# Chapter 21
# Gastrointestinal Complications

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Gastrointestinal (GI) and hepatic complications are common in the hematopoietic stem cell transplant (HSCT) patient. The agents used in the conditioning regimen induce direct disruption of the intestinal barrier as well as indirect damage from cytokine release and a generalized inflammatory state. These events lead to permeation of bacteria and endotoxins through the bowel wall with subsequent organ damage and increased risk for infection. Similarly, HSCT conditioning can directly affect the hepatic parenchyma or hepatic sinusoids. The immunosuppressed state of the HSCT patient also increases the risk for opportunistic infections of the GI tract and liver.

## 21.1 Upper Gastrointestinal

1. Anorexia
   a. Etiology and pathogenesis
      Usual onset during conditioning and first week post-transplant; may last longer in patients with mucositis, infection, or graft-versus-host disease (GVHD). May result from:
      i. Direct emetogenic effect from conditioning therapy
      ii. Delayed gastric emptying
      iii. Circulating inflammatory cytokines directly affecting appetite centers
      iv. Mucositis-related pain and dysphagia
      v. GVHD
      vi. Infection
      vii. Medications

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b. Diagnosis
Most cases are identified by clinical presentation and do not require additional workup. Endoscopic evaluation (i.e., esophagogastroduodenoscopy) with biopsies to identify potential underlying causes is recommended for cases of protracted or prolonged nausea, vomiting, or anorexia after mucositis has resolved.

c. Treatment

i. Conditioning regimens for HSCT include highly emetogenic therapy. Antiemetic prophylaxis during conditioning therapy (see Chap. 6) should aim at minimizing nausea and vomiting and preserving enteral nutrition for as long as possible.
ii. Daily calorie count to determine:

- If adequate nutritional goals are achieved
- If there is a need for enteral or parenteral supplementation (see Chap. 7)

iii. The efficacy of appetite stimulants in the post-transplant setting has not been determined and is generally not recommended. However, if anorexia becomes chronic, one could consider a trial of megestrol (Megace®) acetate oral solution 800 mg po daily or dronabinol (Marinol®) 2.5–5 mg po before lunch and dinner daily. The safety and efficacy of these agents in children have not been established although empiric use has been reported. Consultation with a pediatric pharmacist prior to their use is recommended.

2. Esophagitis/Gastritis

a. Etiology and pathogenesis
Usually presents during conditioning and period of mucositis but may last longer in patients with GVHD. Potential etiologies include:

i. Mucositis
ii. Medications
iii. Poor oral intake
iv. Altered gastric pH
v. "True" peptic ulcer disease

b. Diagnosis
Diagnosis is clinical. Symptoms typically include heartburn and/or epigastric pain.

c. Treatment

i. First line of therapy is elevation of the head of bed and administration of antacids (calcium carbonate, magnesium, or aluminum hydroxide).
ii. H2 blockers (ranitidine, cimetidine, famotidine) should be avoided in the first 100 days post-HSCT due to their myelosuppressive potential.

iii. Proton pump inhibitors may be of utility in patients with gastritis symptoms. However, their use should be reserved for patients failing first-line treatment and limited to 7–10 days, as prolonged use may inhibit the natural antimicrobial barrier and increase the risk for infection.

- Lansoprazole (Prevacid®) 30–60 mg po daily to BID
- Omeprazole (Prilosec®) 20–40 mg po daily to BID
- Pantoprazole (Protonix®) 40–80 mg po daily

iv. Gastric acid blockade therapy can impact the absorption of concurrent oral azole antifungal therapy.

3. Nausea

a. Etiology and pathogenesis
b. Diagnosis
c. Treatment

i. Patients with persistent nausea despite prn antiemetics should receive scheduled antiemetics.
ii. Schedule a dopamine antagonist + a short acting benzodiazepine, e.g., lorazepam (Ativan®) ± diphenhydramine (Benadryl®).
iii. Lorazepam should not be used alone as a scheduled antiemetic unless for anticipatory nausea.
iv. Examples of dopamine antagonists include:

- Prochlorperazine (Compazine®) 5–10 mg po/IV q 6 h
- Metoclopramide (Reglan®) 20 to 30 mg po/IV or qAC and HS
- Droperidol (Inapsine®) 0.625 mg IV q 6 h
- Haloperidol (Haldol®) 0.5–2 mg po/IV q 4–6 h
- Promethazine (Phenergan®) 12.5 mg po/IV q 4–6 h

v. Motion-induced nausea should be treated with either a scopalomine patch (Transderm Scop®) 1.5 mg changed every 3 days, or meclizine (Bonine®, Antivert®) 12.5–25 mg po q 8 h.
vi. These medications have been proven effective for acute nausea, however not in the setting of delayed nausea.
vii. Anticipatory nausea should be treated with lorazepam (Ativan®) or alprazolam (Xanax®) prior to the aggravating factor (e.g., medications, meals, etc.).

## 21.2 Lower Gastrointestinal

1. Diarrhea (see Table 21.1)

a. Etiology and pathogenesis
May present any time during conditioning or post-HSCT. The time of onset may assist in identifying potential etiologies, including:

i. Direct side effect from conditioning and other medications
ii. Mucositis and intestinal epithelial sloughing
iii. Infection
iv. GVHD
v. Pancreatic insufficiency
vi. Brush border disaccharidase deficiency
vii. Malabsorption
viii. Intestinal thrombotic microangiopathy
ix. Mycophenolate mofetil (CellCept®) is a very common inciting agent (through direct mucosal toxicity) and may be very difficult to distinguish from GVHD.

b. Diagnosis
Rule out infection with stool cultures for enteric pathogens. For patients in which diarrhea does not improve after resolution of oral mucositis, consider rectosigmoidoscopy to perform visual inspection and obtain tissue biopsies.

c. Treatment

i. Identify and treat the underlying cause.
ii. Supportive care should focus on hydration and prevention/treatment of electrolyte imbalances.
iii. Bowel rest/restricted diet (low roughage, low residue; low or no lactose (see Appendix 7).
iv. Calculate and replace enteral volume losses with isotonic fluid.
v. Monitor and replace protein losses (albumin, gamma globulin).
vi. Vitamin K depletion associated with chronic diarrhea is common. If the prothrombin time is elevated, vitamin K should be replaced. The dose is 2.5–25 mg IV or SQ (max 10 mg for children); if prothrombin time is not satisfactory within 6–8 h, the dose may be repeated.
vii. Loperamide (Imodium®) 2–4 mg po every 6 h or octreotide (Sandostatin®) may be effective to treat or relieve diarrhea associated with conditioning regimen and GVHD. The recommended octreotide regi-

**Table 21.1** Diarrhea associated with chemotherapy (not GVHD)

| Grade | Diarrhea |
|---|---|
| 1 | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline |
| 2 | Increase of 4–6 stools per day over baseline; IV fluid indicated < 24 h; moderate increase in ostomy output compared to baseline; not interfering with ADL |
| 3 | Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 h; severe increase in ostomy output compared to baseline; interfering with ADLs |
| 4 | Life-threatening consequences (i.e., hemodynamic collapse) |
| 5 | Death |

*GVHD* graft-versus-host disease, *IV* intravenous, *ADL* activities of daily living

men varies. A fixed dose of 500 mcg IV every 8 h for 7 days or 50 mcg (2 mcg/kg) IV TID escalated to continuous infusion at 15 mcg/h (1 mcg/kg/hr) have been reported to have some success in control of diarrhea in the HSCT setting.

viii. Denatured tincture of opium (DTO) has also been used in settings of high-volume diarrhea but should be used with caution as opiate-induced ileus can be observed.

ix. Antidiarrheal agents should not be used in patients with infectious diarrhea; negative C. difficile toxin assay should be ascertained prior to the addition of antimotility agents

2. Gastrointestinal Bleeding

a. Etiology and pathogenesis
Most cases have diffuse areas of bleeding as opposed to a localized site. Causes of GI bleeding include:

i. Thrombocytopenia
ii. Esophageal trauma (from retching)
iii. Esophagitis
iv. Colitis
v. Anal fissures or hemorrhoids
vi. Viral infections
vii. GVHD

b. Diagnosis
Diagnosis is clinical. An esophagogastroduodenoscopy with rectosigmoidoscopy/colonoscopy may aid in identifying the cause of and controlling localized bleeding.

c. Treatment
If possible, treatment of the underlying disorder should be initiated. Symptom control may be achieved with:

i. Platelet support to maintain platelets $\geq 50{,}000/mm^3$.
ii. Packed red blood cells (PRBC) transfusion to maintain hematocrit > 28 %.
iii. Octreotide may provide short-term control.
iv. Control of localized bleeding with endoscopic cautery or embolization.
v. If large-volume acute blood loss occurs, consider desmopressin (DDAVP®) ± aminocaproic acid (Amicar®) or tranexamic acid (Lysteda®), providing the patient has no evidence of hematuria.
vi. The use of recombinant factor VII (NovoSeven®) 90 mcg IV q 2 h to control bleeding in the HSCT setting has not been studied and its routine use is not recommended.
vii. Consider radiologic assessment with angiography or a red cell nuclear scan to identify areas of active bleeding.

## 21.3 Hepatobiliary Diseases

1. Sinusoidal Obstruction Syndrome or Veno-Occlusive Disease (SOS/VOD) of the Liver

   a. Epidemiology
   Incidence is reported at approximately 5–10 %. Severe SOS/VOD frequently leads to multiorgan failure and is associated with day 100 mortality of > 90 %.

   b. Etiology and pathogenesis
   Usually presents during the first weeks following conditioning, prior to engraftment, and results from direct injury to sinusoidal endothelial cells and hepatocytes. Pre-transplant risk factors include:

      i. Older age (or younger age for children)
      ii. Poor performance status
      iii. Female gender
      iv. Advanced malignancy or patients with inherited disorders of metabolism
      v. Reduced pulmonary diffusion capacity (diffusing capacity of carbon monoxide (DLCO))
      vi. Prior hepatic disease (elevated bilirubin or aspartate transaminase (AST), preexisting cirrhosis)
      vii. Prior abdominal radiation
      viii. Use of gemtuzumab ozogamicin (Mylotarg®) within 3 months of conditioning

   c. Transplant risk factors include:

      i. Myeloablative conditioning
      ii. Second HSCT
      iii. Use of high-dose alkylating chemotherapy or total body irradiation (TBI)
      iv. Use of methotrexate for GVHD prophylaxis.

   d. Diagnosis

      i. Clinical picture includes

         - Total bilirubin > 2 mg/dL
         - Weight gain > 5 % from baseline
         - Right upper quadrant tenderness (tender hepatomegaly) ± ascites.

      ii. Abdominal ultrasound with liver Doppler usually shows hepatomegaly, ascites, and, in more advanced cases, reversal of portal flow.
      iii. Liver biopsy is not necessary for diagnosis. If needed to rule out other causes, a transjugular liver biopsy with measurement of hepatic venous pressure gradient should be obtained. More invasive procedures (percutaneous or open biopsy) carry higher risk due to high pressures and potential coagulopathy associated with hepatic synthetic dysfunction.
      iv. Differential diagnoses include sepsis-related cholestasis, other cholestatic liver disease, and GVHD.

e. Treatment

i. Prevention of SOS/VOD is the best "treatment" by recognizing patients who are at risk and, when possible, avoiding exposure to known risk factors (i.e., selection of transplant conditioning regimen).
ii. Ursodeoxycholic acid (Ursodiol®) 300 mg po TID from start of conditioning until approximately 1 week after engraftment has been shown in small randomized studies of prophylaxis to provide benefit in decreasing the severity of SOS/VOD.
iii. Prompt treatment is crucial as the severe form of this disease results in very high rates of mortality.
iv. Supportive care is the treatment of choice, including:

- Maintaining careful fluid (water and sodium) balance
- Providing aggressive diuresis
- Discontinuing/avoiding agents that may exacerbate hepatotoxicity when possible
- Preserving renal blood flow (renal dose dopamine 2–5 mcg/kg/min), if needed

v. Defibrotide is a potent antithrombotic and profibrinolytic agent. A historical-controlled phase III study demonstrated a survival advantage for patients with severe SOS/VOD who receive this drug early in their course. This agent is not commercially available in the USA as of this printing. However, it can be procured under compassionate, emergency use.

2. Acute Hepatitis (also see Chap. 17)

a. Etiology and pathogenesis
May present anytime during conditioning or post-HSCT. The time of onset may assist in identifying potential etiologies which includes:

i. Infection/sepsis
ii. Acute biliary obstruction
iii. Drug-induced toxicity
iv. GVHD

b. Diagnosis

i. Sudden elevation of serum transaminases (AST, alanine transaminase (ALT)).
ii. Blood tests for viral DNA (herpes viruses, adenovirus, hepatitis B, hepatitis C).
iii. Imaging (computed tomography (CT) or ultrasound) may be used to identify fungal abscesses in the setting of disseminated infection.
iv. Liver biopsy may aid in identifying a cause.

c. Treatment
Supportive care, removal of inciting agents when possible (if drug-related), treatment of infection.

i. A prolonged course of antibiotics or antifungals may be required for bacterial or fungal infections.
ii. Acute viral hepatitis may lead to fulminant hepatic failure if not treated promptly. Possible viruses include herpes simplex, varicella, cytomegalovirus, and human herpes viruses (HHV-6 and HHV-8). If the patient is not receiving acyclovir prophylaxis, initiation of empiric treatment is recommended.
iii. Hepatitis B can also present with fulminant hepatic failure. Patients with a previous history of hepatitis B or exposure to a donor with a previous history of hepatitis B are at higher risk. Antiviral therapy should be initiated promptly (lamivudine [Epivir], tenofovir [Viread], or similar). The initiation and further dosing for these agents should be determined with the assistance of the gastroenterologist/hepatologist).

3. Gallbladder Disease and Pancreatitis

a. Etiology and pathogenesis
Biliary sludging is very common in transplant patients and is usually asymptomatic, but may also cause acute acalculous cholecystitis, pancreatitis, or cholangitis. Sludging may result from:

i. Chemotherapy.
ii. Parenteral alimentation with prolonged absence of oral intake.
iii. Antibiotics.
iv. Hyperlipidemia.
v. GVHD.
vi. Infection/sepsis. Consider adenoviral infection, especially in children.

b. Diagnosis
Abdominal ultrasound may reveal gallbladder disease (thickening of gallbladder wall, stones, etc.). Hepatobiliary iminodiacetic acid (HIDA) scan may reveal gallbladder obstruction.

c. Treatment

i. Bowel rest.
ii. Removal of parenteral alimentation, if inciting agent.
iii. Cholecystectomy is infrequently needed.
iv. Endoscopic retrograde cholangiopancreatography (ERCP) is only needed in the case of obstructive cholangitis.

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