Current approach to early gastrointestinal and liver complications of hematopoietic stem cell transplantation

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ABSTRACT

The gastrointestinal (GI) system is one of the most commonly affected sites during a hematopoietic stem cell transplantation (HSCT) due to toxicities of preparative regimens, the accompanying immunodeficiency, and organ damage caused by graft versus host disease. In this review, we focus on early GI and liver complications following autologous (auto-) and allogeneic (allo-) HSCT and clarify both the risk factors and therapeutic strategies. Early GI and liver complications associated with HSCT remain challenging issues. Despite the improvements in this field during the last decade, treatments for these complications still place a significant burden on both patients and the physicians treating these patients. GI and liver complications remain some of the causes of mortality associated with HSCT. For practicing hematologists, oncologists, and gastroenterologists in this field, the awareness and early diagnosis of the GI complications remain important factors to obtain optimal outcomes in this patient population.

Keywords: *Allogeneic hematopoetic stem cell transplantation, graft versus host disease, gastrointestinal system*

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is regarded as a curative treatment option for many hematological diseases (1), and autologous (auto-) HSCT is commonly used to treat multiple myeloma, relapsing lymphomas, and a few solid tumors (2,3). Infections and graft versus host disease (GvHD) are still major causes of mortality and morbidity in the allogeneic setting, despite pivotal advances such as reduced intensity conditioning regimens, more accurate matching techniques, manipulation of graft components and new therapeutic approaches (4). The gastrointestinal (GI) system is one of the most commonly affected sites due to the toxicities of the preparative regimens, the accompanying immunodeficiency, and organ damage by GvHD. Complications in the GI system and liver can be divided into two groups, based on the time of occurrence: early (within 3 months after the procedure) and late (more than 3 months after the procedure). In this review, we focus on early GI and liver complications following auto- and allo-HSCT and clarify both risk factors and therapeutic strategies. Important early GI and liver complications that practicing hematologists, oncologists, and gastroenterologists encounter can further be grouped into pre-engraftment and peri-/post-engraftment complications, according to the timing of engraftment (5,6).

PRE-ENGRAFTMENT COMPLICATIONS

Nausea and vomiting

During the pre-engraftment period (i.e., the first 2 weeks after HSCT), the most relevant causes of nausea and vomiting are the chemotherapeutic agents used in conditioning regimens, with or without body irradiation. The pathogenesis includes stimulation of the chemotherapy trigger zone in the brainstem or cell damage in the GI tract, which results in releasing neuroactive agents and vagal stimulation, both of which activate the vomiting center.

Prevention is more essential than treatment in this stage. Acute emesis prevention (up to 24 hours after chemotherapy) requires combination treatment with corticosteroids or methylprednisolone and 5-hydroxytryptamine-3-receptor antagonists. For delayed emesis prevention (up to 5 days after treatment), corticosteroids or aprepitant are effective agents. Phenothiazines, metoclopramide, lorazepam, haloperidol, dronabinol, and corticosteroids are preferred for this treatment (7).

Diarrhea

Diarrhea is generally observed within 3 months following HSCT. It deteriorates the patient's general health status, but the etiology of diarrhea is complicated. In the pre-en-

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graftment period, diarrhea occurs mostly due to mucosal damage caused by the conditioning regimen, such as alkylating agents, busulfan, and combination regimens or radiotherapy (7).

Neutropenic enterocolitis (NE), also called typhlitis, is a common complication during the pre-engraftment period. In NE, intestinal mucosal injury caused by chemoradiotherapy or intestinal leukemic infiltration leads to intestinal edema and enlarged vessels, and the intestine becomes more vulnerable to bacterial invasion (8). Gram-negative rods, Gram-positive cocci, enterococci, fungi, and viruses are the most commonly detected causes. Patients may present with abdominal pain, diarrhea, fever, nausea, vomiting, or abdominal distention. Computed tomography is generally preferred for diagnosis as a non-invasive method that can show the bowel wall thickening, a dilated colonic segment, pericolonic inflammation, and an inflammatory mass. Because most patients have neutrophil counts <500/μL, conservative management is proposed, including aggressive fluid resuscitation, correction of electrolyte imbalance, bowel rest, abdominal decompression, and broad-spectrum antibiotics (9).

Mucositis

Oral mucositis is a debilitating adverse effect during HSCT and its prevalence varies between 47% and 100%. It is well documented, especially within 5-10 days after initiating a conditioning regimen, mostly with radiation-based myeloablative regimens containing the chemotherapeutic agents busulfan, etoposide, melphalan, and methotrexate, in addition to the use of methotrexate-containing GvHD prophylaxis (10). Pre-existing periodontal disease increases the risk. Viral, bacterial, and fungal etiologies may also cause mucositis. Mucositis may cause pain, dysphagia, decreased oral caloric intake, bleeding, infection, upper airway edema, and obstruction (7). Oral mucositis is graded based on the World Health Organization criteria or the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTAE) (Table 1). Prevention and early treatment strategies reduce the severity of symptoms. Supportive treatments include topical agents such as saline and bicarbonate rinses, mucosal coating agents, topical anesthetics, and topical nystatin, as well as oral cryotherapy with ice chips. The keratinocyte growth factor (palifermin) was approved by the US Food and Drug Administration (FDA) to prevent mucositis (7).

PERI-/POST-ENGRAFTMENT COMPLICATIONS

Acute GvHD

Acute GvHD (aGvHD) is an immune-mediated process that provokes severe immune dysregulation and organ dysfunction following allo-HSCT. Previously, GvHD has been defined on the basis of the time of occurrence: aGvHD in the first 100 days vs chronic GvHD (cGvHD) 100 days after transplantation (6). In 2014, the NIH released new consensus criteria suggesting that aGvHD and cGvHD might be detected outside of these established periods. Late onset/persistent aGvHD occurs after 100 days in the absence of cGvHD, whereas in overlap syndrome, aGvHD and cGvHD may coexist (11). Risk factors for the development of aGvHD include the human leukocyte antigen disparity, increased age of the recipient or donor, female donor, gender disparity, the intensity of conditioning regimens, and the source of the graft (12,13).

Historically, early trials of human marrow grafting failed because of fatal GvHD. In the late 1960s, the compatibility of first dog leukocyte antigen (DLA) and then HLA between donors and recipients, as well as effective drugs to overcome GvHD, were investigated. Allo-HSCT from HLA-identical sibling donors has a significantly lower risk of aGvHD compared to the risk observed with unrelated donors. The higher mortality rates following haploidentical HSCT compared to allo-HSCT from HLA-matched

Table 1. Oral mucositis grading scales

	National Cancer Institute-Common Terminology Criteria for Adverse Events	World Health Organization
Grade 0	Absence of other criteria	Absence of other criteria
Grade 1	Asymptomatic or mild symptoms; interventions not indicated	Oral soreness; erythema
Grade 2	Moderate pain; not interfering with oral intake; modified diet intake	Ulcers, but able to eat solids
Grade 3	Severe pain; interfering with oral intake	Oral ulcers and able to take liquids only
Grade 4	Life-threatening consequences; urgent intervention	Oral alimentation impossible
Grade 5	Death	N/A

siblings are related to higher engraftment failure, higher GvHD rates, and higher relapse risk. Myeloablative regimens are also usually associated with higher incidences of aGvHD compared to the risk observed with reduced intensity regimens. The incidence of aGvHD is similar in peripheral blood and bone marrow as a stem cell source but higher in double-unit umbilical cord transplants (14). The major target tissues of aGvHD are the GI system, liver and skin, occurring in approximately 50% of allo-HSCT recipients. The GI system and liver aGvHD will be discussed in the following section.

Acute GI system GvHD

The frequency of acute GI GvHD among 2500 patients undergoing allo-HSCT was observed to be 54%, but it increased to 63% when combined with liver GvHD (14). In the pathophysiology of GI aGvHD, interactions among a recipient's intestinal epithelium, stroma, immune cells, and luminal microbial flora play important roles. Three phases describe the development of aGVHD: the afferent phase, efferent phase, and effector phase. During the afferent phase, a robust inflammatory response upregulates the secretion of tumor necrosis factor (TNF) alpha, interleukin-1, and interleukin-6 and stimulates antigen-presenting cells. Conditioning regimens or infection damage intestinal tissue, which leads to the translocation of bacterial products (pathogen-associated molecular patterns) into blood or lymphoid tissue and pro-inflammatory danger-associated molecular patterns into the extracellular space (14). Also, goblet cells, Paneth cells, and intestinal stem cells were shown to be reduced in acute GI GvHD. Increased nonrelapse mortality was found to be associated with the loss of Paneth cells and dysbiosis in human studies. Proinflammatory commensal bacterial (e.g., *Enterobacteria* and *Enterococcus*), fungal (*Candida*), and viral (Cytomegalovirus, CMV) infections contribute to the development of acute GI GvHD after injury to goblet cells, which shield the intestinal epithelium (15). In the efferent phase, T-cell trafficking and expansion take place, and effector cells such as neutrophils, natural killer cells, and macrophages contribute to tissue damage in the effector phase (16).

Emerging data suggest that alterations in the intestinal microbiota and microbiome are related to the incidence and severity of GvHD. The human microbiome consists of the bacteria, archaea, viruses, fungi, and other microeukaryotes that live within the host. Intestinal homeostasis relies on interactions between immunologic function and gut microbiota (17) and is maintained by regulatory T cells. The loss of diversity in gut microbiota, and specifically the loss of *Clostridia* species, promotes GvHD. Antibiotic treatment is probably the main factor in the shift of microbiota during the course of transplantation (18).

An aGvHD diagnosis relies on clinical, laboratorial, and histopathologic data. Patients with aGvHD of the upper GI system present with nausea/vomiting, satiety, and anorexia, but aGvHD of the lower GI system presents with diarrhea and abdominal pain after 20 days post-transplant. In the differential diagnosis of upper gut GvHD, nauseating drugs, the effects of the conditioning regimen, herpes virus, *Helicobacter pylori*, and phlegmonous gastritis are important, whereas in lower gut GvHD, the effects of the conditioning regimen, viral infections (e.g., CMV, adenovirus, etc.), bacterial infections (*Clostridium difficile*, etc.), parasitic infections (*Giardia lamblia, Cryptosporidia*, etc.) and drugs should be considered (14,15). Acute GvHD is graded from Stages 1 to 4 based on the clinical severity of symptoms (Table 2). To assess the severity of aGvHD, special markers may be considered, such as fecal alpha-1 antitrypsin, fecal calprotectin, TIM3, sTNFR1, ST2, IL26, and Reg3alpaa (19). However, these markers are not practical to screen for and rarely used in the clinic. Abdominal ultrasonography, color Doppler imaging, and fluorodeoxyglucose-positron emission tomography (FDG-PET) are not feasible noninvasive techniques because the mucosa cannot be visualized directly (20). Therefore, capsule endoscopy and confocal laser endomicroscopy are novel approaches that should be studied further (21). Erythema, friability, and erosions are commonly seen in GI endoscopy edematous mucosa. Today, pathologic evaluation of an endoscopic biopsy is the most definitive method to diagnose acute GI GvHD. The histopathologic hallmark of acute GI GvHD is epithelial

Table 2. Acute graft versus host disease stages

Clinical Stage	Lower GI	Upper GI	Liver (Bilirubin mg/dL)
1	Diarrhea <500 mL/day	Nausea/vomiting	2-3
2	Diarrhea 500-1000 mL/day		3-6
3	Diarrhea 1000-1500 mL/day		6-15
4	Diarrhea >1500 mL/day		>15

apoptosis. The Lerner classification is the most widely used histopathologic scoring system for acute intestinal GvHD based on apoptotic bodies, crypt destruction, and mucosal denudation. According to the NIH Pathology Working Group, biopsy specimens can be reported as *negative for GvHD*, *possible GvHD*, and *likely GvHD* (22). To diminish inter-observer differences in both diagnosis and grading, several other groups have recently created more descriptive diagnostic criteria (23). Indeed, discrepancies of involvement between the upper and lower GI tract biopsies have been reported in up to 45% of patients. Changqing *et al.* demonstrated retrospectively in 110 cases with aGvHD that lower GI tract lesions are more prevalent and severe than upper GI tract lesions (24).

Various T-cell depletion techniques in the graft have successfully reduced the rates of GvHD but increased relapse and rejection rates, for which there are unresolved concerns. Prophylactic antifungal, antiviral, and antibacterial strategies are associated with reduced aGvHD rates. Standard aGvHD prophylaxis consists of a calcineurin inhibitor (e.g., tacrolimus, cyclosporine, etc.) and an anti-metabolite, including methotrexate (MTX), mycophenolate mofetil (MMF), and others. In a systematic review, an MMF/calcineurine inhibitor showed a more favorable toxicity profile than an MTX/calcineurine inhibitor. In myeloablative matched-related donor transplants, MMF-based GvHD prophylaxis was not inferior to MTX-based regimens. Despite recent advances, systemic steroids are still the main treatment option in acute GI GvHD, in combination with nonabsorbable steroids. The prednisone dose varies according to the stage and risk of GvHD from 0.5mg/kg/day to 2mg/kg/day (25,26). Four variables predict mortality during the first 14 days of initial therapy: adult age, failure of initial doses of prednisone, jaundice, and GI bleeding. In steroid failure, which is seen in approximately 25% of patients, antithymocyte globulin (ATG), infliximab, alemtuzumab, MMF, sirolimus, cyclosporine, pulse cyclophosphamide, or extracorporal photopheresis (ECP) might be alternatives, but none of them achieve more than a 50% response (27,28). Intramesenteric steroid administration may be considered as another treatment option (29).

Table 3. Novel approaches in a gastrointestinal graft versus host disease treatment

Novel Approach	Path of Action
IL-22	Increases intestinal stem cells
Histone deacetylase inhibitor	Altering patterns of gene expression, Suppress proinflammatory cytokine production, Enhance natural Treg functions, Regulate epigenetic landscape
SYK inhibitor	Intracellular nonreceptor tyrosine kinase inhibitor ERK and NFAT inhibition
JAK1/2 inhibitor	Inhibition of STAT family Reduction of IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
Mesenchymal stem cell	Modulate central immune compartments, promote T-cells maturation, induce T regs, influence the function of NK cells and suppress dendritic cell maturation.

BMI: body mass index; HP: *Helicobacter pylori*

Novel treatments that appear quite promising (Table 3) include the JAK1/2 inhibitor ruxolitinib, which was administered to 95 pretreated steroid refractory patients with aGvHD, who achieved a 6-month survival of 79% (30). The overall response rate was 81.5% in steroid refractory aGvHD, which was associated with a complete remission rate of 46.3%. However, ruxolitinib treatment has major side effects, including cytopenia and CMV reactivation (31). Another alternative therapy for steroid-refractory aGvHD is infusion of mesenchymal stromal cells (MSCs). MSCs can differentiate into various types of cells and modulate immune responses. Dotoli *et al.* reported results from 46 patients with steroid-refractory aGvHD III/IV. Of these, 50% had clinical improvements, with a 2-year overall survival of 17.4% (22). The effect of prophylactic co-infusion of MSCs and hematopoietic stem cells is still controversial. Lazarus *et al.* showed that the incidence of aGvHD decreased by up to 28% in patients with prophylactic MSC infusion (32). There is currently an ongoing study recruiting participants to evaluate the effect of prophylactic MSCs in patients with aGvHD in a haploidentical HSCT setting (ClinicalTrials.gov identifier NCT03106662). Fecal microbiota transplantation (FMT) is another intervention to restore GI microbiota to reduce the risk of GvHD. Limited clinical data showed encouraging results in *Clostridium difficile* infections, but further prospective trials are needed to evaluate the safety and efficacy of autologous or allogeneic FMT (17).

Acute liver GvHD

The liver is one of the organs most frequently affected by aGvHD. In pathophysiology, endothelial injury with allo-reactive cytotoxic T lymphocytes plays a major role. TNF is the foremost cytokine. CD25 expressing donor T cells can induce GvHD lesions in a mouse model. Humoral immunity also contributes to the process, which was histologically proven by C4d expression in portal vessels and hepatic sinusoids (33). Pan et al. (34) demonstrated that Th1/Th17 imbalance and increased Th1-type reactivation are responsible for acute liver GvHD. A critical attribute of liver GvHD is biliary epithelium damage, including nuclear pleomorphism, loss of nuclear polarity, nuclear overlap, cytoplasmic vacuolization, and eosinophilic infiltration. Ductopenia and apoptosis of small- to medium-caliber bile duct epithelial cells are histopathological lesions that result from the activation of pro-inflammatory cytokines (35). Portal and diffuse lobular inflammation are also detected. In prolonged cases, cholestasis may result in hepatocellular ballooning and feathery degeneration.

Older age, the use of peripheral stem cells, a higher degree of histocompatibility, unrelated donors, and nonmyeloablative conditioning regimens are major risk factors for an increased risk of aGvHD. The diplotype of the glutathionine S-transferase gene, which functions in catabolizing busulfan and the metabolites of cyclophosphamide, is an independent protective factor against aGvHD (54). Some other important predictors of liver GvHD are high hepatic artery resistance index and increased IL-18 (36). Clinical differential diagnosis of hepatic aGvHD includes infections, drug toxicity, sinusoidal obstruction syndrome, iron overload, biliary tract disease, and engraftment syndrome (ES) (14). ES emerges during the neutrophil recovery period after HSCT. It is considered to be a more common complication following auto-HSCT (37,38). Many transplant centers use the diagnostic definition suggested by Spitzer, which contains major and minor criteria (Table 4). Although ES has a self-limited course in most cases, multiorgan failure can sometimes be detected (39). Innate immune cells associated with an increased release of inflammatory cytokines (including IL-1, TNF-alpha, interferon gamma, IL-2 receptor-alpha and TNF-receptor alpha) may play a role in ES. Soluble thrombomodulin, plasminogen activator Type 1 and CRP increase, as well as complement activation, are detected in ES. Post-transplant granulocyte colony stimulation factor therapy has shown a positive correlation with the development of ES. Cyclophophamide exposure has been associated with a reduced risk for ES, but previous exposure to bortezomib or lenalidomine has been linked to a higher risk for ES (40). Chang *et al.* identified younger recipients, male-male transplantations, unrelated donors, cord blood as a stem cell source, ABO major incompatibility, myeloablative conditioning, and TBI (1200 cGy) as risk factors. Immunosuppressive therapy consisting of tacrolimus/methotrexate/ATG may decrease the risk of ES compared to the use of cyclosporine alone (39). It is essential to exclude alternative causes to manage ES. The major treatment is systemic corticosteroids starting with a dose of 1-1.5 mg/kg/day and tapering when symptoms resolve. Additional immune suppressants may be administered in the event of steroid resistance (40).

Table 4. Engraftment syndrome definition criteria

Major	Minor
• A temperature ≥38°C without a defined infectious etiology • Erythrodermic rash not related to any drug, covering a body area over 25% • Non-cardiogenic pulmonary edema accompanied by hypoxia • Diffuse pulmonary infiltrates	• Hepatic dysfunction with either bilirubin ≥2 mg/dL • Transaminase levels ≥2 times normal • Renal failure • Weight gain ≥2.5% of baseline body weight • Transient encephalopathy unexplained by other causes

Liver aGvHD is staged according to serum bilirubin levels (Table 1). Cholestatic jaundice, increased serum levels of alkaline phosphatase, and eosinophilia are the main clinical and laboratory manifestations. Generally, milder elevations in aspartate transaminase (AST) and alanine transaminase (ALT) accompany liver aGvHD, but sharp elevations in AST and ALT with or without jaundice may also be detected in patients with acute liver GvHD. Isolated liver GvHD is more problematic, and persistent jaundice is an independent predictor of GvHD-related mortality (14). Vanishing bile duct syndrome, which is the progressive destruction and disappearance of intrahepatic bile ducts, may be detected as a severe complication of liver GvHD. Liver biopsy is preferred to accurately diagnose liver aGvHD, but it is not recommended and infrequently performed due to the risk of complication. Standard protocols of prophylaxis and treatment are suggested; however, anecdotal evidence shows that pulse cyclophosphamide, ECP, or switching to sirolimus or oral budesonide are more effective methods (14).

Sinusoidal obstruction syndrome

Sinusoidal obstruction syndrome (SOS), formerly known as veno-occlusive disease, is a fatal complication that occurs within the first 35-40 days following myeloablative preparation regimen (e.g., total body irradiation and high dose chemotherapy). The overall incidence of SOS in a recent meta-analysis of 135 studies between 1979 and 2007 was 13.7% (95% confidence interval, 13.3%-14.1%) (41). The incidence varied from 21% to 25% in allogeneic graft recipients to 5% in auto-HSCT (42,43).

In SOS, changes in the hepatic sinusoids induce liver injury and give rise to endothelial injury. Kupffer cells, leukocytes, and mast cells may also play a role in endothelial cell damage, ischemia, and hepatocellular injury, mediated by 5-hydroxytryptamine, prostaglandins, leukotrienes, and free radicals. Increased expression of adhesion molecules such as intracellular cell adhesion molecule, vascular cell adhesion molecule, and procoagulants such as von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) are also detected (44). In the early stages, the subintimal part of the central and sublobular venula thickens due to edema. Fibrous obliteration in central venules occurs by the deposition of fibrinogen and other proteins in the venular walls and perisinusoidal space. Reduction in venous flow, which can be shown in a histological examination, causes serious hepatic congestion and sinusoidal dilatation, ultimately leading to portal hypertension (45). Chronic lesions radiating into the parenchyma develop with persistent SOS and rarely progress to cirrhosis (42).

The presenting symptoms are painful hepatomegaly, weight gain, and fluid retention, and SOS is further characterized by elevated serum bilirubin levels and thrombocytopenia (46). SOS can be defined by the presence of at least two modified Seattle criteria before day 30 post-HSCT: bilirubin ≥2mg/dL, hepatomegaly, and ascites with or without unexplained weight gain of >2% over baseline (47,48). However, the Baltimore criteria narrow the time to 21 post-HSCT days and accept the weight gain of >5% over baseline. A severe SOS generally results in multiorgan failure (42). A retrospective analysis of 136 patients that received HDC with auto-HSCT showed that renal dysfunction and refractoriness to platelet transfusion may occur in severe forms. The recommended clinical grading of SOS is given in Table 5 (48). Although SOS signs are often detected in the first or second week following transplantation, some authors reported later onset of this syndrome. Busulfan, melphalan, or alkylating agents such as thiotepa, especially in the autologous setting, are among the risk factors for the late onset SOS (49,50). In auto-HSCT, the time of appearance of risk factors determines the two patterns of outcomes: Mild forms are associated with early onset (before Day 11), and severe forms, with later onset (after Day 17). Fluid retention may be refractory to diuretic therapy, so half of patients with renal impairment may need dialysis. Due to liver failure, elongation in prothrombin time may be detected. As the disease progresses, severe encephalopathy and interstitial pneumonitis may develop in some patients (51). For differential diagnosis, GvHD, Budd-Chiari syndrome, drug reactions, infections, and heart failure should be excluded (42).

Pre-transplant risk factors of SOS include liver dysfunction (hepatitis, fibrosis, cirrhosis, etc.), hepatic metastases, history of liver radiotherapy, hepatotoxic agents (including herbal remedies, gemtuzumab ozogamicin, melphalan, cytosine arabinoside, and cyclophosphamide), infectious attacks, iron overload, history of stem cell transplantation, and advanced age. Likewise, transplant-related factors include a myeloablative conditioning regimen (TBI, busulfan, and cyclophosphamide), HLA-mismatched related or unrelated donor selection, and the use of methotrexate for GvHD prophylaxis (42,52). In a retrospective analysis of 291 auto-HSCTs for solid tumors and lymphomas, evidence of metastatic liver disease and single high dose-carmustine (≥450 mg/sqm) compared to fractionated doses were detected as pre-transplant characteristics that predict SOS (53,54).

Methods to diagnose SOS, despite practical difficulties, include transjugular liver biopsies and manometric monitoring of hepatic blood flow. A highly specific measurement to identify SOS is a hepatic venous pressure gradient (HVPG) of ≥10 mmHg in a patient without a previous liver disease. However, a normal HVPG does not exclude the diagnosis. Therefore, this method may be required in patients where the clinical diagnosis is not clear (55). In (Doppler) ultrasonography, a variety of abnormalities can be observed, such as gallbladder wall thickening, hepatomegaly, ascites, and reduced or reversed portal flow.

Table 5. Clinical grading of sinusoidal obstruction syndrome

	Mild	Moderate	Severe
Bilirubin, mg/dL	<5	5.1-8.0	>8.0
Liver enzymes (aspartate transaminase, alanine transaminase)	<3×normal	3-8×normal	>8×normal
Weight above baseline	<2%	2%-5%	>5%
Serum creatinine	Normal	<2×normal	>2×normal
Clinical rate of change	Slow	Moderate	Rapid

A few case reports have demonstrated magnetic resonance findings, such as patchy signal enhancement of the liver, hepatomegaly, ascites, hepatic vein narrowing, peri-portal cuffing, and gallbladder wall thickening or hyperintensity. Several studies showed a significant elevation of PAI-1 as a diagnostic marker in SOS that predicted the severity of SOS (56). Proposed biomarkers for predicting endothelial injury include pre- and post-transplant vWF, thrombomodulin, E-selectin, soluble intercellular adhesion molecule-1, and vascular endothelial growth factor, but they are rarely used in practice (57).

It is essential to identify especially high-risk patients and apply effective preventive strategies in both the pre-transplant and peri-transplant periods. Reducing iron overload, preferring reduced-intensity conditions, administering intravenous rather than oral busulfan, using fludarabine instead of cyclophosphamide, adjusting the dose of busulfan, avoiding hepatotoxic drugs, and reconsidering the timing of HSCT in the case of liver dysfunction remain important strategic measures. Prostoglandin E1, pentoxifylline, heparin (unfractioned and low molecular weight), antithrombin, glutamine, and fresh frozen plasma are currently not recommended in the prophylaxis of SOS (55). On the other hand, a systematic review of pooled results of randomized studies demonstrated a reduced risk of SOS in patients receiving ursodeoxycholic acid (relative risk, 0.34; 95% confidence interval, 0.17-0.66).

Salt and water restriction can be combined with diuretics to treat the symptoms of SOS. In severe cases, renal replacement therapy may be required. Studies of SOS treatments showed that the most promising agent is defibrotide (58), which is a new olygodeoxyribonucleotide derivative that has demonstrated increased tPA and thrombomodulin but decreased vWF and the plasminogen activator inhibitor Type 1 expression. Defibrotide reduces the endothelial cell activation, protects endothelial cells from damage, and increases fibrinolysis (59). In its first trial in 1998, 19 patients received defibrotide and achieved a survival rate of 32% at day 100 post-transplantation. As a result of this encouraging data, patients with hepatic SOS were admitted to an international compassionate use program between 1998 and 2009. In a European multicenter compassionate use study, 40 patients participated and demonstrated a 55% complete response (CR) rate with a survival rate of 43% after 100 days (58). The US FDA permitted the use of defibrotide between 2007 and 2011, with which 32% of patients achieved CR, and the overall survival at 100 days was 50%. Therefore, defibrotide was approved by the European Union, as well as the US FDA, to treat adult and pediatric patients with hepatic SOS. The recommended schedule of administration for SOS in daily practice is 4x6.25 mg/kg/day, with a 2-hour intravenous infusion at least for 21 days until signs and symptoms are resolved. The clinical response will be obtained sooner if patients receive defibrotide as soon as SOS is suspected. The successful use of defibrotide following auto-HSCT was also demonstrated in several studies (60). In a study conducted by Shah *et al.*, oral defibrotide cured late-onset SOS after auto-HSCT. Serious adverse events were experienced by 51% of patients, including fatal hemorrhagic adverse events in 5% and fatal hypotension in 0.3% of patients (60).

Several reports have shown the efficacy of glutathione, vitamin E and N-acetylcysteine in treating SOS. Charcoal hemofiltration has been demonstrated to be effective in two adult patients by adsorbing circulating bilirubin and other toxins. Transjugular intrahepatic portosystemic shunts can also be used to decompress the portal circulation, but the results are conflicting. Liver transplantation has also been reported as a treatment option in some subgroups of patients with SOS (60).

Infectious complications

It is crucial to rule out infectious diarrhea, which may be due to bacterial and viral causes. Van Kraaij et al. (61) demonstrated the common causes of infectious gastroenteritis in 13 of 172 stool specimens including rotavirus, adenovirus, *Clostridium difficile, Salmonella,* echovirus, and *Cryptosporidium*. Pala et al. (62) detected the cause of diarrhea in 30.8% of patients. In that study, CMV, *Cryptosporidium, Salmonella, Giardia,* and *Clostridium difficile* were commonly observed pathogens. Management of infectious gastroenteritis is based on prompt diagnosis, effective treatment, and strict application of universal contact precautions.

Cytomegalovirus infection and disease remain the major causes of morbidity and mortality after allo-HSCT. The incidence of CMV organ disease ranges between 15% and 25%. The symptoms and signs of GI GvHD usually overlap with those of CMV gastroenteritis. Bhutani et al. (63) demonstrated in 252 patients that the recipients who had CMV IgG seropositivity and CMV viremia are associated with the development of CMV gastroenteritis. Imaging shows non-specific bowel wall thickening and inflammatory changes, especially in the ileocecal region. Preemptive use of ganciclovir guided by monitoring for CMV viremia is the standard of care.

Clostridium difficile infection (CDI) is a growing epidemiological problem in hospitalized patients. Chopra *et al.* found that CDI was 9-fold more prevalent than in general patients and 1.4-fold higher than cancer patients in HSCT settings. CDI generally occurs 3 to 33 days post-transplant. Several risk factors have been identified for CDI during HSCT, including allogeneic transplants, cord blood as a stem cell source, age greater than 60 years, diabetes, myeloablative conditioning regimens, *Clostridium difficile* colonization, colonization with vancomycin-resistant *Enterococci*, severe mucositis, broad spectrum antibiotics, and GvHD. Severe forms of disease and the prior use of linezolid were linked to death in 14 days of CDI onset in a study from Brazil (64). According to a 2010 update by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America guidelines, a dose of 500 mg metronidazole given orally 3 times per day for 10-14 days is the first drug of choice for an initial episode of CDI. In severe CDI, vancoymycin may be preferred at a dose of 125 mg orally 4 times per day for 10 to 14 days. In treating CDI, vancomycin-containing regimens had lower rates of recurrence compared to metronidazole monotherapy. Finally, Lee et al. (65) showed that three different bacterial taxa (Bacteriodes, Lachnospiraceae, and Ruminococcaceae) were protective and lowered the risk of CDI.

Fungal pathogens may cause severe mortality and morbidity after HSCT. In the early pre-engraftment phase, *Candida* spp. are detected more frequently, whereas late-phase GvHD and its treatment promotes fungal infections (4). *Candida* and *Aspergillus* species usually present with erosive infections of the GI tract, most frequently involving the esophagus. In severe cases, dissemination of fungal infections can result in microabscesses in the liver and can be detected as multiple small, scattered hypoattenuating nodules with CT. As a first-line therapy, voriconazole and amphotericin B are suggested in invasive candidiasis and aspergillosis. Posaconazole, caspofungin, or combination therapy might be considered in refractory patients (4).

In summary, early GI and liver complications of HSCT are still challenging issues. Despite improvements in this field during the last decade, treating these complications still places an important burden on both patients and the physicians treating these patients. GI complications remain some of the causes of mortality associated with HSCT. For practicing hematologists, oncologists, and gastroenterologists in this field, awareness and early diagnosis of the GI and liver complications remain important factors to obtain optimal outcomes in this patient population.

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