19 Gastrointestinal Infections After Solid Organ or Hematopoietic Cell Transplantation

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19.1 Introduction

The gastrointestinal tract is a common site of infection in patients who are immunosuppressed following either solid organ (SOT) or hematopoietic cell transplantation (HCT). Patients undergoing these procedures have many immunosuppressive drugs in common, but hematopoietic cell recipients must also face the toxicity of myeloablative conditioning regimens, absence of cellular immunity pending engraftment, acute and chronic GVHD, and delayed immune reconstitution. Clinical presentations of intestinal infection can be subtle, and diagnosis of specific infections often requires endoscopic biopsy of intestinal mucosa. Noninfectious problems, for example, diverticular bleeding after kidney transplant or intestinal GVHD after allogeneic HCT, may mimic infections and may also coexist with infection.

19.2 Gastrointestinal Infections After Solid Organ Transplantation

The frequency of gastrointestinal complications after SOT is 20–35 %, encompassing graft dysfunction and side effects of immunosuppression including direct side effects, malignancy (often from viral transformation), and infection [1–3] (Tables 19-1 and 19-2). Despite screening measures and antimicrobial prophylaxis, infectious complications remain a major source of morbidity and mortality. Infections occurring in the first month of transplant are distinct from those occurring later. In the first month most infections are those present prior to transplant (e.g., urinary tract infection), those transmitted by the transplanted organ (e.g., CMV infection), and those related to technical complications of the procedure (e.g., ascending cholangitis). After 1 month, opportunistic infections from viruses, fungi, and parasites residing in gastrointestinal reservoirs, immunoprivileged sites, or latent states, along with community-acquired infection, are more likely to occur [4].

19.2.1 Kidney and Kidney–Pancreas Transplant

After renal grafts (KT), gastrointestinal complications, usually infections, are seen in up to 50 % of patients and correlate with long-term survival [47–49]. Intestinal ischemia is more common problem after KT than after other organ transplants, particularly in patients with polycystic kidney disease [50, 51]. A life-threatening infection can lead to discontinuation of immunosuppressive drugs and the renal graft sacrificed, as uremia is treatable by dialysis.

Biliary tract and pancreatic infections (cholecystitis, ascending cholangitis, infected pancreatitis) are common in KT recipients particularly among patients with diabetes [52], related to a high frequency of gallstones and to elevated blood triglycerides, secondary hyperparathyroidism, and medications, (cyclosporine, azathioprine, and prednisone), respectively [53, 54].

Cytomegalovirus (CMV) viremia and gastrointestinal disease are common in KT and KPT, with pancreas recipients at greater risk due to higher levels of immunosuppression [5, 55]. CMV disease is a risk factor for rejection of renal grafts [56]. Preemptive therapy for viremia reduces the frequency of CMV disease [57]; however, after surveillance has ceased, CMV can cause enteritis or pneumonia years after transplant [58]. The peak time for symptoms is about 8 weeks after transplant. In high-risk patients (donor seropositive and recipient seronegative), valganciclovir prophylaxis is now routinely practiced [5, 59]. In high-risk patients receiving prophylaxis kidney retransplant has been identified as a risk factor for developing CMV reactivation [60].

In historical KT recipients there was a 20 % incidence of gastrointestinal hemorrhage likely related to *Helicobacter pylori* infection [61, 62]. With treatment of *H. pylori* before transplant and use of proton pump inhibitors, ulcer formation and hemorrhage are now rare (<5 %) after KT [3].

Five to 10 % of kidney transplant patients require long-term immunosuppressive therapy because of chronic rejection increasing the risk of CMV, EBV, hepatitis viruses, papillomavirus, parasites, and fungi [63, 64]. Severe colitis

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Table 19-1. Microorganism causes of gastrointestinal infection after solid organ transplantation

Organism class	Epidemiology	Clinical presentation/diagnosis	Treatment/prophylaxis
CMV	Most common gastrointestinal infection resulting from reactivation of latent donor or recipient virus [5] Especially common in treatment for organ rejection [4] treatment with mycophenolate mofetil [6] CMV-negative recipients who receive a CMV-positive graft [7–9] and coinfection with immunomodulating viruses, bacteria, or fungi [4, 10] The peak incidence of CMV infection is 4–6 months after transplant once antiviral prophylaxis has been stopped [11]	Gastroenteritis accounts for 80 % of cases of organ-invasive disease [12] The presentation of CMV gastroenteritis varies widely depending on the affected gut segment and can include dysphagia, odynophagia, nausea, vomiting, abdominal pain, GI bleeding, perforation, or diarrhea CMV intestinal infection may also form intraluminal masses, masquerading as a neoplastic lesion [13]	Use of ganciclovir, foscarnet, valganciclovir prophylaxis has significantly reduced the risk [14–18] Prolonged CMV prophylaxis beyond the typical 6 months has also been evaluated in high risk patients to prevent late reactivation of CMV [19] Low risk patients can be placed on surveillance and treated only if positive for CMV DNA, but virologic surveillance can miss CMV gastroenteritis and hepatitis [20]
HSV	HSV1 and HSV2 are the second most common infection resulting from reactivation of latent recipient virus (not donor)	Gastrointestinal manifestation most commonly involves esophageal ulcers presenting as odynophagia, dysphagia, or nausea. Only rarely involves the intestines If left untreated, it can progress to gastrointestinal bleeding and/or perforation Disseminated HSV presenting with fever, leucopenia, and hepatitis can also rarely occur [21]	Prophylaxis with acyclovir, valacyclovir, valganciclovir, or famciclovir has reduced recurrence [22] If antiviral prophylaxis is not used, manifestations of HSV infection can develop in up to 70 % of transplant recipients [21]
EBV	Gastrointestinal manifestations of Epstein–Barr virus (EBV) less common than other herpes viruses	Primary EBV presents more commonly as mononucleosis with fever, pharyngitis, hepatitis, and enlarged lymph nodes in the early postoperative period [23] Secondary EBV presents more commonly in older patients as posttransplant lymphoproliferative disorder, an infiltrative lymphomatous process involving the viscera and central nervous system [24–27]	Reduction of immunosuppression, rituximab, surgery, and/or chemotherapy may be used for lymphoproliferative disorders
HHV-8	Gastrointestinal manifestations of human herpes viruses (HHV-8) less common than other herpes viruses	HHV-8 is oncogenic and can lead to Kaposi's sarcoma, Castleman's disease, and primary effusion lymphomas (a form of non-Hodgkin's lymphoma) involving the gastrointestinal tract and presenting as intestinal bleeding [28]	Reduction of immunosuppression, possibly surgical excision, radiation therapy, or chemotherapy
Enteropathic viruses	Adenovirus, norovirus, rotavirus, and astrovirus until recently have been an underrecognized cause of diarrhea in patients undergoing SOT [29] Shedding can pose an infectious risk to other immunocompromised patients especially in facilities specializing in transplant care [29] Routine testing with PCR for these viruses should be performed in immunosuppressed patients with diarrhea for the purpose of guiding therapy and infection control	Watery non-bloody diarrhea is usually proceeded by nausea, vomiting, and abdominal cramping Can cause both acute and chronic infections and can lead to prolonged symptomatic or asymptomatic viral shedding [29]	A live attenuated vaccine is available for adenovirus types 4 & 7 and rotavirus that can only be administered only prior to transplant [29] There are no vaccines available for norovirus (see Chap. 28) Alcohol disinfectants are not effective for enteric viruses and soap and water should be used Cidofovir or brincidofovir has shown efficacy against adenovirus [29, 30] Nitazoxanide may have activity against norovirus, although no controlled trials have been performed. No antiviral therapies exist for rotavirus or astrovirus

C. difficile	*C. difficile* infection (CDI) represents one of the most common causes of diarrhea in the SOT population and occurs in greater than 10 % of patients [31, 32] Antibiotics and other factors that decrease microbial diversity in the gut microbiota are thought to contribute to the disease by compromising colonization resistance to pathogenic strains of *C. difficile* [33, 34] A hypervirulent strain BI/NAP1/027 has been responsible for many of the outbreaks of CDI and for severe refractory CDI [35]	Watery non-bloody diarrhea often with elevated white count Pseudomembranous colitis on colonoscopy or flexible sigmoidoscopy Diagnosed most often by a positive PCR for DNA coding for *C. difficile* toxins A or B	Treatment usually consists of metronidazole, oral vancomycin, or fidaxomycin [36] Recurrent CDI can be treated with pulsed dose antibiotics [37] Fecal microbiota transplantation has been given in the immunosuppressed population, and in small cases series does not have increased incidence of infectious complications [38] First FMT has cure rates of 78 % in the immunocompromised population and approaches cure rates of 90 % after a second course of FMT [38, 39] Other therapies including investigational antibiotics, monoclonal antibody therapy, vaccine, and microbe-based approaches to treatment are also currently in clinical trials [40] Colonization with nonvirulent strains by administration of spores has been shown to be protective against recurrent CDI [41]
Fungi	Gastrointestinal infections with fungi are most commonly due to *Candida* spp. (*C. albicans*, *C. albicans*, *C. tropicalis*, and *C. krusei*) [42] and less commonly to *Aspergillus* spp Candidal yeast forms can traverse intact small intestinal mucosa into the portal circulation. Mortality from visceral fungal infection is high especially in patients located in the ICU	Gastrointestinal *Candida* infection can manifest as candidal esophagitis presenting most often with dysphagia or odynophagia, sometimes without oral thrush, thus, obviating the need for upper endoscopy for diagnosis Esophageal candidiasis can often present simultaneously with CMV or HSV especially in patients on high levels of immunosuppression In addition, intestinal reservoirs and swallowed yeast forms of *Candida* and aspergillus can translocate the gut leading to peritonitis, fungemia, intra-abdominal abscesses, and invasive mycoses of the liver or pancreas	Antifungal prophylaxis with fluconazole in SOT patients has not been universal due to side effects, emerging resistance, and lack of controlled trials [43] Instead prophylaxis depends on identifying patients that are at high risk for developing infections [44] Fluconazole is more routinely given in liver, lung, pancreas, and intestinal transplants due to the higher incidence of fungal infections [44] Treatment of Candidal infections depends on the specific species, susceptibilities, and nature of infection [44]
Microsporidia	Microsporidia infection is well appreciated in patients with HIV infection, but may be under diagnosed due to low suspicion and lack of detection with routine stool examination in the post-SOT population [45]	Chronic unexplained diarrhea, fatigue, and weight loss Detection of microsporidia requires the use of a modified trichrome stain	Treatment is most often with albendazole
Strongyloides	Pretransplant screening measures of patients that are from or have visited endemic areas (West Indies and Far East) has reduced the prevalence of disseminated strongyloidiasis in the SOT setting	*Strongyloides stercoralis* can lead to fever, abdominal pain, bloody diarrhea, abdominal distension, and nausea Rarely it presents with an acute respiratory illness caused by migration of *S. stercoralis* through the lungs or hyperinfection which is associated with high mortality [46]	Treatment is most often with ivermectin

Table 19-2. Noninfectious causes of gastrointestinal signs and symptoms after solid organ transplantation, by organs transplanted

Kidney and kidney–pancreas	Pancreas	Liver	Heart, lung, and heart–lung	Intestine and intestine–liver
Acute pancreatitis	Acute pancreatitis	Biliary leak	Choledocholithiasis	Anastomotic leak
Biliary leak	Biliary leak	Bowel perforation	Bowel perforation	Graft rejection
Bowel necrosis	Bowel necrosis	Bowel obstruction	Gastroparesis	
Bowel obstruction	Bowel obstruction	Gastrointestinal bleeding	GERD/Dyspepsia	
Choledocholithiasis	Duodenitis	Graft rejection	Pancreatitis	
Duodenitis	Enterocutaneous fistula	Hepatic artery stenosis	Peptic ulcer disease	
Enterocutaneous fistula	Graft vessel thrombosis	Hepatic artery thrombosis	Pseudoobstruction	
Gastrointestinal bleeding	Graft rejection			
Graft rejection	Internal hernias			
Graft vessel thrombosis				
Intestinal ischemia				

and enterocolitis caused by CMV, *C. difficile*, *C. septicum*, cryptosporidia, and enteric bacterial infections have been described in small numbers of KT patients, usually in case reports [65–68].

19.2.2 Pancreas Transplant

Pancreas transplant recipients develop all the infections common to SOT patients, but most of the abdominal problems that develop are related to the surgery and the grafted tissue [69, 70]. *C. difficile* and CMV are most common gastrointestinal infections [71]. Surgical complications are given in Table 19-2 [69] Pancreatitis may develop in the pancreatic portion of the graft, causing nausea and vomiting, bleeding, anastomotic leaks, perforation, and abscesses [69]. Hematuria may be one sign of bleeding of the graft, if bladder drainage is used.

19.2.3 Liver Transplant

Gastrointestinal complications unique to orthotopic liver transplant (OLT) are generally related to the surgery itself (Table 19-2) [72, 73] and recurrence of the underlying liver disease, both infectious (see Chap. 14) and noninfectious.

A higher incidence of bacterial (70 %), viral (20 %), and fungal (8 %) infections are seen in OLT than other solid organ transplants [74, 75], including enteritis, colitis, ascending cholangitis, peritonitis, and intra-abdominal abscess. This high rate of infections may be related to low albumin state (and ineffective opsonization capacity), decreased barrier function of the intestine, disruption of the luminal integrity with transection of the biliary tract, and iron overload [75, 76]. Viral infections are associated with increased bacterial infections [77] and increase the risk of allograft injury and rejection [74, 78].

Most bacterial infections occur within the first 2 months after transplant [75, 79–81]. A range of bacterial prophylactic regiments have met with mixed results in preventing surgical site and deep intra-abdominal infections [75, 82]. Unusual opportunistic infections (Listeria and Mycobacterium) are more prevalent beyond 2 months after transplant [75]. *Clostridium difficile* infects 2.7–15.8 % of OLT recipients leading to high rates of graft loss, total colectomy, and death [75]. OLT patients with hyperbilirubinemia and hypoalbuminemia are at increased risk for bacterial infections (particularly with *Pseudomonas*) in the setting of liver biopsy [83].

CMV infection in OLT recipients is the most problematic viral pathogen, associated with increased morbidity and mortality [84]. Prophylactic use of ganciclovir is associated with an increased incidence of delayed-onset primary CMV disease, associated with increased mortality. Alternatively, surveillance for CMV viremia or DNAemia and preemptive therapy can be effective. Primary CMV infections can occur in OLT patients who were seronegative at the time of transplant [85–87]. A finding of asymptomatic low-level CMV viremia after OLT does not require antiviral therapy, but patients with high-level viremia or CMV disease in the liver, gastrointestinal mucosa, or lungs are treated (see Chap. 25) [88, 89].

Herpes simplex virus, VZV, rotavirus, adenovirus, and norovirus are rarer causes of viral infections in OLT patients. EBV infections and lymphoproliferative syndromes may occur in chronically immunosuppressed OLT recipients. The incidence of adenovirus infection after OLT is 2–6 % and usually involves the transplanted liver, although other organs can be infected in the absence of liver involvement [90, 91]. The incidence of adenovirus infection is lower in isolated OLT than in combined liver and small intestinal transplant [92].

In the past, OLT recipients frequently developed invasive fungal infections with mortality rates ranging from 65 to 90 % [93], related to fungal overgrowth in the gut with translocation. Current rates of fungal infections are less than 10 % [94, 95]. Many risk factors for fungal infection have been identified including dialysis, rejection treatment, CMV infection, biliary tract disease, use of broad-spectrum antibiotics, indwelling Foley catheter, and iron overload [93, 96]. Fungal resistance to fluconazole has led to alternative antifungal regiments (e.g., micafungin and anidulafungin) [97, 98].

19.2.4 Heart, Lung, and Heart/Lung Transplant

Some 50 % of heart (HT), lung (LT), and heart–lung transplantation (HLT) recipients have gastrointestinal complications, with up to 20 % requiring surgery [99–101]. In the first 30 days the most common complications are pancreatitis, gastroduodenal ulcers, pseudoobstruction, and colonic perforation. In the ensuing months diarrhea, gastroesophageal reflux disease (GERD), gastroparesis, dyspepsia, nausea and vomiting, abdominal pain, pancreatitis, CMV, cholelithiasis, ulcers, and hepatobiliary disease are more common [100, 102, 103].

Symptomatic gastroparesis has been described in 25 % of LT recipients and up to 80 % in HLT recipients [104, 105]. The course is often waxing and waning, but in most patients, there is remission of symptoms [104, 106]. Recipients with GERD and/or gastroparesis are at risk for the development of obliterative bronchiolitis [102, 104]. Proton pump inhibitors are useful for reducing reflux; however, if reflux disease is unremitting, laparoscopic fundoplication may be successful [107, 108]. Giant gastric ulcers (>3 cm in diameter) have been described in LT recipients despite use of proton pump inhibitors. Risk factors include bilateral LT, high-dose NSAIDs, high-dose corticosteroids, and cyclosporine. The description of these ulcers suggests decreased mucosal blood flow from stress or CMV endovascular infection rather than NSAIDs as the cause [109, 110].

CMV disease is more frequent after LT and HT than other organ transplants, presenting most often as pneumonia but gastrointestinal CMV infection is also common [9]. LT and HLT recipients have the highest incidence of fungal infection in SOT. Aspergillus is more common than *Candida* species.

Adenovirus infections in LT and HLT patients affect primarily the transplanted organ rather than the gut and carry a high incidence and mortality [111]. HSV, VZV, and EBV cause the same spectrum of problems in cardiac as in other transplantation patients. The most serious complication is EBV-related lymphoproliferative disease. Although most cases are of B-cell origin, T-cell lymphomas have also been described [112].

Patients undergoing LT for cystic fibrosis experience a unique set of gastrointestinal complications [113] including pancreatic insufficiency and secondary biliary cirrhosis which can complicate absorption of immunosuppressive medications such as cyclosporine. Distal intestinal obstruction syndrome occurs in about 20 %. Cystic fibrosis patients may also experience cholecystitis, peptic ulcer disease, GERD, and gallstones. Biliary complications occur more frequently after HT than in the general population. Transplant patients can undergo elective prophylactic cholecystectomy as mortality of biliary disease post transplant is high [114].

19.2.5 Intestine and Intestine: Liver Transplant

Most of the complications of intestinal transplant are related to the underlying intestinal diseases leading to the transplant (usually short bowel syndrome following infarction or extensive Crohn's disease), rejection of the graft, and anastomotic leaks [115]. The level of immunosuppression to prevent rejection of the graft is high, along with the frequency of infection by herpesviruses, bacteria, and fungi. The most common causes of viral enteritis are rotavirus (high-volume watery diarrhea with prolonged viral shedding) [116]; adenovirus (mostly ileal involvement, with severe symptoms) [92, 117, 118]; norovirus (protracted, severe diarrhea) [119]; and CMV (now less common because of ganciclovir prophylaxis but potentially severe) [120]. The presentation of viral infection often overlaps with signs and symptoms of rejection. Hence differentiation between viral infection and rejection is crucial. Two types of malignancy related to immune suppression have been reported, EBV-lymphoproliferative disease and de novo cancers of non-lymphomatous origin [115, 121]. Surveillance for EBV DNA and preemptive treatment reduces the frequency of lymphoproliferative disease. Because the continuity of the intestinal neurons is disrupted by the surgery, intestinal dysmotility and anorexia can be problematic. Gastrointestinal symptoms secondary to de novo food allergy has been reported in three intestinal transplant recipients [122].

19.3 Gastrointestinal Infections Before and After Hematopoietic Cell Transplantation (HCT)

HCT recipients are prone to many of the same gastrointestinal infections as SOT recipients, but noninfectious intestinal complications are much more common after HCT (Table 19-2) [123]. The current approach to gastrointestinal infection after HCT emphasizes pretransplant screening for infection, prophylaxis, early recognition of infection using molecular methods, and preemptive therapy. Compared to past HCT experience, gut infections are now less common and only rarely cause death.

19.3.1 Gastrointestinal Infections Before the Start of Conditioning Therapy

Unlike SOT candidates, HCT candidates are often immunocompromised and have low platelets prior to transplant due to chemotherapy or the underlying disease process, for example, a hematologic malignancy or immune disorder. Pretransplant gastrointestinal problems can be infectious in origin and require evaluation prior to transplant [124].

In addition to the common causes of upper gastrointestinal bleeding (gastroduodenal ulcers related to *H. pylori* or NSAID use, Dieulafoy lesion, erosive esophagitis), upper sources of bleeding can be due to mucosal infection caused by CMV, HSV, VZV, or *Candida* spp. [124]. In addition to the usual causes of colonic bleeding (inflammatory bowel disease, colorectal cancer, telangiectasias, and diverticula),

bleeding can also be due to infection caused by CMV, *Entamoeba histolytica,* Clostridium *septicum* (typhlitis), and rarely *Clostridium difficile.* Ideally intestinal ulcerations should be healed prior to undergoing HCT as bleeding will likely worsen in the setting of more profound thrombocytopenia with conditioning therapy. Interestingly, *H. pylori* infection in one retrospective study inversely correlated with the development and severity of GVHD [125].

Patients with immune deficiency disorders and immunosuppression caused by hematologic malignancy or its treatment may also present with acute onset diarrhea. In addition to the common causes of diarrhea (irritable bowel syndrome, ulcerative colitis, and Crohn's Disease), infectious causes should be given special consideration including *E. histolytica*, *Strongyloides*, *Giardia lamblia*, cryptosporidia, *Clostridium difficile*, CMV, rotavirus, and adenovirus [126–129]. Some infections like Cryptosporidiosis may be resistant to therapy in an immunosuppressed patient [130], but restoration of normal immunity after allogeneic HCT can effect clearance of cryptosporidia [131]. Typhlitis is a syndrome of cecal edema, mucosal friability, and ulceration in neutropenic patients, often associated with polymicrobial sepsis and high mortality if left unrecognized and untreated; its cause is usually intestinal clostridia infection, particularly *C. septicum* [132, 133]. Typhlitis occurs in the setting of induction chemotherapy and is sometimes difficult to distinguish from the direct toxic effects of the chemotherapeutic agents. Typhlitis has become far less frequent since physicians began prescribing empiric antibiotics that cover clostridial organisms in patients with right lower quadrant pain.

Pain near the anal canal in a granulocytopenic patient is due to bacterial infection until proven otherwise. Administration of broad-spectrum antibiotics, including anaerobic coverage, is adequate treatment in most cases, with surgical incision and drainage reserved for progressive infections [134]. Extensive supralevator and intersphincteric abscesses may be present without being apparent on external examination but can be diagnosed by computed axial tomography (CT), magnetic resonance imaging (MRI) or transperineal sonography. Less commonly, perianal inflammation and ulcers may be due to HSV, CMV, and fungal infections [135].

19.3.2 Gastrointestinal Infections During the First Year After HCT

After HCT, gastrointestinal infections are now far less common than gut mucosal and liver injury caused by noninfectious diseases such as the effects of conditioning therapy, medication side effects, and GVHD [136]. This is largely due to prophylactic regimens. We also have a better understanding of some of the factors that predispose patients to GVHD and superimposed infections such as vitamin D deficiency [137]. When infections do occur, they usually develop in the background of these other gut diseases.

High-dose conditioning therapy damages the oropharyngeal and gastrointestinal mucosa, resulting in oral mucositis anorexia, and diarrhea. Oropharyngeal mucositis may extend into the esophagus, causing dysphagia and painful swallowing that mimics infectious esophagitis [138]. Esophageal infections have almost disappeared as problems after transplant because of prophylaxis against HSV, VZV, and *Candida* species and preemptive therapy in patients with CMV DNAemia.

Anorexia and nausea caused by conditioning therapy varies in its intensity (myeloablative regimens causing more severe and more protracted gut mucosal damage) and may persist beyond day 20. These symptoms are also common complications of transplant medications such as calcineurin inhibitors, sirolimus, mycophenolate mofetil, azole antifungal drugs, trimethoprim–sulfamethoxazole, nystatin, and rarely now, amphotericin B. In years past, herpesviruses were common causes of nausea, vomiting, and anorexia [139], but with the exception of sporadic cases of CMV disease, herpesvirus infections of the upper gut have largely disappeared.

Acute GVHD of the intestine and liver is an immunologic disorder that results from donor lymphoid cells reacting against host tissues and usually has its onset 15–40 days after transplant [136, 139–141]. Gut GVHD can occur earlier if prophylactic medications (e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil) are not given, or later, following reduced-intensity conditioning regimens [142]. In most patients, acute GVHD diminishes by day 100, although in some it can be protracted. Intestinal manifestations of acute GVHD include nausea and vomiting, profuse watery diarrhea with protein loss, abdominal pain, bleeding, and ileus [123]. The diagnosis of acute GVHD can usually be made on clinical grounds and confirmed by biopsy of target organs. The syndrome of chronic GVHD occurs 3–9 months after transplantation. Intestinal problems of chronic GVHD include esophageal desquamation and stricture formation, bacterial overgrowth in the small intestine, and chronic cholestatic liver disease [143]. MMF can cause intestinal inflammation and ulcerations in a presentation that is difficult to distinguish from GVHD [144]. Oral potassium replacement among other medications can result in esophageal ulcers. Antibiotic use can lead to alterations in the intestinal flora and promote intestinal domination with certain fungi and gram-negative organisms [145]. This may predispose patients to antibiotic-associated diarrhea, *C. difficile* colitis, *C. septicum* typhlitis, and bacteremia (see Chap. 52).

The most common organisms causing gastrointestinal infection after HCT are viral (CMV, norovirus, adenovirus, rotavirus, and astrovirus) and bacterial (*C. difficile*) and they commonly develop in patients with GVHD [146]. Gut infections that were prevalent 30 years ago have largely disappeared because of changes in practice—low microbial foods during extreme immune suppression, prophylaxis of common infections, and microbial surveillance with preemptive therapies [147]. Before fluconazole prophylaxis, problems formerly caused by fungal infection (esophagitis, enteritis,

portal fungemia, bleeding ulcers, and hepatobiliary disease) were not uncommon [148, 149].

Before the advent of serological testing for CMV and preemptive treatment with ganciclovir, gastrointestinal CMV was the most problematic of the herpes viruses [150]. While valganciclovir prophylaxis showed no advantage over PCR-guided preemptive therapy [151], other next generation therapies with fewer side effects than currently used prophylactic antivirals are in Phase III clinical trials and are likely to be used widely as routine prophylaxis in the near future [30, 152]. CMV disease usually presents as nausea and vomiting between 40 and 60 days after transplantation. CMV may be recovered from ulcerations throughout the intestine even when molecular methods cannot identify CMV in the bloodstream [150]. CMV may also be associated with pancreatitis and infiltration of neural elements in the intestine [153].

Adenovirus usually causes a mild to moderately severe diarrheal illness, but severe disseminated disease, with fulminant hepatitis and necrotizing enteritis, has been reported with some serotypes of the virus [154–158]. Other enteric viruses that cause diarrhea include *astrovirus, norovirus,* and *rotavirus* [129, 141]. EBV-associated posttransplant lymphoproliferative disease (PTLD) has a frequency of about 3 % [159]. It can develop rapidly in HCT patients, infiltrating the stomach, intestine, mesentery, liver, and spleen [160]. Poor treatment response to rituximab is determined by age greater than 30 years, involvement of extralymphoid tissue, GVHD, poor response to immunosuppressive tapers, and unchanged EBV viremia [159].

The risk of parasitic diseases has decreased in the setting of pretransplantation screening and treatment. If patients are discharged to a less-controlled environment, they may acquire parasites such as *Giardia lamblia* and *Cryptosporidium* organisms, particularly from infected children and drinking water [126, 161, 162]. The diagnosis of cryptosporidial infection—often missed with standard microscopy—is best made by PCR of fecal specimens [128].

19.3.3 Gastrointestinal Infections in Long-Term Transplant Survivors

Intestinal and hepatobiliary complications after the first year are far less common than earlier post-transplant; most of these intestinal problems, however, are not related to infection (Table 19-2). Some patients with extensive chronic GVHD have esophageal desquamation, webs, submucosal fibrous rings, bullae, and long, narrow strictures in the upper and mid-esophagus [143, 163, 164]. The most common symptom is dysphagia; some patients present with insidious weight loss, retrosternal pain, and aspiration of gastric contents. Chronic GVHD may cause intractable esophageal disease if not diagnosed and treated promptly. Patients with protracted acute GVHD often have symptoms that wax and wane with intensity of immunosuppressive therapy for up to 15 years after HCT, with each exacerbation similar to the presenting signs of GVHD that occurred earlier after HCT (satiety, poor appetite, nausea, episodic diarrhea, and weight loss) [165, 166]. Sporadic cases of fungal and rarely viral esophagitis may occur in patients with chronic GVHD on immunosuppressive and antibiotic therapy. Esophageal strictures may be sequela of earlier herpes virus infection or mucositis. There are sporadic cases of gut infection with *C. difficile*, CMV, and rarely *G. lamblia*, *Cryptosporidia*, *rotavirus*, and *norovirus*, in long-term survivors [143, 161, 162, 167].

Squamous cell carcinoma of the esophagus has been reported in HCT survivors, usually with concomitant chronic GVHD of the oropharynx [168]. Myasthenia gravis may also complicate chronic GVHD, with dysphagia as its presenting complaint. Intestinal diseases in cell donors have been reported in their recipients, for example, inflammatory bowel disease and celiac sprue [169, 170]. Diarrhea, steatorrhea, and weight loss secondary to pancreatic insufficiency have developed in some HCT survivors [171].

19.4 Intestinal Microbiota in Transplant Patients

The gastrointestinal microbiota plays an important role in the development of infections after both SOT and HCT [172]. Much of our current understanding of the microbiota's role in SOT comes from work in patients who have undergone orthotopic liver transplantation [173, 174]. The microbiota may predispose patients to nonalcoholic steatohepatitis. In cirrhosis, the microbiota produces metabolites including ammonia that contribute to hepatic encephalopathy [175]. Administration of lactobacillus combined with a high fiber diet has been shown to prevent postoperative infections in liver transplantation [176]. A study evaluating the effect of pretransplant rifaximin on the incidence of post-liver transplant infections found no significant difference [82]. In kidney transplants, increased abundance of *Faecalibacterium prausnitzii* has been associated with escalation of tacrolimus levels [177]. The microbiota also influences the immune system's T cell subtypes and likely has direct impacts on transplant outcomes [178].

In HCT the microbiota is impoverished as a result of administration of systemic antibiotics [179, 180], gut inflammation caused by GVHD [179], and possibly other factors. The degree to which the diversity is decreased at the time of engraftment has been shown to predict all cause mortality after allogeneic HCT [181]. An impoverished microbiota may effect mortality by leading to worsened GVHD [179, 182], increased risk of enteric infections [183], and increased risk of bacteremia [145]. Certain probiotic species like *Lactobacillus* spp. have been shown to have an ameliorating effect on the severity of GVHD [182]. Patients with leukemia vs. other forms of hematological malignancy have been

shown to preferentially develop low diversity states with predominance of *Enterococcus,* but the reason is not known [145]. Increased risk of low diversity may also be associated with comorbid autoimmune conditions in which dysbiosis has been shown to be prevalent [184].

19.5 A Problem-Oriented Approach to Diagnosis of Gastrointestinal Infections After Transplant

19.5.1 Heartburn, Odynophagia, and Dysphagia

The organisms responsible for infectious esophagitis are fungi, viruses, and bacteria, but infections caused by multiple types of organisms are common in severely compromised, neutropenic patients [185]. In contrast, less compromised patients with indolent esophageal infections may present with chronic dyspepsia and dysphagia; these patients rarely have deep fungal infections involving the spleen or liver, probably because of adequate neutrophil function. Less well appreciated as symptoms of esophageal infection are nausea, vomiting, and anorexia, which are typical of infection with herpesviruses. With antimicrobial prophylaxis, preemptive therapy, and close monitoring, esophageal infections have become rare and noninfectious causes of esophageal disease relatively more common (Table 19-3).

19.5.1.1 Fungal Esophagitis

C. albicans is the most common infecting fungal organism, but other *Candida* species, other fungi (*Aspergillus, Histoplasma, Cryptococcus, Blastomyces*), and some plant molds may be found in severely immunosuppressed patients [185–187]. *Candida* esophagitis can be asymptomatic when few adherent plaques are present. Diagnosis is by stains of brushed or biopsied lesions at endoscopy; cultures cannot reliably differentiate among normal flora, colonization, and infection [188], but are useful if an unusual pathogen such as an azole-resistant *Candida* species, *Aspergillus* species, dematiaceous fungi, *Mycobacterium tuberculosis*, or bacterial esophagitis is suspected. Rapid viral cultures should be routine when viral esophagitis is in the differential, even when fungal esophagitis is obvious.

19.5.1.2 Viral Esophagitis

HSV, VZV, and CMV cause acute ulcerative esophagitis in the immunosuppressed patient, presenting with excruciating retrosternal pain in some and in others just nausea, anorexia, mild heartburn, or bleeding [185]. Reflux of acid-peptic juice contributes to the persistence of large ulcers. The diagnosis of HSV esophagitis is made by finding rounded 1–3 mm vesicles in the mid- to distal esophagus, the centers of which slough to form discrete, circumscribed ulcers with raised edges. The discrete ulcerations can coalesce into very large ulcers, presenting difficulty in diagnosis when there is near-total denudement of esophageal epithelium. The endoscopist must attempt to identify HSV-containing ulcer margins or islands of squamous mucosa from which to obtain samples. IHC, rapid viral diagnosis, and PCR are essential for diagnosis when routine histology is equivocal [185] especially in patients with gastric stasis, vomiting, or poor salivary flow (common problems after both HCT and heart–lung transplant). VZV causes typical vesicles and necrotizing panesophagitis in severely immunodeficient patients, with diagnosis by immunohistologic staining, rapid viral cultures, and PCR. The esophageal component of VZV infection may be overshadowed by varicella encephalitis, pneumonitis, and fulminant hepatitis. Immunohistochemical staining and PCR are helpful in differentiating VZV infection from HSV. VZV and HSV esophagitis are rare in patients receiving acyclovir

Table 19-3. Noninfectious causes of gastrointestinal signs and symptoms after hematopoietic cell transplantation, in descending order of frequency

Heartburn, odynophagia, dysphagia	Anorexia, nausea, vomiting	Diarrhea	Abdominal pain	Perianal pain	Gastrointestinal bleeding
Acid-peptic reflux	Mucosal injury from conditioning therapy	Mucosal injury from conditioning therapy	Intestinal pseudo-obstruction	Anal fissure	Acute and protracted acute GVHD
Oropharyngeal mucositis from conditioning therapy	Acute and protracted acute GVHD	Acute and protracted acute GVHD	Acute and protracted acute GVHD	Thrombosed external hemorrhoid	Mucosal injury from conditioning therapy
Chronic GVHD	Medications	Medications (see text)	Mucosal injury from conditioning therapy	Levator muscle spasm	Mallory–Weiss tear
Pill esophagitis	Rarely, brain disorders (neurotoxicity, hematomas)	Intestinal lactase, sucrose deficiency	Biliary pain (sludge, stones)		Bleeding from mucosal biopsy site
Peptic strictures			Hemorrhagic cystitis		Gastric antral vascular ectasia
Post-infection strictures			Acute pancreatitis		Bleeding from diverticula
Severe acute GVHD			Liver pain (SOS)		
Intramural hematomas			Intestinal perforation		
			Intestinal infarction		
			Intramural hematomas (intestine, abdominal wall)		

prophylaxis. In contrast, CMV never infects squamous epithelium but rather subepithelial esophageal cells leading to superficial erosions with serpiginous, non-raised borders in the mid- to distal esophagus. As CMV infection progresses, shallow ulcerations may deepen, extend for 10–15 cm, and even become strictured. Multiple biopsies should be obtained from the bases of the esophageal ulcers, as this is where CMV-infected sub-epithelial fibroblasts and endothelial cells reside [189]. Immunohistochemical staining for early, intermediate, and late antigens can confirm the diagnosis of CMV infection when infected cells are neither megaloid nor inclusion-bearing. These histologic and immunohistologic methods, however, are only about half as sensitive as rapid viral culture methods [189]. If a positive PCR result for CMV DNA is not concordant with viral culture, immunohistology, blood assays for CMV DNA, or endoscopic findings, antiviral therapy should be withheld.

19.5.1.3 Bacterial Esophagitis

Oropharyngeal bacteria may cause esophageal necrosis in patients who lack granulocytes following HCT [190]. Esophageal symptoms, fever, and bacteremia are the usual presenting symptoms; tissue Gram stain is needed for diagnosis. Mycobacterial esophagitis usually presents an extension of pulmonary and mediastinal infection caused by *Mycobacterium tuberculosis*; primary esophageal infection has also been described [185, 191].

19.5.1.4 Noninfectious Causes of Esophageal Symptoms

Infections must be differentiated from noninfectious esophageal disorders (Tables 19-2 and 19-3). It may be difficult to discern the dominant cause of esophageal mucosal injury when both infection and another cause of injury are present. Reflux of gastric contents is particularly problematic after lung or heart–lung transplant and in the presence of Roux-en-Y anastomosis in liver transplant patients. Less common causes of esophageal injury include pill esophagitis, intramural hematomas, and graft-vs-host disease after HCT.

19.5.2 Anorexia, Nausea, and Vomiting

Before effective antiviral prophylaxis and preemptive therapy after SOT and HCT, herpesvirus infections of the esophagus, stomach, or intestine commonly caused loss of appetite, nausea, and vomiting in addition to painful swallowing or diarrhea [189, 192, 193]. VZV and CMV infections may involve visceral neurons to produce a pseudo-obstruction picture with distention and vomiting [194]. Gastric ulcers caused by CMV may fail to heal on acid-reducing medications [195]. Nausea and vomiting are common manifestations of community-acquired viral gastroenteritis and intestinal parasitic infection, especially with *G lamblia* and *Cryptosporidium* organisms [161, 162]. In SOT recipients, *H. pylori* infections, particularly those that cause pyloric channel ulcerations, may cause anorexia, nausea, and poor oral intake, without ulcer pain (syndrome pylorique) [2]. Central nervous system infections such as aspergillus are another cause of nausea and vomiting after HCT; other neurologic signs and, symptoms usually dominate the clinical picture. Diagnosis of gastrointestinal infection as a cause of anorexia, nausea, and vomiting is a three step process: (1) Analysis of stool specimens if diarrhea or abdominal pain is part of the clinical presentation; (2) upper endoscopy for diagnosis of herpesvirus and *Helicobacter pylori* infections; and (3) directed examination of organs that declare themselves to be involved, for example, gallbladder ultrasound when right upper quadrant pain is present, serum lipase and pancreatic amylase when there is epigastric pain, and so on [100, 101, 136]. It is not uncommon to recover CMV from endoscopic biopsies of focal esophageal or gastroduodenal lesions, even when there is no detectable virus in the blood stream.

19.5.2.1 Noninfectious Causes of Upper Gut Symptoms

The differential diagnosis of anorexia, nausea, and vomiting encompasses a long list of noninfectious causes (Tables 19-2 and 19-3). Anorexia and nausea are such protean symptoms that medical judgment must dictate when to aggressively pursue their causes. The more immunosuppressed and the sicker the patient, the more aggressive should be the evaluation. In SOT recipients, anorexia and nausea may be due to organ rejection; gastroparesis (after lung transplant); failure of liver, renal, pulmonary, or cardiac function; visceral inflammation (for example, pancreatitis, cholecystitis, and cystitis). Acute GVHD may also develop after organ transplantation, usually presenting with fever, skin rash, and gastrointestinal symptoms [196–198]. After HCT, myeloablative conditioning therapy causes nausea, vomiting, and anorexia that lasts for 2–3 weeks [138]. After HCT day +20, the most common cause of upper intestinal symptoms is acute GVHD, which causes gastric mucosal edema and erythema [139, 199]. Lymphocytic gastritis resembling GVHD can also be seen in about 12 % of autologous graft recipients [200]. Less common causes of anorexia and nausea after day +20 include disorders of gastric emptying, medication intolerance, and central nervous system lesions [139, 201–204].

19.5.3 Diarrhea

The differential diagnosis of infectious diarrhea in a transplant patient encompasses the same pathogens as in the normal host, as well as some that are very uncommon under ordinary circumstances. However, in the acute care setting, exposure of patients to environmental pathogens is rare

except for *C. difficile* and thus, infection by common enteric pathogens is rare, particularly when patients are following dietary guidelines for safe foods. The exception to this rule is in countries where patients may arrive for transplant already infected by bacterial, viral, and parasitic organisms or be exposed to them after discharge [68, 126]. Infectious diarrhea is often accompanied by a constellation of symptoms (fever, abdominal pain, nausea, vomiting), particularly in SOT patients [68, 205].

19.5.3.1 Bacterial Causes

C. difficile is the most common bacterial cause of diarrhea in hospitalized transplant patients. Colitis caused by *C. difficile* in granulocytopenic patients may be paradoxically mild and lacking typical pseudomembranes perhaps because colitis is largely due to a granulocyte response to clostridial toxins [141, 206, 207]. A more typical clinical course and endoscopic appearance may be seen later after HCT and in SOT patients; severity of *C. difficile* colitis in SOT patients is similar to that in nontransplant patients [208]. With the emergence of more virulent strains of *C. difficile*, more severe colitis is being seen [209]. Available therapies include metronidazole, vancomycin, and fidaxomycin [40]. A proposed probiotic treatment for *C. difficile* colitis, *Saccharomyces boulardii*, may itself reach the bloodstream in patients with immune defects and should be avoided in transplant patients [210]. In refractory immunosuppressed cases, treatment with fecal transplantation has been as efficacious as in non-immunocompromised individuals without increase adverse outcomes [38, 39]. Strict infection control measures in the inpatient, outpatient, and home settings are essential to prevent the transmission of *C. difficile* [211, 212], Relapse is common in the presence of immunosuppression, especially with glucocorticoids [208]. *Recurrent C.* difficile colitis can be treated with pulsed antibiotics and in some cases fecal transplantation [37].

Cord colitis syndrome linked to infection with *Bradyrhizobium enterica* [213] and *Bacteroides fragilis* [214] presents clinically as non-bloody diarrhea 3–11 months after cord blood transplant, histologically characterized by epithelioid granulomas and responsive to metronidazole or fluoroquinolones [215, 216]. Infections with organisms such as such as *T. whipplei* may also be involved [217]. Cord colitis appears to be absent in some centers consistent with lack of exposure to these Z-specific gut pathogens [218].

Diarrhea (often bloody) is seen with neutropenic enterocolitis (typhlitis) caused by *C. septicum* [132, 219]. Mycobacteria, *Aeromonas* species, and enterohemorrhagic *E. coli* have been described as causes of diarrhea in immunosuppressed patients [220, 221]. Bacterial infections not obviously involving the intestine may also cause diarrhea, for example, *Legionella* pneumonia [222] and toxic shock syndrome associated with *Staphylococcus aureus* infection.

19.5.3.2 Viral Causes

Viral infections can result in both acute and chronic diarrhea in the compromised host. Of the herpesviruses, only CMV and rarely HSV infection [223] lead to enteritis and diarrhea. (1) CMV may cause profuse watery diarrhea with protein loss [224, 225]; (2) or an inflammatory colitis with bleeding and pain but less voluminous diarrhea [65, 226]. CMV enteritis does not always result in diarrhea—anorexia, nausea, vomiting, bleeding, and perforation may be the only symptoms [13, 185, 195, 227]. Later CMV infection, after discharge from the transplant center, remains an issue [228, 229]. Although CMV can be found by PCR or viral culture of stool, CMV enteritis is best diagnosed by IHC and rapid viral culture of biopsy specimens from involved tissue [189]. A positive PCR for CMV DNA may represent viral excretion without CMV disease.

Some serotypes of adenovirus cause rapidly progressive necrotizing enteritis associated with severe pulmonary, liver, or renal infection where prompt diagnosis and treatment is necessary to prevent death [2, 154, 156, 230, 231]. Other adenovirus isolates appear to cause less severe mucosal disease, leading to dilemmas about the optimal treatment strategy, particularly when immune suppressive drugs must be continued and the treatment has toxicity [154, 157, 158, 232]. Detection of adenovirus in stool by PCR may be useful in high risk patients [233].

Acquired enteric adenovirus infection with self limited diarrhea and transient fever has been reported in up to 18 % of children and 8 % of adults undergoing HCT [154]. Severe adenovirus enteritis and colitis may be associated with mucosal erosions, ulcerations or bleeding, and may cause abdominal pain and tenderness. Endoscopic diagnosis may be difficult when ileal disease predominates. Adenovirus may also cause pancreatitis in HCT (associated with abdominal pain) [154, 156, 234–237]. In SOT, the source and predominant site of adenovirus infection is the transplanted organ, particularly in children in the early posttransplant period, likely because of absent antibody immunity [90, 232, 237]. Early treatment of adenovirus disease with cidofovir in HCT may be associated with better outcomes, though criteria for early treatment are not fully established. Current criteria for treatment include multiorgan involvement (i.e., viral isolation, or histological documentation, from two or more sites), viremia with clinical signs of disease, or significant (endoscopic, histological, or clinical) enteritis, pneumonia, hemorrhagic cystitis or nephritis. Use of surveillance plasma adenovirus PCR, as well as stool and urine testing in patients with diarrhea or hematuria may be valuable in early diagnosis and preemptive therapy, especially in pediatric patients and patients undergoing T cell depleted transplants [238]. Most patients with isolated stool or urinary adenovirus recover spontaneously, but close monitoring for progressive disease may be prudent [234, 235]. Criteria for treatment in SOT are poorly defined because adenovirus viremia in SOT

commonly resolves spontaneously or with reduction of immunosuppressive therapy, especially in children [90, 117, 237, 239].

Other enteric viruses (astrovirus, rotavirus, norovirus, coxsackievirus), acquired through epidemic exposure or nosocomial transmission, may cause diarrhea in transplant patients [68, 141, 240]; this category is likely to increase in prominence as panels of molecular diagnostic tests become available. These viruses can be associated with prolonged viral shedding for weeks after cessation of symptoms [235, 236]. Astrovirus, a common cause of endemic as well as nosocomial diarrhea in children, has been reported after both HCT and SOT, with a frequency of <5 % of patients with diarrhea. In one prospective study, the most common viral cause of diarrhea after HCT was Astrovirus, which caused a self-limited form of diarrhea [141]. In HCT patients, symptoms may include nausea and anorexia in addition to diarrhea [141, 241, 242]. Rotavirus, a common cause of diarrhea-predominant viral gastroenteritis in children in winter months, causes diarrhea lasting 3–9 days. Prolonged and profuse watery diarrhea of 2 or more weeks' duration is the main symptom attributable to Rotavirus in transplant patients, where the frequency of infection varies widely from center to center (0–1.5 % in adults, higher in children) [116, 243–245]. Other symptoms reported in HCT patients include vomiting, abdominal pain, anorexia, fever, and abnormal liver tests, but without severe enteritis or mortality [244, 246, 247]. Fecal shedding can continue for three or more months after clinical illness. Nosocomial transmission likely accounts for many infections especially on pediatric units [244, 247]. Norovirus is the major cause of adult epidemic viral gastroenteritis [129]. Clues to diagnosis include epidemic exposure and rapid onset of transient vomiting followed by prolonged watery diarrhea [248, 249]. With the exception of CMV, some viruses for which there are no commercial diagnostic tests, rare cases of mycobacterial infection, and EBV-related lymphoproliferative disease involving the small intestine, almost all of the infectious causes of diarrhea can be discovered by analysis of stool specimens using bacterial and viral cultures, PCR (adenovirus, norovirus, cryptosporidia), ELISA (rotavirus, astrovirus, *G. lamblia*, *C. difficile* antigen), and microscopic examination (parasitic diseases, fungal overgrowth). If the lesion is out of the reach of an endoscope, the diagnosis of EBV-related lymphoproliferative disease can be based on finding EBV DNA in the bloodstream and a mass consistent with lymphoma on imaging.

19.5.3.3 Fungal Causes

In the minimally compromised patient, intestinal fungal overgrowth can be a cause of watery diarrhea [250]. In the absence of antifungal prophylaxis, patients with prolonged granulocytopenia may develop diarrhea caused by mucosally invasive fungal infections [251]. Wide use of azoles in the peritransplant period has eliminated gastrointestinal infections caused by *Candida albicans*, but mucosal infection by molds and other *Candida* species can now be seen [252].

19.5.3.4 Parasitic Causes

Parasitic infections have probably been under diagnosed as a cause of chronic diarrhea in transplant recipients because of insensitive tests [68]. Accurate tests for organisms such as *Giardia lamblia*, *Cryptosporidium*, *Enterocytozoon bieneusi*, *Isospora belli*, and *Strongyloides stercoralis* are now available [128, 130, 253–256]. Cryptosporidial infection may mimic GVHD after HCT [127]. Cryptosporidial infections can be eliminated if the underlying immune deficiency disappears [131]. *Strongyloides stercoralis* enteritis may become exacerbated during immunosuppressive therapy, causing diarrhea and hyperinfection syndrome [238]. *Blastocystis hominis* and *Enteromonas hominis*, long believed to be innocuous commensal parasites, have been blamed for persistent diarrhea in some immunodeficient patients.

19.5.3.5 Noninfectious Causes (Tables 19-2 and 19-3)

Noninfectious causes of diarrhea that are common to all transplant patients include magnesium salts to correct renal magnesium wasting; mucosal toxicity caused by mycophenolate mofetil [144] or brincidofovir, an investigational broad-spectrum antiviral agent [30]; the pro-motility side effects of the macrolides tacrolimus and sirolimus [257, 258]; and antibiotics that depress the colonic flora (removing the ability of these bacteria to salvage carbohydrate and thus, causing osmotic diarrhea after carbohydrate ingestion). The gut toxicity of mycophenolic acid delayed release tablets is considerably less than that of MMF [259]. After HCT, diarrhea is caused by mucosal injury from myeloablative conditioning regimens and from acute GVHD [141].

19.5.4 Abdominal Pain

Pain caused by some intestinal infections and intra-abdominal infection resulting from perforation may be a harbinger of a rapidly fatal illness in immune suppressed patients [47, 136, 260, 261]. Perforation is most common in the gastroduodenal region and the colon but can occur at any site in the intestine. Plain abdominal X-rays and helical CT will determine whether a perforation has occurred but the site of perforation can remain obscure. Causes of perforation include CMV infection, fungal infection, necrosis of transmural tumors, trauma, and diverticula [2, 47, 226, 261, 262]. Diverticular perforation is particularly common in renal transplant patients [263]. CMV and VZV can also involve neural plexi, causing ileus and abdominal distention [153, 194, 264]. Severe abdominal pain is often the first manifestation of disseminated VZV

infection, which may progress to fulminant hepatitis. PCR for VZV DNA in the bloodstream is the most useful diagnostic test for visceral VZV infection in the absence of skin lesions [265]. Early recognition and institution of acyclovir therapy result in improved survival [194].

Other focal infections of the intestinal tract that present with abdominal pain include phlegmonous gastritis, appendicitis, infections caused by clostridia organisms (*C. difficile, C. perfringens, C. septicum*), and *Aspergillus* vasculitis [266]. Most immunosuppressed patients with appendicitis have right lower quadrant pain, but in some the usual presentation is masked by corticosteroids and the lack of granulocytes. Typhlitis is a localized infection of the cecum and right colon, caused by clostridia toxins (usually *C. septicum*) and closely related to granulocytopenia [132]. Typhlitis has been rarely observed after solid organ transplantation, probably because of preserved granulocyte function [267]. Consideration of this diagnosis should prompt empiric use of antibiotics (imipenem, oral vancomycin) that cover both clostridia organisms and colonic flora that are translocating into pericolic tissues, and surgical consultation in the event of progression [268]. Cecal CMV ulcerations, fungal infection, and acute GVHD in HCT recipients may present similarly but do not have the same poor prognosis as clostridial typhlitis [269, 270].

A radiologic diagnosis of pneumatosis intestinalis (gaseous infiltration of the intestinal mucosa, usually the colon) is likely to be made in a patient with pain who undergoes abdominal plain film or computed tomography, and it does not necessarily represent a severe form of enteritis. In some cases, there may be air in the peritoneal cavity, mediastinum, and portal vein in addition to the intestinal mucosa. Pneumatosis intestinalis has been described in organ recipients and HCT patients. Disease associations have been with viral enteritis (particularly CMV) and GVHD. The abdominal examination and clinical course in many patients is surprisingly benign. There are, however, catastrophic processes that present with gas in intra-abdominal tissues (intestinal infarction, bowel obstruction, and clostridia infections) that must be differentiated on clinical, microbiologic, and occasionally surgical grounds from the more benign form of pneumatosis intestinalis [271].

EBV lymphoproliferative disease occurs in both solid-organ and HCT recipients on high-dose immunosuppressive therapy. Lymphoid infiltrates may present as abdominal pain, ileus, and bleeding. PCR for EBV DNA in the bloodstream may allow preemptive reduction of immunosuppressive drugs and use of rituxan to forestall development of tissue invasion with transformed immunoblasts.

19.5.4.1 Noninfectious Causes (Tables 19-2 and 19-3)

Many episodes of abdominal pain after SOT or HCT are not caused by infection but instead by conditions such as intestinal pseudo-obstruction (caused by mu-opioid and anticholinergic drugs), pancreatitis, cystitis, biliary stone disease, and in HCT patients, the toxicity of myeloablative conditioning therapy, acute GVHD, liver pain caused by sinusoidal obstruction syndrome, and intramural hematomas involving the gut or abdomen. The initial approach to diagnosis of the cause of abdominal pain in an immunosuppressed patient must be tempered by the knowledge that intra-abdominal catastrophes may occur without extreme signs and symptoms and that the time from presentation to death can be very short. Paradoxically, there is also a danger of physicians overreacting to severe abdominal pain from a cause that seldom results in morbidity, for example, intestinal pseudo-obstruction related to mu-agonist opioids, an intramural hematoma of the sheath of the rectus abdominus muscle, or narcotic bowel syndrome.

19.5.5 Perianal Pain

Perianal pain in a granulocytopenic patient is assumed to be caused by bacterial infection of perianal tissues until proven otherwise, and thus, this is a more a problem for HCT patients than after SOT. Infections can be a difficult problem to recognize because there may be little in the way of pus but instead only a painful cellulitis. These infections are usually polymicrobial (aerobic and anaerobic bacteria), arising either from anal crypts or from tears in the anal canal [272]. Extensive supralevator and intersphincteric abscesses may also occur without being apparent on external examination. Early antimicrobial treatment has led to a marked decrease in the need for surgery. If an obvious abscess is present, antibiotics, incision, and drainage usually result in relief of pain and resolution of the abscess [273]. If there is evidence of tissue necrosis, a more aggressive surgical approach may be needed to prevent a fatal outcome. Perineal examinations may be limited by severe pain and by a risk of bacteremia if the patient is granulocytopenic. CT, MRI, and rectal endoscopic ultrasound give accurate views of the anatomy involved if there is a true abscess; the predictive value of a negative imaging test for an abscess is high.(302) However, if an imaging test suggests an abscess or clinical examination suggests infection in a perirectal space, an experienced colorectal surgeon should examine the patient under conscious sedation or anesthesia, with an eye toward surgical drainage if a significant abscess is discovered.

HSV causes painful chronic mucocutaneous ulcerations in patients with immunodeficiency syndromes, especially those with T-lymphocyte defects [274]. In the perianal area, the appearance is of multiple superficial ulcers with raised borders. When these ulcers coalesce and become macerated and secondarily infected, it is often difficult to identify them as viral. In contrast to decubiti, HSV perianal ulcers are painful, have scalloped borders, and occur away from pressure points. The diagnosis is best made by rapid viral culture. Acyclovir treatment is effective, but secondary bacterial or fungal infection may delay healing. Recurrence is common unless acyclovir is continued or immunosuppressive therapy decreased.

19.5.5.1 Noninfectious Causes (Tables 19-2 and 19-3)

There are few noninfectious causes of pain in the perianal area in transplant patients aside from anal fissures, a thrombosed external hemorrhoid, and unusual disorders of smooth muscle (levator muscle spasm, proctalgia fugax). Persistent diarrhea may lead to painful maceration of perianal skin and secondary infection by bacteria and fungi.

19.5.6 Gastrointestinal Bleeding

In the era before effective antimicrobial prophylaxis, viral ulcerations were the most common cause of bleeding in both HCT and organ transplant patients, but in the current era, bleeding from viral ulcers has become uncommon [5, 275]. CMV ulcers in the esophagus are usually shallow, but those in the gastroduodenal, small bowel, and colonic mucosa are deeper and capable of eroding into large vessels [65, 84]. CMV may also cause diffuse gastritis or enteritis similar to that seen in inflammatory bowel disease [58, 223, 276, 277] and rarely present as mass lesions [13]. Duodenal or gastric ulcers that appear to be typical peptic lesions may harbor CMV in the ulcer base and may fail to heal on standard ulcer therapy [195, 278]. If ulcers are in the midgut, a radionuclide blood pool scan or capsule endoscopy can localize the bleeding site, allowing angiographic control or surgical resection if the ulcer is truly solitary and continues to bleed. Endoscopic hemostasis of bleeding CMV ulcers can occasionally be achieved, but this must be accompanied by antiviral therapy; CMV ulcers often require 2–3 weeks for mucosal lesions to heal following effective therapy [193].

HSV may present as bleeding from coalescent herpetic esophageal ulcers without symptoms referable to the esophagus [279]. HSV causes gastric and intestinal necrosis only rarely, usually in patients on high-dose immunosuppressive therapy [223]. VZV causes esophagitis similar to that caused by HSV and occasionally gastric ulcers, but not intestinal mucosal necrosis. EBV does not cause direct ulceration, but in transplant patients, it may lead to a lymphoma-like immunoproliferative disease may present with bleeding submucosal nodules as well as diffuse mucosal infiltration with immunoblasts [223, 280, 281]. Some serotypes of adenovirus cause extensive intestinal mucosal necrosis as well as fulminant hepatitis and multiorgan failure in HCT patients; prompt treatment can be effective [154–158].

Esophageal and intestinal fungal infections are now very uncommon causes of serious bleeding in transplant patients [251, 275]. Exceptions are patients with prolonged granulocytopenia in whom deeper penetration of fungal organisms, particularly molds, can erode into large submucosal blood vessels, leading to massive bleeding [252].

Aside from *H. pylori*-associated ulcers in SOT recipients [3], bacterial gut infection as a cause of severe bleeding is rare. Pseudomembranous colitis caused by *C. difficile* may also present as bleeding, especially in patients with a low platelet count [141, 206]. Bloody diarrhea also occurs with typhlitis (*C. septicum* infection), especially if platelet counts are low [282].

19.5.6.1 Noninfectious Causes (Tables 19-2 and 19-3)

Both SOT and HCT recipients may come to their respective transplant procedures with gut lesions that may bleed after transplant. Minor bleeding after HCT usually disappears when platelet counts stabilize [283]. The current frequency of severe bleeding after HCT is less than 2 %, almost all of which is due to noninfectious causes (GVHD, gastric antral vascular ectasia, mucosal biopsy sites) [275, 283, 284]. Bleeding after SOT is more likely to be caused by infection, especially CMV- and *H. pylori*-related ulcers [72]. Noninfectious causes of severe bleeding include diverticular bleeding (particularly after renal transplant), portal hypertension-related lesions after liver transplant [72], and bleeding from anastomoses (choledochojejunostomy after liver transplant, intestinal anastomoses after pancreatic or intestinal transplant), and ischemic colitis.

Severe intestinal bleeding, defined as enough bleeding to lead to hemorrhagic shock or a fall in hematocrit by >10 % or transfusion requirement of 2 units of blood per day, leads to two imperatives—one is to stop the bleeding and the other to make a diagnosis of the lesion that is bleeding—particularly if the cause is an infection that is not being treated. In practice, this means endoscopic evaluation of the upper intestinal tract, or the colon, or both, and blood-pool radionuclide scans, angiographic studies, or capsule endoscopy when endoscopy cannot localize the bleeding lesion.

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