Abdominal Pain in the Immunocompromised Patient—Human Immunodeficiency Virus, Transplant, Cancer

Jonathan McKean, MD, Sarah Ronan-Bentle, MD, MS*

KEYWORDS

- Immunocompromised
- Immunosuppressed
- Human immunodeficiency virus
- Cytomegalovirus
- Necrotizing enterocolitis

KEY POINTS

- Immunocompromised patients include those with human immunodeficiency virus, malignancy, and organ transplant and present frequently to emergency departments with abdominal pain.
- Opportunistic infections are a common cause of abdominal pain in the immunocompromised patient and include cytomegalovirus, mycobacterium avium complex, and abdominal tuberculosis.
- Abdominal pain can also be caused by complications from surgery in transplant patients such as nosocomial infections, including pneumonia or urinary tract infection.
- Maintaining a broad differential diagnosis is required in immunocompromised patient evaluation.
- Emergency department evaluation of immunocompromised patients includes assessment of electrolytes and cross-sectional abdominal imaging.
- Emergency department disposition is most often admission.

INTRODUCTION

Immunocompromised patients include those with chronic illnesses being treated with immunomodulatory medications and those with the more severe form caused by impairment of a patient’s own immune responses. Box 1 lists examples of immunosuppressed states. In immunocompromised patients, abdominal pain is a nonspecific
symptom arising from extra-abdominal or retroperitoneal pathologic conditions, including genitourinary or pulmonary etiologies. Diagnosis of peritonitis in immunosuppressed patients is delayed because of delayed presentation and lack of definitive physical examination findings. This is all secondary to the inability to mount an immune response. It is important to maintain vigilance and a broad approach in these patients.

### HUMAN IMMUNODEFICIENCY VIRUS/AIDS

Patients with chronic immunosuppression secondary to human immunodeficiency virus (HIV)/AIDS who have abdominal pain warrant significant consideration when being evaluated in the emergency department. Although the advent of highly active antiretroviral therapy (HAART) has greatly diminished the incidence of opportunistic infections in this population, the emergency provider must still have a high index of suspicion owing to potential poor adherence to medication regimens and unknown HIV/AIDS status. Furthermore, because HAART has resulted in increased survival in those with this disease, further diagnostic challenge is presented in an aging and elderly HIV population.

### Diagnostic Considerations

This article focuses on patients with known HIV as provided in the patient’s history, but it is important to consider the possibility of an undiagnosed HIV infection with the appropriate clinical picture or historical risk factors. In the acute infectious setting, primary HIV may preferentially deplete CD4 cells in the gastrointestinal tract, with up to 60% of T lymphocytes being found in that distribution. Abdominal pain,
nausea, vomiting, and diarrhea may ensue. Unknown, untreated HIV infection may also result in significantly depleted CD4 count and subsequent opportunistic infection. If HIV status is known, the degree of immunosuppression is helpful in developing a comprehensive differential diagnosis, including the risk of opportunistic infections and neoplastic processes. Chart review for the patient’s latest CD4 count and a current complete blood count with differential is helpful.

**Opportunistic Infections**

Intra-abdominal infection is always a consideration a cause of abdominal pain or other symptoms including nausea, vomiting, and diarrhea in the immunosuppressed patient. Positive HIV status in a patient with such symptoms should result in further risk stratification for opportunistic infections. However, because HIV-positive individuals are certainly susceptible to flora responsible for infections in immunocompetent individuals, it is important to include appropriate antibiotic coverage of enteric gram-negative rods and anaerobes.

**CYTOMEGALOVIRUS**

Cytomegalovirus (CMV) is a common infection found in the gastrointestinal tract of HIV-positive patients, and the colon is the most common site of involvement (47%). Common presenting symptoms include abdominal pain, anorexia, fever, diarrhea, and weight loss. CMV has also been linked to appendicitis. CD4 count is an important consideration in this infection, as patients with a count less than 50 cells per international unit are at higher risk for life-threatening complications, namely, perforation of the colon and rarely the small bowel. CMV ileocolitis with subsequent bowel perforation or other surgical complications is reported to be responsible for most emergency laparotomies in AIDS patients and directly responsible for the deaths in 54% to 87% of all such patients. Initial presentation may be insidious with isolated hematochezia as the only symptom. Thus, a high index of suspicion is recommended in these patients owing to the potentially devastating outcomes. Diagnostics in the emergency department rely on computed tomography (CT) imaging for evaluation of colitis or ulceration, with further inpatient diagnostics as needed. CT imaging in CMV often shows transmural colonic wall thickening, spanning from isolated involvement in recto-sigmoid or cecal regions to pan-colitis, with small bowel involvement typically presenting in terminal ileum. A 3- to 6-week course of ganciclovir or foscarnet is recommended treatment; however, because histopathology confirmation is often required, patients suspected of this disease will benefit from admission to the hospital for further studies and monitoring regardless of CT findings in the emergency department.

**MYCOBACTERIUM AVIUM COMPLEX**

Mycobacterium avium complex (MAC) is an opportunistic infection that involves the gastrointestinal tract. MAC is seen in patients with a CD4 count of less than 100 cells per international unit. In the context of a low CD4 count, CT imaging shows significant involvement of lymphoid tissue and mesenteric lymph nodes, splenomegaly, and small bowel thickening predominantly involving the jejunum. In contrast, CMV involves mesenteric lymphadenopathy only 16% of the time. Secondary to antibiotic resistance, in treatment of MAC, it is recommended to initiate antibiotic therapy with double antibiotic coverage of clarithromycin and ethambutol.
ABDOMINAL TUBERCULOSIS

Increasing in frequency in developed countries, abdominal tuberculosis (ATB) should be considered in the HIV population with less severe immunosuppression (200–500 CD4 cells per international unit). Elucidating historical risk factors for contraction of this infection may raise suspicion. Although the abdomen is a less common anatomic location for this infection, it is disproportionately found to be present in immunosuppressed patients. Eighty percent to 85% of HIV patients with ATB will have no signs of pulmonary involvement. Up to 90% of cases favor the ileocecal region as the site of infection with presenting symptoms of right lower quadrant pain or mass. Classically, ATB presents in a wet form with ascites or a dry form with adhesions and possible obstruction. Current recommendations suggest a minimum of a 6-month multidrug therapy for treatment, consisting of ethambutol, rifampin, isoniazid, and pyrazinamide for 2 months followed by 4 months of isoniazid and rifampin.

AMEBIC COLITIS

Parasitic infections with ameba may be considered in the HIV-positive patient with a travel history or recent immigration from geographic regions with high incidences, including India, Africa, and parts of South and Central America. Those at risk for obtaining this infection include HIV-positive people, those younger than 50 years, men who have sex with men, and commercial sex workers. Amebic colitis secondary to this infection bears mentioning, as it is difficult to differentiate from other infectious colitis sources both through clinical examination and CT imaging. However, it is treatable with metronidazole. Intestinal collections of this infection may be misinterpreted as a nonspecific mass or cancer on CT.

OTHERS

- Hepatitis C has a high co-infection rate with HIV transmission (10%–40%) and is more likely to be acutely symptomatic compared with HIV-negative patients.
- Gastrointestinal infections with Salmonella and Campylobacter are more likely in HIV-positive patients. Notably, these patients are more likely to have a systemic infection (20%–40%) from Salmonella compared with immunocompetent patients.
- Acalculous cholecystitis is a more prevalent cause of abdominal pain in immunosuppressed patients than in immunocompetent patients. In HIV patients, acalculous cholecystitis is most often caused by infection from Listeria, CMV, Cryptosporidium, and microsporidia.
- Hepatitis causing right upper quadrant pain can be caused by multiple opportunistic infectious agents including CMV and MAC.

Treatment Regimen Complications

Protease inhibitors cause side effects of abdominal pain, nausea, vomiting, and diarrhea, which are often self-limited. In a patient who has more significant abdominal pain, particularly epigastric/right upper quadrant pain, pancreatitis should be considered. Pancreatitis has been implicated in HAART, although newer-generation medications are less likely to cause it. It is thought that protease inhibitors may contribute to pancreatitis secondary to hyperlipidemia; however, pathophysiology of pancreatitis in HIV likely has multiple contributing factors.

Nucleoside reverse transcriptase inhibitors, including zidovudine, lamivudine, stavudine, and didanosine adversely affect mitochondrial DNA polymerase owing to
structural similarity to reverse transcriptase. Because oxidative phosphorylation and fatty acid chain transport across mitochondrial membrane may be affected, increasing anaerobic metabolism and lactic acidosis can result. Unfortunately, there is no established timeline for onset of symptoms, with cases being reported between months 1 to 20 of therapy. Management of mitochondrial toxicity and lactic acidosis is supportive; with discontinuation of offending agents, one may also consider the addition of metabolic precursors for reactions affected by inhibition of mitochondrial enzymes including thiamine, carnitine, and riboflavin.

**Other Complications**

In addition to infectious precipitants and medication regimen complications, one must consider gross physical intra-abdominal abnormalities as cause of abdominal pain in the HIV-positive patient presenting to the emergency department. Bowel perforation may be present secondary to infectious or inflammatory bowel disease. Small bowel obstruction may be present secondary to adhesions from these infections or from masses secondary to B-cell lymphoma, Kaposi sarcoma, or tuberculosis. With potential for such serious complications, a high index of suspicion is required in the evaluation of these patients.

**SOLID ORGAN TRANSPLANT**

Solid organ transplantation presents a dynamic diagnostic challenge with regard to abdominal pain in the emergency department. These patients are exposed to risks that may change based on chronologic time from surgery or immunosuppressive course. Complications from these risks may manifest as acute or chronic abdominal pain; one clinical center’s experience has found abdominal pain, in addition to fever, was the most frequent presenting complaint to the emergency department among their patients after liver transplant. In patients with a primary intra-abdominal transplant site, including pancreas, liver, and kidney, it behooves the emergency provider to thoroughly evaluate even mild abdominal pain for potentially serious conditions.

**Diagnostic Considerations**

As with other classes of immunosuppression, the transplant patient on immunosuppressive therapy certainly raises concern for infection as a cause of abdominal pain. Furthermore, inhibition of appropriate inflammatory response threatens to blunt symptoms and physical examination findings that would normally be much more striking, which leads to more frequent perforation of appendicitis in liver transplant patients compared with an immunocompetent cohort. There should be a low threshold for CT imaging in the emergency department for these patients.

**Infections**

For the solid organ transplant patient presenting to the emergency department with abdominal pain, infection should be high on the differential diagnosis. Although much discussion focuses on rare and atypical infectious processes, it is important to remember that often it is the same offending agent as in immunocompetent patients. Evaluation for diverticulitis, cholangitis, and other conditions and prompt administration of antibiotics for the usual pathogens is recommended. The timeline from the patient’s surgical procedure and initiation of immunosuppressive therapy may help narrow differential diagnosis.
**First month**
In the first month after surgery, suspicion should be highest for nosocomial infections related to the hospital stay and surgery. Incision cellulitis, intra-abdominal abscess, fungal infection, urinary tract infection, hospital acquired/ventilator-associated pneumonia, Clostridium difficile, or bacteremia secondary to central line placement should be explored.21

**Months 1 to 6**
Generally, within this timeframe the patient undergoes the greatest immunosuppression and is at the highest risk for opportunistic infections. Acute viral, such as CMV, and bacterial infections similar to those discussed previously for HIV-related abdominal pain may all be present in posttransplant patients during this time.

**Months 6 to 12**
Variability in immune response is seen in this group of patients. For those whose graft has taken well and require less pharmacotherapy to prevent rejection, this period represents a risk of infection similar to those in immunocompetent patients, such as community-acquired pneumonia and urinary tract infections, which present as abdominal pain. Other patients requiring a more intensive antirejection regimen continue to have a higher risk for opportunistic infections.

Seropositivity for certain viral strains including CMV, hepatitis C, and Epstein Barr virus have also been associated with a greater propensity for concomitant infections secondary to immunomodulation.21,22

**Other Postoperative Complications**
In addition to infection, other posttransplant diseases result in new-onset abdominal pain. Aside from known risks after abdominal surgery, such as adhesions and small bowel obstruction, the solid organ transplant patient may present with rare or unique causes of abdominal pain. The following list is by no means comprehensive, but rather a representation of the possible complications that may ensue.

**Pancreatitis**
After transplant of the pancreas, there is an expected early phase of pancreatitis known as physiologic acute graft pancreatitis related to reperfusion of the organ that occurs between 30 minutes and 72 hours after the procedure. With such an early onset, this response is managed during postoperative inpatient course. However, graft pancreatitis may have more delayed presentations. Generally, within the first 3 months after transplant, patients are at risk for early acute graft pancreatitis, presenting with abdominal pain and systemic inflammatory response. Most of these cases (60%–70%) result from vascular thrombosis to the graft or other causes including infection or immunologic response.23 Clues to this diagnosis include laboratory markers for pancreatic inflammation and dysfunction (elevated amylase/lipase levels and hyperglycemia) with confirmatory CT imaging.

Pancreatitis is also found with disproportionate frequency in renal transplant patients compared with the general population and a significant increase in associated mortality.24 Multiple suggested contributors to the development of pancreatitis among renal transplant patients include immunosuppression, hyperlipidemia, and viral infections. As with other causes of abdominal pain in the immunosuppressed patient, pancreatitis in transplant may present with subdued symptoms and examination findings in the setting of advanced disease, perhaps contributing to the increased mortality in this cohort.
**Graft-versus-host disease**
Graft-versus-host disease is a rare disease with a mortality rate greater than 85% in liver transplant patients. More commonly associated with hematopoietic stem cell transplants, this disease develops in solid organ transplants because of the presence of lymphoid tissue in the donor organ. Not only is the disease itself rare in this population, abdominal pain as the presenting symptom is also atypical. The skin and gastrointestinal tract are the most commonly affected areas; skin rash with diarrhea or abdominal pain in the posttransplant patient, particularly within 2 to 6 weeks after the procedure, should raise suspicion.

**Abdominal compartment syndrome**
After large solid organ transplant, such as liver transplant, bowel edema, ascites, and organ donor/recipient size mismatch can lead to increased intra-abdominal pressure. Although more likely to be managed in the inpatient setting after initial surgery, worsening ascites or other causes of increased abdominal pressure as an outpatient may result in an emergency department visit for abdominal compartment syndrome. Bladder pressure may be measured as a barometer for this condition. With pressures greater than 25 mm Hg, insertion of a Foley catheter and nasogastric tube for bladder and stomach evacuation can start treatment. Pressures greater than 35 mm Hg require more definitive management with decompressive laparotomy.

Many other cases are reported of postsurgical complications in the solid organ transplant patient population, ranging from diaphragmatic hernia to renal transplant torsion to aortoenteric fistula presenting with hematochezia. These are rare but potentially serious causes of abdominal pain and other gastrointestinal complaints that the emergency provider may encounter.

**CHEMOTHERAPY/NEUTROPENIA**

**Diagnostic Considerations**
Patients with various malignancies have increased frequency of visits to the emergency department, and the frequency of emergency department visits increases near the end of life. Of patients presenting with oncologic-related complaints, the most common presenting symptoms were gastrointestinal followed by pain. Gastrointestinal manifestations can be directly related to the disease burden of the cancer or to complications of cancer treatment.

**Opportunistic Infections**
Those infections common to other immunocompromised patients including those with HIV/AIDS and posttransplant patients are also common in patients undergoing chemotherapy for treatment of malignancy. These include *C difficile* pseudomembranous colitis, CMV, and herpes simplex virus.

Neutropenic enterocolitis (NEC) or typhlitis is a disease that is increasingly recognized as the most common intestinal pathologic condition in patients presenting with the triad of neutropenia, fever, and abdominal pain after receiving antineoplastic chemotherapy. The incidence of NEC is not known, as it is likely underdiagnosed. In hospitalized patients with hematologic malignancies and solid organ malignancies, the pooled incidence was reported at 5.2%. However, the true incidence is likely 50% in this population. In addition, mortality rates are more than 50% because of complications such as colonic perforation and overwhelming sepsis.

The pathophysiology is not well understood. Some years ago, NEC was thought to remain within the ileocecal region because of the decreased vascularity of this portion of the colon. In published reports incorporating cross-sectional imaging studies with
histopathology, NEC was found to be widely distributed throughout the colon, with only 28% of cases isolated to the cecum.34

Similar to posttransplant patients, patients who have undergone bone marrow transplant or have lymphoma are at risk of graft-versus-host disease, which affects the gastrointestinal tract.

In addition to the opportunistic infections and entities related to neutropenia specifically, patients undergoing chemotherapy have abdominal pain, vomiting, and diarrhea related to direct cytotoxic effects of the chemotherapy.

Other specific intra-abdominal conditions that occur more commonly in patients with colorectal cancer than in emergency department patients without cancer include bowel perforation and obstruction.

Other Immunocompromised Patients

In addition to the above-described conditions, it is important to be mindful of patients who present to the emergency department who are mildly or moderately immunocompromised because of other comorbidities or medications. See Table 1 for a description of conditions and medications that contribute to a relative state of immunocompromise. Recognizing that these medications contribute to a relative state of immunosuppression should alert the care provider to the unreliability of the abdominal examination and the need for additional laboratory evaluation and cross-sectional imaging. Early treatment should include volume replacement in addition to symptom control.

The evaluation of abdominal pain in the immunocompromised patient remains challenging. Many patients, whether they have a history of HIV or malignancy or transplant will require cross-sectional imaging of the abdomen and pelvis in the emergency department. Administration of broad-spectrum antibiotics should be considered early. Admission for continued resuscitation and subspecialty consultation or intervention is the usual course.

PEARLS AND PITFALLS

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REFERENCES


