps, diarrhea, fever, headache, nausea, vomiting, chronic diarrhea	Contaminated water, food or food contact surfaces
Anisakis simplex	12 h-days	Abdominal pain, vomiting, coughing	Saltwater fish
Giardiasis	1 week	Abdominal pain, diarrhea, fever, cramps	Water, raw vegetables and fruits
Cryptosporidium	1–12 days	Abdominal cramps, watery diarrhea, mild fever	Contaminated food or water
Cyclospora cayetanensis	1–14 days	Abdominal cramps, watery diarrhea, fatigue, loss of appetite, nausea, weight loss, vomiting	Contaminated raw products (berries, basil, lettuce)

The most common clinical symptoms of *Campylobacter* infections include diarrhea (frequently bloody), abdominal pain, fever, headache, nausea, and/or vomiting. In transplant recipients, bacteremia is more frequent in the general population, with a mortality rate >20% [9, 10].

The symptoms of *Salmonella enteritidis* infection usually appear 12–72 h after infection and include fever, abdominal pain, diarrhea, nausea, and sometimes vomiting. In SOT recipients, bacteremia is common (20–30% of cases vs. 3–4% in non-transplant recipients) [3].

Escherichia coli foodborne disease is generally self-limiting, but it may lead to a life-threatening disease including hemolytic uremic syndrome (HUS). Symptoms of disease include abdominal cramps and diarrhea, which may be bloody. Fever and vomiting may also occur.

Symptoms of staphylococcal food poisoning usually develop within 30 min to 6 h of ingestion. Commonly patients suffer from vomiting, nausea, stomach cramps, and diarrhea. The illness cannot be transmitted to other persons and usually lasts for only 1 day.

Clostridium perfringens infection usually begins suddenly 6–24 h after ingestion and lasts for less than 24 h. Patients have diarrhea and abdominal cramps but usually no fever or vomiting.

Cryptosporidiosis is usually self-limited but in SOT recipients can be chronic with weight loss, electrolyte imbalances, and extraintestinal complications. It causes up to 20% of diarrhea episodes in SOT recipients in developing countries [11].

5.1.3 Microbiological Studies

In SOT recipient, microbiological studies should be performed, especially in cases where the illness persists [12]. In SOT patients with diarrhea, testing for *C. difficile*, norovirus by PCR, bacteria by stool culture, and *Giardia* and *Cryptosporidium* by EIA are recommended as first-line testing; supplemental testing with ova and parasites if at risk for parasite exposures, such as modified acid-fast stain, is useful for the identification of oocysts of the coccidian species (*Cryptosporidium*, *Cystoisospora*, and *Cyclospora*), which may be difficult to detect with routine stains such as trichrome. Multiplex PCR for viral, bacterial, and parasitic pathogens are now available and may have increased sensitivity with respect to the standard tests. Fresh stool samples for culture and analysis provide the highest yield. Stool examination for parasites generally is indicated for patients with suggestive travel histories, chronic diarrhea, and unresponsiveness to antimicrobials.

5.1.4 General Approach

Oral rehydration and symptomatic treatment are the cornerstone of the treatment of foodborne diseases. Unlike immunocompetent patients, transplant recipients frequently need antimicrobials. This is the case for *Salmonella* and *Campylobacter* infections. The empiric antimicrobial therapy in adults should be either a fluoroquinolone such as ciprofloxacin, or azithromycin, depending on the local susceptibility patterns and travel history. Giardiasis can be treated either with tinidazole or nitazoxanide; this last one is the first choice to treat cryptosporidiosis. Cyclosporiasis and yersiniosis are treated with trimethoprim-sulfamethoxazole. Antibiotics should be avoided in cases of STEC, as they may increase the risk of HUS. Antibiotics are also not indicated in toxin-mediated disease. Caution should be made to possible interactions of antimicrobial agents and immunosuppressants. There is no specific therapy for norovirus infection beyond hydration and antimotility; variable success has been seen with the use of immunoglobulin, breast milk, and nitazoxanide [13]. Immunosuppression therapy should be reduced as much as it is safe. However, there is no evidence of beneficial effects of immunosuppression reduction for norovirus infection. Antimotility agents may delay clearance of toxins; therefore, they should be used with caution in SOT recipients. Bismuth subsalicylate should be avoided for decreased renal function.

5.1.5 Prevention of Foodborne Diseases

Prevention is essential in reducing the cases of foodborne illness [14]. Some foods are more associated with illnesses than others (see Table 5.1). Transplant recipients and caregivers should pay particular attention to local recommendations when outbreaks occur to avoid exposure to contaminated foods.

According to the World Health Organization, there are five key rules for food safety [15]:

1. Hands should be washed before and often during food preparation and after going to the toilet. Surfaces and equipment used for food preparation should be washed and sanitized and protected from insects, pests, and other animals.
2. Raw and cooked food and the equipment and utensils used to prepare them need to be separated.
3. Food should be cooked thoroughly, especially meat, poultry, eggs, and seafood. Soups and stews should come to a boil, making sure that they have reached 70 °C. Cooking meat and poultry with a thermometer is advisable.
4. Food needs to be kept at safe temperatures (<5 °C or >60 °C). Cooked food should not be left at room temperature >2 h. Frozen food should not be thawed at room temperature.
5. Only safe water and raw materials should be eaten. Milk must be always pasteurized or boiled, and fruits and vegetables need to be washed if eaten raw and if possible peeled.

5.2 Travel Advice

Travel to tropical or developing countries poses substantial risk to transplant recipients, particularly during periods of maximal immunosuppression [16]. Plans to travel should be discussed at least 2 months before the travel, ideally in a Travel Medicine Clinic with specific transplant protocols. In this visit several issues need to be addressed:

1. Net State of Immunosuppression

Time since transplantation is the first issue to consider. Most authorities recommend avoid traveling to high-risk destinations during the first year of the transplant [17]. The net state of immunosuppression needs also to be considered. Recent episodes of rejection, changes in the immunosuppressive regime, and comorbidities increase the risk and severity of travel-related infections.

2. Graft Function and Medication

It is important that a SOT recipient who is planning to travel is in a stable situation. Patients should take a summary of his/her medical history, a signed copy of their medication list, and sufficient supply of medication as hand luggage. It is advisable to investigate healthcare facilities abroad in the event of an emergency in the area visited.

3. Travel Itinerary

Updated travel advisories should be obtained, as disease risks are not stable over time. The travel itinerary and specific travel plans need to be assessed, considering the specific areas of travel within the country, the activities planned (business vs. leisure), travel's length, and the type of accommodation [18]. Patients should be counseled about cancelation and travel insurance as well.

4. Advice on Minimizing the Risk of Illness

Insect-transmitted infections can be life-threatening in SOT recipients. The application several times a day of an insect repellent containing diethyltoluamide (DEET) is advised. It is also recommended clothing to cover the arms, ankles, and legs despite temperature conditions and the use of mosquito netting [19].

Walking barefoot and swimming in freshwater should be avoided, to reduce the risk of some parasitic infections such as strongyloidiasis, schistosomiasis, or hookworm infection. Leptospirosis may be transmitted through contact with water contaminated with rodent's urine.

Sunscreen lotions and avoidance measures are advised as SOT recipients are at increased risk of skin cancer and photosensitivity [20].

Patients should practice strict hand hygiene and maintain good food safety practices to avoid infections transmission (see foodborne diseases prevention).

To decrease the risks of endemic fungi, the SOT recipients traveler should minimize exposure to outdoor dust, travel in enclosed air-conditioned vehicles, and avoid buildings with active construction. Activities with high risk of aerosolization of spores such as caving or dirt biking must also be avoided.

Travelers to malarial areas should take malaria chemoprophylaxis based on antimalarial drug resistance at the destination and the potential drug interactions [17]. Mefloquine and chloroquine may increase calcineurin inhibitor levels and the risk of arrhythmias when given with TMP/SMX or tacrolimus. Atovaquone-proguanil has less interactions [19]. It must be noted that no antimalarial drug is 100% protective and must be combined with the use of personal protective measures.

Evidence supporting prophylaxis against leptospirosis is ambiguous; however, the CDC recommends doxycycline if high-risk exposures (i.e., floods, heavy rainfall, and recreational water activities [17]).

Traveler's diarrhea in a SOT recipient may lead to renal failure, drug toxicity, and graft dysfunction. Although prophylactic antibiotics can be employed, especially in short travels, the potential of breakthrough diarrhea and side effects usually outweigh the potential benefits. SOT recipients should travel with azithromycin or a fluoroquinolone to be used in cases of traveler's diarrhea.

5.3 Posttransplant Vaccines

Vaccine-preventable diseases are important causes of morbidity and mortality after SOT. Vaccines should generally be given pretransplant where possible [21]. Posttransplant patients can receive inactivated vaccines (Table 5.2). Live-attenuated vaccines are generally avoided with some exception.

Table 5.2 Routine and travel vaccination (highlighted) for the posttransplant patient

Inactivated vaccine	Risk/condition	Dosing schedule
TdaP (tetanus, diphtheria, acellular pertussis)	All	One dose—if not received in the last 10 years
Pneumococcal vaccines:Prevnar13 (PCV13)Pneumovax (PPV23)	All	*Persons who have never had pneumococcal vaccine*: Give one dose of Prevnar13 and Pneumovax at least 8 weeks later *Persons who have previously had Pneumovax*: Wait a minimum of 1 year from the last Pneumovax and give Prevnar13. Then give one dose of Pneumovax 5 years from previous dose and a minimum of 8 weeks from Prevnar13 dose. No further Pneumovax boosters are recommended
Hepatitis B	All (if anti-HBs negative)	Check anti-HBs, and if negative, start three-dose series 0, 1, 6 months Use high-dose hepatitis B vaccine (40 μg Recombivax)
Influenza	All	Annually—use injectable vaccine High-dose vaccines or two standard doses 5 weeks apart may have greater immunogenicity
HPV	Men ≤26 years and MSM of any age,Women ≤45 years of age	Three doses at 0, 2, 6 months
HiB (*Hemophilus influenzae*)	Asplenia or hyposplenia;lung transplantation	One dose
Hepatitis A	All	Two doses at 0, 6 months
Shingles (inactivated)	Age ≥50 years and VZV IgG positive	Two doses at 0, 2–6 months
Meningococcal A, C, Y, W-135	Asplenia or hyposplenia, travel to meningitis-endemic area,complement deficiencyEculizumab use	Two doses of quadrivalent vaccine 8 weeks apart (Menactra or Menveo)
Meningococcal B	Eculizumab use	Two doses of vaccine 8 weeks apart
Rabies	Extensive ongoing close contact with animals	Three doses intramuscular at 1, 7, 21–28 days

Table 5.2 (continued)

Inactivated vaccine	Risk/condition	Dosing schedule
Typhoid (*Salmonella typhi*)	Travel to areas of typhoid transmission	One dose Use inactivated parenteral vaccine
Dukoral	For prevention of traveler's diarrhea	Two oral doses 6 weeks apart Available in some countries only
Live vaccine		
Varicella	VZV IgG negative	Two doses 6 weeks apart Select posttransplant patients on minimal immunosuppression, normal lymphocyte count, close follow-up
MMR	Contraindicated	
Shingles (live-attenuated)	Contraindicated	
Yellow fever	Contraindicated	Small series post-SOT suggests it is safe although data are limited

Vaccine responses are generally reduced compared to healthy controls especially early posttransplant or rejection treatment, particularly if lymphocyte-depleting therapies or rituximab is utilized. In general, vaccination can be started any time after 1 month posttransplant; however, immunogenicity may be diminished with higher doses of immunosuppression. Vaccinations may be routine (e.g., pneumococcal, influenza, hepatitis B) or given in specific circumstances (e.g., meningococcal, rabies). Pneumococcal conjugate vaccine contains protein-conjugated polysaccharides from 13 common serotypes of pneumococcus and is immunogenic in SOT recipients [22, 23] polysaccharide pneumococcal vaccine covers an additional 10 serotypes and is also recommended for SOT recipients. Appropriate intervals are required between the vaccines (Table 5.2). Posttransplant, high-dose hepatitis B vaccine containing 40 μg antigen per dose should be used for optimal seroconversion. Anti-HBs should be determined after 2–4 weeks after vaccination. Combined hepatitis A and hepatitis B vaccines could be used but generally contain <40 μg of hepatitis B antigen and may be less effective. If response is inadequate, an additional three-dose series can be attempted. Influenza vaccine should be provided annually; recent studies have shown that either high-dose vaccine or two doses of standard doses of inactivated influenza vaccine 5 weeks apart may have greater immunogenicity in SOT recipients compared to standard regime [24, 25]. Recently a new inactivated shingles vaccine has been authorized for persons ≥50 years of age who have immunity to varicella. There are currently no published data in SOT recipients with this vaccine.

Meningococcal vaccines should be given to those with risk factors only. In transplantation, specific situations warranting meningococcal vaccine include splenectomy and the use of eculizumab. In patients who undergo planned splenectomy, two doses of meningococcal quadrivalent vaccine should be given with the last one being at least 2 weeks prior to surgery. For unplanned splenectomy, vaccination can be started after postoperative recovery. Response rates may be better if vaccines are given prior to splenectomy. In some parts of the world, there is an increased incidence of meningococcal B disease [26]. A separate vaccine for the B strain is

available and can also be given in cases of splenectomy. Meningococcal vaccine has an approximately 50% seroresponse rate in transplant recipients although data in this population post-splenectomy are lacking [27, 28].

Use of the terminal complement inhibitor eculizumab is shown to predispose to fatal meningococcal sepsis. Therefore, two doses of meningococcal quadrivalent vaccine should be given prior to initiating eculizumab. Similar to splenectomy, meningococcal B vaccine can also be given. Meningococcal disease has occurred despite vaccination, and therefore for additional protection, antibiotic prophylaxis is recommended. Agents for chemoprophylaxis include amoxicillin or ciprofloxacin given for the duration of eculizumab and continuing for 3 months after the last dose of eculizumab.

Inactivated travel vaccines include injectable typhoid and oral cholera vaccine. Live vaccines should be avoided in the posttransplant period although published literature in pediatric patients suggests that select posttransplant patients could safely receive live varicella vaccine [29]. Not enough data are available to recommend other live vaccines. A yellow fever vaccine waiver is generally required for SOT recipients traveling to yellow fever-endemic areas. Serology is only routinely available for certain vaccine-preventable diseases and includes hepatitis A and B, rabies, varicella, measles, mumps, and rubella.

Close contacts of transplant patients can receive the most necessary vaccines including live vaccines. Live vaccines contraindicated in close contacts are oral polio and smallpox vaccines due to the risk of transmission. For other live vaccines, the risk of transmission of attenuated pathogens is minimal. Frequent handwashing should be practiced after contact with infants and children who have received live vaccines including rotavirus, varicella, and MMR vaccines. Healthcare workers who work with SOT patients should be up-to-date on all vaccines.

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