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Acute graft-versus-host disease of the gut: considerations for the gastroenterologist

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Abstract

Haematopoietic stem cell transplantation (HSCT) is central to the management of many haematological disorders. A frequent complication of HSCT is acute graft-versus-host disease (GVHD), a condition in which immune cells from the donor attack healthy recipient tissues. The gastrointestinal system is among the most common sites affected by acute GVHD, and severe manifestations of acute GVHD of the gut portends a poor prognosis in patients after HSCT. Acute GVHD of the gastrointestinal tract presents both diagnostic and therapeutic challenges. Although the clinical manifestations are nonspecific and overlap with those of infection and drug toxicity, diagnosis is ultimately based on clinical criteria. As reliable serum biomarkers have not yet been validated outside of clinical trials, endoscopic and histopathological evaluation continue to be utilized in diagnosis. Once a diagnosis of gastrointestinal acute GVHD is established, therapy with systemic corticosteroids is typically initiated, and non-responders can be treated with a wide range of second-line therapies. In addition to treating the underlying disease, the management of complications including profuse diarrhoea, severe malnutrition and gastrointestinal bleeding is paramount. In this Review, we discuss strategies for the diagnosis and management of acute GVHD of the gastrointestinal tract as they pertain to the practising gastroenterologist.

Haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option for patients with haematological malignancies (such as leukaemia, lymphoma, myeloma and myelodysplasia) and non-malignant diseases (such as haemoglobinopathies, aplastic anaemia and immune deficiency syndromes)[1]. In the USA, >8,000 patients received

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Author contributions

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Competing interests statement

J.F. and J.L. declare that they have a patent application for a biomarker array discussed in this Review (Title: Method of predicting graft versus host disease. Provisional Application No: 62/411,230; Filing Date: 10/21/16). The other authors declare no competing interests.

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allogeneic HSCT in 2013 (REF. 1). Before HSCT, patients commonly undergo conditioning therapy, which comprises treatment with preparative chemotherapy to eradicate diseased haematological cells, provide an immuno-suppressed environment for donor cell engraftment and prevent the rejection of haematopoietic progenitor cells from the donor, which are subsequently infused[1]. In autologous HSCT, donor cells are obtained from the patient, frozen and infused after conditioning chemo-therapy[2]. In allogeneic HSCT, donor cells are derived from a healthy donor with varying degrees of HLA matching with respect to the recipient[2]. Haematopoietic stem cells are most commonly obtained from the bone marrow, peripheral blood or umbilical cord blood[1]. The period between conditioning therapy and donor cell engraftment is typically 10–12 days and is marked by profound neutropenia, particularly in the setting of myeloablative conditioning[3].

Graft-versus-host disease (GVHD) occurs when alloreactive T cells from the donor attack healthy tissues in the recipient and arises almost exclusively in patients who have undergone allogeneic HSCT[3]. Following allogeneic HSCT, functional reconstitution of the immune system occurs gradually over several months, during which time immunosuppressive prophylaxis of GVHD is gradually tapered if GVHD does not develop[4]. Patient outcomes and survival after HSCT depend upon the underlying disease as well as individual patient factors[4]. The two most common underlying causes of death after allogeneic HSCT are disease relapse and GVHD[5].

The NIH criteria subcategorize GVHD into classic acute GVHD, which has defining features and occurs within 100 days after transplantation; persistent, recurrent or late acute GVHD, which presents with the features of acute disease but occurs more than 100 days after transplantation; classic chronic GVHD, which can occur at any time after transplantation, has defining characteristics and lacks the features of acute disease; and an overlap syndrome, which includes features of both chronic and acute GVHD[6,7]. The incidence of acute GVHD varies with respect to several clinical variables, with cumulative incidence rates ranging from 40–80% of HSCT recipients[8]. Risk factors for acute GVHD include differences in histocompatibility between donor and recipient, patient age, source of donor cells, conditioning and prophylaxis regimens used and graft manipulation techniques[9]. The most common tissues affected by acute GVHD are the skin, liver and gastrointestinal tract. Gastrointestinal acute GVHD is the most difficult of these conditions to treat and is the greatest cause of GVHD-related mortality[9]. Although reports vary, the cumulative incidence of gastrointestinal acute GVHD might be as high as 60% (REF. 8). Although hepatic manifestations are relatively less common than skin and gastrointestinal conditions, gastroenterologists might be tasked with their management, for which we refer the reader to a review of the hepatobiliary manifestations of GVHD[10].

In this Review, we focus our discussion on the gastro intestinal manifestations of acute GVHD, as this condition is often the most severe and therefore poses substantial diagnostic and therapeutic challenges. For an overview of chronic GVHD and its management, we refer the reader to two review articles[9,11]. We discuss the aspects of gastrointestinal acute GVHD that are most pertinent to the practising gastroenterologist, including pathophysiology, endoscopic characteristics, diagnosis, risk stratification, treatment, management of complications and supportive care. Importantly, we pay special attention to the latest

paradigm-shifting developments in the study of gastrointestinal acute GVHD, including the role of gut dysbiosis in pathogenesis, data regarding endoscopic diagnosis, the search for novel biomarkers and changes in staging and risk stratification.

Pathophysiology

The pathophysiology of acute GVHD is incompletely understood. Donor T cell responses and inflammatory cytokines are the most studied immune components that mediate tissue damage. Downregulation or inhibition of the recipient regulatory T (T_{reg}) cell response and upregulation of the recipient effector T cell response, which is possibly exacerbated by treatment with immunosuppressive regimens, contributes to the lack of tolerance of allogeneic donor cells to recipient tissues[12]. Dysfunction in recipient antigen-presenting cells also influences immune activation in acute GVHD[12]. In the gut, emerging evidence suggests that the immune dysregulation observed in acute GVHD leads to further perturbation of the intestinal epithelium, specifically intestinal stem cells, Paneth cells and goblet cells[13].

Imbalances in the gut microbiota are also likely to have an important role in the development of acute GVHD of the gastrointestinal tract; conditioning regimens, broad-spectrum antibiotics, immunosuppressants and the introduction of foreign lymphocytes from the donor profoundly alter the composition of the gut microbiota[14–16]. The degree of microbial imbalance has been shown to correlate with long-term outcomes and transplant-related mortality in gastrointestinal acute GVHD[15]. Moreover, *Clostridium difficile* has been implicated as a potential trigger of immune dysregulation that might contribute to the development of acute GVHD via local immune activation[17]. As the complex interplay between the immune system and the gut micro-biota is further elucidated, the intestinal bacteria might become novel therapeutic targets in the management of gastrointestinal acute GVHD. Gut dysbiosis has been observed in both acute GVHD and IBD[18,19]. Moreover, acute GVHD and IBD share clinical, histopathological and genetic features[20,21]. For example, polymorphisms in *NOD2*, which encodes the intracellular bacterial sensor nucleotide-binding oligomerization domain-containing protein 2 (NOD2), are associated with IBD and might also be linked with acute GVHD development in candidate gene studies[20,21]; however, the latter observation remains to be fully validated.

A striking consequence of the immune dysregulation observed in acute GVHD is a multifactorial disturbance of the gut mucosal barrier, which manifests with severe secretory diarrhoea[22]. The immune-mediated destruction of the intestinal mucosa leads to a failure of fluid resorption, particularly in the ileum, and is largely responsible for voluminous diarrhoea in patients with acute GVHD[22,23]. In addition, the destruction of mucosal cells at the brush border and consequent reduction in luminal levels of disaccharidase enzymes creates an osmotic effect due to the passage of unabsorbed carbohydrates[22,23]. Dysbiosis depletes the gut of bacterial populations, which might otherwise mitigate this effect via metabolism of these luminal polysaccharides[23]. Furthermore, compromise of brush border tight junctions (also known as zonulae occludentes) in the setting of a vigorous inflammatory response can lead to substantial mucosal protein loss, therefore drawing fluid into the intestinal lumen via oncotic pressure[24]. Moreover, inflammatory-cell-mediated

destruction of apical bile salt transporters in the ileal brush border leads to bile acid malabsorption and might lead to bile salt diarrhoea[25]. Finally, a number of the agents that are used to prevent and treat acute GVHD and its complications are themselves cathartic agents, most notably the motilin agonist tacrolimus, mycophenolate mofetil (MMF) and magnesium salts[25]. In some instances, these agents might contribute to the voluminous diarrhoea that is frequently observed in acute GVHD.

Diagnosis

As discussed in this section, serological markers, radiology and endoscopy all have roles in the evaluation of patients with suspected acute GVHD of the gastrointestinal tract. Although these tools help to confirm the diagnosis or screen for alternative or coexisting pathologies, the diagnosis of acute GVHD ultimately depends on classic clinical features and the exclusion of alternative diagnoses[26].

Signs and symptoms.

Acute GVHD can affect any segment of the gastrointestinal tract and manifest with nonspecific symptoms. In the oropharynx, mucositis — which is characterized by oral pain, odynophagia, anorexia, blistering, aphthae and gingivitis — might be a manifestation of either acute GVHD or the result of myeloablative conditioning therapy[27,28]. Conditioning regimens are the predominant cause of mucositis in the initial 2–3 weeks after HSCT, with acute GVHD becoming a common culprit thereafter[28]. Severe oral and oesophageal involvement might lead to bleeding, super-infection and, rarely, airway obstruction[29]. Although isolated acute GVHD of the oesophagus is rare, it might present with odynophagia, dysphagia or chest pain[30,31]. The earliest manifestations of gastroduodenal acute GVHD can be insidious and include loss of appetite, early satiety, dyspepsia and weight loss[32–34]. Recognizing these symptoms might offer the best chance for early intervention, which could potentially alter the clinical course of the disease. Symptoms might progress to severe nausea, incessant vomiting, epigastric pain and upper gastrointestinal bleeding[32–34]. Importantly, before engraftment, chemotherapy-induced toxicity and opportunistic infections can cause gastrointestinal manifesta tions similar to those of acute GVHD. In addition, it is not uncommon for drug toxicity, acute GVHD and infections to coexist[35].

Acute GVHD of the lower gastrointestinal tract, which affects both the small and large intestine, manifests with abdominal pain and diarrhoea[36]. The occurrence of diarrhoea 2 weeks after HSCT is the most common presenting symptom of lower gastrointestinal acute GVHD; however, notably, diarrhoea can develop at any time after engraftment[36]. The diarrhoea is secretory, occurs independently of oral intake and can be profound and incessant, with up to several litres of output per day[36]. Although initially watery, the stool might turn mucoid owing to loss of transmucosal proteins and might be bloody in the setting of mucosal denudation[37]. Moreover, small intestinal mucosal injury and protein loss due to acute GVHD can lead to malabsorption and malnutrition[38]. Paradoxically, severe disease can lead to paralytic ileus, either spontaneously or as a result of analgesic and anti-motility agents such as morphine, loperamide or diphenoxylate[36].

The incidence of severe gastrointestinal bleeding after HSCT has markedly declined owing to improvements in fungal, antiviral and acute GVHD prophylaxis. The cumulative incidence of gastrointestinal bleeding of any severity has been reported as 9%, and as 2% for severe gastrointestinal bleeding[37,39]. Although patients who have received HSCT can certainly present with causes of gastrointestinal bleeding that are not related to the transplantation (such as oesophagitis, peptic ulcer disease, angiodysplasia, diverticulosis and haemorrhoids), acute GVHD remains the most common aetiological factor[40]. Predisposing factors to gastrointestinal bleeding in acute GVHD include prolonged thrombocytopenia, an advanced stage of acute GVHD, the presence of thrombotic microangiopathy and secondary infection[39]. Importantly, severe gastrointestinal bleeding in acute GVHD is an independent predictor of mortality, with mortality approaching 40% (REF. 37).

Imaging findings.

Imaging findings in acute GVHD are nonspecific and of limited clinical utility. Nonetheless, CT scan with intravenous and oral contrast reveals abnormal mucosal enhancement of thickened bowel segments in the majority of patients with acute GVHD[41,42]. The distribution of bowel wall thickening in acute GVHD can be patchy or diffuse. Of note, small intestinal involvement is present in ~75% of cases, which aids in the exclusion of pathologies such as *C. difficile* colitis[41,42]. Focal thickening of the ileum and right colon wall might suggest typhlitis (also known as neutropenic enterocolitis)[42]. The degree of bowel wall thickening in acute GVHD is typically moderate, while severe thickening is more commonly observed in patients with a coexisting infection or typhlitis[41]. In rare circumstances, CT scan might also reveal pneumatosis intestinalis (intramural bowel gas) with multiple thin-walled, air-filled pockets in the colonic submucosa or subserosa[43]. Magnetic resonance enterography (MRE) represents an alternative method for assessing gastrointestinal GVHD, and findings are similar to those obtained using CT scan[44]. In addition, contrast-enhanced ultrasonography (CEUS) and PET–CT are non-invasive modalities that are currently being investigated for the assessment of gastrointestinal tract involvement in GVHD[45,46].

Biomarkers.

The search is underway for effective bio-markers that anticipate a patient's risk of developing acute GVHD, diagnose the disease at its earliest stages, estimate the prognosis and predict response to treatment. Several promising biomarkers have been identified, although none have yet been validated to guide diagnosis or treatment. Of the inflammatory bio markers that are elevated in GVHD, those with the greatest relevance to GVHD of the gastrointestinal tract are suppression of tumorigenicity 2 (ST2; also known as IL-1RL1, T1 and IL-33R), regenerating islet-derived protein 3α (REG3α), TNF receptor 1 (TNFR1) and T cell immunoglobulin and mucin domain-containing protein 3 (TIM3; also known as HAVcr-2).

The two most informative biomarkers for acute GVHD are ST2 and REG3α. ST2 is shed from activated T cells and might function as a decoy receptor for IL-33, therefore inhibiting the IL-33-dependent induction of a pro-inflammatory phenotype in T cells[47]. REG3α is secreted primarily by Paneth cells and functions as an antimicrobial peptide and regulator of

Gram-positive bacteria in the gut[47]. A large study (n = 1,287) that utilized a two-biomarker signature measuring ST2 and REG3α concentrations in the blood 1 week after HSCT identified patients who were at high risk of developing lethal GVHD (~20%) and reported a cumulative incidence of 6-month non-relapse mortality (NRM) of 28% in the high-risk group compared with 7% in the low-risk group ($P < 0.001$)[48]. Compared with the low-risk group, high-risk patients had a significantly greater GVHD-related mortality (4% versus 18%, $P < 0.001$) and risk of severe gastrointestinal acute GVHD (8% versus 17%, $P < 0.001$). The Ann Arbor (AA) scoring system, which originally combined the plasma concentrations of three biomarkers (TNFR1, REG3α and ST2) to define three distinct risk groups at the symptomatic onset of acute GVHD, can also now be defined successfully by only two biomarkers, REG3α and ST2 (REF. 49). The AA scores identify patients who will later develop acute GVHD of the lower gastrointestinal tract but who present with only a rash. Patients who present with only skin involvement at the time of diagnosis are classified as AA3 (high risk) by their bio-marker profiles and are twice as likely to develop gastrointestinal acute GVHD compared with patients who are classified as AA1 (low risk)[49]. The two-biomarker AA algorithm is superior to the three-biomarker algorithm, as it can accurately identify more patients who are at low risk, which is perhaps a result of the adoption of a commercial enzyme-linked immunosorbent assay (ELISA) that has increased sensitivity for detection of ST2, the best single biomarker, compared with that used when the initial three-biomarker AA algorithm was developed[48]. Although promising, this algorithm is currently best used in the context of a clinical trial, as it has not yet been demonstrated that a therapeutic intervention based on the biomarker risk can change long-term outcomes. Further refinements, including an increase in the positive predictive value (perhaps through serial monitoring) will be required before the widespread adoption of biomarkers to guide clinical practice.

Of the two other serum biomarkers for gastrointestinal GVHD, levels of TNFR1 (a membrane receptor for TNF that is cleaved into a soluble form after ligand binding) also strongly correlates with the overall severity of acute GVHD, response to treatment, NRM and survival[50,51]. In smaller studies, high serum concentrations of TIM3, an activation marker on $CD4^+$ T cells that regu lates macrophage function, have been shown to predict the development of severe GVHD, and high levels of ST2 and TIM3 have been correlated with 2-year NRM and overall survival in patients with GVHD[52,53].

In addition, numerous inflammatory markers (such as erythrocyte sedimentation rate and C-reactive protein (CRP) levels), angiogenic markers (such as follistatin and angiopoietin 2) and microbiota-derived metabolites (such as butyrate) are under active investigation as biomarkers; however, these markers are non-specific to gastrointestinal acute GVHD[54–56]. In small studies, faecal calprotectin levels were demonstrated to have potential as a diagnostic tool[57,58]. Citrulline levels have also been shown to correlate with enterocyte damage[59]. Finally, serum albumin levels might be a potential prognostic biomarker, possibly as a surrogate for the degree of protein-losing enteropathy or for nutritional status[22,24,60].

Endoscopic findings.

Endoscopic findings in acute GVHD vary broadly, which reflects the phases of progressive mucosal inflammation, including normal mucosa, mucosal oedema, mild erythema, mucosal erosions, superficial ulcerations, severe mucosal sloughing and mucosal denudation[61,62]. (FIG. 1) Studies using the magnification endoscopy with water immersion technique have demonstrated the presence of short, blunted villi in the mucosa of the duodenum and ileum and mucosal oedema, erosion, and 'tortoiseshell-like' mucosa in the colon[63]. The most commonly used system for the classification of endoscopic findings in acute GVHD is the Freiburg Criteria[64] (TABLE 1). However, the diagnostic reliability of endoscopic findings is unclear; studies have reported diagnostic sensitivities and specificities of 34–89% and 65–79%, respectively, when compared with histological diagnosis[64–66]. In addition, some studies have shown that the concordance between the macroscopic and histological findings in acute GVHD are as low as 38.9% and that a difference of two grades or more is observed in 28% of cases[64–67]. Accordingly, mucosal biopsy is necessary for a reliable diagnosis, and both endoscopically normal and abnormal mucosa should be sampled[68,69]. It is worth reiterating that although the diagnosis of acute GVHD should be confirmed with biopsy of the affected organ or tissue when possible, the diagnosis is ultimately made on the basis of clinical findings. In addition, biopsies should not delay the management of the disease in patients who have classical clinical features of acute GVHD[26,70].

Oesophagogastroduodenoscopy (EGD) and colonos-copy are both appropriate diagnostic approaches and can be chosen based on the patient's most prominent symptoms. One study reported diagnostic accuracies of 67–80% for EGD, 58–80% for sigmoidoscopy, 83–87% for colonoscopy, 87–100% for ileocolonoscopy and 92–93% for EGD with sigmoidoscopy[64]. However, several studies have reported that biopsies from the distal colon yield the highest sensitivities for detecting acute GVHD, ranging from 82% to 95% (REFS 67,71). It has also been demonstrated that very few diagnoses of isolated upper gastrointestinal acute GVHD would be missed by performing lower endoscopy alone[72]. Thus, owing to its diagnostic yield, safety and the non-requirement for sedation, flexible sigmoidoscopy with biopsy might be considered the initial endoscopic test of choice[73,74]. Notably, such an approach might not detect superimposed cytomegalo-virus infection, which might be scattered throughout the bowel or localized to the ascending colon[75]. In our clinical practice, we generally do not use purgatives in patients who have received HSCT and who are undergoing lower endoscopy; the volume of diarrhoea in this patient population usually allows for adequate inspection of the mucosa without the need for additional bowel cleansers. Importantly, newer data suggest that upper and lower endoscopy have similar diagnostic yields, even in patients who present with diarrhoea[76,77]. If EGD is performed in such patients, duodenal biopsies have a diagnostic yield higher than other sites of the upper gastrointestinal tract[78]. However, the endoscopist must be aware of the risk of biopsy-induced duodenal haematoma[79].

Owing to the often patchy or diffuse distribution of endoscopic findings in acute GVHD in the gastrointestinal tract, a common pitfall in diagnosis is the failure to obtain biopsy samples from multiple sites. The American Society of Gastrointestinal Endoscopy (ASGE) suggests two potential approaches in patients with suspected GVHD[80]. The first is to obtain

four biopsy samples from the rectosigmoid and the descending colon. If this method is non-diagnostic, an EGD with four biopsy samples from the gastric antrum, gastric body, duodenum and distal oesophagus is recom mended. An alternative approach is to perform ileo colonoscopy to obtain four biopsy samples from each anatomic segment of the colon[80]. Our recommendation (BOX 1; FIG. 2) in patients with diarrhoea and suspected acute GVHD is to perform lower endoscopy (advancing the scope as far proximally as can be safely performed), taking biopsy samples from each colonic segment and any discrete lesions. We perform EGD with biopsies from each anatomic segment in patients with a negative finding on colonoscopy and symptoms consistent with upper gastrointestinal involvement (such as dyspepsia, nausea, vomiting, epigastric pain or upper gastro intestinal bleeding). We recommend that biopsy specimens from different locations be placed in separate containers with 10% buffered formalin to enable disease localization. As with routine endoscopic biopsies, specimen orientation by the gastroenterologist is not required[80].

The precise site of endoscopic biopsy is also important. In general, we recommend that biopsy of areas of sloughed mucosa should be avoided, as they are less likely to be diagnostic. In addition, biopsy of frankly ulcerated areas might be difficult for the pathologist to interpret, as they contain necrotic cells that lack specific histological features. In the stomach, there is evidence that the use of PPIs might artificially increase the number of apoptotic bodies in the antrum, but not in the fundus, which might obscure the histopathological diagnosis of acute GVHD. Thus, the acquisition of fundic biopsies should be considered in patients receiving treatment with PPIs[81].

If discrete ulcers are identified during endoscopy and superimposed cytomegalovirus infection is suspected, biopsies of the ulcer base are essential owing to the cytopathic effect of cytomegalovirus in endothelial cells, ganglion cells and other mesenchymal cells[82]. Adequate tissue sampling is again vital, as studies have demonstrated that the sensitivity of performing three, six and ten biopsies is 80%, 90% and 99%, respectively[82]. Endoscopic features of herpes simplex virus (HSV) infection in the oesophagus include vesiculation and ulceration[83]. These ulcers tend to be multiple, well circumscribed, uniform and smaller than those observed during cytomegalovirus infection. Although HSV colitis is rare, it can mimic the endoscopic features of acute GVHD, cytomegalovirus or other forms of colitis. Endoscopic findings in HSV colitis might include mucosal oedema, erythema and well-demarcated ulcers of variable size and depth, with or without purulent exudate, that are often separated by normal-appearing mucosa[84]. HSV infection is more likely to be detected by sampling the edge of an ulcer, as HSV infects squamous epithelial cells[83]. Biopsy material for viral culture can be stored in containers with viral transport medium, and PCR can be used to test for the presence of viral pathogens[85].

In patients with acute GVHD who fail to respond to first-line treatment, repeat endoscopy might be needed to re-evaluate the stage of disease, assess response to therapy and exclude alternative or superimposed diagnoses. In one study, approximately one-quarter of patients who were unresponsive to first-line acute GVHD treatment were found to have cytomegalovirus infection following repeat endoscopy[86]. A second study reported that 71% of patients with ongoing symptoms had histological findings on repeat endoscopy that

differed from those of the initial endoscopic procedure, which led to changes in therapy in 77% of such patients with ongoing symptoms[87].

Endoscopy with mucosal biopsy is generally safe in patients with acute GVHD. However, bleeding from biopsy sites and intra-mucosal haematomas in the setting of thrombocytopenia have been reported[79]. In a systematic review of the safety of endoscopic procedures in patients with thrombocytopenia (not exclusively with GVHD), the overall bleeding rate was found to be 1.9–2.9% (REF. 88). According to the ASGE guidelines, a platelet count >50 × 10^9/L is recommended before endoscopy with biopsy, and a count >20 × 10^9/L is recommended for diagnostic endoscopy[89,90]. Although data are lacking, frank perforation due to endoscopic biopsy is rare[91]. Finally, although patients with neutropenia after HSCT are at a higher risk of clinically relevant bacteraemia, there are insufficient data in the literature to support or oppose the use of prophylactic antibiotics before endoscopy with biopsies in patients with absolute neutrophil counts <500 cells/μl (equivalent to >0.5 × 10^9/L)[92].

Small bowel capsule endoscopy has also been evaluated as a diagnostic tool in acute GVHD. The disease distribution identified by capsule endoscopy ranges from scattered lesions to contiguous enteritis[93]. Findings include normal mucosa, diffuse erythema, mucosal oedema, erosions and ulceration[93]. In one small trial that involved a cohort of 13 patients, capsule endoscopy showed high sensitivity (100%) and negative predictive value for diagnosis of acute GVHD[94]. Another study suggested that capsule endoscopy can serve as a diagnostic modality that spares the need for EGD in patients who have a high likelihood of small bowel acute GVHD and a high risk of complications from endo scopy[95]. Nevertheless, we recommend against using capsule endoscopy owing to the lack of specificity for acute GVHD compared with conventional endoscopy, the inability to obtain tissue biopsy samples and the potential risk of capsule retention in patients with diffuse enteritis. Another emerging modality is confocal laser endomicroscopy (CLE), which enables *in vivo* histo-logical assessment to be performed during endoscopy, therefore obviating the need for biopsy. Several small studies have shown that CLE has excellent sensitivity and specificity for the diagnosis of acute GVHD[96,97].

Histopathological findings.

The most common histo-logical finding in acute GVHD is epithelial cell apoptosis; as intestinal stem cells are targets of the disease, the most prominent histological manifestation is apoptotic bodies in the regenerative compartment of the crypt[98,99]. Crypt dropout (effacement of the crypt epithelium) is more widespread in high-grade disease and involves dropout of individual crypt cells in low-grade specimens (grade 2) and entire crypts or multiple contiguous crypts in high-grade specimens (grade 3)[100] (FIG. 3). The highest-grade histopathology (grade 4) demonstrates mucosal sloughing and loss of the epithelium[101]. In addition, the number of Paneth cells — which are primarily located next to stem cells in small intestinal crypts — inversely correlates with the risk of mortality in acute GVHD[102]. Accordingly, the quantification of Paneth cells on duodenal biopsy might aid in establishing the diagnosis and in prognosticating disease severity. Although high-grade histopathology,

particularly grade 4, is specific for acute GVHD, it might be difficult to distinguish low-grade acute GVHD from alternative diagnoses such as medication toxicity[103].

The most commonly used histological classification for acute GVHD is a four-tiered grading system[104] (TABLE 2). Grade 1 histology is identified in 90% of patients with acute GVHD, grade 2 histology in 2%, and grades 3 or 4 in 30% combined[104]. Importantly, a single pathological specimen might contain focal areas of varying grade, making definitive grading difficult and probably introducing some element of subjectivity to the final pathological grade assignment in these instances. However, despite well-defined grading schema, histological grade has not been shown to correlate with clinical manifestations of disease[105]. In addition, with the exception of grade 4 histology, which portends a poor prognosis, histological grade is not predictive of treatment response, morbidity or mortality[36,105]. More so, because of the patchy, diffuse distribution of GVHD, the absence of histological findings should not preclude treatment in the appropriate clinical setting.

Staging and prognosis

Several clinical staging systems have been proposed to classify the severity of acute GVHD. Historically, these have included the Glucksberg and the International Bone Marrow Transplant Registry (IBMTR) grading systems[106]. Both systems were updated by Przepiorka *et al.*[107] to include skin, liver and both upper and lower gastrointestinal involvement (BOX 2). Grading is based solely on clinical features, and endoscopic, histological and radiological findings are not taken into account. Note that patients might be classified with high-grade acute GVHD if skin or liver stage is advanced, despite having either absent or minimal-stage gastrointestinal involvement.

Overall, the clinical stage and grade of acute GVHD correlates with treatment response and mortality, with high scores being associated with poor patient outcomes[36,108]. In a large retrospective cohort study in patients who received an allogeneic HSCT for chronic myeloid leukaemia, the transplant-related mortality for grades 0–IV acute GVHD was 28%, 27%, 43%, 68% and 92%, respectively[109]. Another study demonstrated a relative risk of acute GVHD-related mortality of 2.28 for grades III–IV compared with grade II disease[110]. In 2015, MacMillan and colleagues[111] proposed a novel risk score for acute GVHD that used multiple regression analysis to stratify patients into standard-risk and high-risk groups. By use of this model, high-risk patients were shown to be much less likely to respond to initial corticosteroid therapy and had at least a twofold increased risk of mortality. The authors proposed that patients who were deemed high risk should be considered for more intensive first-line therapy than corticosteroids alone.

There are several important limitations to the current grading schemas for acute GVHD. First, the systems are not based on data from validated clinical trials. Second, they do not take into account the dynamic nature of the disease and usually reflect only maximal disease severity. Finally, they are calculated retrospectively and thus cannot be used as a prognostic tool. Some investigators have proposed that a scoring system based on an area under a receiver operating characteristic (ROC) curve model of disease activity might better reflect disease activity and enable more accurate prognostication of NRM[112].

In addition to standardized staging, clinical features have been used to predict outcomes in acute GVHD. Severe gastrointestinal bleeding, hypoalbuminaemia and serum biomarker levels (including ST2, REG3α, TNFR1 and TIM3) are associated with increased mortality in acute GVHD[37,60]. A study demonstrated that a composite of clinical features — including jaundice, age >18 years, lack of response to corticosteroids and gastrointestinal bleeding — correlated with poor outcomes in patients with acute GVHD[113]. Another composite score that included timing of onset, disease severity at diagnosis and visceral organ involvement was reported to be associated with poor survival[110]. By use of radiography, the presence of diffuse small bowel thickening and of pneumatosis intestinalis portended a poor prognosis in patients with acute GVHD[43,114].

Differential diagnosis

Given the nonspecific presentation of acute GVHD, a broad differential diagnosis should be considered when evaluating patients with gastrointestinal complaints following HSCT (TABLE 3). The timing of symptom onset is a key consideration; conditioning therapy is the most common cause of gastrointestinal symptoms in the period immediately following HSCT and is the most likely cause of diarrhoea during the first 3 weeks. Thereafter, acute GVHD becomes more common[36]. After engraftment, it is not unusual for both acute GVHD and conditioning therapy-induced gastrointestinal symptoms to coexist or for one to transition into the other. Diarrhoea secondary to conditioning regimens is typically self-limited and less severe than in acute GVHD[91].

In addition to myeloablative conditioning regimens, ongoing immunosuppressive prophylaxis can cause adverse gastrointestinal effects. Mycophenolate acid (MPA), an inhibitor of purine synthesis in lymphocytes, can cause a colitis that is difficult to distinguish from acute GVHD[115]. MPA is available in two formulations: the prodrug MMF and the sodium salt, enteric-coated mycophenolate sodium (EC-MPS)[116]. Gastrointestinal symptoms occur in nearly half of patients who receive MMF therapy[115]. The most frequent complaint with MMF is watery, voluminous diarrhoea that starts 2–4 weeks follow ing initiation of therapy[115]. Findings on endoscopy range from normal mucosa to ulceration and mucosal sloughing. Notably, rectal sparing is observed almost universally in MMF-induced colitis[115]. Moreover, the histology of MMF-induced colitis closely resembles that of acute GVHD; however, eosinophilia and the absence of apoptotic micro-abscesses are more common in MMF-induced colitis[117]. Initial treatment of MMF-induced colitis consists of dose reduction or discontinuation of the medication. Alternatively, some centres utilize EC-MPS, which might improve gastrointestinal tolerability compared with the standard formulation MMF[116].

Infections account for 10–15% of cases of diarrhoea in the period following HSCT[36,118], and enteric viral infections are more common than bacterial infections in this setting[119]. Gastrointestinal cytomegalovirus infection should be considered in all patients who receive HSCT (FIG. 4). Cytomegalovirus infection can present as diarrhoea, abdominal pain, odynophagia or fever occurring weeks to months after HSCT[86]. Diarrhoea is bloody in half of such cases[120]. Similar to acute GVHD, lesions might be found endoscopically anywhere along the gastrointestinal tract with prominent mucositis, mucosal ulceration and

sloughing[86]. As patients with active gastrointestinal cytomegalovirus infection might demonstrate negative serum PCR results, intestinal biopsy is required for definitive diagnosis[36]. Owing to the fact that histological findings might mimic those of acute GVHD and that characteristic cytomegalovirus inclusions might be difficult to identify with haematoxylin and eosin (H&E) staining, immunohistochemical staining (typically antibodies targeting the cytomegalovirus tegument component pp65 or other early or immediate early cytomegalovirus antigens) or viral culture (with subsequent confirmatory PCR testing) should be performed[121]. Timely diagnosis and therapy are crucial, as cytomegalovirus infection is an independent predictor of mortality in patients who receive HSCT[86,122]. In addition, varicella zoster virus (VZV) is another possible viral pathogen that might confound the diagnosis of acute GVHD, whereby disseminated VZV infection presents with abdominal pain, diarrhoea and transaminitis that might precede dermatological manifestations[121].

A number of non-culturable viruses can cause severe diarrhoea in post-HSCT patients[123,124]. These viruses, including adenovirus, astrovirus, rotavirus and noro-virus, predominate during the winter, are often health care-associated and might cause severe and prolonged illness following HSCT[123,124]. Upon infection with these viruses, severe diarrhoea might develop with or without upper gastrointestinal symptoms. Viral gastroenteritis and acute GVHD can sometimes coexist, and viral gastroenteritis might be predisposing to or worsen the symptoms of acute GVHD[124]. A growing number of reports suggest that norovirus infection can result in severe, and occasionally life-threatening, complications in patients who are immunocompromised[125]. Norovirus is highly transmissible, and outbreaks can spread rapidly within health care centres. PCR-based testing of stool samples is the standard confirmatory test in suspected cases of norovirus gastroenteritis. Endoscopic findings are variable and might include normal mucosa or severe erythema. Histological assessment might demonstrate villous blunting and prominent cytotoxic lymphocytosis[125].

Among bacterial pathogens, *C. difficile* is perhaps the most common and most worrisome. The incidence of *C. difficile* infection among patients who receive allogeneic HSCT ranges from 12 to 27% and is associated with increased mortality[17,126,127]. Predisposing factors to *C. difficile* infection include age >60 years, allogeneic HSCT, chemotherapy before conditioning therapy, severe acute GVHD, use of broad-spectrum antimicrobials and prior vancomycin-resistant enterococci colonization[126]. Clinically, *C. difficile* infection can be indistinguishable from acute GVHD[36,128]. Endoscopically, pseudo-membranes are typically absent in *C. difficile*-infected immuno suppressed patients, making *C. difficile* infection more difficult to endoscopically distinguish from acute GVHD[129]. Various treatment guidelines recommend antibiotic therapy with oral metronidazole for mild to moderate cases of *C. difficile* infection, and oral vancomycin for severe cases[130]. Notably, these guidelines rely on severity scores that utilize white blood cell count, serum creatinine concentrations and serum albumin levels, which might be problematic in the post-HSCT population[17].

Typhlitis due to *Clostridium septicum* infection is characterized by inflammation of the caecum and presents with fever and right lower quadrant abdominal pain 2–4 weeks following cytotoxic chemotherapy or conditioning chemotherapy, at which point neutrophil

counts are at their nadir[131]. In contrast to acute GVHD, typhlitis most often presents before bone marrow engraftment. If typhlitis is suspected, imaging must be performed and might reveal bowel wall thickening and mucosal enhancement, predominantly in the ileocaecal region[132]. If detected, empirical therapy with broad-spectrum antibiotics should be initiated and surgical consultation should be considered[132]. Initial antibiotic coverage must be active against *C. septicum*, *Pseudomonas aeruginosa* and other colonic microbiota that might translocate through a bowel wall that has been compromised by clostridial toxins[133]. Typical empirical regimens include piperacillin–tazobactam monotherapy, cefepime in combination with metronidazole, or ceftazidime with metronidazole.

Cord colitis syndrome (CCS) is a proposed clinical entity that presents as a persistent diarrhoeal illness in ~10% of patients who receive cord blood transplantation and causes a granulomatous inflammation of the upper and lower gastrointestinal tract[134]. CCS is considered a diagnosis of exclusion once acute GVHD and demonstrable infectious aetiologies have been ruled out[134]. Although the syndrome is responsive to antibiotics, a causative pathogen has not been definitively identified[135]. CCS most often presents several months following cord blood transplantation with watery diarrhoea and fever. Colonoscopy reveals erythematous mucosa with or without ulceration, and biopsy demonstrates chronic active colitis, frequently with associated granulomas[136]. This clinical entity remains controversial, as studies have suggested that CCS is not a histopathologically distinct disease from acute GVHD[137,138].

Management

Once alternative causes of post-HSCT gastro intestinal symptoms have been thoroughly considered and excluded and a diagnosis of acute GVHD has been established, prompt treatment should be initiated. Following HSCT, patients should receive GVHD prophylaxis, and those who later develop GVHD should be assessed for the adequacy of their prophylactic regimen, with adjustment as required. First-line treatment regimens consist of systemic and/or oral non-absorbable corticosteroids. Unfortunately, non-response to first-line treatment is common, and data regarding the effectiveness of various second-line treatment modalities is limited. Supportive care throughout the duration of illness is of critical importance and focuses on symptomatic management[139].

Prophylaxis of acute GVHD.

Prophylaxis of acute GVHD is based upon suppression of the engrafted cytotoxic T cell-mediated immune response. Factors considered in selecting a prophylactic regimen include the underlying malignancy, the chemotherapy regimen used for conditioning, the extent of HLA discordance between the donor and recipient, the susceptibility of the patient to infection and the desire of the physician to balance graft immunosuppression with the desired graft-versus-tumour effect[140]. A common prophylactic regimen consists of a course of methotrexate combined with a prolonged tapering dose of a calcineurin inhibitor[141,142]. Among patients who receive less aggressive conditioning regimens, methotrexate might be replaced with MMF or EC-MPS (to avoid methotrexate-related toxicity)[143,144]. Patients who receive an unrelated donor HSCT or an HLA−mismatched transplantation are at greater risk

of developing acute GVHD, and such patients can undergo T cell depletion or post-transplantation treatment with cyclophosphamide, which might reduce the incidence of acute GVHD[145,146].

Treatment of acute GVHD.

The initial step in the management of acute GVHD is the evaluation of the patient's prophylactic regimen[147]. Among patients who discontinue prophylaxis, the prophylactic regimen can be restarted; in patients still receiving prophylaxis, drug levels can be optimized via dosage increase if serum drug levels are low.

The mainstay first-line treatment strategy for gastrointestinal acute GVHD comprises corticosteroids[147]. A common starting regimen with systemic corticosteroids is prednisone or methylprednisolone at doses of 1–2 mg/kg per day in divided doses (typically every 12 hours). For patients with less severe disease (grade II), initial treatment with a lower dose of prednisone (1 mg/kg/day) has also been shown to be effective[148]. Conversely, corticosteroid doses >2 mg/kg/day do not provide additional therapeutic benefit across grades of severity[149]. At any grade of severity, concomitant use of oral non-absorbable corticosteroids, such as budesonide or beclomethasone, might improve response rates and also helps to moderate the dose of systemic cortico steroid therapy[150,151]. For patients with mild to moderate disease severity, monotherapy with oral beclomethasone dipropionate is a reasonable initial therapeutic approach[152]. In patients with mild to moderate colonic acute GVHD, we have also prescribed budesonide MMX (Cosmo Pharmaceuticals NV), an oral formulation that uses a multi-matrix system to extend budesonide release throughout the colon, which has been studied in patients with ulcerative colitis[153]. Corticosteroids are generally continued for several weeks and slowly tapered to prevent relapse[154]. Patients who demonstrate disease progression at day 5 of treatment, or no improvement by day 7, are deemed steroid-refractory and are likely to require second-line agents[147,154].

A substantial proportion of patients with acute GVHD fail to respond to first-line corticosteroids. In a study from 2015, 31% of standard-risk patients and 57% of high-risk patients were steroid-refractory.[111] There are also data showing that patients with lower gastrointestinal involvement are at particularly high risk of non-response[155]. Unfortunately, there is an insufficient amount of quality data to guide the management of patients who fail to respond to corticosteroids, and their outcomes are generally poor[139]. Several second-line therapies are currently available to treat patients who are steroid-refractory, including lymphocyte-depleting agents, cell cycle inhibitors, antimetabolites, TNF antagonists, inhibitors of leukocyte trafficking, antibodies directed against various interleukins, extra corporeal photopheresis and others[139]. A detailed discussion of second-line therapies is beyond the scope of this article, and we direct the reader to a relevant review[139].

Supportive care and management of gastrointestinal complications in acute GVHD.

In addition to immunosuppressive therapies, treatment of acute GVHD includes symptomatic management of nausea, vomiting, mucositis, dysphagia, diarrhoea, abdominal pain, bleeding and malnutrition. Patients with severe disease might be placed on bowel rest ('*nil per os*' (NPO)) to prevent exacerbation of symptoms. However, oral intake should be

resumed as soon as the patient can tolerate it to prevent gut atrophy. Nausea secondary to upper gastro intestinal acute GVHD might be initially managed with 5-hydroxytryptamine 3 ($5\text{-}HT_3$) receptor antagonists[156]. Low-dose corticosteroids are also effectively used as prophylactics[157]. Other agents for symptomatic management include phenothiazines, metoclopramide, lorazepam, haloperidol and dronabinol. Aprepitant, a neurokinin 1 receptor antagonist, is effective for symptomatic management; however, it should be noted that aprepitant interacts with various immunosuppressants, as it is a substrate and a moderate inhibitor of human cytochrome P450 3A4, which has a crucial role in the hepatic metabolism of calcineurin inhibitors[158].

Oropharyngeal mucositis, dysphagia and odynophagia can lead to anorexia and malnutrition; supportive measures include the use of topical anaesthetics. Viscous lidocaine is included in formulations known as ‘magic mouthwashes’, which contain components such as antibiotics, antifungals, antihistamines, steroids and coating agents. Saline solution has been shown to be as effective as a ‘magic mouthwash’ for analgesia and healing of mucositis[159]. In addition, antiseptic mouth rinses such as chlorhexidine gluconate aid in the prophylaxis of oral superinfection but might also exacerbate symptoms of mucositis. For symptoms of oesophagitis, the mainstay of therapy is PPIs[158]. Although coating agents such as sucralfate are often used in conjunction with PPIs, there is little evidence to support their efficacy, and there is concern that they might decrease the absorption of other medications; thus, they are not recommended by expert guidelines[160].

Chronic abdominal pain related to acute GVHD is difficult to treat. The pain is attributed to inflammation, oedema, increased mucosal friability and ileus[161]. The use of NSAIDs and paracetamol might be limited by bleeding and hepatotoxicity risks, respectively. Therefore, opioid analgesics (morphine, hydro morphone and so on) are often necessary. Opioids should be used with caution in patients with acute GVHD, as they can further impair neuromuscular activity, hinder gut propulsion and inadvertently exacerbate pain[162]. In an effort to combat these adverse effects, the μ-opioid receptor antagonist methylnaltrexone might be used pre-emptively[163]. Alternatively, buprenorphine, a μ-opioid receptor partial agonist and a κ-opioid receptor and δ-opioid receptor antagonist, might offer analgesia with less frequent and less severe adverse gastrointestinal effects[164]. Finally, non-narcotic analgesics such as GABA analogues, serotonin–noradrenaline reuptake inhibitors and tri-cyclic anti depressants might have a role as adjuncts for neuropathic gastrointestinal pain[162].

The management of diarrhoea is one of the greatest challenges in acute GVHD (TABLE 4). Anti-diarrhoeal agents should be initiated after infection is excluded, as decreasing stool output might delay clearance of pathogenic bacteria and their associated toxins, thus lengthening the disease course[165]. Loperamide is the initial anti-diarrhoeal agent of choice, but if ineffective, octreotide or tincture of opium might be used and titrated to elicit the desired response[166]. The combination of atropine and diphenoxylate is a commonly used anti-motility agent; however, it must be used with caution, as it can provoke ileus (pseudo-obstruction)[167]. A trial of pancreatic enzyme supplementation might also be considered, as there is evidence that acute GVHD can cause pancreatic insufficiency[168,169]. The addition of a bile-acid-binding resin (known as a bile acid sequestrant) might also be beneficial[168,169]; however, such agents should be used judiciously, as they can interfere with the absorption of

other medications. Stool output must be measured diligently, and anti-motility agents should be tapered as soon as diarrhoea begins to subside to prevent the development of ileus[59].

Patients who receive HSCT commonly develop macronutrient and micronutrient deficiencies secondary to profound gastrointestinal symptoms, systemic inflammation, protein-losing enteropathy and medication toxicity[59]. Malnutrition and hypoalbuminaemia are well-established factors associated with poor prognosis and thus must be addressed[60]. Patients should receive formal nutritional evaluations to determine their need for supplemental enteral and/or parenteral nutrition. Oral feeding is preferable in order to maintain both intestinal function and the mucosal barrier and concomitantly avoids the potential complications of total parenteral nutrition (TPN)[170]. However, TPN might be the only available option for patients with severe diarrhoea and an inability to tolerate sufficient oral intake. If TPN is initiated, an early re-introduction of oral intake leads to improved nutritional outcomes[171].

Gastrointestinal bleeding secondary to acute GVHD typically results from diffuse mucosal oozing of blood and is rarely amenable to endoscopic intervention[158]. Nonetheless, endoscopic evaluation is warranted to exclude lesions that might be treatable. The mainstay of therapy for acute GVHD-related haemorrhage include supportive therapy to correct thrombocytopenia and coagulopathy, acid suppression and treatment of GVHD[158]. Continuous infusion of octreotide has been studied for the treatment of GVHD-related gastrointestinal bleeding, but its efficacy is lost when the drug is discontinued[172]. In the setting of ongoing bleeding that cannot be managed with conservative approaches, cases of successful arterial embolization have been reported[173]. Another technique is intra-arterial platelet transfusion[174]. Surgical management is typically not feasible, given the diffuse nature of the disease and the high surgical risk of these patients.

Conclusions

Although the pathophysiology of acute GVHD remains to be fully elucidated, acute GVHD seems to be largely a result of dysregulated cell-mediated immunity, which prompts an aggressive cytotoxic response by donor lymphocytes. Emerging evidence suggests that imbalances in the gut microbiota probably also have an important role in the development of acute GVHD of the gastrointestinal tract. Although serological markers, radiology and endoscopy all have important roles in the evaluation of patients with gastrointestinal acute GVHD, the diagnosis ultimately depends on identification of classical clinical features and the exclusion of alternative diagnoses. Given the nonspecific presentation of acute GVHD, a broad differential diagnosis should be considered and should include the effects of myeloablative conditioning regimens, ongoing immunosuppressive prophylaxis, viral infection and bacterial infection (particularly with *C. difficile*). Endoscopic findings might vary broadly and reflect the phases of progressive mucosal inflammation. Although the diagnosis of acute GVHD should be confirmed using tissue biopsy when possible, the diagnosis is ultimately made on the basis of clinical findings, and biopsies should not delay the management of the disease in patients who present with classic clinical features. Biopsy samples from the distal colon yield the highest sensitivities for detecting acute GVHD and should be obtained from multiple sites given the typically patchy, diffuse nature of the

disease. The histological grade of biopsy specimens has not been shown to correlate with clinical manifestations of disease and is not predictive of treatment response, morbidity or mortality. Several novel biomarkers have been identified that might help anticipate the risk of developing acute GVHD, diagnose the disease at earlier stages, estimate the prognosis and predict response to treatment; however, to date, none have been integrated into routine clinical practice. First-line treatment regimens for acute GVHD consist of corticosteroids; higher dose corticosteroids are not superior to more moderate dosages, and the use of oral, non-absorbable corticosteroids can help to further reduce systemic dose requirements. Failure to respond to first-line treatment is common and should prompt the re-evaluation of the patient for possible alternative or concomitant diagnoses. Although a number of second-line treatments are available, outcomes among corticosteroid non-responders remains dismal.

Accordingly, acute GVHD of the gastrointestinal tract is a major challenge in the clinical management of patients with haematological malignancies who receive HSCT. In spite of ongoing advances, GVHD remains a common occurrence at centres that perform HSCT. Severe gastrointestinal acute GVHD has a poor prognosis and can be catastrophic if it is not expediently diagnosed and treated. Although the diagnosis and treatment of acute GVHD generally falls within the realm of the haematologist and oncologist, the involvement of the gut necessitates the consultation of a gastroenterologist. Gastroenterologists have a central role in both diagnosis and risk stratification of acute GVHD of the gut via endoscopy and tissue biopsy. They also manage gastro intestinal complications, including gastro intestinal bleeds, and can guide aspects of supportive care such as treatment of diarrhoea and malnutrition. A collaborative, multidisciplinary approach involving haematologists, gastroenterologists and pathologists is most likely to lead to improved outcomes in the vulnerable population of patients with acute GVHD of the gut.

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Allogeneic HSCT

Transplantation in which a patient receives haematopoietic stem cells from a genetically similar, but not identical, donor.

Autologous HSCT

Transplantation in which a patient's haematopoietic stem cells are harvested, stored for the duration of the patient's conditioning regimen, and later returned to that same patient for re-engraftment.

Myeloablative conditioning

The complete or near complete depletion of native bone marrow cells via the administration of cytotoxic chemotherapy such as cyclophosphamide, often along with radiation therapy.

Oesophagogastroduodenoscopy

A diagnostic endoscopic procedure used to visualize, and sometimes intervene upon, regions of the upper gastrointestinal tract, down to the level of the duodenum.

Small bowel capsule endoscopy

A procedure in which a capsule containing a wireless camera is ingested by a patient and used to visualize areas of the small bowel that are difficult to access using conventional endoscopy.

Unrelated donor HSCT

A type of allogeneic transplant in which the donor is not related to the patient.

HLA-mismatched transplantation

A type of allogeneic transplantation in which the HLA typing of the donor and recipient are not identical.

Key points

- Acute graft-versus-host disease (GVHD) of the gastrointestinal tract is a common complication in patients after haematopoietic stem cell transplantation (HSCT) that results in considerable morbidity and mortality
- As the clinical, serological and radiographical findings in gastrointestinal acute GVHD are nonspecific, a broad differential diagnosis should be considered, particularly potential infectious causes and chemotherapeutic or immunosuppressant toxicity
- Expedient endoscopy and histopathology are helpful in excluding possible conditions that mimic gastrointestinal acute GVHD; nevertheless, the diagnosis is ultimately based on clinical criteria
- Several novel diagnostic, prognostic, risk and predictive biomarkers have been identified for gastrointestinal acute GVHD; however, none have yet been integrated into routine clinical practice
- Upon diagnosis of gastrointestinal acute GVHD, timely first-line therapy with systemic corticosteroids (such as prednisone or methylprednisolone) and/or oral non-absorbable corticosteroids (such as beclomethasone or budesonide) is crucial
- Acute GVHD leads to substantial gastrointestinal symptom burden, including profuse diarrhoea, abdominal pain, severe malnutrition and gastrointestinal bleeding; providing supportive and palliative care is a critical role of the gastroenterologist

Proposed endoscopic approach in suspected acute GVHD

Numerous variables must be taken into account when considering an endoscopic evaluation in a patient following haematopoietic stem cell transplantation (HSCT). This box summarizes our recommendations for the pre-procedural and post-procedural considerations. It also provides our proposed endoscopic approach in patients after HCST who are being evaluated for gastrointestinal acute graft-versus-host disease (GVHD).

Pre-endoscopy

Optimize haemodynamics and pulmonary status

- Ensure platelet count is $>50 \times 10^9$/L and international normalized ratio (INR) is <1.5
- No bowel preparation is necessary for lower endoscopy
- No antibiotic prophylaxis is necessary

Endoscopic approach

- For diarrhoea-predominant disease:
  - Lower endoscopy, advancing the scope to the furthest proximal extent as can be accomplished safely
  - Biopsies of any discrete lesions and random biopsies of mucosa in each colonic segment
  - If the above are non-diagnostic, consider oesophagogastroduodenoscopy (EGD) with biopsies from each anatomic segment
- If upper gastrointestinal symptoms are most prominent:
  - EGD with biopsies from each anatomic segment
  - If the above is non-diagnostic, consider lower endoscopy, advancing the scope to the furthest proximal extent as can be accomplished safely and obtaining biopsies accordingly

Post-endoscopy

- Clear communication between the gastroenterologist and pathologist regarding the differential diagnosis
  - Assess for GVHD, superimposed cytomegalovirus infection, and so on
- Monitor response to treatment and consider repeat endoscopy if there is no clinical improvement

Clinical staging and grading of acute GVHD

The severity of acute graft-versus-host disease (GVHD) is classified according to the stage of individual target organ involvement and the overall grade, which takes into account the stages of each organ system. The clinical stage and grade of acute GVHD correlate with treatment response and mortality.

Clinical stage of acute GVHD

Stage	Target organ			
	Skin (active erythema only)	Liver (serum total bilirubin)	Upper gastrointestinal	Lower gastrointestinal (stool output)
0	No active (erythematous) rash	<2 mg/dL (<34.21 μmol/L)	No or intermittent nausea, vomiting or anorexia	• Adult: <500 mL per day • Child: <10 mL/kg per day
1	Maculopapular rash, <25% BSA	2–3 mg/dL (34.21–51.31 μmol/L)	Persistent nausea, vomiting or anorexia	• Adult: 500–999 mL per day • Child: 10–19.9 mL/kg per day
2	Maculopapular rash, 25–50% BSA	3.1–6 mg/dL (53.02–102.62 μmol/L)	–	• Adult: 1,000–1,500 mL per day • Child: 20–30 mL/kg per day
3	Maculopapular rash, >50% BSA	6.1–15 mg/dL (104.33–256.56 μmol/L)	–	• Adult: >1,500 mL per day • Child: >30 mL/kg per day
4	Generalized erythroderma (>50% BSA), plus bullous formation and desquamation (>5% BSA)	>15 mg/dL (>256.56 μmol/L)	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of volume)

Overall clinical grade of acute GVHD (based upon the most severe target organ involvement)

Grade	Criteria
0	No stage 1–4 of any organ involvement
I	Stage 1–2 skin involvement, without liver, upper gastrointestinal or lower gastrointestinal involvement
II	Stage 3 skin involvement and/or stage 1 liver involvement and/or stage 1 upper gastrointestinal involvement and/or stage 1 lower gastrointestinal involvement
III	Stage 2–3 liver involvement and/or stage 2–3 lower gastrointestinal involvement with stage 0–3 skin involvement and/or stage 0–1 upper gastrointestinal involvement
IV	Stage 4 skin, liver or lower gastrointestinal involvement, with stage 0–1 upper gastrointestinal involvement

BSA, body surface area. Tables from REF. 107, Macmillan Publishers Limited.

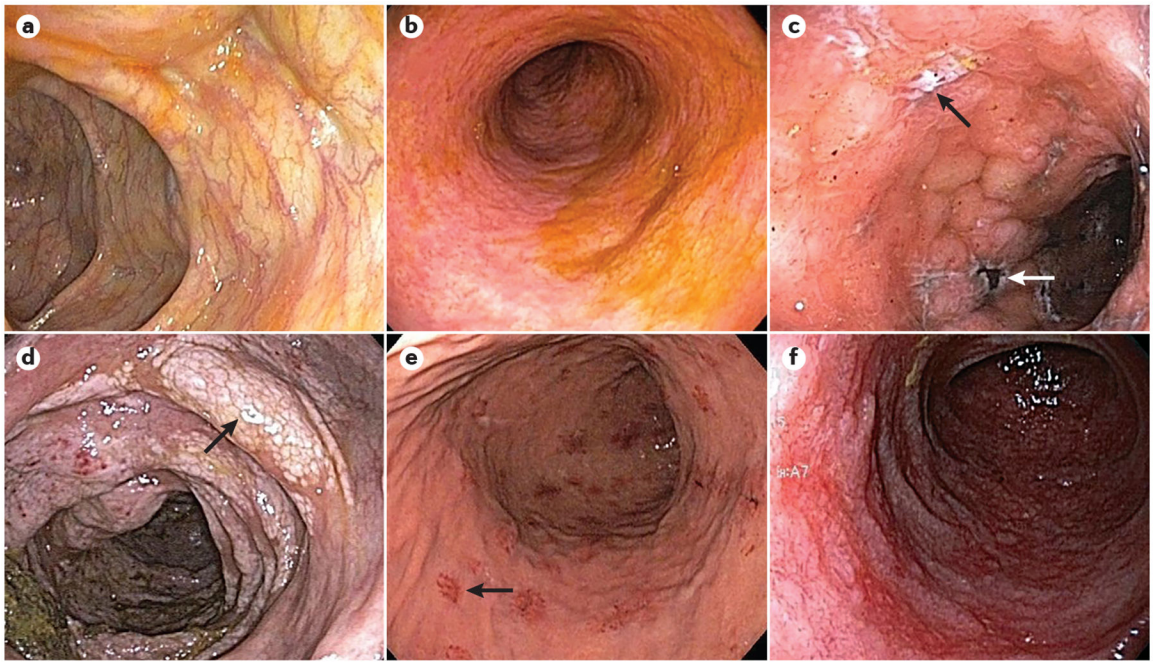

Figure 1 |. Endoscopic findings in acute GVHD of the gastrointestinal tract.

Endoscopic images depict various endoscopic findings in acute graft-versus-host disease (GVHD) of the gastrointestinal tract. **a** | Colonic mucosa with a normal appearance following haematopoietic stem cell transplantation (HSCT) in a patient with diarrhoea. Non-targeted biopsies revealed mild acute GVHD. **b** | Sigmoid colonic mucosa with mucosal oedema, loss of normal haustra and complete loss of vascularity following HSCT in a patient with diarrhoea. Biopsies revealed mild acute GVHD. **c** | Colonic mucosa with oedema, exudates, deep ulcers (black arrow) and areas of necrotic tissue (white arrow) in a patient following HSCT with biopsies confirming severe acute GVHD. **d** | Colonic mucosa with oedema, friability, loss of vascularity and white plaques (arrow) in a patient following HSCT. Biopsies revealed moderate acute GVHD and pneumatosis intestinalis. **e** | Upper endoscopy in a patient with nausea and epigastric pain following HSCT, showing patchy, raised erythematous lesions (arrow) as well as localized superficial mucosal erosions. Biopsies of the lesions revealed mild acute GVHD. **f** | Duodenal mucosa in a patient with severe epigastric pain following HSCT, revealing loss of normal plicae circulares, the presence of friable and oedematous mucosa and a complete loss of normal vascularity. Biopsies revealed severe acute GVHD.

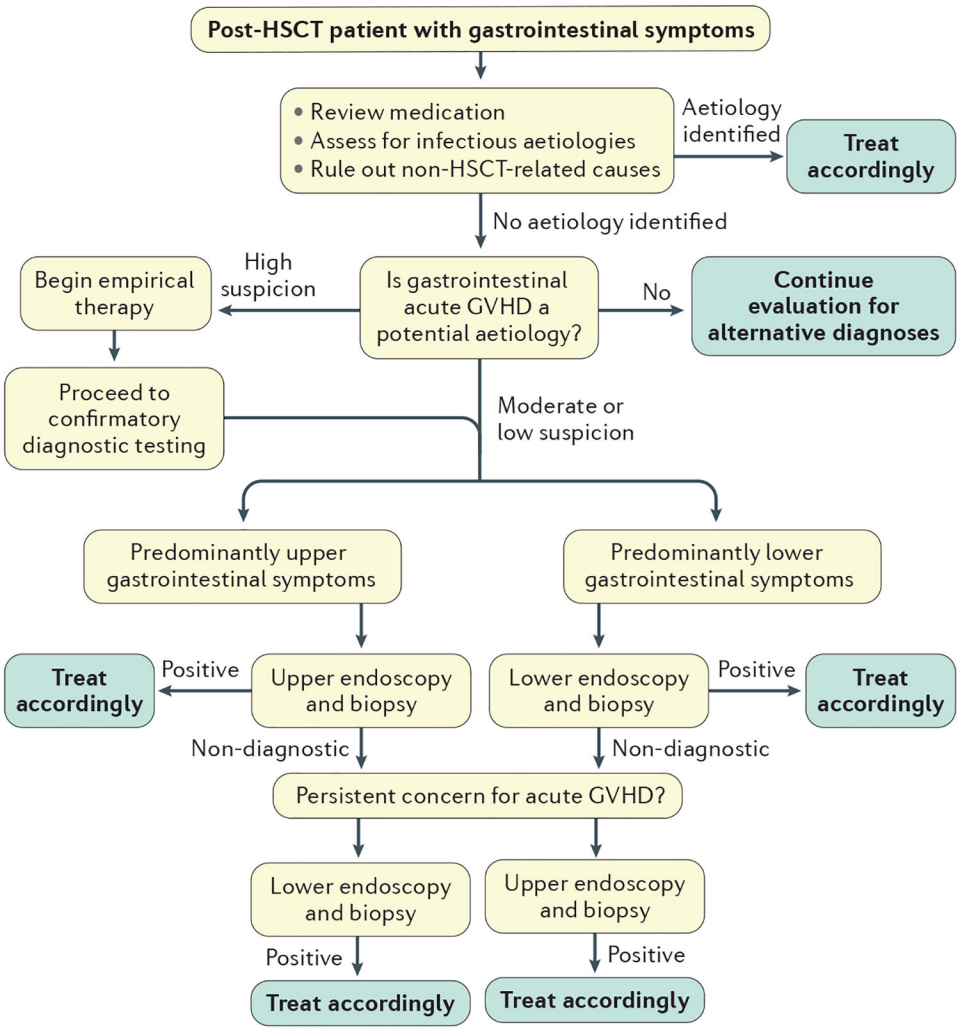

Figure 2 |. Recommended diagnostic algorithm for patients with suspected gastrointestinal acute GVHD after HSCT.

Post-haematopoietic stem cell transplantation (HSCT) patients who develop gastrointestinal symptoms must be carefully evaluated. The initial step is to review medications that might cause gastrointestinal adverse effects, assess for acute infection and rule out non-transplant-related gastrointestinal illness. If these aetiologies are excluded, graft-versus-host disease (GVHD) must be considered as a potential aetiology. If there is a high suspicion for gastrointestinal acute GVHD, empirical treatment can be initiated as the diagnostic work-up is undertaken. If there is a moderate or low suspicion for gastrointestinal acute GVHD, an endoscopic evaluation should be undertaken in accordance with the patient's predominant symptoms (upper or lower gastrointestinal). Once a diagnosis is established, treatment should be promptly initiated. If the initial study is non-diagnostic but gastrointestinal acute GVHD is still a concern, further endoscopic evaluation should be undertaken. Once a diagnosis is established, appropriate therapy must be initiated. First-line therapy for GVHD typically includes corticosteroids.

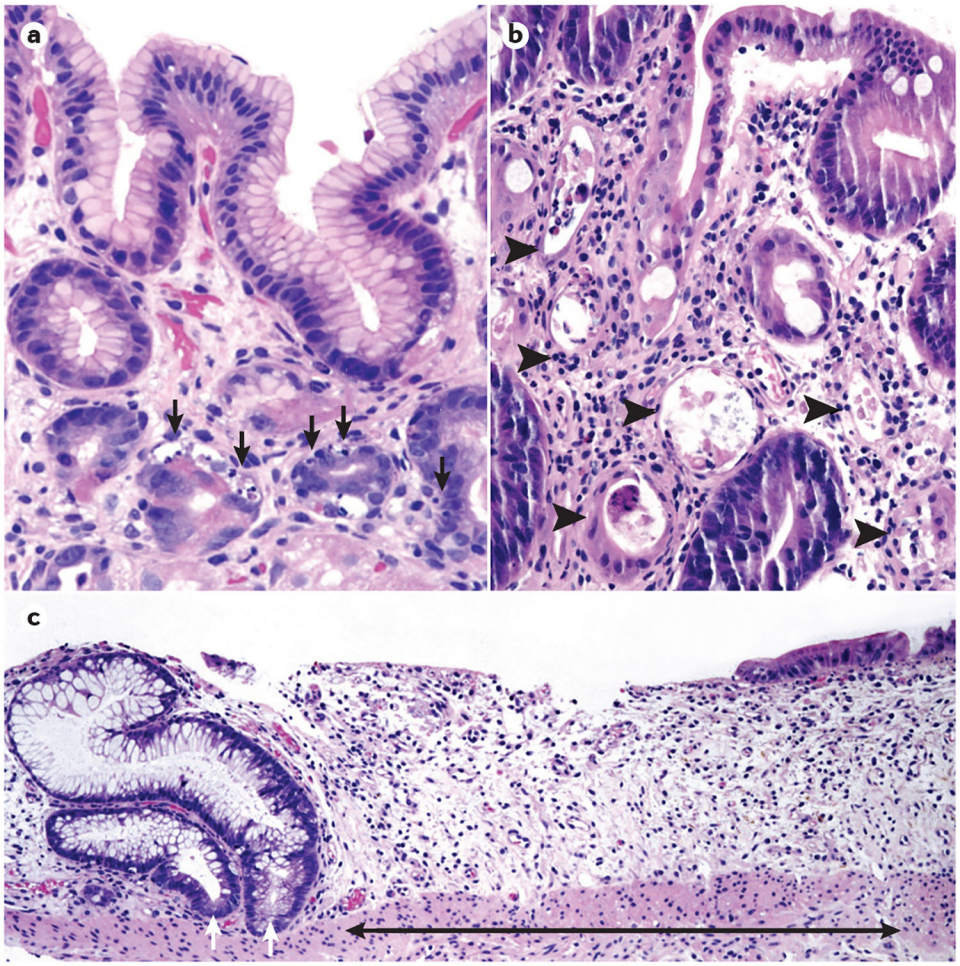

Figure 3 |. Histopathological findings in GVHD of the gastrointestinal tract.
Haematoxylin and eosin (H&E) staining of acute graft-versus-host disease (GVHD) of the gastrointestinal tract, illustrating common histopathological findings. **a** | Oxyntic mucosa of the stomach showing apoptotic epithelial cells in multiple crypts (black arrows, ×200). The nuclei of the apoptotic cells shrink in size, the chromatin condenses and nuclear fragmentation occurs. **b** | Colonic mucosa depicting multiple withered and necrotic crypts (arrow heads, ×200). **c** | Colonic biopsy showing areas of extensive crypt loss (black arrow). The remaining two crypts (white arrows) show reactive epithelial changes (×100).

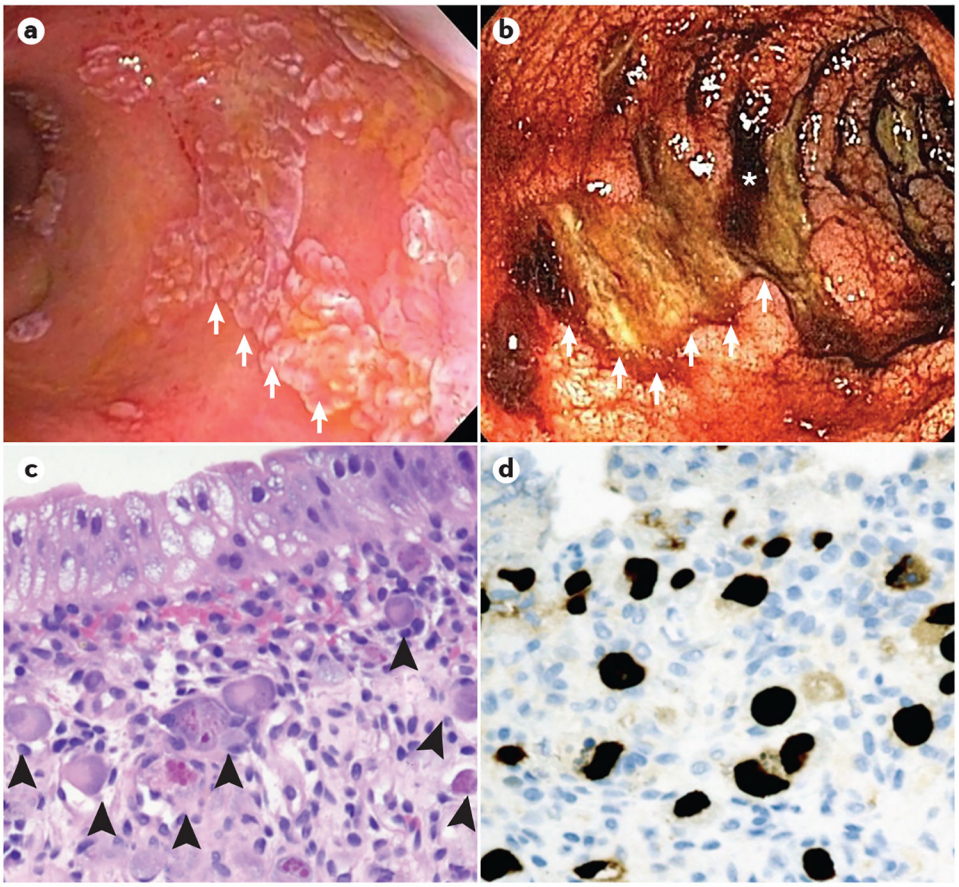

Figure 4 |. Gastrointestinal cytomegalovirus infection following HSCT.

Endoscopic and histopathological images from patients with acute graft-versus-host disease (GVHD) of the gastrointestinal tract, depicting cytomegalovirus infection in the post-haematopoietic stem cell transplantation (HSCT) setting. **a** | Colonoscopy in a patient following HSCT with established severe acute GVHD who is unresponsive to corticosteroids. Numerous raised white plaques (white arrows) are present throughout the colon. Biopsy samples of the lesions revealed extensive cytomegalovirus-infected cells and positive immunostaining for cytomegalovirus proteins. **b** | Colonoscopy in a patient following HSCT with severe acute GVHD and profuse haematochezia. Large, deep ulcers in the transverse colon (white arrows, which trace the rim of an ulcer), areas of active bleeding (asterisk) and diffusely oedematous colonic mucosa are seen. Biopsies of the mucosa revealed acute GVHD, whereas biopsies of the ulcer base stained positive for cytomegalovirus proteins by use of immunohistochemistry. **c** | Haematoxylin and eosin (H&E)-stained slide showing an area of a colon with crypt loss and multiple cytomegalovirus-infected endothelial cells (arrowheads, ×200). The cytomegalovirus-infected cells have large, smudgy, eccentric nuclei with prominent intranuclear and intracytoplasmic inclusions. **d** | Immunohistochemical staining of cytomegalovirus proteins (typically cytomegalovirus tegument component pp65) highlights cytomegalovirus-infected endothelial cells (dark brown immunostaining, ×200).

Table 1 |

Grading endoscopic severity in gastrointestinal acute GVHD

Grade	Freiburg Classification for endoscopic findings[64]
1	Normal mucosa or the absence of higher-grade findings
2	Spotted erythema or initial aphthous lesion
3	Aphthous lesions or focal erosions
4	Confluent defects, ulcerations and/or complete denudation of the mucosa

Table from REF. 64, Macmillan Publishers Limited.

Table 2 |

Grading histological severity in gastrointestinal acute GVHD

Grade	Histological classification
1	Isolated apoptotic epithelial cells without crypt loss
2	Crypt necrosis, withering and individual crypt loss
3	Contiguous areas of multiple crypt loss
4	Extensive crypt dropout with denudation of the epithelium

Data from REF. 99 and REF. 104.

Table 3 |

Differential diagnosis for acute GVHD of the gastrointestinal tract

Aetiology	Differential diagnosis
Anorexia, dysphagia, nausea and vomiting	
Iatrogenic	• Conditioning chemotherapy (cyclophosphamide, busulfan, cytarabine, melphalan) • Immunosuppressants • Radiation • Antibiotics • Opioids • Pill-induced oesophagitis
Infectious	• Cytomegalovirus, HSV, VZV • Candida • Bacterial
Inflammatory	• Peptic oesophagitis • Peptic stricture
Anatomical	• Bowel obstruction (mass lesion, haematoma) • Ileus, colonic pseudo-obstruction
Abdominal pain	
Iatrogenic	• Conditioning chemotherapy-induced enteritis • Medication-induced constipation, ileus
Infectious	• Bacterial • Viral • Parasitic • Liver abscess
Inflammatory	• Peptic ulcer disease • Typhlitis • EBV lymphoproliferative disease
Hepatic, biliary, pancreatic	• Acute pancreatitis • Acute (acalculous) cholecystitis • Ascending cholangitis • Sinusoidal obstruction syndrome
Vascular	• Haematoma • Intestinal infarction
Genitourinary	• Haemorrhagic cystitis • Infectious cystitis • Nephrolithiasis
Diarrhoea	

Aetiology	Differential diagnosis
Iatrogenic	• Conditioning chemotherapy (melphalan, cytarabine, alkylating agents) • Immunosuppressants (tacrolimus, MMF) • Antibiotics • Magnesium supplements
Infectious	• Cytomegalovirus, EBV, adenovirus, rotavirus, astrovirus, norovirus • Enteric pathogens, MAC, *Clostridium septicum* • Clostridium difficile • Giardia lamblia, Cryptosporidium hominis, Entamoeba histolytica, Strongyloides stercoralis
Other	• Cord colitis syndrome • Thrombotic microangiopathy • Disaccharidase deficiency • Bile salt malabsorption • Pancreatic insufficiency

EBV, Epstein–Barr virus; HSV, herpes simplex virus; MAC, *Mycobacterium avium* complex; MMF, mycophenolate mofetil; VZV, varicella zoster virus.

Table 4 |

Management of diarrhoea in gastrointestinal acute GVHD

Medication	Dosing
Loperamide	• Start at 4 mg initial dose, followed by 2 mg four times daily • Titrate dose based on response to 4 mg four times daily • Maximum daily dose is 16 mg
Diphenoxylate–atropine	• Use with caution to prevent ileus • Start at one tablet (containing diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg) four times daily • Titrate dose based on response to two tablets four times daily • Maximum daily dose is eight tablets
Octreotide	• Start at 50 μg subcutaneously three times daily • Based on response, titrate by 100 μg per dose every 48 hours • Maximum of 500 μg per dose; maximum daily dose is 1,500 μg
Tincture of opium	• Contains morphine 10 mg/mL • Start at 10–15 drops in water every 3–4 h • Titrate dose based on response • Maximum dose based on adverse effects
Pancrelipase	• Start at 500 lipase units/kg per meal • Titrate dose based on response • Doses >10,000 lipase units/kg per day should be used with caution
Cholestyramine	• Start at 2 g twice daily • Based on response, titrate dose by 4 g per day every 4 weeks • Maximum daily dose is 24 g