

# Gastrointestinal complications of oncologic therapy

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## SUMMARY

Gastrointestinal complications are common in patients undergoing various forms of cancer treatment, including chemotherapy, radiation therapy, and molecular-targeted therapies. Many of these complications are life-threatening and require prompt diagnosis and treatment. Complications of oncologic therapy can occur in the esophagus (esophagitis, strictures, bacterial, viral and fungal infections), upper gastrointestinal tract (mucositis, bleeding, nausea and vomiting), colon (diarrhea, graft-versus-host disease, colitis and constipation), liver (drug hepatotoxicity and graft-versus-host disease), and pancreas (pancreatitis). Treatment of the different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication.

**KEYWORDS** drug hepatotoxicity, drug-induced enterotoxicity, graft-versus-host disease, infectious esophagitis, neutropenic enterocolitis

## REVIEW CRITERIA

A thorough literature search was performed using MEDLINE/PubMed search engines with secondary review of cited publications. Prospective and retrospective studies, clinical trials as well as review articles were included. The following key terms were used for selection of articles: "esophagitis", "esophageal strictures", "drug-induced diarrhea", "*Clostridium difficile* colitis", "neutropenic enterocolitis", "constipation", "graft versus host disease", "radiation proctitis" and "drug-induced liver toxicity" and "liver injury", "chemotherapy-induced nausea and vomiting", "mucositis". The search was performed in January 2008 for references published in 1970 and later, and was restricted to full papers in English.

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## INTRODUCTION

Various nonsurgical oncologic treatments are currently available, including chemotherapy, radiotherapy, and molecular-targeted therapies. Although many oncologic treatments are effective, they frequently have adverse effects, a considerable number of which affect the gastrointestinal tract. Any part of the gastrointestinal tract can be affected, including the esophagus (esophagitis, strictures, bacterial, viral and fungal infections), upper gastrointestinal tract (mucositis, bleeding, nausea and vomiting), colon (diarrhea, graft-versus-host disease [GVHD], colitis and constipation), liver (drug hepatotoxicity and GVHD), and pancreas (pancreatitis). Many of these gastrointestinal adverse effects differ in severity between individuals, but they can be life-threatening and must be quickly identified and treated. In some instances, oncologic treatment will need to be adjusted to minimize the development of severe gastrointestinal complications. Monitoring of the oncologic treatment for each patient in relation to associated adverse effects is, therefore, essential and requires efficient communication between oncologists and gastroenterologists to ensure that the most effective oncologic treatment is administered whilst any gastrointestinal adverse effects are managed.

This Review discusses some of the gastrointestinal complications that can arise as a result of various oncologic treatments, including esophagitis, diarrhea and constipation, neutropenic enterocolitis, GVHD, radiation proctitis, drug hepatotoxicity, nausea and vomiting, gastrointestinal perforation, fistula formation, arterial thrombosis and bleeding, acute pancreatitis, and oral mucositis. The pathologic mechanisms underlying each complication are discussed, along with the symptoms, methods of diagnosis and treatment options.

## ESOPHAGITIS

Esophagitis in patients with cancer can be caused by the cytotoxic effects of chemotherapy and radiation, or by infection with viral, fungal or

**Table 1** Common causes of esophagitis in patients receiving oncologic therapy.

Causative agent	Diagnosis	Symptoms	Endoscopic/histologic appearance	Treatment
<i>Candida albicans</i>	Endoscopy, biopsy	Odynophagia, dysphagia	White plaque-like lesions, surrounding erythema on esophageal walls	Systemic antifungal treatment (e.g. fluconazole, itraconazole, voriconazole, echinocandins)
HSV	Endoscopy, biopsy, IHC	Odynophagia, dysphagia, nausea, vomiting, heartburn, epigastric pain, fever. Symptoms of coexistent herpes labialis or presence of oropharyngeal ulcers	Small vesicles, coalescing to form ulcers	Aciclovir, foscarnet sodium
CMV	Endoscopy, biopsy	Odynophagia, dysphagia, nausea, vomiting, heartburn, epigastric pain, fever	Linear or serpiginous ulcers	Intravenous ganciclovir, foscarnet sodium
VZV	Endoscopy, biopsy	Odynophagia, dysphagia, nausea, vomiting, heartburn, epigastric pain, fever. Symptoms of coexistent disseminated herpes zoster	Ulcers similar to HSV ulcers	Intravenous aciclovir
Polymicrobial, oral flora	Endoscopy, biopsy,	Odynophagia, dysphagia	Clusters of bacteria mixed with necrotic epithelial cells in biopsy samples	Broad-spectrum antibiotics
Radiation treatment (e.g. of lung and esophageal cancers)	Endoscopy	Odynophagia, dysphagia, chest pain	Erythema, edema and friability of the mucosa; ulcerations, stricture formation	Lidocaine hydrochloride, PPIs, endoscopic dilation, SEPS

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; IHC, immunohistochemistry; SEPS, self-expanding plastic stents; VZV, varicella-zoster virus.

bacterial organisms (Table 1), the risk of which is often increased in immunocompromised cancer patients.<sup>1</sup> Other causes of esophagitis that are common in patients with cancer include GERD, pill-induced injury, and GVHD in hematopoietic stem-cell transplant recipients. Prompt endoscopic evaluation and biopsies are recommended when esophagitis is suspected in an immunocompromised patient, to enable early diagnosis and therapy.<sup>2</sup>

### Fungal infections

Esophageal candidiasis is one of the most common infections in immunocompromised patients, and is most often caused by *Candida albicans*. Patients with esophageal candidiasis usually complain of odynophagia and/or dysphagia. Of note, the absence of oropharyngeal thrush does not exclude a diagnosis of esophageal candidiasis. An empiric trial of antifungal therapy is appropriate when patients present with classic symptoms such as odynophagia and/or dysphagia, but endoscopy should be performed and biopsy samples taken if symptoms do not improve approximately 72 h after treatment initiation.<sup>1</sup>

On endoscopy, esophageal candidiasis is identified by white plaque-like lesions with

surrounding erythema covering the esophageal walls. Esophageal biopsies or brushings should be taken and used to confirm the presence of invasive yeast or hyphal forms of *C. albicans*.

Treatment of esophageal candidiasis in immunocompromised patients requires systemic antifungal therapy, and it should never be managed with topical agents in this setting. Fluconazole (100–200 mg daily for 14–21 days) is effective at eradicating *Candida* infections and is the treatment of choice for most patients with esophageal candidiasis.<sup>3</sup> Itraconazole oral solution (200 mg daily) and voriconazole (200 mg twice daily) might be as effective as fluconazole.<sup>4,5</sup> Voriconazole can be used for the treatment of infections unresponsive or refractory to fluconazole therapy.<sup>6</sup> Itraconazole use has been associated with considerable nausea and has the potential to interact with other drugs because it inhibits the cytochrome p450 enzymatic system.

The echinocandins—caspofungin, micafungin and anidulafungin—are also very effective for the treatment of *Candida* esophagitis.<sup>7–9</sup> They are administered intravenously and are used to a larger extent in hospitalized patients. Another antifungal drug, amphotericin B, is no longer recommended because of its toxicity profile.

### Viral infections

Viral infections of the esophagus are caused by herpes simplex virus (HSV), cytomegalovirus (CMV), and rarely, varicella-zoster virus (VZV). Presenting symptoms include odynophagia, dysphagia, and less frequently nausea, vomiting, heartburn, epigastric pain and fever. Some patients with HSV esophagitis might have coexistent herpes labialis or oropharyngeal ulcers.<sup>10</sup>

Diagnosis of esophageal viral infection is by endoscopy and biopsy. In the early stage of infection, HSV lesions can appear as small vesicles; these eventually coalesce to form large ulcers that are usually less than 2 cm in size.<sup>11</sup> CMV causes ulcers that are linear or serpiginous and deeper than HSV-related ulcers. VZV can produce esophagitis in adults with herpes zoster, usually in the setting of disseminated infection.<sup>2</sup>

Endoscopically, VZV ulcers are similar to those caused by HSV, and distinction requires immunohistochemistry or culture of biopsy specimens. Biopsy samples taken from the edge of an HSV-related ulcer will show intranuclear inclusions and multinucleated giant cells. Inclusions can also be detected by immunohistochemistry, by using monoclonal antibodies to HSV. Biopsy samples taken from patients with CMV infection show intranuclear inclusions in fibroblasts and endothelial cells. Immunohistochemistry with anti-CMV antibodies is also helpful for diagnosis.

For patients with HSV esophagitis, aciclovir (400 mg orally five times daily for 14–21 days or 5 mg/kg intravenously every 8 h for 7–14 days) is the therapy of choice. Foscarnet sodium is reserved for those patients infected with aciclovir-resistant HSV strains or those who do not respond to aciclovir treatment. Famciclovir or valaciclovir can be considered in patients able to tolerate oral therapy, although there is limited clinical experience with these drugs for the treatment of HSV-associated esophagitis.

VZV esophagitis is initially treated with intravenous aciclovir as these patients usually have disseminated infection. After clinical improvement, patients can be switched to any of the oral agents mentioned above for HSV esophagitis.

CMV esophagitis can be treated with intravenous ganciclovir (5 mg/kg twice daily) or foscarnet sodium (90 mg/kg twice daily) for 3–6 weeks.<sup>12–14</sup> Whether maintenance treatment is needed once the initial infection has been cleared is controversial. Valganciclovir is an oral agent that is rapidly absorbed and

hydrolyzed to ganciclovir. Although valganciclovir has been approved for the treatment of CMV retinitis in patients with AIDS and is used for prophylaxis against CMV infection in solid-organ transplant recipients, its role in CMV gastrointestinal disease has not been studied. At a dose of 900 mg daily, valganciclovir produces systemic exposure to a dose equivalent to that of intravenous ganciclovir at 5 mg/kg.<sup>15</sup> Anecdotal reports suggest that oral valganciclovir can effectively treat CMV esophagitis once odynophagia has been improved by intravenous ganciclovir, and patients can tolerate oral medication. Other groups have suggested that oral valganciclovir should be used as maintenance therapy in patients who have had a relapse of CMV infection in the gastrointestinal tract. Additional studies are, however, needed to make specific recommendations concerning the use of valganciclovir for the treatment of CMV esophagitis.

### Bacterial infections

Bacterial esophagitis can occur in immunocompromised patients and is usually polymicrobial, being derived from oral flora.<sup>2</sup> Diagnosis is made by endoscopic biopsies that demonstrate the presence of bacteria clusters mixed with necrotic epithelial cells. Treatment with broad-spectrum antibiotics is usually successful.

### Radiation-induced esophagitis

Radiation-induced esophagitis can occur during radiation treatment of lung and esophageal cancers. The severity of esophagitis generally increases with radiation dose and with the combined use of some chemotherapeutic agents such as doxorubicin hydrochloride, bleomycin, cyclophosphamide and cisplatin.<sup>16,17</sup>

Patients with radiation-induced esophagitis often complain of odynophagia, dysphagia, and chest pain. Endoscopy can reveal erythema, edema and friability of the mucosa, as well as ulcerations and stricture formation. Treatment includes the use of viscous lidocaine hydrochloride and PPIs to prevent further acid-related injury.

Strictures are managed by endoscopic dilation, and strictures refractory to endoscopic dilation can be managed by the placement of self-expanding plastic stents (SEPS) (Figure 1). SEPS are similar in concept to expandable metal stents, however, SEPS have the advantage of being able to be repositioned, and removed

once the stricture has resolved. Clinical data suggest that temporarily placed SEPS can be curative for esophageal strictures in up to 80% of patients who have benign esophageal lesions.<sup>18,19</sup> The most common complication of SEPS is migration of the stent, which can occur in up to one-third of patients.<sup>20</sup> In patients with tracheo-esophageal fistula occurring secondary to esophageal cancer, covered stents (either self-expanding metal or plastic stents) are the treatment of choice, and can achieve fistula closure in 70–100% of patients.<sup>21</sup>

## DIARRHEA

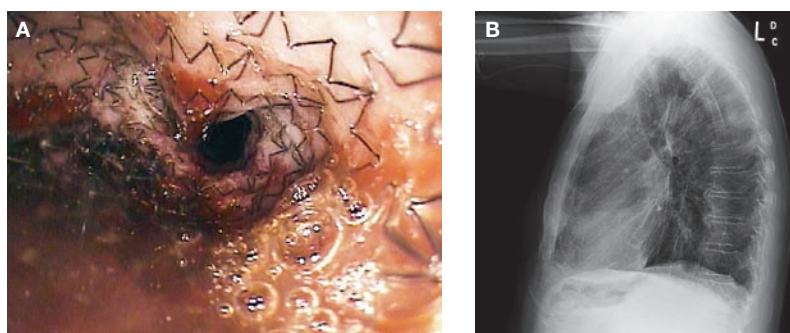
Diarrhea is a common complication of cytotoxic therapy (Box 1), and occurs most commonly in cancer patients treated with fluoropyrimidines (particularly 5-fluorouracil [5-FU]), irinotecan hydrochloride, methotrexate or cisplatin. The diarrhea can be debilitating and in severe cases can even be life-threatening. The onset of diarrhea can lead to cancer treatment delays, reduced quality of life, and diminished drug compliance. In fact, diarrhea is the dose-limiting factor and the major toxic adverse effect of regimens containing a fluoropyrimidine and/or irinotecan hydrochloride.

Other causes of diarrhea in patients undergoing cancer treatment include radiation therapy, small-molecule therapy, monoclonal antibody therapy, neutropenic enterocolitis, and *Clostridium difficile* colitis. Neutropenic enterocolitis is discussed separately to diarrhea because of its unique setting. GVHD in patients who have received an allogeneic hematopoietic stem-cell transplant is also associated with severe diarrhea and is discussed in more detail later in the Review.

### Chemotherapy-induced diarrhea

The severity of chemotherapy-induced diarrhea is often described, particularly for study purposes, using the National Cancer Institute Common Toxicity Criteria (NCI CTC).<sup>22</sup> Grading is based on the number of stools passed per day, the passing of nocturnal stools, and the need for parenteral support or intensive care.

The severity and prevalence of diarrhea caused by 5-FU treatment is increased by the addition of leucovorin (also known as folinic acid) to the treatment regimen. Diarrhea is reported in up to 50% of patients receiving weekly 5-FU/leucovorin combined treatment. Moreover, the severity of the diarrhea can worsen when 5-FU



**Figure 1** Use of a self-expanding esophageal stent to manage an esophageal stricture. (A) Endoscopic view of a self-expanding stent deployed in the esophagus. (B) Chest radiograph showing the stent deployed in the esophagus.

### Box 1 Common causes of diarrhea in patients receiving oncologic therapy.

#### Fluoropyrimidines

- 5-Fluorouracil
- Capecitabine

#### Irinotecan hydrochloride

#### Oxaliplatin

#### Small-molecule EGFR inhibitors

- Erlotinib

#### Small-molecular VEGF inhibitors

- Sorafenib

#### Monoclonal antibodies directed against EGFR

- Cetuximab

#### Radiation therapy

#### Graft-versus-host disease

#### *Clostridium difficile* infection

Abbreviations: EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

is administered by bolus injection as opposed to intravenous infusion. Other factors that can raise the risk of 5-FU-induced diarrhea include female sex, the presence of an unresected primary tumor, previous episodes of chemotherapy-induced diarrhea, and treatment during the summer season.<sup>23,24</sup>

Irinotecan hydrochloride can cause an early-onset diarrhea accompanied by abdominal cramping, lacrimation, salivation, and other symptoms that seem to be mediated by cholinergic receptors. These symptoms can be effectively treated with atropine as well as loperamide hydrochloride.<sup>25</sup> The late-onset diarrhea associated with irinotecan hydrochloride is unpredictable and can occur at all dose levels. It

is seen less frequently when irinotecan hydrochloride is given every 3 weeks rather than weekly.<sup>20</sup> Diarrhea caused by the combined treatment regimen of irinotecan hydrochloride, 5-FU and leucovorin has been reported to be substantially more severe compared with diarrhea caused by 5-FU and leucovorin without irinotecan hydrochloride.<sup>26–28</sup>

Capecitabine is an oral fluoropyrimidine that is converted to 5-FU by a series of enzymatic reactions. One of the major dose-limiting toxicities of capecitabine is diarrhea. There seems to be regional differences in tolerance to capecitabine, with more serious adverse events reported in the US compared with other parts of the world.<sup>29</sup> These regional variations might be due to genetic polymorphisms, lifestyle or possibly differences in dietary folate intake.<sup>29</sup>

Diarrhea also occurs frequently in patients with cancer treated with regimens combining 5-FU, leucovorin and oxaliplatin, particularly when 5-FU is administered as a weekly or daily bolus.<sup>30,31</sup>

#### **Diarrhea induced by small molecules and monoclonal antibodies**

Diarrhea is also common in patients with cancer receiving small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. For example, grade 1–2 diarrhea as defined by the NCI CTC has been reported in up to 56% of patients receiving erlotinib.<sup>32</sup> Another small-molecule inhibitor of tyrosine kinases in the vascular endothelial growth factor (VEGF) pathway, sorafenib, has been associated with diarrhea in approximately 34% of patients.<sup>33</sup> Unlike the small-molecule EGFR inhibitors, cetuximab, which is a chimeric monoclonal antibody that binds EGFR, has been reported to cause diarrhea of any grade in only 12.7% of patients and grade 3 diarrhea in only 1.2% of patients.<sup>34</sup>

#### **Radiation-induced diarrhea**

Radiation therapy can injure the gastrointestinal mucosa. The extent of injury and associated diarrhea usually peaks 1–2 weeks after initiation of irradiation. Worsening diarrhea occurs when radiation is given in combination with chemotherapy, for example with 5-FU for the treatment of rectal cancer.<sup>35</sup> Patients presenting with severe diarrhea, fever or neutropenia following chemoradiation should be admitted to hospital for a diagnostic work-up and treatment.

#### **Treatment of chemotherapy-induced and radiation-induced diarrhea**

The treatment of chemotherapy-induced or radiation-induced diarrhea involves aggressive oral rehydration and electrolyte replacement and the use of pharmacologic agents to reduce fluid loss and decrease intestinal motility. Opioid agonists are a basic component of therapy. Loperamide hydrochloride (Imodium®; Johnson & Johnson, New Brunswick, NJ) and diphenoxylate (Lomotil®; G.D. Searle & Co., Skokie, IL) are the agents most commonly used to treat diarrhea. For mild-to-moderate diarrhea, an initial dose of 4 mg loperamide hydrochloride should be given, followed by a further 2 mg every 4 h or after every stool. Severe cases of diarrhea or irinotecan-hydrochloride-induced diarrhea often require a more aggressive regimen, with an initial dose of 4 mg loperamide hydrochloride followed by a further 2 mg every 2 h or 4 mg every 4 h until the patient has been diarrhea-free for 12 h.<sup>36,37</sup>

Octreotide—a synthetic long-acting somatostatin analog—has been used as second-line therapy in patients who do not respond to opioids. The recommended initial dose of octreotide is 100–150 µg given subcutaneously three times daily, or 25–50 µg every hour if given as an intravenous infusion.<sup>37</sup> Octreotide can be titrated to higher doses (500–2,500 µg three times daily) for the treatment of those individuals who do not respond to lower doses.<sup>38,39</sup>

Other agents have been used as adjunctive therapy in the treatment of mild-to-moderate chemotherapy-induced and radiation-induced diarrhea, including absorbents such as kaolin and charcoal, deodorized tincture of opium, paregoric, and codeine phosphate.

#### **Stem-cell-transplantation-associated diarrhea**

Patients undergoing stem-cell transplantation can suffer from diarrhea caused by the conditioning regimen, GVHD or to an infection related to immunosuppressive therapy. Pretransplant conditioning regimens (including total body irradiation and/or a combination of chemotherapeutic agents) can injure the intestinal mucosa as discussed above, causing a secretory diarrhea that resolves after mucosal restitution. Recipients of allogeneic stem-cell transplants can also develop GVHD, which usually starts 3 weeks or longer after transplantation. GVHD and its associated diarrhea are discussed in a separate section in more detail.

### ***Clostridium difficile* diarrhea**

*C. difficile* infection is the most common cause of infectious diarrhea in hospitalized patients.<sup>40</sup> Although commonly associated with the use of antibiotics, risk factors for *C. difficile* colitis also include bowel surgery, an immunocompromised state and any process that suppresses the normal gastrointestinal flora, including chemotherapeutic agents.

Patients with cancer undergoing chemotherapy are also predisposed to *C. difficile*-induced diarrhea even in the absence of antibiotic therapy.<sup>41</sup> Use of methotrexate, doxorubicin hydrochloride and cyclophosphamide is frequently associated with *C. difficile* infection.<sup>41</sup> Clinical presentation of *C. difficile* infection can vary from mild diarrhea without colitis, to colitis with systemic manifestations, pseudomembranous colitis with or without protein-losing enteropathy, or fulminant colitis with the development of toxic megacolon.

A diagnosis of *C. difficile*-related diarrhea is established by detecting the presence of *C. difficile* toxin in stool or by identifying pseudomembranous colitis on endoscopic evaluation (Figure 2). Endoscopically, pseudomembranes can be seen as adherent yellow plaques that vary in diameter from 2 mm to 10 mm. The intervening mucosa can appear normal or mildly erythematous.<sup>40</sup> The rectum and sigmoid colon are typically involved, but in approximately 10% of cases colitis is only present in the more proximal colon and can be missed during sigmoidoscopy.

The stool cytotoxin assay is a tissue culture assay based on the induction of cell rounding by *C. difficile* toxin in stool filtrate, and is considered the gold standard for diagnosis. It has a high sensitivity (94–100%) and specificity (99%),<sup>42</sup> however, it is costly and it takes 2–3 days to complete. More rapid and inexpensive enzyme-linked immunosorbent assays (ELISAs) with similar sensitivity (70–90%) and specificity (99%) can also be used.<sup>43</sup> These ELISAs detect the most common enterotoxin produced by *C. difficile*, toxin A, but do not detect toxin B. If an initial stool immunoassay test is negative, repeating a stool ELISA or supplementing it with a cytotoxicity assay can increase the sensitivity for diagnosis.<sup>44</sup>

Standard therapy for *C. difficile*-associated diarrhea is oral metronidazole or oral vancomycin. Metronidazole at a dose of 500 mg three times daily given either orally or intravenously for 10–14 days is as effective as oral vancomycin given at a dose of 125 mg four times daily.<sup>45</sup>

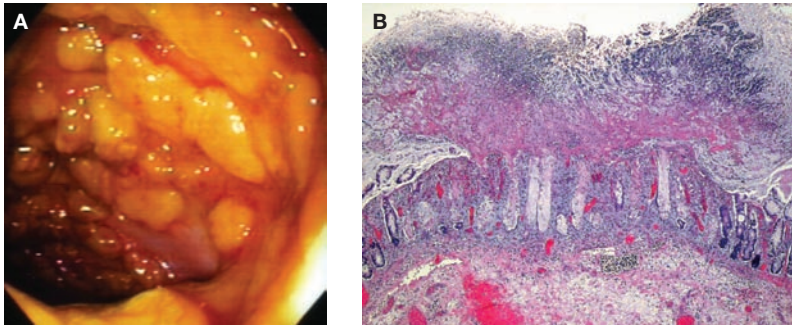
However, metronidazole has some advantages over vancomycin including its lower cost and the fact that it can reduce selection of vancomycin-resistant enterococci. Metronidazole is, therefore, considered by many to be the initial therapy of choice in nonsevere cases of *C. difficile*-induced diarrhea.

In patients with severe *C. difficile* infection and signs of systemic toxicity, the recommended treatment regimen is initial therapy with vancomycin 125 mg orally four times daily, with escalation of the dose at 48 h intervals up to 500 mg four times daily if patients fail to improve. If patients do not respond to oral vancomycin, the addition of intravenous metronidazole 500 mg every 8 h, or vancomycin retention enemas (0.5–1 g of vancomycin dissolved in 1–2 l of normal saline every 4–12 h), should be considered.<sup>46</sup>

Relapse of *C. difficile*-induced diarrhea is common, occurring in up to 10–25% of all patients with *C. difficile* infection. Relapses usually occur within 1–3 weeks after termination of initial therapy, and are probably caused by failure to eradicate the organism rather than development of antibiotic resistance.<sup>40</sup> First relapses should be treated with a second 10–14 day course of oral metronidazole or vancomycin.<sup>47</sup> If a patient relapses after taking a second course of antibiotics, different approaches have been suggested, including tapered or pulsed antibiotic therapy, and the use of anion-binding resins such as colestyramine or colestipol hydrochloride alone or in combination with vancomycin.<sup>48</sup>

### **NEUTROPENIC ENTEROCOLITIS**

Neutropenic enterocolitis is a clinical syndrome in neutropenic patients that is characterized by fever and right lower quadrant pain. The disease has been reported in children and adults with leukemia, multiple myeloma, aplastic anemia, myelodysplastic syndrome, granulocytopenias from other causes or AIDS, and after immunosuppressive therapy for solid malignancies and transplants.<sup>47,49</sup> The true incidence of neutropenic enterocolitis is unknown. In a systematic review of 145 published articles, a 5.3% pooled incidence rate of neutropenic enterocolitis was reported in a population that included adults hospitalized for the treatment of hematologic malignancies or aplastic anemia or who were receiving high-dose chemotherapy for the treatment of solid tumors.<sup>50</sup>



**Figure 2** Pseudomembranous colitis. (A) Plaque-like 'pseudomembranes' adherent to the colonic mucosa, as observed by colonoscopy. (B) Photomicrograph of a typical lesion with a 'volcano-like' appearance with luminal inflammatory exudate.

### Pathogenesis and symptoms

A combination of factors might be involved in the pathogenesis of neutropenic enterocolitis, including mucosal injury by cytotoxic drugs, neutropenia and impaired host defense against intestinal organisms.<sup>51</sup> Histologic examination of biopsy samples can reveal a thickened bowel wall, edema, mucosal ulcerations, focal hemorrhage and mucosal or transmural necrosis.

Numerous bacterial and/or fungal organisms have been identified in surgical specimens and peritoneal fluid from patients with neutropenic enterocolitis, including Gram-negative rod bacteria, Gram-positive cocci, enterococci, anaerobes (e.g. *Clostridium septicum*) and *Candida* species.<sup>49,51</sup> Leukemic or acute inflammatory infiltrates have only rarely been identified in these patients.<sup>47</sup>

Patients with neutropenic enterocolitis present with profound neutropenia, fever and abdominal pain, particularly in the right lower quadrant. Other presenting symptoms can include abdominal distension, nausea, vomiting and watery or bloody diarrhea.

### Diagnosis and treatment

The presentation and clinical findings of neutropenic enterocolitis can be nonspecific, and therefore differential diagnoses must be considered, including pseudomembranous colitis, other infectious colitis, colonic pseudo-obstruction, acute appendicitis and ischemic colitis.

A diagnosis of neutropenic enterocolitis is usually made by performing imaging studies—CT is preferred to ultrasound or plain abdominal films. CT is also useful in ruling out other processes that can mimic neutropenic

enterocolitis. Abnormal findings on CT and ultrasound that are indicative of neutropenic enterocolitis include a fluid-filled, dilated cecum, a right lower quadrant inflammatory mass and pericecal fluid or inflammatory changes in the pericecal soft tissues.<sup>51</sup> Plain films of the abdomen often show nonspecific findings, but they can occasionally reveal a distended cecum with dilated adjacent loops of small bowel, thumbprinting or pneumatosis intestinalis.<sup>52</sup>

Treatment of neutropenic enterocolitis is mostly supportive and consists of bowel rest and the administration of intravenous fluids and broad-spectrum antibiotics.<sup>51</sup> Cytopenias and coagulopathy associated with oncologic treatment should also be corrected since neutropenia contributes to the pathogenesis of the disease and coagulopathy can be associated with blood loss from mucosal hemorrhage. Strong consideration should also be given to the use of recombinant granulocyte colony-stimulating factor (G-CSF) to hasten leukocyte recovery, as normalization of neutrophil counts might contribute to the resolution of neutropenic enterocolitis.<sup>52,53</sup> Surgery has been recommended for patients with persistent gastrointestinal bleeding despite correction of cytopenias and coagulopathy.<sup>52,54</sup> Surgery is also recommended for patients with perforation or clinical deterioration despite pharmacologic therapy.<sup>52,54</sup>

### CONSTIPATION

Constipation is a common problem in patients undergoing cancer treatment. In this setting, constipation is usually caused by a combination of poor oral intake, decreased physical activity, and the action of drugs such as opioid analgesics or antiemetic agents, which slow intestinal transit time. Constipation has also been reported in patients taking vinka alkaloids, in particular vincristine and thalidomide.<sup>55,56</sup>

Impaction, bowel obstruction and colonic pseudo-obstruction must be ruled out before initiating therapy for constipation. Electrolyte abnormalities and other reversible causes should be corrected first. Drugs that cause constipation should be discontinued if possible. Laxatives, with or without stool softeners, can also be used in the initial treatment of constipation. Stimulant laxatives such as bisacodyl and senna alter electrolyte transport by the intestinal mucosa and increase intestinal motor activity. If these agents are not effective, osmotic agents such as lactulose or sorbitol can be effective at

improving stool frequency and consistency.<sup>57</sup> Polyethylene glycol solutions (without electrolytes) are available in powder form and have been found to be effective at improving chronic constipation.<sup>57</sup> The use of drugs to improve colonic transit has been disappointing. Metoclopramide seems to be ineffective, and tegaserod (a 5-hydroxytryptamine receptor agonist) has been removed from the market because of concern regarding its cardiovascular adverse effects.

### **GRAFT-VERSUS-HOST DISEASE**

GVHD is classified as either acute or chronic on the basis of the time to disease onset following transplantation. Acute GVHD disease onset occurs within the first 100 days of hematopoietic stem-cell transplantation, whereas chronic disease is defined as disease onset after 100 days following transplantation. This classification is somewhat arbitrary because a continuum of clinical findings can be observed in patients with acute or chronic GVHD.

#### **Acute graft-versus-host disease**

Acute GVHD has been reported in 9–50% of patients who receive allogeneic hematopoietic stem-cell transplants from a human leukocyte antigen (HLA)-identical sibling. In acute GVHD, involvement of the gastrointestinal tract is characterized by voluminous watery diarrhea and abdominal cramping (Box 1). The diarrhea is secretory and can frequently become bloody.<sup>58</sup> Patients can also present with upper gastrointestinal tract symptoms (dyspepsia, food intolerance, nausea, vomiting and anorexia) in the absence of lower gastrointestinal symptoms.<sup>59</sup>

Biopsies are helpful for making a diagnosis of acute GVHD. The most consistent histologic feature of acute GVHD is apoptotic cell death,<sup>60</sup> but this feature is not specific to this entity, and is also present in other conditions. The area of the gastrointestinal tract that should be targeted for endoscopic biopsies for the diagnosis of acute GVHD is a topic of debate. Early publications suggest that rectal biopsies provide the highest diagnostic yield,<sup>61</sup> while other studies have found that biopsies of the stomach<sup>62</sup> and small bowel<sup>63,64</sup> are most sensitive regardless of whether the patient presents with upper or lower gastrointestinal symptoms. Until data from prospective studies are available, we recommend that biopsies be taken from the stomach, duodenum and rectum when

patients are referred for evaluation of potential acute GVHD.

#### **Chronic graft-versus-host disease**

Chronic GVHD can occur in up to 50% of patients who survive long-term after receiving a transplant from an HLA-identical sibling.<sup>65</sup> The esophagus is the most common site of involvement in patients with chronic GVHD, and these patients can develop painful esophageal ulcerations, webs, rings and strictures.<sup>66</sup> The oral mucosa can be dry, resulting in ulceration and pain. The small bowel and colon are not as frequently involved as in acute GVHD, but when they are involved, patients can present with diarrhea, malabsorption, fibrosis of the submucosa and sclerosis of the intestine.<sup>66,67</sup>

The liver is commonly involved in acute and chronic GVHD. Pathology can reveal extensive bile duct damage with bile duct atypia and degeneration, epithelial cell dropout and lymphocytic infiltration of small bile ducts leading to cholestasis.<sup>68,69</sup> Biopsy is the only method to diagnose GVHD of the liver and to rule out other entities in the differential diagnosis, such as veno-occlusive disease, infection or drug toxicity. A liver biopsy is rarely performed for diagnostic purposes, as biopsies from skin or gastrointestinal tract can be easily obtained with less risk and a high diagnostic yield.

#### **RADIATION PROCTITIS**

Patients receiving radiation therapy to the abdomen and pelvis for the treatment of gynecologic, genitourinary, gastrointestinal and other malignancies are at risk of developing acute and chronic intestinal injury. In the rectum and distal colon, acute radiation injury usually occurs within 6 weeks of beginning therapy and is characterized by diarrhea, rectal urgency, tenesmus and, occasionally, rectal bleeding. These symptoms usually resolve within 6 months without the need for therapy.<sup>70</sup>

Chronic radiation proctitis or coloproctitis has a delayed onset, occurring on average a year or later after exposure to radiation. This type of chronic injury is caused by obliterative endarteritis and chronic mucosal ischemia resulting in epithelial atrophy and fibrosis. The end result of this process is stricture formation and bleeding within the colon and rectum. Patients with radiation proctitis can present with diarrhea, bleeding, tenesmus, urgency, difficulties with defecation and less commonly fecal incontinence.



**Box 2** Advantages and disadvantages of treatment options for radiation proctitis.

**Sucralfate enemas**

Some reports of improved symptoms (including bleeding) without adverse effects

**Argon plasma coagulation**

Easy, safe and inexpensive  
Improvement in bleeding and anemia after approximately 2.9 endoscopic sessions

**Argon or Nd:YAG lasers**

Expensive  
Successful in controlling bleeding

**BICAP or heater probe**

Might cause greater tissue injury

**Surgery**

Considered for intractable symptoms such as strictures, pain or bleeding

**Other (hyperbaric oxygen, short-chain fatty acid enemas, rectal instillation of formaldehyde)**

Some reports of improved symptoms

Abbreviations: BICAP, bipolar electrocoagulation; Nd:YAG, neodymium-doped yttrium aluminium garnet.

The diagnosis of radiation proctitis is made by colonoscopy or sigmoidoscopy. Endoscopic findings include mucosal edema, erythema, friability and the presence of telangiectasias. In severe cases, mucosal ulcerations and strictures can be observed.<sup>71</sup>

Treatment for radiation proctitis should focus on the pattern of symptoms (Box 2). Some patients will present mostly with pain, diarrhea and tenesmus and others exclusively with bleeding. Sucralfate, administered orally or topically, has been reported to improve symptoms (including bleeding) without causing considerable adverse events;<sup>72,73</sup> however, studies investigating the efficacy of this drug have largely been uncontrolled. Other treatments that have shown some benefit in small clinical trials include hyperbaric oxygen,<sup>74</sup> short-chain fatty acid enemas,<sup>75</sup> and rectal instillation of formaldehyde.<sup>76</sup>

Various thermal endoscopic therapies have also been used successfully to treat bleeding associated with radiation proctitis, including argon plasma coagulation (APC), argon and Nd:YAG (neodymium-doped yttrium aluminium garnet) lasers, bipolar electrocoagulation and heater probes. APC uses energy transmitted to tissue by ionized argon gas and has gained popularity because of ease of application, safe depth of

penetration, low cost compared with laser treatment, and wide availability. The benefits of APC for the treatment of radiation proctitis have been shown in several case series.<sup>77–79</sup> Patients treated with APC have improvement in bleeding and anemia after a median of 2.9 treatment sessions.<sup>80</sup> Lasers such as argon and Nd:YAG successfully control bleeding, but are expensive and not widely available. Bipolar electrocoagulation and heater probes are also effective for the treatment of radiation proctitis, but might cause more tissue injury compared with APC or lasers.

Surgery should be considered in patients with intractable symptoms such as strictures, pain or bleeding.<sup>81</sup> In summary, the selection of treatment for radiation proctitis should be based on the type and severity of symptoms as well as local expertise.

## DRUG HEPATOTOXICITY

Patients undergoing chemotherapy require careful assessment of liver function both before and during therapy. If liver function test results are abnormal, the etiology must be defined promptly and as clearly as possible. In addition to drug reactions, there are multiple potential causes of abnormal liver function test results in patients undergoing chemotherapy, including tumor progression, infection or the presence of coexisting hepatic disease.

### Hepatitis

Patients with pre-existing liver disease can be more susceptible to drug-induced hepatotoxicity. Chemotherapy (including the use of monoclonal antibodies) can lead to reactivation of HBV and its associated disease.<sup>82–84</sup> Risk factors for HBV reactivation include HBV surface antigen and HBV envelope antigen seropositivity, detectable HBV DNA before chemotherapy, male sex, diagnosis of lymphoma or breast cancer, and use of steroids.<sup>82,85,86</sup>

Prophylactic treatment with lamivudine seems to be beneficial in preventing HBV reactivation, or reducing the severity of HBV-related disease in patients undergoing cytotoxic chemotherapy.<sup>87</sup> Newer agents for treatment of hepatitis B are available, but there are currently no studies concerning their use for prophylaxis in the setting of cancer chemotherapy or stem-cell transplantation. For short-term prophylaxis (less than 6 months), lamivudine is a reasonable choice for treatment because the risk of developing

lamivudine resistance during this time frame is extremely low. If, however, therapy is required for longer than 6 months, the use of either adefovir dipivoxil or entecavir instead of lamivudine is recommended.<sup>71</sup>

The relationship between chemotherapy and HCV reactivation is less clear than for HBV infection. It seems that the presence of HCV infection increases the risk of having abnormal liver function test results,<sup>88</sup> however, severe flares of clinical hepatitis are extremely rare.

### Idiosyncratic hepatotoxicities

Most hepatotoxic drug reactions are idiosyncratic and are due to either hypersensitivity mechanisms or host metabolic idiosyncrasy.<sup>89</sup>

#### *Alkylating agents*

Alkylating agents are uncommonly associated with hepatotoxicity. With the exception of cyclophosphamide and ifosfamide, patients receiving alkylating agents generally do not require a dose reduction because of hepatotoxic adverse effects. Cyclophosphamide is infrequently hepatotoxic and its effect is probably due to an idiosyncratic reaction. On rare occasions, diffuse hepatocellular destruction and massive hepatic necrosis associated with cyclophosphamide use have been described.<sup>90</sup> Other alkylating agents (including melphalan, chlorambucil, nitrogen mustards and busulfan) are not dependent upon the liver for their metabolism and are not frequently associated with hepatotoxicity.

#### *Antimetabolites*

The antimetabolites commonly seen in clinical use include cytarabine, 5-FU, 6-mercaptopurine (6-MP), azathioprine, 6-thioguanine and methotrexate. Hepatic metabolism has an important role in the processing of these drugs, and dose reductions are usually necessary in patients who develop liver dysfunction.

Cytarabine is used for the treatment of acute myelogenous leukemia, and on rare occasions has been associated with cholestasis, which seems to be reversible.<sup>91</sup> Only rare reports of hepatotoxicity have been noted with use of intravenous 5-FU; however, hepatotoxicity can be more common when 5-FU is administered in combination with ascaricides.<sup>92</sup> Intra-arterial administration of the 5-FU metabolite floxuridine (fluorodeoxyuridine [FUdR]) has been associated with two types of toxicity—one suggestive of hepatocellular injury, and the

other consistent with sclerosing cholangitis.<sup>93–95</sup> 6-MP is often used as a maintenance therapy in acute lymphoblastic leukemia, and two patterns of toxicity associated with its use have been reported—hepatocellular injury and cholestasis.<sup>96</sup> Hepatotoxicity caused by 6-MP occurs more commonly when a daily dose of 2 mg/kg is exceeded. Azathioprine is a nitroimidazole derivative of 6-MP. Toxicity with azathioprine is less common and less dose-dependent than with 6-MP. Three different patterns of toxicity associated with azathioprine have been described—a hypersensitivity reaction, an idiosyncratic cholestatic reaction, and endothelial cell injury with development of elevated portal pressures, veno-occlusive disease and peliosis hepatis.<sup>97</sup>

High-dose methotrexate therapy has been associated with reversible elevations in the levels of aminotransferases.<sup>98</sup> It is interesting to note that patients taking long-term, low-dose methotrexate therapy for psoriasis or rheumatoid arthritis are at risk of developing hepatic fibrosis and cirrhosis; however, the risk is low in patients who receive less than 1.5 g of methotrexate as a cumulative dose.<sup>99</sup>

#### *Antitumor antibiotics*

The antitumor antibiotics include doxorubicin hydrochloride and daunorubicin. Doxorubicin hydrochloride can cause hepatocellular injury and steatosis, and dose reduction has been recommended in patients with cholestasis to avoid further toxicity.<sup>100</sup> Similar guidelines are recommended for daunorubicin.

#### *Neoadjuvant regimens*

Combinations of 5-FU and oxaliplatin or irinotecan hydrochloride are used as neoadjuvant therapy in patients with colorectal cancer before resection of liver metastases. These neoadjuvant regimens have been associated with steatosis, hepatic vascular injury and nodular regenerative hyperplasia.<sup>101–104</sup> Veno-occlusive disease has been seen with dacarbazine,<sup>105</sup> 6-MP,<sup>106</sup> azathioprine,<sup>107,108</sup> cyclophosphamide,<sup>109</sup> busulfan,<sup>110</sup> and following treatment with ABVD (doxorubicin, bleomycin, vinblastine sulphate, dacarbazine) for Hodgkin's disease.<sup>111</sup>

## OTHER COMPLICATIONS

### **Nausea and vomiting**

Nausea and vomiting frequently occur after administration of chemotherapeutic agents. The likelihood of developing nausea and vomiting

**Table 2** Other gastrointestinal complications associated with oncologic therapy.

Complication	Common causes	Treatment
Nausea and vomiting	Chemotherapy	Antiemetic agents (5-HT <sub>3</sub> receptor antagonists, NK-1-receptor antagonists, corticosteroids), metaclopramide hydrochloride, butyrophenones, phenothiazines, cannabinoids, olanzapine
Gastrointestinal perforation, fistula formation, arterial thrombosis and bleeding	Bevacizumab (monoclonal antibody against VEGF)	Surgery for perforation of fistula formation. Usually supportive care for bleeding
Acute pancreatitis	Causes unrelated to cancer (gallstone, alcohol) and cancer-related (metronidazole, sulfonamides, tetracycline, furosemide, thiazides, estrogen, tamoxifen and chemotherapy agents)	Supportive: NPO, bowel rest, intravenous fluids or TPN if needed, nasogastric tube suction if needed
Oral mucositis or ulceration of the mucosal lining of the oropharynx	Radiation, chemotherapy for solid malignancies and patients undergoing hematopoietic stem-cell transplantation	Palifermin (patients with hematologic malignancies)

Abbreviations: 5-HT<sub>3</sub>, 5-hydroxytryptamine-3; NK-1, neurokinin-1; NPO, nil per os; TPN, total parenteral nutrition; VEGF, vascular endothelial growth factor.

following chemotherapy depends on several factors including the chemotherapy dose and the intrinsic emetogenicity of a given agent.<sup>112</sup> The emetogenic potential of intravenously administered antineoplastic agents can be assigned to five levels, ranging from minimal or less than 10% risk (e.g. bevacizumab) to a high or greater than 90% risk (e.g. cisplatin).<sup>105</sup> Emesis can be acute (i.e. occurring within the first 24 h of receiving chemotherapy) or delayed.

Various antiemetic agents are now available for the prevention and treatment of chemotherapy-induced nausea and vomiting (Table 2). These include agents with a high therapeutic index such as 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists (e.g. ondansetron, granisetron, dolasetron, tropisetron, palonosetron), neurokinin-1-receptor antagonists (e.g. aprepitant) and corticosteroids (usually used in combination with other agents). Agents with a low therapeutic index are also used, such as metaclopramide hydrochloride, butyrophenones, phenothiazines, cannabinoids and olanzapine. The preferred agent and regimen depends on the emetogenic level of a given chemotherapeutic drug. For drugs with a low emetogenic risk, antiemetics are given only before chemotherapy, while antiemetics are provided before and after chemotherapy for those chemotherapy drugs with a high emetogenic risk (levels 3 or higher).

#### Gastrointestinal perforation, fistula formation, arterial thrombosis and bleeding

Gastrointestinal perforation, fistula formation, arterial thrombosis and bleeding have been reported with bevacizumab, a monoclonal antibody against VEGF (Table 2).<sup>113</sup> Intestinal perforation has been reported in 1–2% of patients treated with bevacizumab for metastatic colorectal cancer.<sup>114,115</sup> Risk factors associated with perforation include an intact primary tumor, prior irradiation, acute diverticulitis, intra-abdominal abscess and gastrointestinal obstruction.<sup>116</sup>

#### Acute pancreatitis

Acute pancreatitis in patients with cancer or in those who have undergone hematopoietic stem-cell transplantation can be caused by conditions present in the general population, including gallstones and alcohol. However, other etiologies should be taken into consideration when managing cancer patients who have acute pancreatitis, including their medications and chemotherapeutic agents (Table 2).

Drug-induced pancreatitis has no distinguishing clinical features, and therefore taking a careful drug history and excluding other etiologies are essential to make a diagnosis. Some of the most common drugs known to cause acute pancreatitis include metronidazole, sulfonamides, tetracycline, furosemide, thiazides, estrogen and tamoxifen.<sup>117,118</sup> The last two drugs might act via the induction of hypertriglyceridemia.<sup>119,120</sup>

During the course of chemotherapy, pancreatitis has been reported with the use of azathioprine,<sup>121</sup> ifosfamide,<sup>122</sup> prednisone,<sup>123</sup> cytosine arabinoside,<sup>124</sup> and various regimens of combination chemotherapy including vinca alkaloids, methotrexate, mitomycin, 5-FU, cyclophosphamide, cisplatin and bleomycin.

### Oral mucositis or ulceration of the oropharynx

Oral mucositis or painful ulceration of the mucosal lining of the oropharynx occurs frequently in individuals undergoing radiation and chemotherapy for solid malignancies, and has been reported in up to 98% of individuals undergoing hematopoietic stem-cell transplantation (Table 2).<sup>125</sup> Palifermin, a recombinant human keratinocyte growth factor decreases the incidence and duration of mucositis in patients with hematologic malignancies who are receiving chemotherapy and requiring stem-cell transplantation support, and has been approved by the FDA for this indication. Results from phase I and II trials investigating the use of palifermin in patients receiving chemotherapy for solid tumors are also encouraging.<sup>125</sup>

### CONCLUSIONS

Cancer is a important problem worldwide, and although new and improved treatment options are increasingly available, many of these can cause adverse effects and these frequently involve the gastrointestinal tract. Chemotherapy and radiation therapy regimes have increased in complexity, with greater therapeutic effectiveness achieved by using combination therapies. As discussed, these combination therapies often result in the development of more severe complications, including esophagitis, diarrhea and drug-induced hepatotoxicity, all of which reduce quality of life and, in the case of diarrhea and hepatotoxicity, can be life-threatening. The immunocompromised state induced by oncologic therapy is also an important pathologic mechanism underlying the development of gastrointestinal complications, with an increased risk of infection leading to complications such as esophagitis and diarrhea. Similarly, neutropenic enterocolitis can be caused by drug cytotoxicity and an impaired host defense to intestinal organisms. GVHD affects a considerable proportion of patients who survive long-term following an allogenic hematopoietic stem-cell transplant, and can also have severe consequences.

The gastroenterologist has an important role in managing the gastrointestinal complications associated with various cancer treatments. It is, therefore, of importance that gastroenterologists are aware of the adverse effects of oncologic therapies and maintain communication with the treating oncologist so that the cancer and gastrointestinal adverse effects can be managed as effectively as possible.

### KEY POINTS

- Gastrointestinal complications of oncologic therapy are common and can affect all organs of the gastrointestinal tract; they are often life-threatening
- Treatment of gastrointestinal complications of oncologic therapy should be individualized to take into account the patient's status and disease pathophysiology
- Gastrointestinal complications of oncologic therapy are often multifactorial, involving direct toxicity and secondary events resulting from the immunosuppressive properties of given agents
- Gastrointestinal complications of therapy must be differentiated from signs and symptoms of underlying disease

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**Competing interests**

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