Gastrointestinal and Genitourinary Infections

Ana Paula Velez, John N. Greene, and Jorge Lamarche

Abstract Gastrointestinal infections in neutropenic patients are common especially in the setting of mucotoxic chemotherapy. In this setting common enteric pathogens can easily gain access to the bloodstream and cause bacteremia and severe sepsis. Additionally, other gastrointestinal infections commonly seen in immunocompetent patients such as *clostridium difficile* colitis can often complicate the clinical picture in neutropenic patients given the broad use of antibiotics.

Genitourinary infections in neutropenic patients occur as a complication of indwelling foley catheters, mucosal inflammation and anatomical abnormalities of the genitourinary tract. Although the pathogenesis is similar to the immunocompetent population, the infections are more frequent and severe in neutropenic patients.

In this chapter, we will discuss the most common type of gastrointestinal and genitourinary tract infections in neutropenic patients.

Keywords Candida esophagitis · HSV esophagitis · CMV esophagitis · Neutropenic colitis · Typhlitis · *Clostridium difficile* colitis · Proctitis · Diverticulitis · Hepatitis B and C virus · Hemorrhagic viral cystitis

Esophagitis

Neutropenic patients are particularly predisposed to develop infectious esophagitis given the chemotherapy induced mucositis, radiation therapy, immunosuppression, steroid use and prophylactic antibiotics. In this section, we will review the most

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common cause of esophagitis including candida, herpes simplex (HSV) and cytomegalovirus (CMV). Other causes of esophagitis such as pill esophagitis, radiation and eosinophilic esophagitis, as well as other non-infections causes of esophagitis are not within the scope of this book.

Candida Esophagitis

Candia albicans is the most common type of *candida spp* that cause candida esophagitis but other type of *candida spp.* such as *c. glabrata, c. kruseii, and c. tropicalis* can also cause esophagitis in neutropenic patients [1].

Clinical symptoms of candida esophagitis include odynophagia and retrosternal pain. Oral or soft palate thrush may be a clue on physical examination, but is not always present [2].

The diagnosis of candida esophagitis is by endoscopy. White plaques are seen attached to the esophageal mucosa (Fig. 1). Mucosal samples demonstrate yeast and pseudohyphae. Cultures reveal *candida spp*.

The treatment of candida esophagitis is with empiric systemic antifungals based on the above symptoms. If the symptoms do not improve in 72 hours, endoscopy should be performed to rule out other causes of esophagitis [3].

The use of topical antifungal agents to treat candida esophagitis should be avoided. Systemic fluconazole is the agent of choice. Fluconazole resistant candida esophagitis should be suspected if the symptoms do not improve, especially patients who have been on prophylactic fluconazole, voriconazole, posaconazole, or isavuconazole. In such cases micafungin or amphotericin should be considered. The recommended length of treatment is 14–21 days [4].

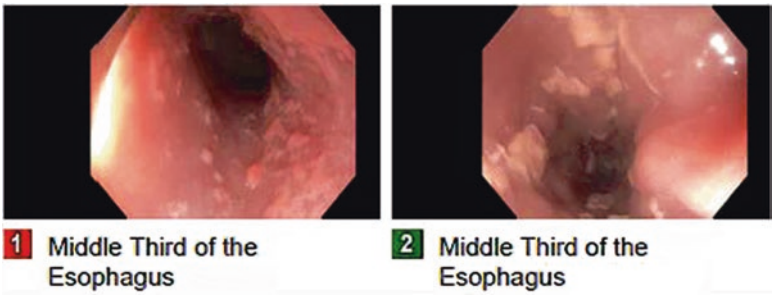

Fig. 1 Endoscopic picture demonstrating candida esophagitis

Herpes Simplex Virus Esophagitis

The majority of Herpes Virus Simplex (HSV) esophagitis are due to HSV1, but HSV2 can also be isolated [5]. Patients usually complaint of dysphagia, odynophagia, retrosternal pain with or without fever [6]. In addition, intractable hiccups has also been described [7].

On physical examination, oral vesicles or ulcers may be present, but not always as the infection may be deeper in the esophagus.

The diagnosis of HSV esophagitis relies on endoscopic observation of small coalescent ulcers less than 2 cm in diameter (Fig. 2). Biopsy of the suspicious lesions should be taken to confirm the diagnosis. Histopathology of the tissue demonstrates multinucleated giant cells. The tissue should also be sent for HSV stains and culture.

Qualitative PCR from the tissue samples can be used, but this technique is highly sensitive and can be associated with asymptomatic viral shedding that does not necessarily correlates with clinical findings especially if no ulcers are visualized [8].

The treatment of HSV esophagitis in neutropenic patients should be for 14–21 days. Famciclovir or valacyclovir can be used. If the patient is not able to tolerate medications by mouth, IV acyclovir can be prescribed.

Acyclovir by mouth is often used, but may not be as convenient as oral famciclovir or valacyclovir because the absorption is less predictable and it has to be taken several times a day.

If the patients do not respond to initial therapy, HSV resistant virus should be suspected. In such cases, the initial therapy may have to be changed to foscarnet. If biopsy samples are available, they should be tested for thymidine kinase gene mutation. This mutation is associated with HSV resistance to valacyclovir and famciclovir [9].

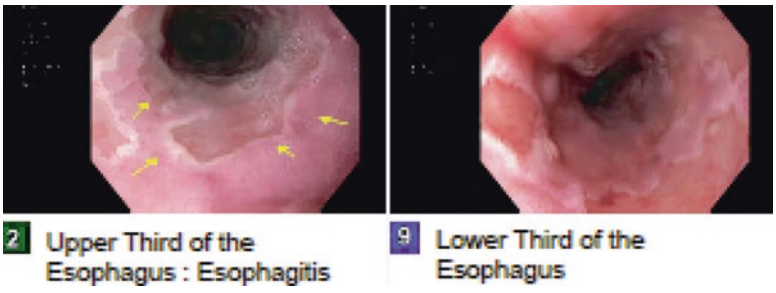

Fig. 2 Endoscopic picture of HSV esophagitis

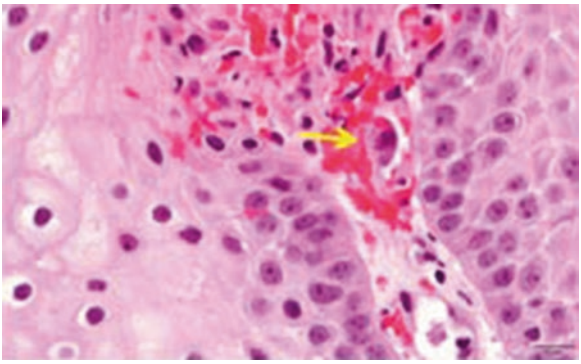

Fig. 3 Typical intranuclear and intracytoplasmic inclusions with the characteristic cytomegalic cells

Cytomegalovirus Esophagitis

Cytomegalovirus (CMV) esophagitis is the second most common type of CMV infection after CMV colitis in immunosuppressed patients. In cancer patients, risk factors include radiation therapy, chemotherapy, and immunosuppression therapy. Clinical manifestations are similar to HSV and candida esophagitis including, odynophagia, dysphagia, retrosternal chest pain, nausea and vomiting [10].

The diagnosis of CMV esophagitis is by endoscopic evaluation of the lesions and biopsy with tissue samples assessed for histopathology. The lesions are typically linear or shallow erosions. Tissue biopsy reveals the typical intranuclear and intracytoplasmic inclusions with the characteristic cytomegalic cells (Fig. 3). CMV PCR in blood may not useful because it does not always correlate with organ disease [11, 12].

The treatment for CMV esophagitis is ganciclovir, or its prodrug valganciclovir. Other options particularly for CMV resistant virus include foscarnet or cidofovir. The last 2 options are only reserved for patients who are intolerant or resistant to ganciclovir given their potential nephrotoxicity [13–15].

Colitis, Proctitis and Diverticulitis

Neutropenic patients are particularly predisposed to develop different causes of colitis. Prophylactic antibiotics, chemotherapy, and radiation therapy can be associated with mucositis and enteritis. Enteric flora and previous colonizing bacteria can cause local infection and translocate to the blood stream.

Neutropenic colitis known as typhlitis, and *clostridium difficile* colitis are the most common type of colitis in neutropenic patients and will be reviewed here. Other infectious causes of colitis such as CMV, adenovirus, rotavirus, norovirus, and parasitc colitis are not within the scope of this chapter.

Neutropenic Colitis

Typhlitis is a life threatening enterocolitis that occurs mainly in neutropenic patients. The pathogenesis is poorly understood, but it is believed that chemotherapy induced mucosal injury, and motility dysfunction with bacterial overgrowth causing secondary bacterial infection may play a role. The most common affected area is the cecum followed by the ascending colon and the terminal ileum. It has been postulated that the distensibility of the cecum and limited blood supply may facilitate the bacterial overgrowth [16–18].

Typhlitis is usually a polymicrobial infection with several bacteria involved including *Klebsiella spp*, *E. coli, Streptococcus viridans, Enterococcus spp*, *Pseudomonas*, and *Candida spp. Clostridium spp* particularly *clostridium septicum* play an important role and may be associated with increased mortality [17–19].

Clinical manifestations include right lower abdominal distention, abdominal cramps, nausea, vomiting, watery or bloody diarrhea sometimes with hematochezia, and fever. The symptoms usually develop after the 3rd week of chemotherapy [19].

The diagnosis is usually clinical based on the above symptoms. Computed tomography (CT) of the abdomen and pelvis can confirm the diagnosis and rule out complications such as pneumatosis intestinalis and perforation. CT may reveal colonic wall thickening and cecum dilation (Fig. 4). Plain abdominal x ray lacks sensitivity but may reveal dilation of the cecum and ascending colon with intramural gas [17, 19].

The treatment of typhlitis is initially conservative with bowel rest, nasogastric suction, and parenteral nutrition if necessary. Systemic antibiotics such as piperacillin tazobactam, or cefepime plus metronidazole or ceftazidime plus metronidazole, or meropenem, imipenem or doripenem are indicated. Surgical therapy is only indicated when clinical deterioration is imminent despite the above measures. Other indications for surgical therapy include persistent bleeding despite correction of coagulopathies or bowel perforation [19].

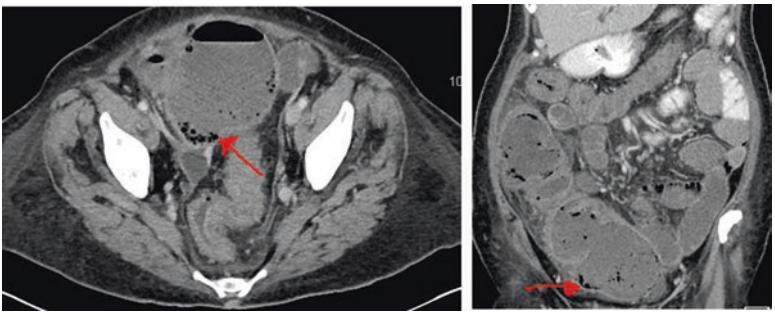

Fig. 4 CT of the abdomen and pelvis of a patient with neutropenic colitis with significantly dilated cecum and ascending colon. There is air within the bowel wall in the ascending colon to the level of the splenic flexure

Clostridium Difficile *Associated Disease*

Clostridium difficile associated disease is an important cause of morbidity and mortality in neutropenic patients. Chemotherapy, prophylactic antibiotics, mucositis, prolonged hospitalization, use of proton pump inhibitors, and immunosuppression predispose this population to develop *Clostridum difficile* associated disease. A multicenter survey reported that hospital acquired *Clostridium difficile* infection was twice as common in the cancer population compared with the general population [20].

The clinical diagnosis of *Clostridium difficile* associated disease represents a challenge in neutropenic patients because chemotherapy associated enteritis may have similar symptomatology. Some studies have shown that less than half of cancer patients with *C. diff* associated diarrhea have the classical symptoms including fever and abdominal pain [20].

The diagnosis of severe *Clostridium difficile* associated disease in neutropenic patients may be difficult to assess since these patients lack typical leukocytosis. In addition, they may have chronic kidney disease. In such patients, clinical judgment to treat as severe disease is a bedside decision.

Treatment and microbiologic diagnosis of *Clostridium difficile* in neutropenic patients follows the same recommendation as for non-neutropenic patients. Unfortunately, high risk neutropenic patients require prophylactic antibiotics which cannot be discontinued.

Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of *Clostridium difficile*. If access to vancomycin or fidaxomicin is limited, then metronidazole for an initial episode of nonsevere *Clostridium difficile* infection is acceptable.

Oral vancomycin with or without intravenous metronidazole is the ideal treatment for severe and complicated *Clostridium difficile* associated disease. The use of probiotics to prevent Clostridium difficile associated disease is not endorsed by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). In addition, there is concern for possible bloodstream infection with the use of probiotics in the neutropenic population [20, 21].

Classically, the length of treatment of *Clostridium difficile* associated disease is 10–14 days. However in neutropenic patients, treatment often needs to be continued while receiving prophylactic antibiotics to prevent relapse. In such cases, oral vancomycin 125 mg po bid can be used after 14 days of initial therapy while the patient remains on other antibiotics [22]. Metronidazole is not an ideal option for chronic prophylaxis to prevent *Clostridium difficile* because of the potential neurotoxicity when given beyond 28 days.

Fecal microbiota transplant is widely used in immunocompetent patients with recurrent *Clostridium difficile* associated diarrhea. In immunocompromised patients its use has not yet been accepted because of concern for donor related infections and bacterial translocation from the gastrointestinal tract to the blood stream [20].

Proctitis

Perirectal inflammation in neutropenic patients may occur as a result of mucosal inflammation from chemotherapy, diarrhea, bleeding hemorrhoids, or from perirectal furuncles. Perirectal wounds can later develop into rectal fissures or perirectal abscesses. Small peri-rectal wounds can lead to blood stream infections. Given the anatomic location, these infection are usually polymicrobial. Bacteria involved are often *E coli*, *Klebsiella spp*, *Pseudomonas spp*, *Enterobacter spp*, *Citrobacter spp*, *Proteus mirabilis*, *anaerobes spp*, *Enterococcus spp*, *Streptococcus viridans*, *Staphylococcus aureus* and *Candida spp*. Molds are rare but can also be found [16].

Symptoms include fever, severe peri-anal pain that can be associated with constipation.

Diagnosis is usually clinical. If there is any concern for peri-anal or peri-rectal abscess, a CT of the pelvis should be ordered to evaluate its extent. In such cases, surgical consultation is indicated. In neutropenic patients, the timing and indication of surgery may have to be balanced with the risks for bleeding and poor wound healing [23].

Systemic antibiotics such as vancomycin in addition to piperacillin tazobactam, cefepime with metronidazole, ceftazidime with metronidazole, meropenem, imipenem or doripenem are indicated. The initial antibiotic regimen can be narrowed to cover specific bacteria isolated once the patient is more stable and blood and perirectal cultures are finalized.

Diverticulitis

Diverticulitis results from microscopic or macroscopic perforation of a diverticulum due to local inflammation. In neutropenic patients with diverticulosis, the inflammation may be precipitated by enteritis from chemotherapy and constipation. Complicated diverticulitis can lead to abscess formation (Fig. 5), perforation and fecal peritonitis.

Given the above reasons, immunosuppressed patient are often at risk for complicated and recurrent diverticulitis.

The treatment of diverticulitis should include antibiotics to cover anaerobic organisms and enteric gram negative rods including Pseudomonas. Antibiotics such as piperacillin tazobactam, or cefepime plus metronidazole or ceftazidime plus metronidazole, or meropenem, imipenem or doripenem are indicated. A low threshold for surgical treatment in immunosuppressed patients is endorsed by the 2014 Guidelines by the American Society of Colon and Rectal Surgeons, but further study revealed increasing morbidity following surgical therapy in patients receiving chemotherapy [24, 25].

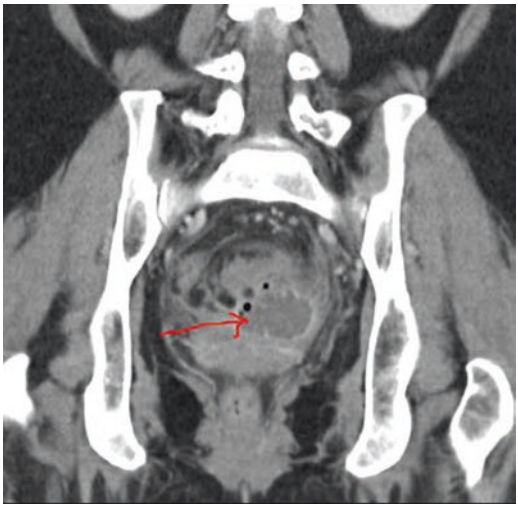

Fig. 5 CT of a patient with diverticulitis and sigmoid abscess

The decision of surgical treatment should be individualized balancing the risk vs benefits considering the acute illness, overall medical condition, chances of healing and or eradicating the infection with medical therapy alone.

Cholecystitis and Cholangitis

Cholangitis and cholecystitis in neutropenic patients just as in the general population results from cholelithiasis. It can also result from malignant lesions of the biliary tract. As a result, enteric gram negative rods, and anaerobic bacteria can translocate into the bloodstream causing sepsis.

The clinical symptoms include fever, right upper quadrant abdominal pain and jaundice if obstructive cholangitis is present. Treatment includes relieving the obstruction of the biliary tree if present and systemic antibiotics [26].

Antibiotics such as piperacillin tazobactam, or vancomycin and cefepime plus metronidazole or vancomycin and ceftazidime plus metronidazole, or vancomycin and meropenem, imipenem or doripenem are indicated.

Hepatitis

Hepatitis B virus (HBV) and hepatitis C (HCV) are very common viruses worldwide. In oncologic patients, HBV reactivation ranges between 30% and 80% depending the chemotherapy regimen.

The Center of Disease Control (CDC) recommends screening for HBV in all patients receiving cytotoxic or immunosuppressive therapy. Patients who have hepatitis B surface antigen (HBsAg) or who are hepatitis B core antibody (HBcAb) positive and receive chemotherapy regimens with anti CD20 agents, TNF alpha inhibitors, and anthracyclines are at higher risk for reactivation. In these patients HBV prophylaxis should be considered. Ideal regimens for HBV prophylaxis include tenofovir, entecavir adefovir and lamivudine [26–28].

HCV reactivation in cancer patients has not been well studied and little is known about the need for prophylaxis, but newer therapies can ensure cure in 12 weeks decreasing morbidity and mortality in this population. The National Comprehensive Cancer Network (NCCN) guidelines recommends that all patients receiving chemotherapy or immunosuppressive therapy should be screened and treated for HCV particularly if the life expectancy is greater than 12 months [26, 27].

Other viruses such as Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV) and Adenovirus can also cause severe hepatitis in neutropenic and immunosuppressed patients, but are rare outisde of the allogeneic stem cell transplant population . These infections are not within the scope of this chapter.

Genitourinary Tract Infections

Neutropenia, chemotherapy, mucosal inflammation and indwelling foley catheters increase the susceptibility for developing genitourinary infections (GU) infection. Although the pathogenesis is similar to the immunocompetent population, the infections are more frequent and severe in neutropenic patients.

Unfortunately, in this population, the diagnosis represents a challenge because the signs and symptoms of inflammation may be absent and the sensitivity of pyuria may be low [29].

The presence of a foley catheter increases the risk of bacteriuria 5–10% per day. The most common organisms that cause urinary tract infections include enteric gram negative rods such as *E coli, klebsiella pneumoniae*, and *Proteus mirabilis. Staphylococcus saprophyticus* is also a common pathogen [30].

In neutropenic patients, other bacteria such as *Enterococcus* and *Pseudomonas spp* can also cause GU infections. Rarely molds including *Fusarium spp* may be involved [31].

The treatment of urinary tract infections in neutropenic patients should be directed towards the isolated organism. The duration may be longer to prevent recurrent infection while the patient is still neutropenic.

Antimicrobial treatment should also be given for patients with prolonged and profound neutropenia and asymptomatic bacteriuria because of the high risk of bacteremia.

Hemorrhagic viral cystitis is an important cause of morbidity and mortality in transplant patients but is rarely seen in neutropenic patients without transplant. The viruses commonly involved are BK, Adenovirus, and CMV.

Key Points

Disease	Organisms	Antibiotics
Esophagitis	Candida, HSV, rarely CMV	Fluconazole if Candida. Famciclovir, or Valacyclovir. If HSV, and Ganciclovir if CMV.
Typhlitis, diverticulitis	*Klebsiella spp*, *E. coli*, *Streptococcus viridans*, *Enterococcus spp*, *Pseudomonas*, *Candida spp*, *Clostridium spp* and other anaerobes	Piperacillin tazobactam. Cefepime plus metronidazole. Ceftazidime plus Metronidazole. Meropenem, or Imipenem or Doripenem.
Proctitis	*E coli*, *Klebsiella spp*, *Pseudomonas spp*, *Enterobacter spp*, *Citrobacter spp*, *Proteus*, *anaerobes*, *Enterococcus spp*, *Streptococcus viridans*, *Staphylococcus aureus* and *Candida spp*. Molds are rare but can also be found	Vancomycin plus Piperacillin Tazobactam. Vancomycin plus Cefepime and Metronidazole. Vancomycin plus Ceftazidime and Metronidazole. Vancomycin and Meropenem, Imipenem or Doripenem until susceptibilities are available.
Clostridium difficile colitis	*Clostridium dificile*	Oral Vancomycin or Fidaxomicin. If access to Vancomycin or Fidaxomicin is limited, then Metronidazole for initial episode of nonsevere *Clostridium difficile* infection. Oral vancomycin with or without intravenous Metronidazole for severe and complicated *Clostridium difficile* associated disease.
Cholecystitis and Cholangitis	Enteric gram negative rods, anaerobic bacteria	Piperacillin tazobactam. Vancomycin and Cefepime plus Metronidazole. Vancomycin and Ceftazidime plus Metronidazole. Vancomycin and Meropenem, Imipenem or Doripenem

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