SURGICAL MANAGEMENT OF BENIGN AND MALIGNANT COLORECTAL DISEASE IN THE IMMUNOSUPPRESSED PATIENT

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Immunosuppression can be attributed to primary or acquired causes or immunosuppressive medications [see Table 1]. Primary immunodeficiency disorders can have gastrointestinal manifestations with chronic or recurrent infections or inflammatory colitides that may resemble inflammatory bowel disease. This review discusses the surgical management of colorectal problems that arise in patients with acquired and medication-related etiologies of immunosuppression.

Surgical management of the immunosuppressed patient usually requires a multidisciplinary approach with clinicians who are treating the underlying disease causing the immunocompromised state. The risks of surgical intervention must be carefully weighed against the potential benefits, and it is important to maintain focus on the bigger picture to optimize outcomes.

The preoperative evaluation of the immunosuppressed patient requires a high index of suspicion as many patients are sicker than they appear on examination due to the blunting of peritoneal signs and inability to mount an immune response.

Intraoperative management of patients who are immunosuppressed must involve consideration of poor wound healing capabilities and the greater morbidity and mortality associated with infectious complications. Surgeons performing colorectal operations in immunosuppressed patients may have a lower threshold for fecal diversion because of the serious sequelae of anastomotic leak.

Postoperative management of immunosuppressed patients often involves a multidisciplinary approach to manage the underlying disease process and immunosuppressive medications.

Immunosuppressive Medications

This section discusses the various medications that can cause immunosuppression with regard to their mechanisms of action, the risks they pose to surgical patients, and the perioperative management of these patients.

IMMUNOSUPPRESSIVE MEDICATIONS FOR INFLAMMATORY BOWEL DISEASE

The primary goals of medical therapy for inflammatory bowel disease are to induce remission, improve quality of life, and reduce the need for operative intervention. Over the last three decades, the medical management of inflammatory bowel disease has enjoyed significant progress with the introduction of cyclosporine in the 1980s and biologics in the late 1990s. The types of medications that are typically used to treat ulcerative colitis and Crohn disease are detailed here [see Table 2].

A significant proportion of patients with Crohn disease and ulcerative colitis will proceed to surgical intervention for disease that is refractory to medical management. Population-based studies demonstrate that two thirds of patients with Crohn disease and one third of patients with ulcerative colitis will undergo at least one operation.5,6 Another one third of these patients will undergo a subsequent operation within 1 year of their initial operation.7 Perioperative and postoperative continuation of immunosuppressants and immunomodulators for inflammatory bowel disease can increase patients’ susceptibility to infections and poor wound healing, which must be weighed against the risk of disease recurrence.8–10

Corticosteroids

Surgical patients may be on long-term or short-term steroids for a variety of autoimmune or inflammatory conditions, and surgeons must be aware of the perioperative management of these patients to be prepared for the potential complications. Steroids are part of the maintenance immunosuppressive regimen for many organ transplant recipients. In patients with inflammatory bowel disease, they may induce remission and be discontinued when

Table 1 Causes of Immunosuppression

<table>
<thead>
<tr>
<th>Primary causes</th>
<th>Acquired causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA or IgM deficiency</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>Burns</td>
</tr>
<tr>
<td>Complement disorder</td>
<td>Cancer, especially Hematologic Malignancies</td>
</tr>
<tr>
<td>T cell deficiency</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>NK cell deficiency</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td>Combined cellular and humoral immunodeficiency</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Leukocyte adhesion molecular defects</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Phagocytic dysfunction</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Acquired causes</td>
<td>Medication/treatment</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Burns</td>
<td>Radiation</td>
</tr>
<tr>
<td>Cancer, especially Hematologic Malignancies</td>
<td>Steroids</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Medications for inflammatory bowel disease, rheumatoid arthritis, and other inflammatory disorders</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Immunosuppressive medication for transplantation</td>
</tr>
</tbody>
</table>

NK = natural killer.
patients transition to nonsteroid maintenance therapy, although a significant proportion of patients have steroid-dependent disease (28% of patients with Crohn disease and 22% of patients with ulcerative colitis).7

**Mechanism of action** Corticosteroids exert immunomodulatory and antiinflammatory effects through impairment of macrophage function by inhibition of antigen processing and T cell activation. They also attenuate the inflammatory response through decreased production of cytokines, including interleukin-1 (IL-1), IL-2, IL-6, interferon gamma, and tumor necrosis factor–α (TNF-α).11 Among patients undergoing colorectal operations, the most common indication for systemic steroid therapy is inflammatory bowel disease.

**Risks to the surgical patient and clinical management** Systemic corticosteroid therapy increases the risks of wound complications as well as other side effects that may complicate postoperative management.

**Wound healing** Due to the inhibitory effect on the inflammatory response, systemic corticosteroid therapy impairs wound healing. An important surgical consideration is the decision whether to create a primary anastomosis in a patient who is on systemic corticosteroids.

Some surgeons argue that patients with steroid-dependent ulcerative colitis who have been on high-dose steroids for a significant period of time may benefit from a staged surgical approach to reduce the potential for postoperative complications. They recommend total abdominal colectomy with end ileostomy as a first procedure as it gives these patients the opportunity to wean off steroids and recover their wound healing capabilities before undergoing proctectomy with an ileal pelvic pouch. However, others have seen no difference in infectious complications between patients who are on systemic steroids and those who are not, and, as such, advocate that preoperative systemic steroid therapy does not necessarily warrant a staged approach.3,12,15,16

**Adrenal insufficiency** Adrenal insufficiency is a potentially fatal complication that can cause postoperative cardiovascular collapse and is more likely to occur in patients with a higher average daily dose of steroids and who have been on them for a longer period of time.17,18 Giving high-dose corticosteroids in the perioperative period is the standard of care for patients who are either currently on systemic corticosteroids or have been treated with corticosteroids within the past year.9,19,20 Patients taking 5 mg of prednisone per day or less, alternate-day corticosteroids, or any dose of corticosteroids for less than 3 weeks are unlikely to have adrenal suppression and therefore may not require “stress-dose” steroids.21-24 Patients taking 20 mg daily or more of prednisone (or its equivalent) for more than 3 weeks or who have features of Cushing syndrome likely have a suppressed hypothalamic-pituitary-adrenal axis and should be considered for stress-dose steroids in the perioperative period.

A commonly used perioperative steroid regimen for patients undergoing colectomy or proctocolectomy for medically refractory ulcerative colitis is detailed here [see Table 2].

### Table 2 Immunosuppressive Medications for Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Potential Complications</th>
<th>Perioperative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Systemic (prednisone)</td>
<td>Inhibit inflammatory response and cytokine expression via several mechanisms</td>
<td>Wound infection or dehiscence</td>
<td>Stress-dose steroids with steroid taper</td>
</tr>
<tr>
<td></td>
<td>Nonsystemic (budesonide)</td>
<td>High affinity for glucocorticoid receptor by low systemic activity due to first-pass metabolism in liver</td>
<td>Less likely to cause complications than systemic steroids</td>
<td>Continue if clinically indicated; no need for stress-dose steroids</td>
</tr>
<tr>
<td>5-ASAs</td>
<td>Mesalamine, sulfasalazine</td>
<td>Modulates local chemical mediators of inflammatory response</td>
<td>Nausea, headache, fever, rash, pancreatitis, pneumonitis</td>
<td>Continue if clinically indicated</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>Azathioprine</td>
<td>Inhibits purine ring biosynthesis, decreasing synthesis of DNA</td>
<td>Liver and bone marrow toxicity</td>
<td>Stop at least 2 weeks preoperatively; restart (if clinically indicated) at 2–4 weeks postoperatively, as long as no ongoing infectious or wound healing complications</td>
</tr>
<tr>
<td></td>
<td>6-Mercaptopurine</td>
<td>Active metabolite of azathioprine</td>
<td>Liver and bone marrow toxicity</td>
<td>Stop at least 2 weeks preoperatively; restart (if clinically indicated) at 2–4 weeks postoperatively, as long as no ongoing infectious or wound healing complications</td>
</tr>
<tr>
<td>Biologics (anti-TNF-α antibody)</td>
<td>Infliximab, adalimumab, certolizumab pegol</td>
<td>Monoclonal antibody inhibits TNF-α</td>
<td>Possible increased risk of infectious complications</td>
<td>Stop at least 2 weeks preoperatively; restart (if clinically indicated) at 2–4 weeks postoperatively, as long as no ongoing infectious or wound healing complications</td>
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5-ASA = 5-aminosalicylic acid; TNF-α = tumor necrosis factor–α.
Table 3}, but clinicians may be able to reduce the dosage and/or taper off the steroids more quickly for patients who have been on lower corticosteroid doses before surgery (prednisone < 20 mg per day) or had tapered off corticosteroids completely within the year, or are undergoing a smaller operation, such as an ileostomy closure rather than a colectomy.

It is important to maintain a high index of suspicion as adrenal crisis may manifest similarly to other postoperative events. Aside from hypotension refractory to fluids, patients may also experience fatigue, abdominal pain, nausea, vomiting, decreased ileostomy output, or increased ileostomy output.25,26 Adrenal insufficiency or steroid withdrawal in the immediate postoperative period may occur even in patients who receive appropriate stress-dose steroids.27 Some patients may need a higher dose, whereas others may not tolerate the taper well, and still others may not absorb prednisone adequately, especially if they have an ileus or a high-output ileostomy. Recent evidence suggests that low-dose steroids for patients with recent or current exposure to systemic corticosteroid therapy are sufficient to prevent adrenal insufficiency in the postoperative period.24–26

Other considerations	Other side effects of concern to the clinician caring for the postoperative patient on systemic steroids include hyperglycemia, hypertension, fluid and electrolyte imbalance, and psychological effects.35 Because steroids can induce a rise in the white blood cell count due to demargination, clinicians will need to rely on other data to determine if a surgical patient has an infection. A confounding factor is that steroids can also blunt the signs and symptoms of intra-abdominal infections, increasing the risk of missed or delayed diagnoses for preoperative conditions such as bowel perforation and postoperative complications such as anastomotic leaks.

5-Aminosalicylic Acid Agents

There is no current evidence to suggest that 5-aminosalicylic acid (5-ASA) agents such as mesalamine and sulfasalazine increase perioperative morbidity. Therefore, they can be continued unless the patient has decreased glomerular filtration. 5-ASA agents should be discontinued the day prior to surgery and resumed 3 days after surgery.36

Immunomodulators

The predominant immunomodulators used to treat inflammatory bowel disease are the thiopurines—azathioprine and 6-mercaptopurine (6-MP)—which are used to maintain steroid-induced remission for patients whose disease does not respond to aminosalicylates. Ideally, the introduction of azathioprine or 6-MP will allow steroids to be tapered successfully.

Mechanism of action The metabolites of 6-MP ultimately become incorporated into the DNA, subsequently blocking DNA replication and purine synthesis. This causes inhibition of T lymphocytes. Azathioprine is a purine analogue and the prodrug of 6-MP and has the same effect as 6-MP.

Risks to the surgical patient and clinical management Thiopurines may have an effect on wound healing. We recommend that these medications be held at least on the day of surgery and, if renal function remains normal, resumed within 2 weeks for patients with Crohn disease to prevent recurrence. The other immunomodulators that are used less frequently for inflammatory bowel disease (cyclosporine, methotrexate, and tacrolimus) are discussed in the section on transplant medications.

Biologics

Biologic therapy with infliximab for the treatment of Crohn disease was approved in 1998 and then approved for ulcerative colitis in 2005. Adalimumab and certolizumab are two additional therapies that have been approved for Crohn disease. These medications are used to induce and maintain remission in patients with inflammatory bowel disease refractory to other medications, as well as other autoimmune conditions, such as psoriasis and rheumatoid arthritis.

Mechanism of action Infliximab, adalimumab, and certolizumab are monoclonal antibodies targeted at TNF-α, a cytokine with a major role in the inflammatory response, especially in ulcerative colitis and Crohn disease. These medications are thought to cause apoptosis of inflammatory cells that express TNF-α.

Risks to the surgical patient and clinical management The increased rate of postoperative morbidity with corticosteroids37–41 has been well documented, whereas the surgical consequences of cyclosporine and biologic agents remain more controversial.37–40 Some authors have found no increase in the rate of postoperative complications with the use of preoperative cyclosporine42–44 or infliximab45,46 among patients with inflammatory bowel disease, or more specifically those with Crohn disease.40,41,47–49 Other authors have

Table 3 Sample Steroid Taper for Patients Who Are on Prolonged High-Dose Systemic Corticosteroid Therapy prior to Colectomy for Medically Refractory Ulcerative Colitis

<table>
<thead>
<tr>
<th>Time from Operation</th>
<th>Recommended Steroid Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of surgery</td>
<td>Hydrocortisone 100 mg IV before operation, hydrocortisone 100 mg IV q. 8 hr</td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>Hydrocortisone 50 mg IV q. 8 hr</td>
</tr>
<tr>
<td>Postoperative day 2 until tolerating a diet</td>
<td>Hydrocortisone 25 mg IV q. 8 hr</td>
</tr>
<tr>
<td>When tolerating a diet</td>
<td>Hydrocortisone 25 mg IV q. 8 hr and prednisone 20 mg p.o.</td>
</tr>
<tr>
<td>For next 5-7 days</td>
<td>Prednisone 20 mg p.o. daily</td>
</tr>
<tr>
<td>Every 5-7 days</td>
<td>Decrease prednisone by 2.5–10 mg every 5-7 days</td>
</tr>
</tbody>
</table>

IV = intravenous.
found that although infliximab alone does not increase postoperative complications, the use of both infliximab and cyclosporine together before colectomy is associated with high surgical morbidity in those patients undergoing ileal pouch-anal anastomosis (IPAA) for ulcerative colitis.50 Still others found a significant increase in the anastomotic leak rate, pouch-specific and infectious complications following IPAA for ulcerative colitis, and increased short-term postoperative complications when infliximab was administered preoperatively.31,52

The results of a meta-analysis examining the postoperative risks for patients on biologic agents suggests that infectious complications may be slightly increased in patients undergoing operations for Crohn disease but not for ulcerative colitis [see Figure 1].53 Also under debate is the surgical management of patients on anti-TNF-α therapy. Some groups argue for a lower threshold for fecal diversion and a staged approach to total proctectomy with IPAA. Other centers argue that preoperative anti-TNF-α therapy in patients with ulcerative colitis has not and should not increase the number of three-stage pouches.12,54,55

Other Considerations

Patients on immunosuppressive medications for inflammatory bowel disease may have an increased risk of developing cancer such as melanoma and nonmelanoma skin cancers. There is an increased risk of non-Hodgkin lymphoma in patients treated with thiopurines and anti-TNF-α therapy.56 Patients who are diagnosed with cancer may benefit from a lower dose of immunosuppression for the inflammatory bowel disease until the cancer is under control with surgical resection and/or chemotherapy. Chemotherapy may even help control bowel symptoms, but if patients do experience a flare in symptoms, then a multidisciplinary approach is necessary to find a strategy to optimize outcomes.57

IMMUNOSUPPRESSIVE MEDICATIONS FOR TRANSPLANTATION

Organ transplant recipients are typically on a combination regimen of medications to prevent graft rejection. The most common immunosuppression medications are detailed here [see Table 4]. Transplant recipients who need subsequent operations may be at higher risk for wound complications, and we discuss the surgical challenges presented by some of these medications.

Cyclosporine

Cyclosporine is used for both transplant immunosuppression and induction of remission in severe inflammatory bowel disease.

Mechanism of action Cyclosporine is a calcineurin inhibitor that binds to cyclophilin and inhibits transcription and translation of cytokines, especially IL-2.

Risks to the surgical patient and clinical management Preoperative cyclosporine has not been shown to have any detrimental effects during or after surgery.42–44 But patients are at much higher risk for opportunistic infection and deterioration of renal function, so it is important to monitor cyclosporine levels after surgery if the drug is to be continued for other clinical reasons.

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) inhibitors are primarily used in solid-organ transplantation and include everolimus and sirolimus. Other mTOR inhibitors are also used to treat renal cell carcinoma.

Mechanism of action These medications inhibit IL-2-induced T lymphocyte proliferation. mTOR inhibitors prevent the activity of fibroblasts and endothelial cells and thus prevent wound healing. They also inhibit angiogenesis, inflammation, and growth factor production.

Risks to the surgical patient and clinical management mTOR inhibitors have been shown to impair wound healing in patients undergoing solid-organ transplantation, with increased rates of wound dehiscence, incisional hernia, and infection.58 These wound complications can be seen in as many as 40% of organ transplant recipients treated with these agents.59,60 Transplant patients who then require a subsequent operation are subject to an elevated risk of wound complications. Therefore, mTOR inhibitors should be discontinued and replaced with another mode of immunosuppression at least 7 days prior to the operation and restarted 1 to 2 weeks after the operation or until the wound heals adequately. Some clinicians may choose to switch the patient entirely to another regimen several weeks prior to an elective general surgery operation.61 Surgeons may also choose to delay staple removal for an additional 2 or 3 weeks to allow for complete healing of the skin incision.

Management of Benign Colorectal Diseases in Immunocompromised Patients

DIVERTICULITIS

The incidence of acute diverticulitis is increasing in Western populations.62 Although most patients have an uncomplicated disease course, older patients, patients with multiple comorbidities, patients taking nonsteroidal antiinflammatory drugs,63,64 and immunocompromised patients65 are at higher risk for complicated disease and perforation.61–64 In immunocompetent patients, diverticulitis classically manifests with abdominal pain and tenderness, fever, and leukocytosis. However, immunocompromised patients may present with

Figure 1 Mucocutaneous separation around a diverting ileostomy for a malnourished patient with severe fistulizing perianal Crohn disease who had been on adalimumab. As is the case with many patients, it is likely that a multitude of factors contributed to poor wound healing.
minimal symptoms or physical findings, mandating a high index of suspicion [see Figure 2].

Immunocompromised patients are more likely to fail nonoperative management with antibiotics and require operative intervention for their disease process. This higher failure rate may result from an impaired ability to “wall off” the perforation and contain the infection, thus allowing ongoing infection and inflammation. Postoperatively, immunocompromised patients have significantly higher morbidity (65% versus 24% for immunocompetent patients) and mortality (39% versus 2% for immunocompetent patients) because immunocompromised individuals have an increased morbidity and mortality from diverticulitis, it is recommended that surgeons have a lower threshold to proceed to resection in these patients than they would for immunocompetent patients. This may be particularly pertinent in the transplant patient population, which has a higher rate of complicated diverticulitis compared with the general population (40% versus 15%), a higher rate of surgical resection, and a higher mortality from diverticulitis. Colorectal or anorectal problems occur in 6% of patients who have had heart or heart-lung transplantation, and most of these are attributed to diverticulitis; the majority of patients with diverticulitis after transplantation undergo surgical resection. The incidence of diverticular perforation in kidney transplant patients is equal to that of the general population, but perforation in these patients carries greater morbidity and mortality.

Transplant patients who require sigmoid colectomy for diverticulitis—whether urgent or elective—have a longer hospitalization than nontransplant patients. Those who undergo urgent resection also have poorer survival than nontransplant patients undergoing urgent resection, with 19% mortality versus 0%.

### Table 4 Immunosuppressive Medications for Transplant Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action</th>
<th>Potential Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Prednisone</td>
<td>Inhibits inflammatory response and cytokine expression via several mechanisms</td>
<td>Wound infection or dehiscence</td>
</tr>
<tr>
<td>Calcineurin</td>
<td>Cyclosporine</td>
<td>Binds to cyclophilin, inhibits calcineurin-dependent transcription and translation of cytokine genes, particularly IL-2</td>
<td>Nephrotoxicity, increased rates of infection (CMV, bacterial pneumonias, and fungal sepsis)</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus (FK-506)</td>
<td>Binds to FK-binding protein, inhibits calcineurin-dependent transcription and translation of cytokine genes, particularly IL-2</td>
<td></td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>Sirolimus</td>
<td>Binds to FK-binding protein, inhibits IL-2 and IL-6-driven events, which reduces T cell activation</td>
<td>Impaired wound healing</td>
</tr>
<tr>
<td>Purine synthesis inhibitors</td>
<td>Mycophenolate mofetil (MMF)</td>
<td>Inhibits inosine monophosphate dehydrogenase, inhibiting the de novo pathway for guanine nucleotide biosynthesis, preventing proliferation of B and T cells</td>
<td>GI disturbances, neutropenia, viral infections, impaired wound healing</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Azathioprine</td>
<td>Inhibits purine ring biosynthesis, decreasing synthesis of DNA</td>
<td>Bone marrow suppression, liver impairment, and cholestatic jaundice</td>
</tr>
<tr>
<td>Depleting antibodies</td>
<td>ATG (polyclonal)</td>
<td>Depletes T cells</td>
<td>Cytokine release syndrome, PTLD, increase in infectious complications</td>
</tr>
<tr>
<td></td>
<td>OKT3 (monoclonal)</td>
<td>Depletes T cells</td>
<td>Skin reaction, fatigue, fever, myalgia, pulmonary edema, increased infectious complications</td>
</tr>
</tbody>
</table>

ATG = anti-thyroglobulin antibody; CMV = cytomegalovirus; GI = gastrointestinal; IL = interleukin; mTOR = mammalian target of rapamycin; PTLD = posttransplantation lymphoproliferative disease.

Figure 2  Computed tomographic scan showing an intra-abdominal abscess in a patient on systemic chemotherapy who had minimal signs or symptoms of infection. Aside from a mild tachycardia (90 beats/min, from baseline in the 70s), she had no abdominal pain or tenderness even on deep palpation, fever, or leukocytosis. Percutaneous drainage was not possible as the abscess was surrounded by loops of small bowel. She was treated with broad-spectrum antibiotics and laparoscopic sigmoid colectomy with primary anastomosis 6 weeks later.
Because of these poor outcomes, patients awaiting organ transplantation who have had a bout of acute diverticulitis may be considered for elective sigmoid colectomy to avoid a recurrence post-transplantation when they are on immunosuppression, although this is controversial. Patients with chronic renal failure, especially those with polycystic kidney disease, have a particularly high risk of perforation in recurrent diverticulitis, so sigmoid colectomy may be considered after antibiotic treatment of the initial episode. However, most patients awaiting organ transplantation are high-risk surgical candidates, so this challenging decision must be made on a case-by-case basis.

In the case of suspected acute diverticulitis in an immunosuppressed patient, we recommend computed tomography to confirm the diagnosis and assess for complications such as fecal peritonitis or abscess and reduction of immunosuppressive therapy if possible. Patients with a free perforation and fecal peritonitis should proceed expeditiously to sigmoid colectomy with end colostomy. Those with an associated abscess should be treated with antibiotic therapy and percutaneous drainage if necessary; if they fail to improve, then proceed to sigmoid colectomy with end colostomy, but if they respond well, then they may undergo colonoscopy in 6 weeks followed by consideration for elective sigmoid resection with colorectal anastomosis. Patients with uncomplicated diverticulitis should be treated with antibiotic therapy. If they improve, then they may undergo colonoscopy in 6 weeks followed by consideration for elective sigmoid resection with colorectal anastomosis; if they do not improve, then they will require sigmoid colectomy on that admission.

APPENDICITIS

Immunocompromised patients presenting with signs and symptoms suspicious for acute appendicitis present a complex diagnostic and management dilemma as they may have a variety of other etiologies for their symptoms and are at higher risk for postoperative complications.

Acute Appendicitis in Immunocompromised Patients

Patients with the HIV infection are more likely to develop appendicitis than those in the general population. Risk factors include the absence of highly active antiretroviral therapy (HAART) and younger age. Patients with AIDS who underwent appendectomy were more likely than patients without AIDS to have postoperative morbidity and mortality in a population-based study. Unlike patients with HIV, organ transplant recipients rarely develop appendicitis. However, if they do undergo appendectomy for appendicitis, they are more likely to develop complications and require longer hospitalization.

Nonbacterial Causes of Acute Appendicitis in Immunocompromised Patients

Cryptosporidiosis has been reported as a rare entity causing inflammation of the appendix in patients with HIV or AIDS. Patients who undergo appendectomy and are found incidentally to have cryptosporidiosis on pathologic analysis should therefore be tested for HIV and other causes of immunocompromise.

Hematologic malignancies such as acute myeloid leukemia and lymphoma have also been reported to present as acute appendicitis. Pathologic examination of the appendectomy specimen will demonstrate a leukemic or lymphomatous infiltration of the appendix.

Typhlitis, which is discussed later in this review, can present with right lower quadrant pain and radiologic evidence of appendiceal and cecal inflammation. Clinicians must have a high index of suspicion for typhlitis in patients on chemotherapy and consider this on the differential before performing an operation.

Clostridium difficile Colitis

The overall incidence of Clostridium difficile colitis has more than doubled in the last decade, and the prevalence of C. difficile is higher in immunocompromised patients than in the general population. C. difficile is responsible for 20 to 30% of antibiotic-associated diarrhea and 50 to 75% of cases of antibiotic-associated colitis and is now the leading cause of nosocomial diarrhea. Risk factors for C. difficile infection include antibiotic use, use of corticosteroids, use of proton pump inhibitors, hospitalization, and immunosuppression. Patients present with watery diarrhea, leukocytosis, and possibly abdominal pain and fever. The diagnosis of C. difficile infection is confirmed with polymerase chain reaction (PCR), which is superior to detection of C. difficile toxin. The first-line treatment for mild infection is oral metronidazole and oral vancomycin or fidaxomicin for severe C. difficile. Refractory or relapsing infection can be treated with fecal microbiota transplantation, although this treatment is not yet widely available. Severe toxic C. difficile colitis may require emergent colectomy.

Most patients who are colonized with C. difficile are asymptomatic due to their humoral IgG response to the bacteria. However, when this normal immune response is blunted, as it is in HIV-positive patients and transplant recipients, the susceptibility to this infection is much greater. The rate of symptomatic C. difficile infection is as high as 34% among lung transplant patients. Thus, all transplant patients with new-onset diarrhea should undergo testing for C. difficile and aggressive treatment if it is positive.

Patients with inflammatory bowel disease have a significantly higher outpatient carrier rate of C. difficile of 10% compared with 2% in the general population. These patients tend to experience increased severity of their underlying inflammatory bowel disease and require more aggressive medical treatment to control symptoms. Concurrent C. difficile infection in the setting of ulcerative colitis also causes an increased risk of colectomy within 1 year of infection and increased mortality from colitis. C. difficile infection must be ruled out in patients experiencing an acute flare of inflammatory colitis before the escalation of immunosuppressive therapy.

Cytomegalovirus Colitis

Acute cytomegalovirus (CMV) colitis in patients with severe inflammatory bowel disease is not uncommon. The clinical presentation of this infection can be quite similar to that seen with a flare of colitis due to inflammatory bowel disease. The diagnosis of CMV colitis is made with endoscopic biopsy and analysis by inclusion bodies on
hematoxylin-eosin staining or positive immunohistochemistry, the latter of which is more sensitive.

A significant proportion of patients with ulcerative colitis have been infected at some point with CMV. A prospective observational study demonstrated that 70% of patients with moderate to severe ulcerative colitis are positive for CMV IgG, although most of these patients did not have an active infection as determined by antigen and PCR levels and therefore did not require antiviral therapy. The presence of CMV in the colon has been shown to blunt the effect of medical therapy on the underlying inflammatory condition.

Patients with ulcerative colitis and high CMV DNA loads in colonic tissue were found to have more medically refractory colitis than those with low CMV DNA loads in colonic tissue. However, none of these patients with high DNA loads had CMV by immunohistochemistry, the standard method of diagnosis of acute infection (see Figure 3). A clinical model for identifying patients with inflammatory bowel disease who are more likely to have CMV infection was developed and includes medically refractory inflammatory bowel disease or colonic ulcers seen on endoscopy and treatment with steroids or immunomodulators. These medications in the presence of severe ulcerative colitis are thought to cause reactivation of CMV colitis. Diagnosis of CMV by immunohistochemistry should be a routine part of the evaluation of patients with an exacerbation of their inflammatory bowel disease or disease that is refractory to medical management. Prior to escalating immunosuppressive therapy such as biologic therapy, CMV infection must be excluded as the flare in symptoms may potentially be treatable with antiviral therapy.

CMV colitis can also occur in patients who have undergone transplantation and patients with immunosuppression due to hematologic disorders.

### Colorectal Problems Related to Neutropenia

Patients with hematologic disorders or malignancies and those on chemotherapy may have bouts of neutropenia related to the natural history of their disease and treatment regimens. Many of these patients will develop conditions that warrant a surgical opinion and possibly surgical intervention.

### Anorectal Problems

Anorectal pathology such as perianal abscesses and fistulas and anal fissures commonly occur in immunocompetent patients as well as immunocompromised patients.

#### Perianal Abscesses and Fistulas

Perianal abscesses occur frequently in neutropenic patients and may present with perianal or anal pain, fever, and perhaps drainage. A particular challenge in this population is that the neutropenia may result in an inability to create pus, which can mislead clinicians expecting purulent drainage. Therefore, perianal processes where one would expect purulence must be considered abscesses and treated accordingly. This population of patients is more likely than immunocompetent patients to experience bacteremia and sepsis due to a perianal abscess and therefore require prolonged antibiotic therapy. Almost a third of patients with leukemia and a perianal abscess have recurrent perianal abscesses. The management of these infections depends on the presence of a fluid collection, diagnosed by clinical examination or, in some instances, by imaging. If there is a suspicious fluid collection, surgical drainage in the operating room is preferable over bedside drainage for several reasons: many of these patients also have thrombocytopenia, and bleeding can be prevented with the use of electrocautery; if there is a fistula, then a draining seton can be placed at the time of drainage, thus preventing recurrent abscess formation. The placement of Pezzer drains in large cavities can allow the surgeon to make a smaller incision in these patients who are unable to heal large open wounds.

At the time of drainage, an inspection of the anal canal should be performed to look for an internal fistula opening. If there is an intersphincteric tract, then drainage of the intersphincteric collection with fistulotomy should be performed. However, a transspincteric tract should not be managed with fistulotomy, even in the case of a posterior or superficial fistula tract that would normally be amenable to a fistulotomy, because patients in this condition are unable to heal large open wounds. A better strategy is to place a draining seton and wait several weeks to months for resolution or stability of the patient’s hematologic problems before proceeding with definitive treatment of the fistula.

#### Anal Fissures

Patients undergoing chemotherapy may be particularly prone to the development of anal fissures because of the increased risk of diarrhea as a side effect of treatment. Severe anal pain and anal bleeding are common symptoms, and physical examination may reveal a skin tag and a fissure. Treatment consists of optimizing stool consistency and sitz baths first; topical therapies are next, with calcium channel blocker or nitroglycerine-based ointments. In
immunosuppressed patients, lateral internal sphincterotomy should be avoided if possible due to the potential infectious and wound healing complications.

**Neutropenic Enterocolitis**

Patients with neutropenic enterocolitis (also called typhilitis) present with fever, nausea, vomiting, diarrhea, and abdominal pain. The incidence of neutropenic enterocolitis is on the rise, a phenomenon attributed to more aggressive chemotherapy regimens. Examination may reveal findings similar to those with acute appendicitis, with right lower quadrant rebound tenderness. Hallmark radiologic findings include bowel wall thickness of greater than 4 mm. Distinguishing neutropenic enterocolitis from other causes of abdominal pain can be challenging. Other infectious etiologies, such as *C. difficile* infection, must be ruled out.

These patients require aggressive treatment to control the infection with broad-spectrum antibiotics, improve the neutrophil count, and correct coagulopathy. Clinical deterioration on maximal medical therapy, hemorrhage, and bowel perforation are indications for surgical intervention.

**Colorectal surgical considerations in patients undergoing chemotherapy**

Patients undergoing treatment with chemotherapeutic agents often require surgical intervention during the course of treatment. If a patient requires an emergent colorectal operation while on chemotherapy, one can expect a higher risk of wound problems and anastomotic leak; therefore, fecal diversion rather than primary anastomosis is preferable in this setting as the septic consequences of an anastomotic leak can be fatal in such patients. Chemotherapy can be resumed in 2 to 4 weeks provided that there are no lingering wound healing or infectious complications. In the case of a patient requiring an elective colorectal operation, one should wait at least 2 weeks after the cessation of chemotherapy before performing an operation; for agents such as bevacizumab, 4 weeks is recommended to reduce the risk of wound infection [see Figure 4].

**Bevacizumab and Bowel Perforation**

Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor used to treat a variety of cancers, including colorectal cancer. It was found to significantly increase the risk of gastrointestinal perforation, with a relative risk of 2.14, accounting for a 0.9% incidence. Mortality among those with perforation was 21.7%. Higher doses of bevacizumab increase the risk of perforation, as does a diagnosis of colon cancer with a relative risk of 3.1 and renal cell carcinoma with a relative risk of 5.7.

**Enterocolitis Due to Ipilimumab**

Ipilimumab is a monoclonal antibody that targets cytotoxic T lymphocyte-associated antigen 4 and is used to treat metastatic melanoma and renal cell carcinoma.

Enterocolitis occurs in over a fifth of patients undergoing treatment with this drug and is its most common major toxicity. It presents with severe diarrhea and can be treated with corticosteroids or infliximab. Patients who fail to respond to medical management may progress to bowel perforation or hemorrhage, which are indications for surgical intervention.

**Neoplastic Colorectal Problems in Immunocompromised Patients**

**Human Papillomavirus-Associated Anorectal Problems**

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States as 80% of sexually active people will be exposed to it. The majority of patients infected with HPV are able to clear the infection; those with persistent infection are at risk for a variety of neoplasms depending on the location and strain. HPV-16 and HPV-18 are the most common high-risk strains of the virus and are the etiologic agents for the vast majority of anal cancer cases; HPV-6 and HPV-11 are the most common low-risk strains and are responsible for anal condyloma. The etiologic agents, method of diagnosis, and treatments for the various manifestations of HPV are summarized here [see Table 5].

**Anal HPV Infection in Immunosuppressed Patients**

The prevalence of HPV infection in HIV-positive men who have sex with men (MSM) is 91% for all strains of HPV, 81% for high-risk strains of HPV, and 36% for HPV-16, the most common cause of invasive cancer. The prevalence of anal HPV infection is 57% in HIV-negative MSM.

Given that a quarter of pretransplantation patients have anal HPV infection and 15% of pretransplantation patients...
have anal HPV infection with high-risk strains, it is reasonable to screen these patients before and after transplantation for anal dysplasia or malignancy.101

**Anal Condyloma**

Anal condyloma is predominantly due to infection with HPV-6 and HPV-11.102 Compared with the general population, immunosuppressed patients carry an increased risk of condylomatous lesions throughout the body, and over half of HIV-positive men develop genital warts. The treatment of anal condyloma ranges from topical therapies, including podophyllin, bichloroacetic acid, trichloroacetic acid, and imiquimod, to surgical treatments of excision and fulguration. Immunosuppressed patients have a higher risk of recurrence than immunocompetent patients.103

**High-Grade Squamous Intraepithelial Lesion**

There are several terms referring to the entity of high-grade anal dysplasia that is thought to be the precursor lesion of anal squamous cell carcinoma. These include anal intraepithelial neoplasia types 2 and 3, high-grade anal intraepithelial neoplasm, and anal carcinoma in situ. In 2013, standardized terminology was recommended, and per those recommendations, we refer to this as high-grade squamous intraepithelial lesion (HSIL).104

The incidence of HSIL in organ transplant recipients is 6.3 per 100,000 person-years, a much higher rate than the general population, corresponding to a standardized incidence ratio (SIR) of 11.6. The median age at diagnosis of HSIL in this population is 43 years, and the mean interval of time between transplantation and the diagnosis of HSIL is 4.4 years.105 The type and level of immunosuppression appear to be related to the risk of developing HSIL as transplant patients who were treated with corticosteroids have over quadruple the incidence of HSIL as those who were not and patients receiving a second transplant have almost double the incidence.

The incidence of HSIL is even higher among patients with AIDS, with an SIR of 68.6 in men and 33 in women.106 Among HIV-positive MSM, 41% have abnormal anal cytology, and over half of these patients were found to have HSIL.100

The rates of HSIL in the anus have increased significantly in recent years, whereas the rates of preinvasive squamous lesions of the cervix, vagina, and penis have declined. The incidence of HSIL has increased by 16% per year in men and 7.3% in women.107

Patients who are taking immunosuppressive medications or who have HIV are at increased risk for not only developing low-grade squamous intraepithelial lesion (LSIL) or HSIL but also for experiencing progression from LSIL to HSIL or from dysplasia to invasive cancer and extensive HSILs.108,109 Immunocompetent patients are much less likely to experience progression from HSIL to invasive cancer.

There is considerable debate regarding the treatment strategy for HSIL, with some adopting a watch-and-wait approach in patients with HSIL and others advocating for treatment of dysplastic lesions. The former group argues that excision causes morbidity without a proven benefit as only a fraction of patients with HSIL will progress to invasive cancer, and these cases are usually successfully treated with chemoradiation therapy.110 In contrast, those who support a more aggressive strategy argue that HSIL is indeed a precursor to anal cancer; treatment of HSIL can effectively control the disease and thereby prevent the development of invasive cancer.111,112

High-resolution anoscopy (HRA) can be a useful tool for the diagnosis and treatment of HSIL. HRA is based on the same technique and principles of colposcopy to diagnosis cervical dysplasia as 3% acetic acid and sometimes Lugol solution are applied to the anal canal mucosa so that lesions that turn acetowhite with a distinct vascular pattern become apparent. These suspicious lesions can be directly biopsied and destroyed with the aid of a high-resolution operating microscope.113 Other treatment modalities are topical imiquimod or topical fluorouracil, but these were found to have higher recurrence rates than destruction of dysplastic lesions with electrocautery.114

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**Table 5**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiologic Agent</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal HPV infection</td>
<td>Any HPV strain</td>
<td>Anal Papanicolaou smear with abnormal cytology</td>
<td>Expectant management vs HRA</td>
</tr>
<tr>
<td>Anal condyloma</td>
<td>Most commonly HPV-6 and -11, but also other low- and high-risk strains</td>
<td>Verrucous perianal and anal lesions</td>
<td>Chemical or surgical destruction</td>
</tr>
<tr>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
<td>Low-risk or high-risk strains</td>
<td>Biopsy</td>
<td>Expectant management with close follow-up for high-risk patients</td>
</tr>
<tr>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
<td>Most commonly HPV-16 and -18, also other high-risk strains</td>
<td>Biopsy</td>
<td>Controversial: expectant management vs topical treatment vs HRA with targeted destruction</td>
</tr>
<tr>
<td>Anal squamous cell carcinoma</td>
<td>Most commonly HPV-16 and -18, also other high-risk strains</td>
<td>Biopsy</td>
<td>Chemoradiation, salvage APR for persistence or recurrence</td>
</tr>
</tbody>
</table>

APR = abdominoperineal resection; HPV = human papillomavirus; HRA = high-resolution anoscopy.
Women with HSILs should be referred to a gynecologist to undergo evaluation for cervical intraepithelial neoplasia due to the high rate of concomitant disease.

**Anal Cancer**

Like HSIL, the incidence of invasive anal squamous carcinoma in solid-organ transplant recipients is higher in the organ recipient population than in the general population, with an incidence of 12.3 per 100,000 person-years, corresponding to an SIR of up to 5.8-10 times the risk that nontransplant recipients face.\(^{115}\) The median age at diagnosis of the anal cancer is 54, and the average time from transplantation to diagnosis of anal cancer is 5.3 years.\(^{105,116,117}\) Patients who were treated with azathioprine were almost twice as likely to develop anal cancer than transplant recipients who were not, and undergoing a second transplantation doubled the incidence of invasive anal cancer.\(^{106}\)

Patients with HIV have an even higher risk of invasive anal squamous cell cancer, with an SIR of 29 to 50 compared with patients without HIV.\(^{117,118}\) Patients with AIDS have a particularly high incidence, with an SIR of 34.6 in men and 14.5 in women.\(^{106}\)

Similar to the trends seen in HSIL, the incidence of invasive anal squamous cell cancer has also increased in recent years, whereas invasive cancers of the cervix, vagina, and penis have decreased. The annual percent change in men is 3.6% and in women is 2.3%.\(^{107}\) Since the introduction of HAART, the SIR of anal cancer has increased, presumably because patients are living longer with HIV.\(^{118}\)

Despite these high rates of invasive anal cancer, there is considerable debate over whether high-risk populations should undergo routine screening for anal cancer, with some authors arguing that the practice is not cost-effective.\(^{119}\) The American Society of Colon and Rectal Surgeons’ practice parameters recommend that anal Papanicolaou smears may be useful in detection and follow-up but warn that there is a high false negative rate.\(^{120}\)

**Prevention of HPV Infection**

The quadrivalent HPV vaccine prevents infection with the four most common strains of HPV—types 6, 11, 16, and 18.\(^{121}\) Vaccination against HPV has reduced the rates of LSIL and HSIL in the MSM population and is thought to potentially help reduce the risk of anal cancer in a double-blind study.\(^{122,123}\)

The Advisory Committee on Immunization Practices recommends routine vaccination at age 11 or 12. The vaccination series can be started at age 9, and those who were not vaccinated at the routine age of 11 or 12 can undergo vaccination through the age of 26. The same recommendations apply for immunocompromised patients. Those who are already infected with HPV and are under the age of 27 should still undergo vaccination to protect against infection with other strains of the virus, although the vaccine will not affect the existing infection.\(^{124}\) The efficacy of vaccination in patients over age 26 has not yet been determined but is undergoing evaluation.

**Colorectal Cancer in Immunocompromised Patients**

Although there is a higher risk of colorectal cancer in patients who are solid-organ transplant recipients with an SIR of 1.69, there was no increased risk in patients with HIV or AIDS.\(^{117}\) Before patients undergo transplantation, it is important to screen for malignancies such as colorectal cancer as immunosuppression can accelerate the growth and spread of neoplasms.

**Kaposi Sarcoma**

Infection with human herpesvirus 8 (HHV-8) is a necessary cause of Kaposi sarcoma, an AIDS-defining cancer that can affect the gastrointestinal tract, among other locations. Although cancers that are not considered to be AIDS-defining cancers (such as anal squamous cell cancer) have been on the rise in the era of HAART, AIDS-defining cancers such as Kaposi sarcoma have declined from an SIR of 272 in the pre-HAART era to a current SIR of 23.\(^{118}\) Transplant patients also have an increased incidence of Kaposi sarcoma with an SIR of 208.\(^{117}\)

Kaposi sarcoma frequently involves the gastrointestinal tract but is usually asymptomatic; patients who do have symptoms present with gastrointestinal bleeding and diarrhea.\(^{125}\) Diagnosis of gastrointestinal Kaposi sarcoma can be difficult because the lesions are often submucosal. When they are endoscopically apparent, they may appear as multifocal sharply demarcated, bluish-red lesions throughout the upper and lower gastrointestinal tract.\(^{126}\) Histologic findings demonstrate proliferating spindle cells and positivity for CD31, CD34, and HHV-8 markers.

The differential diagnosis for lower gastrointestinal bleeding in patients with AIDS should include Kaposi sarcoma along with non-Hodgkin lymphoma and CMV colitis, as well as colorectal diagnoses that commonly affect the general population, such as hemorrhoids, fissures, diverticulosis, and colorectal cancer.\(^{127}\)

**Conclusions**

Immunosuppressed patients are not only particularly prone to several colorectal diseases, such as HPV-related neoplasms, CMV colitis, and perineal infections, but they also present a unique set of challenges for management of common colorectal diseases such as diverticulitis. This review has covered the clinical and surgical management of many of these scenarios, but there are many more potential cases involving immunosuppression and colorectal disease. The key points for optimal management of these complex patients are using a multidisciplinary team approach, having a high index of suspicion for sepsis, and minimizing the risks of wound healing and other infectious complications.

**Financial Disclosures:** Cindy Kin, MD, Amy Lightner, MD, and Mark Welton, MD, MHCM, have no relevant financial relationships to disclose.

**References**


