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50.1 Introduction

The gastrointestinal (GI) tract is one of the systems most commonly affected by transplant complications. It is due to the high vulnerability of the gut mucosa composed of dividing cells, which are susceptible to chemotherapy-induced damage, rich vasculature, constant contact with intestinal microflora, and high content of immune-competent cells. Therefore, when evaluating symptoms from the GI system, various possible causes must be taken into account, especially drug toxicity, infections, and graft-versus-host disease. In this chapter selected GI complications most frequent after HSCT will be presented. The GI aGVHD was already discussed in Chaps. 43 and 44 and infectious causes in Chaps. 38 and 39.

50.2 Nausea/Vomiting

50.2.1 Definitions

Nausea: a disorder characterized by a queasy sensation and/or the urge to vomit.

Vomiting: a disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.

50.2.2 Types

Acute onset: within 24 h of chemotherapy administration (peak at 4–6 h) lasting for 24–48 h.

Delayed onset: occurs more than 24 h after chemotherapy (peak at 2–3 days) lasting for prolonged period of time.

50.2.3 Pathophysiology

1. Direct activation of the vomiting center in the brain stem by chemotherapy, which triggers target organs in GI tract.
2. Damage to the GI mucosa, causing vagal stimulation and neurotransmitter (serotonin, neurokinin-1, dopamine) release causing reflexive stimulation of the vomiting center.
3. Radiotherapy-induced neurotransmitter release stimulating vomiting center concomitant with brain edema.

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50.2.4 Causes

Induced directly by conditioning chemoradiotherapy

TBI, TLI, cranio-spinal irradiation

Chemotherapy drugs (NCCN 2017):

- High emetic risk (frequency > 90%):
CY >1500 mg/m², BCNU >250 mg/m²
- Moderate emetic risk (frequency 30–90%):
bendamustine, BU, BCNU ≤250 mg/m²,
CY ≤1500 mg/m², MEL
- Minimal to low emetic risk (frequency < 30%):
VP, TT, FLU, MTX ≤50 mg/m²

Drugs: opioids, CNI, nystatin, AmB, voriconazole, itraconazole, TMP-SMX, MMF

GVHD

Hepatic disease: GVHD, VOD, viral hepatitis

Infection: CMV, HSV, VZV, fungal, bacterial, norovirus, rotavirus, parasites

Adrenal insufficiency

Pancreatitis

50.2.5 Diagnosis

Based on symptoms.

50.2.6 Grading (CTCAE v4.0 [NCI 2009])

<i>Nausea</i>	
Grade 1	Loss of appetite without alteration of eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration, or malnutrition
Grade 3	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated
<i>Vomiting</i>	
Grade 1	1–2 episodes (separated by 5 min) in 24 hs
Grade 2	3–5 episodes (separated by 5 min) in 24 h
Grade 3	≥6 episodes (separated by 5 min) in 24 h, tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences, urgent intervention indicated

50.2.7 Treatment

Prevention of nausea/vomiting is the mainstay of clinical management since treatment frequently proves ineffective. Delayed nausea should be

treated with scheduled antiemetics for 2–4 days after completion of chemotherapy.

50.2.8 Prophylaxis

Choice of drugs depends on the use of drug with highest emetogenic potential (NCCN 2017):

High emetic risk	Serotonin (5-HT ₃ antagonist) (patients should be monitored for QT corrected prolongation) <ul style="list-style-type: none"> • Short-acting: ondansetron 3 × 8 mg IV on days of chemo +24–48 h, granisetron, dolasetron • Long-acting: palonosetron 0.25 mg IV, may be repeated every 3 days Plus Neurokinin-1 receptor antagonists, e.g., aprepitant Plus/minus Dexamethasone 2–10 mg IV (as required for a short duration)
Moderate emetic risk	Serotonin (5-HT ₃) antagonists (as above) Plus/minus Dexamethasone 2–10 mg IV
Low emetic risk	Serotonin (5-HT ₃) antagonists (short acting, as above) Metoclopramide Prochlorperazine
TBI	Serotonin (5-HT ₃) antagonists (short- or long-acting, as above) Dexamethasone (4 mg/d or 4 mg bid)

50.2.9 Other Nausea/Vomiting

Breakthrough treatment	Addition of a different class anti-emetic drug Prochlorperazine (10 mg IV q6h) Haloperidol (1–2 mg q4h) Metoclopramide (0.5–2 mg/kg IV q6h) Olanzapine Scopolamine transdermal patch Corticosteroids Lorazepam
Anticipatory nausea/vomiting	Prevention of nausea/vomiting by efficient prophylaxis at every treatment Strong smell avoidance Behavioral therapy Lorazepam, alprazolam

50.3 Diarrhea

50.3.1 Definitions

A disorder characterized by frequent and watery bowel movements.

50.3.2 Physiopathogeny

Depending on the cause.

50.3.3 Causes

The diarrhea in preengraftment period is most frequently caused by toxicity of conditioning. In post transplant period, aGVHD must be taken into consideration. The risk of infectious causes persists for the whole time with bacterial causes predominating relatively earlier than viral infections.

Chemotherapy and radiation therapy-related toxicity

Acute GVHD

Intestinal infections:

- *Clostridium difficile*
- Viral (CMV, VZV, rotavirus, norovirus, astrovirus, adenovirus)
- Parasitic (giardia, strongyloides, cryptosporidium)
- Fungal (candida)

Medications (antibiotics, mycophenolate mofetil, oral nutritional supplements)

Transplant-associated microangiopathy

Other: pancreatitis/pancreatic insufficiency, lactose intolerance/disaccharidase deficiency, malabsorption, inflammatory bowel disease, liver and gallbladder disease

50.3.4 Diagnosis

The standard workup for diarrhea after HSCT includes stool cultures, tests for *Clostridium difficile* toxin A and B, *Clostridium* antigen, stool and/or blood tests for viruses, and, when negative, endoscopy with biopsy for aGVHD and CMV. However, when these tests are proven negative, a broad area of causes must be considered (Robak et al. 2017).

Stool examination and microbiological workup

- *C. difficile* toxin, antigen, culture
- Parasites (giardia, strongyloides, cryptosporidium)
- Viruses (CMV, VZV, rotavirus, norovirus, astrovirus, adenovirus)
- Fungi (culture)

Sigmoidoscopy/colonoscopy ± gastroscopy

- Histopathology for GVHD, cryptosporidium, and CMV
- Viral, parasitic/bacterial cultures

Biochemistry (triglycerides, amylase, lipase),

GVHD biomarkers (calprotectin, REG3- α) (Rodriguez-Otero et al. 2012; Ferrara et al. 2011)

Ultrasound, CT (in GVHD distal ileum or proximal colon most likely involved)

Capsule endoscopy

50.3.5 Grading

When the diagnosis of gut aGVHD is established or suspected, aGVHD grading should be used as described in Chap. 43. Otherwise, (CTCAE v4.0) grading should be used (NCI 2009).

Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
Grade 3	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated

50.3.6 Treatment

Targeted, according to the known or suspected cause, consider overlap with another pathology (e.g., aGVHD with gut CMV infection)

Ancillary: modification of diet

- Lactose- or gluten-free
- Restricted diet (low roughage, low residue, low or no lactose)
- Temporarily nothing per os and TPN

Avoid fluid loss and dyselectrolytemia

Monitor and replace protein losses (albumin, gamma globulin)

Loperamide 2–4 mg p.o. every 6 h if associated with toxicity of conditioning or GVHD

Octreotide

50.4 Esophagitis/Gastritis

50.4.1 Definitions/Symptoms

Heartburn and/or epigastric pain observed most frequently during conditioning and period of mucositis.

50.4.2 Causes

Mucositis, medications, altered gastric pH, peptic ulcer disease, and fungal esophagitis.

50.4.3 Diagnosis

Based on clinical symptoms \pm endoscopy.

50.4.4 Treatment

Depending on the cause, elevation of the head of bed, and consideration of proton pump inhibitors and other symptomatic treatments (e.g., alginate, antacid, and topical local anesthetics, such as oxetacaine for mucositis). May require systemic analgesia if patient unable to swallow.

50.5 GI Bleeding

50.5.1 Definitions/Symptoms

May appear as melena, hematemesis or bloody stool, or emergence of normocytic anemia.

50.5.2 Causes

Thrombocytopenia, esophageal trauma, esophagitis, colitis, anal fissures or varices, viral infections, GVHD, and plasma coagulation impairment.

50.5.3 Diagnosis

Esophagogastroduodenoscopy, colonoscopy, and angioCT.

50.5.4 Treatment

Treatment of underlying disorder

Symptomatic

- Platelet transfusion to $>50 \times 10^9/L$
- RBC transfusion
- Fresh frozen plasma, fibrinogen concentrates, vitamin K supplementation
- Octreotide
- Endoscopic cauterization or embolization

When massive blood loss

- Desmopressin
- Tranexamic acid
- Recombinant factor VII

50.6 Typhlitis

50.6.1 Definitions/Symptoms

Necrosis of usually large intestinal wall associated with chemotherapy toxicity and bacterial overgrowth.

Occurs within 30 days after HSCT, patients usually complain of pain in right lower abdominal quadrant, often with associated fever.

Additionally, nausea, emesis, increased abdominal wall tension, and watery bloody diarrhea may occur (Robak et al. 2017).

50.6.2 Causes

Toxicity/infection.

50.6.3 Diagnosis

Clinical and abdominal ultrasound or CT: bowel wall thickening usually limited to single region, e.g., ileocecal or ascending colon; may be associated with perforation and air within intestinal wall.

50.6.4 Treatment

Antibiotics and bowel rest. Avoid surgical intervention.

50.7 Pancreatic Disease

50.7.1 Definitions/Symptoms

Pancreatic insufficiency and atrophy or acute pancreatitis.

50.7.2 Causes

Medications (prednisone, tacrolimus), stones, and pancreatic GVHD.

50.7.3 Diagnosis

Insufficiency and atrophy: low serum trypsinogen, high fecal elastase-1, and possible atrophy in imaging. Acute pancreatitis: elevated lipase and amylase, elevated fecal fat, and edema in ultrasound/CT.

50.7.4 Treatment

When insufficiency: enzyme replacement.

50.8 Chronic Esophageal GVHD

50.8.1 Definitions/Symptoms

Dysphagia to solid food, chest discomfort, and aspiration (Jagasia et al. 2015; Robak et al. 2017)

50.8.2 Diagnosis

Barium meal: mid/upper esophageal strictures, webs, rings, bullae, and desquamation. Endoscopy: as above, erythematous, friable sloughed mucosa.

50.8.3 Treatment

When severe and chronic, need serial dilations and enteral tube placement or esophagectomy.

Key Points

The workup and management of GI complications after HCT follow general medical approach; however the most frequent scenarios remain characteristic for this patient population. The most common causes include toxicity of drugs, especially those used for conditioning, infection, and/or graft-versus-host disease:

- Nausea/vomiting or diarrhea occurring before engraftment is most likely caused by toxicity of conditioning, while after engraftment, GVHD needs to be considered, especially in allo-HSCT setting.
- For the whole post transplant period, infectious causes should also be considered with bacterial or fungal causes predominating in the neutropenic period and viral reactivations/infections in the later phases.
- Importantly, inflammation caused by infection may become a trigger to GVHD, while GVHD is frequently followed by infection; therefore, overlapping scenarios always need to be taken into account.
- GI GVHD is frequently a diagnosis of exclusion (especially in patients with other overlapping causes which may impact on laboratory investigations). However, it should always be considered when symptoms persist despite extensive workup and/or directed treatment.

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