Gastrointestinal Complications of Transplant Immunosuppression

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At a time when the judicious use of a broad range of immunosuppressive drugs has ensured excellent patient and organ survival rates after kidney transplantation, attention is focusing on strategies to minimize their side effects. Almost all immunosuppressive medications are associated with some form of gastrointestinal (GI) complication (1–6). The majority of these complications fall into one of several general categories: infections, mucosal injury and ulceration, biliary tract diseases, diverticular disease, pancreatitis, and malignancy (Table 1).

An understanding of the GI morbidities related to transplantation permits the development of systematic strategies to reduce and manage these disorders. In this article, we provide an overview of the GI complications arising from the use of immunosuppressive medications and review common prophylactic and treatment approaches.

Infections

By suppressing the body’s defensive immune functions, all immunosuppressive regimens can lead to increased rates of systemic or localized infections including those of the GI tract. These infections may be bacterial, viral, fungal, or parasitic and may infect one or more gut segments between the mouth and anus. The following discussion is not intended to be comprehensive but will instead indicate those representative infectious entities that most commonly affect transplant recipients.

Viral Infections

Infections with cytomegalovirus (CMV) and herpes viruses are very common in transplant recipients. They are very costly and can cause significant morbidity and mortality. We are not going to discuss some other viruses, such as adenoviruses, respiratory syncytial virus, influenza virus, and polyoma virus, which can cause serious infections in the immunocompromised host, because GI involvement with these viruses is not common.

CMV Infection. CMV infection occurs in a large proportion of transplant patients and is the most common viral cause of clinical disorders in these patients. The incidence of enteric and/or gastric infection is remarkably high, affecting a substantial portion of patients, especially during the first 6 to 12 mo after organ transplantation. Sakr et al. (7) studied 140 liver transplant recipients before and after transplantation for the presence and the absence of CMV enteritis. They demonstrated that, although only one patient had evidence of enteric CMV infection before transplant, the incidence of CMV enteritis posttransplant was 27.7% in the cyclosporine (CsA)-treated group and 20% in the tacrolimus-treated group. Interestingly, patients treated with tacrolimus in this particular study had less severe enteric CMV infection compared with CsA-treated patients. CMV-related infections may be systemic, in which case patients typically present with viremia and constitutional symptoms and almost always with accompanying leukopenia; they may be localized or tissue-invasive. CMV can affect any segment of the GI tract. The symptoms and signs depend on the affected gut segment and may include dysphagia, odynophagia, nausea, vomiting, abdominal pain, GI bleeding, perforation, or diarrhea. CMV infection can also mimic many other entities such as ischemic colitis, intestinal pseudo-obstruction, toxic megacolon, and colon carcinoma (8). Pancreatitis, especially in recipients of CMV-positive pancreatic allografts, has also been reported (9).

If we look at individual immunosuppressive drugs in detail, it was suggested by several studies that there is an association between mycophenolate mofetil (MMF) and tissue-invasive CMV, especially of the GI tract (6,10). All three pivotal MMF trials reported information on increase in tissue-invasive CMV infection without specific reference to the GI tract (6,11,12). In the US trial, tissue-invasive CMV disease was more common in the MMF groups, with rates of 7% for azathioprine (AZA) group, 11% for MMF 2 g/d, and 12% for MMF 3 g/d (11). Serious GI events appeared to be more common in the two smaller MMF studies, but interpretation requires a more detailed analysis of the raw data (10,13). In one study, 57% of patients treated with MMF had either dose reductions or interruptions due to adverse events, especially diarrhea, nausea, vomiting, and leukopenia (13). In addition, 6.5% of patients discontinued medication because of noninfectious GI events, and 6.5% were diagnosed with tissue-invasive CMV of the GI tract, compared with 0% for the AZA group. In the other study reported by Hebert et al. (10), 21% of patients had gastritis,
Table 1. Gastrointestinal complications after transplantation

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duodenitis, or esophagitis, and 11% had either duodenal or esophageal ulceration. In the same study, CMV disease of the GI tract developed in 11% (2 of 19 patients) after they started receiving MMF. However, as both of these small studies were of graft rescue in refractory acute rejection with high-dose steroid use, higher rates of adverse events are not unexpected. Patients in graft rescue trials tend to be heavily immunosuppression before switching to the salvage regimen, which may contribute to increased rates of certain infections, including CMV. In addition, MMF-treated patients seemed to experience more upper GI events that required investigation by endoscopy with biopsy in these rescue trials (13). Thus, it is also likely that more MMF patients underwent a biopsy, which might introduce a detection bias for CMV.

Recently, two studies have added to the controversy over the link between CMV disease and MMF dosing. A small, uncontrolled study with a total of 62 patients by Kaplan et al. (14) describes patients receiving maintenance MMF therapy (with either CsA or tacrolimus in addition to prednisone) who presented with persistent midepigastric pain. Endoscopy with biopsy revealed that 90% of these patients had evidence of CMV infection in the small intestine or gastric mucosa. The authors demonstrated that an MMF dose of >2 g/d coupled to therapy with tacrolimus (versus CsA) showed a trend toward an increased relative risk for abdominal pain although the association was not statistically significant. Only transplantation from a CMV-positive donor into a CMV-negative recipient and the presence of leukopenia were independent risk factors for the development of abdominal pain in this particular study. In agreement with this observation a case-controlled study of 31 CMV patients matched with 102 control patients demonstrated that that MMF dose of 2 g/d was not an independent risk factor for CMV viremia or tissue invasion in renal allograft recipients (15). The stepwise logistic regression analysis identified the presence of past rejection episodes and a CMV-positive donor as the only significant factors.

Information on CMV infection in FK506 studies is incomplete but suggestive of modest rates. In one of the large studies, tissue-invasive CMV, not specified for site, was diagnosed in 6.8% of CsA and 9.3% of FK506 patients (1). In another study, CMV infections were diagnosed in 16.6% of CsA patients and 13.5% of FK506 patients, with 2% of FK506 patients discontinuing study drug because of CMV versus none in the CsA group; possible tissue invasion was not specified (16).

Any patient, especially in the early posttransplantation setting or during intensive immunosuppression for rejection, presenting with fever, nausea, vomiting, diarrhea, and laboratory findings of leukopenia and/or increased liver enzymes should undergo endoscopy and biopsy to assess the possibility of CMV enteritis. Failure to identify enteric CMV at an early stage could allow spread to critical organs, such as lung and liver, and perforation of the infected viscus with disastrous consequences (7). Typical endoscopic findings of tissue-invasive CMV of the digestive tract are shallow, erythematous erosions or localized ulcers. However, these visual findings are not specific, so biopsy is essential. CMV inclusion bodies or positive CMV cultures are sometimes obtained from biopsy samples of patients who are negative for visual endoscopic findings; the relevance of such biopsy findings is unclear. Demonstration of CMV in peripheral blood by direct detection of antigenemia or by PCR technique provides a great tool for diagnosis of early active CMV infection. Prophylaxis for CMV infection after transplantation was reviewed extensively elsewhere (17). Studies for CMV prophylaxis that rely exclusively on acyclovir have produced inconsistent results. Among CMV-positive liver transplant recipients, 2 g/d of oral acyclovir for 16 wk after transplantation was significantly better than placebo in preventing CMV disease (CMV incidence was 5% in the acyclovir group and 27% in the placebo group) (18). In contrast, among 18 renal transplant patients who received oral acyclovir in dosages from 600 to 4000 mg/d for 4 to 7 mo after transplantation, CMV disease developed in 12 patients (67%), leading the researchers to conclude that other strategies of CMV prophylaxis should be sought (19). Studies using acyclovir in combination with ganciclovir have generally produced good results. In a series of 170 consecutive kidney transplantations, prophylaxis with acyclovir, combined with ganciclovir during acute rejection and in cases of delayed graft function, gave good protection against CMV infections and prevented CMV disease (20). Among 167 liver transplant patients randomized to either 120 d of antiviral prophylaxis with acyclovir 800 mg orally four times daily or 14 d of ganciclovir (5 mg/kg) intravenously every 12 h followed by oral acyclovir 800 mg four times daily, the sequence of ganciclovir followed by acyclovir was more effective than acyclovir alone in reducing CMV infection and disease (21). Other studies suggest that ganciclovir can be used effectively alone for CMV prophylaxis. Among 44 renal transplant patients randomized to either placebo or 750 mg of oral ganciclovir twice daily for 12 wk after renal transplantation, ganciclovir had a significant impact on the occurrence of CMV infections during the first 9 mo posttransplantation, irrespective of the CMV status of donor or recipient and of treatment for acute rejection episodes (22). In another study of kidney transplant patients randomized to receive either oral acyclovir (800 mg four times daily) or oral ganciclovir (1000 mg three times daily) for 3 mo, ganciclovir-treated patients had a much lower rate of CMV infection during a mean of 14.4 mo of follow-up (23). The cumulative infection rate at 6 mo was 35.9% for acyclovir and 2.5% for ganciclovir. Similar results were reported in liver transplant recipients (24). A recent study of valacyclovir among 616 D+/R− and R+ renal transplant patients randomized to either placebo or 2 g of valacyclovir...
four times daily for 90 d demonstrated that valacyclovir significantly reduced the occurrence of CMV disease at 6 mo (25). Although, none of these studies demonstrated specifically that GI involvement of CMV is decreased with general CMV prophylaxis, an intensive prophylactic strategy to decrease the morbidity and mortality from CMV infection is particularly important and necessary in the high-risk (recipient negative/donor positive) patient group. In established CMV infection, ganciclovir is the drug of choice for treatment in all organ transplants followed by foscarnet. Ongoing trials of valganciclovir, an orally administered valine ester of ganciclovir, will provide information whether this agent would be effective for CMV prophylaxis or treatment in transplant recipients.

**Herpes Simplex Virus.** Herpes simplex virus (HSV) is second only to CMV among viral agents that cause clinical infection in transplant patients. It usually presents as a reactivation of the latent virus mostly within the first 6 wk after transplantation. HSV can affect many parts of the GI tract. In addition to mild, ulcer-like mucocutaneous lesions, especially in the oral cavity and pharynx, another common site for infection is the esophagus, with one group reporting esophagitis in 5 of 221 renal transplant patients (2.2%) over an 8-yr period (26). All cases developed during the treatment of acute rejection with high-dose steroids and antilymphocyte preparations. Patients with HSV infection after transplantation usually present with odynophagia or dysphagia as well as orocutaneous HSV lesions, although the orocutaneous complaints in some patients may develop after the appearance of esophagitis. Endoscopy can reveal shallow ulcers surrounded by typical vesicles, discrete or coalescent ulcers, and pseudomembranous lesions mimicking a cutaneous senile lesion. It is a common belief that symptoms of odynophagia or dysphagia in the setting of intensive immunosuppression must be investigated endoscopically without delay as untreated herpetic ulcers can progress to hemorrhage, which may even be fatal, or to esophageal perforation. Because endoscopic appearance may vary, endoscopic biopsy for histology, immunohistochemistry, and viral cultures is necessary. Transplant physicians must have a high level of suspicion during periods of increased immunosuppression for HSV infection. Simple mucocutaneous lesions can be treated with a short course of oral acyclovir. Extensive and more serious cases may need to be treated with IV acyclovir or ganciclovir when there is also concomitant CMV or Epstein-Barr virus (EBV) infection.

**Fungal Infections**

Because of several risk factors, such as frequent antibiotic therapy, steroid use, hyperglycemia, indwelling catheters, and impaired cellular immunity, opportunistic fungal infections are very common, especially the first couple of months after surgery in transplant recipients. Although many fungal infections can affect the GI tract, candidiasis is the most common.

**Candidal Infection.** Candidal infection most typically presents in the immunosuppressed transplant patient as esophagitis with or without oral thrush. Risk factors associated with invasive candidal infections include administration of broad-spectrum antibiotics, recent treatment for acute rejection with high-dose steroids or antibodies, and the presence of a Roux-en-Y choledochojejunostomy in patients with liver transplantation. Candida esophagitis usually presents with odynophagia or dysphagia. Less commonly, patients may present with fever, heartburn, epigastric pain, or GI bleeding. Lesions may include superficial erosions, ulcers, and white nodules or plaques. Identification of lesions is important because the infection may be severe and necrotizing, which may result in perforation (27). Perforation with formation of tracheoesophageal fistulas has also been reported (28).

The responsible species is most commonly either *Candida albicans* or *Candida tropicalis* (4). Fungal infection may occur in conjunction with systemic CMV infection. Of a series of 66 CMV-positive liver transplant recipients, candidal esophagitis developed in 3 (29). The diagnosis of candidal infections is made by fungal cultures or histopathologic examination of appropriate specimens. Therapy includes topical antifungal preparations (nystatin, amphotericin B oral solutions) and oral or intravenous antifungal agents. Liposomal amphotericin B preparations are less nephrotoxic than the regular amphotericin B but are more expensive.

Different transplant programs have different incidences of invasive fungal infections; therefore, prophylaxis may vary from one program to another. For prophylaxis of upper GI fungal infection, the use of nystatin swish and swallow every 6 h for 6 mo after induction and after each rejection treatment has been described as well as oral clotrimazole and oral amphotericin B in renal transplant recipients as effective (5). In 212 liver transplant recipients who received fluconazole (400 mg/d) until 10 wk after transplantation, fungal colonization decreased significantly compared with placebo (28% versus 90%) (30). In addition, proven fungal infection occurred in 43% of placebo recipients but in only 9% of fluconazole recipients (P < 0.001). Interestingly, infection and colonization by organisms intrinsically resistant to fluconazole did not increase, which is a concern because of the potential for the emergence of fluconazole-resistant *Candida* species in patients given prophylactic fluconazole. No hepatotoxicity was observed in this particular group of patients. It has been recommended to monitor serum cyclosporine levels closely in patients treated with prophylactic fluconazole because of the interaction between the two drugs. For liver transplant recipients, it was suggested to use the prophylactic fluconazole only in high-risk groups of patients, such as recipients with previous CMV infection, multiple transfusions, and retransplantation (31). The optimal duration of prophylaxis and the antifungal agent are still not standardized.

**Bacterial Infections**

Bacterial infections of the GI tract are not uncommon in transplant recipients. Examples include *Yersinia enterocolitica* and *Clostridium difficile* colitis. Such infections may be more prevalent in patients with systemic CMV infection (29). *Yersinia* septicemia can occur especially in patients with iron loading, diabetes mellitus, chronic liver disease, OKT3 use, and high aluminum store, which might contribute an additional risk factor to immunosuppression (32,33). Patients usually
present with GI symptoms, such as diarrhea and abdominal tenderness, and rarely with erythema nodosum, arthritis, myocarditis, meningitis, and acute renal failure. Antibiotic treatment is efficient to cure the disease.

Although its true incidence among transplant recipients is not well known, the overall incidence of *C. difficile* colitis was recently reported as 8%, with 16% in the pediatric kidney transplant group, 15.5% in the combined kidney-pancreas group, and 3.5% in the adult-kidney only group by West et al. (34). In this particular study, young recipient age (<5 yr), female gender, treatment of rejection with monoclonal antibodies, antibiotic use, and intra-abdominal graft placement increased the incidence of disease. Transplant recipients can be asymptomatic carriers of *C. difficile* but can also develop diarrhea, intestinal obstruction, abscess, and toxic megacolon. Treatment with oral metronidazole in less severe cases and vancomycin in severe *C. difficile* colitis is very effective.

**Parasitic Infections**

Another consequence of immunosuppression is susceptibility to infection by protozoan or metazoan parasites. Microsporidia are obligate intracellular protozoan parasites. GI infection due to microsporidia is the most common cause of diarrhea in patients with HIV infection. Gumbo et al. (35) described four cases in which microsporidial infection led to unexplained chronic diarrhea, fatigue, and weight loss in solid organ transplant recipients. The authors speculated that microsporidial infection is underdiagnosed because suspicion is low and the organism is not detected by routine stool examination. Since patients can remain infected for several years, with intermittent symptomatic periods, it has been suggested that transplant recipients with chronic, unexplained diarrhea in the late post-transplantation period should have stools examined with a modified trichrome stain, which can detect microsporidia. Infection with the nematode *Strongyloides stercoralis* has been reported to lead to fever, abdominal pain, bloody diarrhea, abdominal distension, nausea, and vomiting in renal transplant recipients. Rarely, patients can present with acute respiratory illness caused by the migration *S. stercoralis* through the lungs. Hyperinfection can occur and is associated with high mortality (36). The diagnosis should especially be considered in patients from endemic areas such as the West Indies or the Far East. Interestingly, the risk of hyperinfection in transplant recipients markedly decreased in the CsA era. It is recommended that any potential living donor with a history of infection with *S. stercoralis* should be examined for the presence of larvae in stools and urine. Before transplantation, treatment with thiabendazole should be instituted until the infection is eradicated. In the case of a transplant recipient, thiabendazole or ivermectin should be prescribed (37,38). Although thiabendazole competes for metabolism sites in the liver with xanthine-type drugs (theophylline, caffeine), there is no interaction with calcineurin inhibitors. There are no reported drug interactions between ivermectin and calcineurin inhibitors in the literature, but immunocompromised hosts may require repeated treatment with this drug for complete recovery. Microsporidial infections respond well to treatment with metronidazole (35).

**Helicobacter pylori Infection**

*H. pylori* plays an important role in gastritis and peptic ulcer disease in the general population. In a study by Ozgur et al. (39), the prevalence of *H. pylori* was 70% and 60% in renal transplant recipients and hemodialysis patients, respectively. Gastritis was seen in 65% of renal transplant patients compared with 19% in hemodialysis patients, suggesting other factors contributing to increased levels of gastritis in transplant recipients. Teenan et al. (40) examined 33 renal transplant recipients by endoscopy 2 to 4 mo after transplantation and identified 16 patients with duodenitis, 10 patients with gastritis, and 4 patients with gastric ulcer. *H. pylori* was found in the gastric antrum of 16 patients (48%) and was strongly associated with symptomatic dyspepsia, gastritis, and peptic ulceration. Although this was a small study, there was no relationship between *H. pylori* colonization and either cyclosporine levels or steroid dose. *H. pylori* infection is also widely prevalent among heart transplant recipients, but its prevalence is not higher than that seen in the general population. Huwez et al. (41) studied 47 heart transplant recipients with endoscopy to assess the opportunistic infections of the GI tract. *H. pylori* was found in 23 (49%) patients; 17% had gastritis, 17% had duodenitis, 30% had reflux disease. Eight (35%) of these *H. pylori*–positive patients had GI symptoms, and infection recurred or persisted in half of the patients treated with triple therapy; this is a lower eradication rate than the general population, which raises the possibility of immunosuppression hindering the clearance of *H. pylori*. We recommend full investigation, including endoscopy with biopsies, in patients with possible *H. pylori* infection before treatment with antibiotics.

**Mucosal Injury and Ulceration**

**Diarrhea**

In addition to infectious causes, diarrhea can be caused by certain immunosuppressive drugs. The three large trials involving tacrolimus, comprising a total of almost 1500 patients, suggest that GI side effects are more common with tacrolimus than CsA (1,2,16). All three trials show increased rates of tacrolimus-associated diarrhea; in two of the three, the difference was substantial (2.2 times and 1.5 times, respectively) (2,16). All three trials also suggest that nausea and vomiting are more common with tacrolimus. Dyspepsia and constipation also appear somewhat more common with tacrolimus, as does abdominal pain. Possibly adding to a dosage-dependent effect on adverse events is the fact that 30 of the 268 tacrolimus patients in the US liver transplant trial were 12 yr of age or younger. The severity of tacrolimus-associated GI side effects is uncertain. Some reports suggest that these GI problems have a relatively mild course, which can generally be managed with dosage reduction. For example, in the study by Mayer et al. (16), none of the 303 patients in the tacrolimus groups had their study medication discontinued because of a GI event. In the study by Pirsch et al. (1), only 3 (1.5%) of 205 tacrolimus patients crossed over to CsA because of GI events. However, other reports suggest that GI events due to tacrolimus may be more severe and difficult to manage. In one study, 7 (6%) of 122 patients taking tacrolimus had unusually serious GI out-
comes, with 6 requiring prolonged parenteral nutrition to deal with the secondary effects of anorexia (42).

Two large trials with MMF demonstrated rates of diarrhea in the MMF groups to be between 1.3 and 1.9 times those in the AZA groups (6,11). In many event categories, the highest rates were found in the MMF 3-g/d group, which suggests a dose-dependent effect. According to The Us Renal Transplant Mycophenolate Mofetil Study, the rates of drug discontinuation specifically attributable to GI adverse events were 6.7% for AZA, 3.6% for MMF 2 g/d, and 8.4% for MMF 3 g/d at 3-yr follow-up (43).

A number of possible mechanisms for MMF-associated diarrhea have been proposed, such as inhibition of colonic crypt cell division possibly due to immune-mediated mechanism as well as loss of normal villous structure in the duodenum (44,45). There are also a few reports of nausea and diarrhea with rapamycin use in the literature (46–48).

Dose manipulation, reduction of total dosage, and/or dose splitting (e.g., changing two times daily dosing to four times daily) of certain immunosuppressive drugs, such as MMF and tacrolimus, is an important strategy to manage GI toxicities, particularly diarrhea, in transplant recipients. In many patients, such manipulations reduce the intensity and duration of symptoms (6,10,49).

Ulceration of the GI Tract

Multiple factors contribute to ulcer formation in transplant patients. Examples include the stress of surgery, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), the use of steroids, and the possible impairment of native gastroduodenal cytoprotection due to an AZA- or MMF-induced slowing of intestinal cell turnover (50). In kidney transplantation, a number of additional ulcer-producing factors may come into play, such as increased gastric acid secretion during posttransplantation dialysis, the possible ulcer-causing effect of heparin used during dialysis, and elevated postoperative histamine and gastrin levels (50).

The role of steroids in peptic ulcer is still controversial. A meta-analysis of a large number of patients on steroids by Conn et al. (51) revealed that peptic ulcer was a rare complication of corticosteroid therapy. On the other hand, another study by Steger et al. (50) demonstrated that there was a trend for those patients treated with methylprednisolone for rejection to develop more ulcers or inflammatory lesions. It is most likely that the development of peptic ulcer in transplant recipients is multifactorial. In the modern transplant era, upper GI ulcers have an overall low incidence after renal transplantation. For example, in a series of 1034 renal transplants in patients receiving CsA-based immunosuppression and antacids as the sole routine ulcer prophylaxis, 33 patients experienced a total of 41 endoscopy-proven ulcers, of which 15 bled and 1 (perforated) was fatal. Of the 41 ulcers, 19 (46%) were duodenal, 17 (42%) were gastric, and 5 (12%) were esophageal (5). Although the overall incidence is low, ulcers tend to occur at highly variable and unpredictable intervals (5). Further complicating diagnosis is the fact that steroids frequently mask the clinical symptoms of ulcers (and other GI disorders) and thereby delay diagnosis and treatment (5). In fact, many ulcers in transplant recipients are entirely asymptomatic. In one study, only 39% of patients (7 of 18) with endoscopically proven ulcers had symptoms (50). However, in cases of GI perforation and peritonitis among steroid-maintained patients, clinical findings of fever and abdominal pain develop with some consistency, occurring in 91% and 84%, respectively, in one series (52).

GI bleeding, when it occurs, is often secondary to ulceration. Among 1000 consecutive liver transplantations, there were 92 episodes of GI bleeding in which endoscopic diagnoses were made (53). Of these 92 episodes, ulcers (gastric, duodenal, or esophageal) were the most common cause of bleeding (25 of 92 episodes), the second most common cause being non-CMV enteritis (gastritis, colitis, duodenitis, esophagitis, or ileitis): 24 of 92 episodes.

In lung transplant recipients, giant gastric ulcers (defined as gastric ulcers with a diameter ≥3 cm) may occur. These large ulcers are associated with high morbidity and mortality secondary to bleeding and may develop despite routine use of H₂-receptor antagonists (3). Possible factors contributing to these ulcers are reported as bilateral lung transplantation, high-dose oral NSAIDs for at least 1 wk after transplantation, high-dose intravenous steroids for acute rejection, and CsA immunosuppression. A retrospective study of kidney transplant recipients by the same authors did not find giant gastric ulcers, making it uncertain whether these large ulcers are specific to lung transplantation. We believe that NSAIDs should not be used in transplant recipients.

There are no demographic or clinical features that readily identify all patients at increased risk of upper GI ulcers. Therefore, a high degree of clinical suspicion is called for, coupled with a low threshold for endoscopy with tissue sampling for histology, microbiology, and virology (5). In fact, ulcers may be both common and frankly asymptomatic in the renal transplant setting, yet may cause significant morbidity or mortality when they become apparent. One center used routine endoscopy 7 to 14 d after transplantation, even when H₂-receptor antagonists are used routinely (50). In view of the decreased incidence and severity of peptic ulcer in recent years, routine endoscopy in asymptomatic patients is not recommended in transplant recipients.

Prophylaxis against posttransplantation GI ulceration may include one or more methods designed to reduce acid secretion or protect the mucosa from the effects of acid. These methods include H₂-receptor antagonists (e.g., ranitidine), proton-pump inhibitors (e.g., omeprazole), coating agents (e.g., sucralfate or bismuth-containing agents), and prostaglandins (misoprostol).

For example, one group used ranitidine, sucralfate, or omeprazole for approximately the first 3 mo after transplantation (without specifying criteria, if any, for choice of agent and without giving efficacy data) (10). One pediatric group reported using acid-reducing therapy for at least the first year after transplantation; specifically, ranitidine 0.8 mg/kg per dose intravenously three times daily starting at transplantation and converting to omeprazole or lansoprazole dose by weight.
when the child tolerates oral medication without a nasogastric feeding tube (54).

In one series, prophylaxis of severe GI bleeding after renal transplantation with omeprazole was at least as effective as ranitidine (55). The researchers noted additional advantages, such as prolonged effect and a simple dosage, which does not require any adjustment on the basis of graft function development. In another study, misoprostol (prostaglandin E₁ analogue), when used in combination with antacid and ranitidine, was more effective than the combination of antacid and ranitidine, either alone or with bismuth, in preventing peptic ulcer disease in kidney transplant patients (56).

Attempts to protect against ulcers can complicate immunosuppressive management by several mechanisms. CsA levels may be altered by concomitant administration of cimetidine or ranitidine, and cimetidine may falsely elevate serum creatinine levels by blocking the tubular secretion of creatinine. Routine treatment with sucralfate can hinder absorption of CsA. Proton-pump inhibitors (e.g., omeprazole) can alter CsA levels, and both H₂-antagonists and proton-pump inhibitors may, by reducing acid secretion, alter upper gut flora and thus potentially increase the chance of colonization with undesirable organisms (e.g., causing fungal esophagitis) (5). Because of these possible complications, some transplantation groups do not routinely provide ulcer prophylaxis.

Endoscopy is important not only in diagnosis but also in treatment. Many bleeding gastric ulcers can be controlled with endoscopic procedures such as injection of epinephrine or alcohol, use of heater probes, or vicaps electrodes (57). In a series of 41 consecutive, endoscopy-proven ulcers, 96% were successfully managed nonsurgically (5). Because medical management of identified ulcers is almost always successful, surgical management should be considered only for primary surgical indications (e.g., perforation) or failure of medical or endoscopic therapy. In the subset of patients who require surgical intervention for bleeding gastric ulcers, a technique involving simultaneous laparotomy and endoscopy may obviate the need for gastrotomy, thus reducing the risk of surgical contamination (57).

Diverticular Disease

Diverticular disease has been reported in up to 42% of patients with ESRD (58). Complicated diverticulitis defined as diverticulitis involving free perforation, abscess, phlegmon, or fistula after renal transplantation was reported as 1.1% in a recent study by Lederman et al. (59). In this particular study, clinical presentation varied from asymptomatic pneumoperitoneum to generalized peritonitis. It has also been reported that renal transplant recipients with polycystic kidney disease had increased incidence of gastrointestinal diverticular disease and colonic perforation without any clear explanation (59,60). However, even when risk factors are known, predicting colonic complications has proved difficult. In a series of 1186 renal transplants performed at Vanderbilt University, we found that pretransplantation colonic screening of older patients (>50 yr) was ineffective in predicting posttransplantation colonic complications (61). For example, in this particular study, we identified 20 cases of diverticular disease among older patients, more than a quarter of which were associated with adult polycystic disease. None of these 20 patients underwent pretransplantation colectomy, and none developed posttransplantation symptomatic colon disease. Most of these patients were younger at the time of transplantation so would not have received screening studies. On the basis of these findings, we recommended abandoning the practice of pretransplantation colonic screening in asymptomatic patients >50 yr of age. Screening should be done selectively in certain transplant candidates, especially patients with polycystic kidney disease, with documented active diverticulitis/complications or symptoms suggestive of diverticular disease by either barium enema or colonoscopy.

Perforations

Perforations of any part of the GI tract can occur in transplant patients, although the colon may be the most common site. In one series of 1401 consecutive renal transplants, 30 patients (2.1%) had a total of 34 episodes of colonic perforation, 13 (38%) of which were fatal (52). The causation is often multifactorial, with lower GI perforation often secondary to a combination of diverticular disease and impairment of GI histologic integrity due to NSAIDs, steroids, and other immunosuppressive agents (8).

Two patterns of lower GI perforation have been reported by Stelzner et al. (52) in renal transplant patients, with one pattern occurring early after transplantation and the other usually occurring late. In the early pattern, perforation occurs most commonly in patients with renal failure who are undergoing dialysis and have had heavy immunosuppression, particularly with corticosteroids. These early perforations are considered to be largely attributable to diverticulitis or CMV colitis. In the late pattern, perforation may occur years after transplantation and is thought to be largely attributable to diverticulosis or malignancy, such as clinically unrecognized lymphoma. The authors acknowledge that these patterns are not fully inclusive, and a variety of other factors have been associated with lower GI complications. Steroids have been implicated as a cause of spontaneous colonic perforation in otherwise normal population as well as transplant recipients (62,63). A recent report suggests that MMF may be associated with colonic ulceration in a few patients (64). Fungal infections such as mucormycosis have also been reported as a cause of gastric perforation in transplant recipients (65). In recent years, new antibiotics, more sensitive diagnostic modalities, such as computed tomography scan, early and aggressive surgery, and corticosteroid-sparing regimens helped to decrease the incidence and severity of colonic perforation.

Biliary Tract Disease

Organ transplant recipients are at high risk for complications of biliary calculi. Cholecystectomy after transplantation is often carried out emergently and has a high mortality rate (66). In a study of 178 heart, lung, or heart-lung transplant recipients, 65 (37%) had documented biliary tract disease, including thickened gall bladder wall, sludge, dilated bile ducts, gallblad-
Pancreatitis

Acute pancreatitis (AP) is an uncommon but a very serious complication in transplant recipients. The incidence of AP has been reported to be 3 to 5.7% in orthotopic liver transplant recipients, with a mortality rate of up to 64% (71,72). Underlying factors to each episode of pancreatitis were identified as biliary manipulation, history of recent ingestion of alcohol, hepatitis B infection, and malignancy in the region of the pancreas. In renal transplant recipients, AP was reported to be 1 to 2.3% with a high mortality rate up to 100% (73,74). CMV, hypercalcemia, alcohol, cholelithiasis, and immunosuppression are the most common precipitating factors for AP. A 30-fold difference in the incidence of AP between the heart transplant recipients and nontransplant cardiopulmonary bypass patients (3.0 versus <0.1%; \( P < 0.05 \)) in a recent study reported by Herline et al. (75). There was an eightfold difference in mortality between the transplant patients with and without pancreatitis (33% versus 4%), although this did not reach statistical significance in this particular study. It has been reported in both animal studies and human clinical trials of transplantation that for AP in transplant recipients.

Posttransplantation lymphoproliferative disorder (PTLD) can involve GI tract up to 10% of transplant recipients. Unfortunately, PTLD involvement of the GI tract is not readily accessible as abnormal lymph node enlargements for early diagnosis. Acute abdomen from perforation or obstruction and GI bleeding can occur late in the disease process. In a retrospective study of 172 pediatric liver transplant recipients, GI symptoms occurred in 38.5% of EBV-infected patients and 43% of patients with GI symptoms (mostly GI bleeding) developed PTLD (86). O’Connor et al. (87) evaluated 24 pediatric liver transplant recipients with abdominal pain, vomiting, hematemesis, anemia, growth failure, and suspected PTLD. In six patients, endoscopy revealed the characteristic finding of raised, rubbery, and erythematous lesion with a central ulceration (B lymphocytes + EBV on biopsy) located predomina ntly in the colon or stomach. Authors recommended endoscopy and biopsy in transplant recipients who have GI symptoms associated with positive EBV serologies to rule out PTLD.
Low-grade, gastric mucosa-associated lymphoid tissue–type lymphomas are also reported in transplant recipients (88). These lymphomas are rare, can be associated with *H. pylori*, and are treated with a variety of modalities, including reduction of immunosuppression, antibiotics, surgery, and chemotherapy.

A clinical suspicion is mandatory for the diagnosis of PTLD in transplant recipients, especially in the GI tract. Endoscopy is the most useful tool for diagnosis and treatment of PTLD involving GI tract as well as monitoring the response to therapy. When PTLD is diagnosed, treatment includes lowering or cessation of immunosuppression, antiviral agents, surgery, and chemotherapy as well as new modalities, such as treatment with anti-CD19 or anti-CD20 antibodies. The discussion of treatment of PTLD in detail is beyond the scope of this review.

**Conclusion**

There are several GI complications of immunosuppressive agents that are seen frequently in transplant recipients. Differences between the large immunosuppressive drug trials in such areas as methodology, definitions of events, and drug combinations make cross-study comparisons problematic and leave open the possibility that published data do not accurately indicate relative rates of immunosuppressant-specific GI adverse events. It may also be true that perceptions regarding the relative frequency of GI side effects among immunosuppressants have to some extent been skewed by reduced rates of toxicities of some of the newer immunosuppressive drugs, which could lead to greater clinical emphasis on the GI events by both physician and patient.

Whatever immunosuppressive regimen is used, certain precepts of GI prophylaxis and management apply to reduce the incidence and impact of the clinical entity. Antiviral and/or antifungal as well as ulcer prophylaxis should be considered always with cognizance of the side effects of these approaches. Because most transplant patients are taking steroids, which can obscure or even completely mask clinical findings, a high level of suspicion is needed, especially in patients receiving high-dose steroids to proceed to detailed GI evaluation with clinical hints. Suspicious GI findings, even apparently mild ones, should be investigated aggressively, which, as a practical matter, means endoscopy with biopsy. Failure to identify evolving but initially asymptomatic conditions can have life-threatening consequences, such as enteric perforation. When diarrhea or other GI events occur, drug discontinuation is generally not necessary if dosage manipulations, such as dose splitting and dosage reduction, can reduce the event to acceptable levels. In regimens containing MMF or AZA, temporary drug interruption followed by dosage manipulation may, if necessary, allow a patient to continue on an effective and otherwise safe immunosuppressive regimen (6). Steroid withdrawal after kidney transplantation might be another option to consider with recent addition of very potent drugs, such as MMF and rapamycin, to transplant armamentarium in patients with serious steroid-related GI complications. We believe, as experience with immunosuppressive agents continues to grow, that prophylaxis and treatment of GI complications will also improve and reduce the consequences of these management problems in transplant recipients.

**References**

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