

How I treat acute graft-versus-host disease of the gastrointestinal tract and the liver

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Treatment of acute graft-versus-host disease (GVHD) has evolved from a one-size-fits-all approach to a more nuanced strategy based on predicted outcomes. Lower and time-limited doses of immune suppression for patients predicted to have

low-risk GVHD are safe and effective. In more severe GVHD, prolonged exposure to immunosuppressive therapies, failure to achieve tolerance, and inadequate clinical responses are the proximate causes of GVHD-related deaths. This article presents

acute GVHD-related scenarios representing, respectively, certainty of diagnosis, multiple causes of symptoms, jaundice, an initial therapy algorithm, secondary therapy, and defining futility of treatment. (*Blood* 2016;127(12):1544-1550)

Introduction

Acute GVHD is a still enigmatic, sometimes untreatable systemic disease of gastrointestinal mucosa, small bile ducts, hepatocytes, skin, lungs, and kidneys.¹ Even though GVHD is an iatrogenic illness, its pathogenesis is not completely understood, and deaths from GVHD are a continuing obstacle to successful transplantation.² Here, I summarize my approach to acute GVHD of the gut and liver (Table 1) through illustrative cases.

Case discussions

Patient 1

Patient 1, who was well engrafted and eating well at day 15 after a myeloablative allograft, developed anorexia, bilious vomiting, and loose stools at day 27. Antiemetic medications lessened the vomiting but not other symptoms; esophagogastroduodenoscopy at day 35 showed markedly edematous mucosa in the gastric antrum, with patchy erythema near the pylorus; sigmoidoscopy revealed normal-appearing mucosa. Fecal specimens and mucosal biopsies were negative for viruses; histology showed nonspecific inflammation in the pyloric gland area. No therapy was given; symptoms persisted.

Discussion: patient 1. Near certainty of GVHD diagnosis, a prerequisite for starting treatment that carries risk, can be achieved by combining a high pretest likelihood of GVHD with negative evidence of infection; consistent findings on physical examination, gut imaging, and endoscopic examination of gut mucosa; and typical histologic changes in intestinal crypts and small bile ducts.³ Histology alone, however, is not the gold standard for diagnosis because of sampling error, patchiness of GVHD-related abnormalities, and absence of early histologic abnormalities in both gut and liver GVHD.^{4,5} The appearance of gut mucosa, combined with gastrointestinal tract imaging, offers a global view of gut GVHD that can be more accurate in diagnosis than millimeter-sized biopsies.⁶ Mucosal histology is complementary to other findings, rather than contradictory.

In the 1970s, diarrhea and abdominal pain were the only recognized gut GVHD symptoms. By the 1990s, more than 80% of patients with satiety, anorexia, nausea, and vomiting after day 20, often in the absence of significant diarrhea, had biopsy-proven upper-gut GVHD.⁷ Patients with GVHD can soldier through meals, but they are seldom hungry and get little pleasure from eating. GVHD involving the small intestine and colon is termed lower-gut GVHD. Diarrhea >1 L/d is caused by failure of retrieval of luminal fluid by the ileum. Diarrheal volumes in GVHD are also increased by downregulation of brush-border disaccharidases (diarrhea after lactose/sucrose ingestion), failure of ileal bile salt resorption (bile-salt diarrhea), the motilin-agonist tacrolimus, and lack of colonic bacterial salvage of malabsorbed carbohydrate. GVHD diarrheal fluid has an elevated protein content, sometimes seen as precipitated ropy material. Gut protein loss often precedes symptoms, suggesting loss through mucosal tight junctions and not weeping of serum from ulcerated mucosa.^{8,9} A decrease in serum albumin ≥ 0.5 g/dL is a useful marker of impending lower-gut GVHD.¹⁰ The pain of lower-gut GVHD is caused by distention with luminal fluid and transmural edema, worsened by μ -agonist opioids and anticholinergic drugs, which cause pseudo-obstruction. Upper-gut GVHD without evidence of gut protein loss, jaundice, or higher-volume diarrhea has a significantly better prognosis than lower-gut GVHD.^{11,12}

Common mimics of upper-gut GVHD are listed in Table 2. I endoscope all patients who have persistent satiety/nausea/vomiting/anorexia after day 20, especially those with risk factors for CMV disease. Upper-gut GVHD seldom resolves spontaneously, and having a nauseated patient wait for treatment seems unnecessary. At our center, the distribution of gut stages 1, 2, 3, and 4 among 1554 recent patients was 84%, 7%, 6%, and 3%, respectively, with the majority of those with stage 1 gut GVHD having mostly upper-gut symptoms (Table 1) (G.B.M., unpublished observations). We also see upper-gut GVHD in $\sim 10\%$ of autologous graft recipients¹³; I tend to wait until after \sim day 25 for endoscopy, particularly among myeloma patients transplanted after high-dose melphalan, as their mucosal damage can take longer to resolve.

Table 1. Frequency of acute GVHD of the gut and liver among 2500 patients undergoing first allogeneic transplants

	Frequency	Percent
Overall: gut ± liver GVHD	1580/2500	63
Gut + liver GVHD	200/2500	8
Gut GVHD, no liver GVHD	1354/2500	54
Liver GVHD, no gut GVHD	26/2500	1
Skin GVHD present	22/2500	0.88
Skin GVHD absent*	4/2500	0.16
No gut or liver GVHD	920/2500	37

Patients undergoing first allogeneic transplants at the Fred Hutchinson Cancer Research Center and Seattle Cancer Care Alliance from July 1, 2003, through December 31, 2014 (G.B.M., unpublished observations).

*These 4 patients had acute GVHD of the liver but no gut or skin GVHD. Their severity of liver disease was stage 1 (peak total serum bilirubin 2-3 mg/dL) in 2 patients, stage 2 (>3-6 mg/dL) in 1 patient, and stage 4 (>15 mg/dL) in 1 patient.

The differential diagnosis of diarrhea-abdominal pain in an allograft recipient is narrow (Table 2).³ Biopsy is not necessary when the pretest probability of GVHD is high, skin GVHD is present, the risk of CMV infection is low, and a screening panel for gut infection is negative. I have the bias that patients destined to develop high- and very high-risk GVHD (Figure 1) should have endoscopic and histologic proof of GVHD, if not at onset then certainly at a time of failure of initial treatment.

Endoscopic biopsy and testing of fecal samples can eliminate infection as a cause of symptoms and can find changes of GVHD that carry prognostic information (Table 3).¹⁴⁻³² In upper-gut GVHD, edematous mucosa is often more impressive than histologic changes.⁴ More severe cases are characterized by erythema, friability, and erosions in the pyloric gland area, often accompanied by a pool of bile and retained food in the stomach. The duodenum may or may not have similar changes but, in severe cases, may be denuded of mucosa. I take 4 to 6 biopsies from areas of erythema, erosion, or ulcer plus 4 to 6 biopsies from the pyloric gland area irrespective of appearance, with biopsies also sent for viral culture. Biopsies lifted off the biopsy forceps are unrolled, flattened, and placed in fixative. Four-micron serial sections perpendicular to the plane of mucosa allow examination of 30 to 50 serial sections. At the base of crypts, GVHD histologic features include apoptotic epithelial cells, “missing” epithelial cells, crypt loss, and karyorrhexic debris (Table 3).^{4,33,34} The rate of false-negative histology in upper-gut GVHD is significant; what the endoscopist sees as mucosal edema, erythema, and friability is often invisible to

the pathologist. Although systems of grading of endoscopic appearance and histologic changes are available, only the most severe findings have much predictive value (Table 3).³⁵

For evaluation of diarrhea-abdominal pain, I start with upper endoscopy even in patients with diarrhea.³⁶ Unless there is florid gastroduodenal GVHD, I also biopsy the rectosigmoid mucosa, even if normal in appearance, without cleansing enemas or oral solution preparation. In some circumstances, the diagnostic yield is higher with cecal/ileal biopsies than with gastric/duodenal/rectosigmoid biopsies.³⁵ Ulcerated tissue cannot be read as GVHD, but in the absence of infection, GVHD is the most likely diagnosis, particularly when apoptotic crypt cells are seen in intact adjacent mucosa. Histology also has problems with false-positive results (residual conditioning therapy toxicity, infection, MMF, or brincidofovir toxicity). The advent of molecular testing for gut pathogens largely obviates the need for immunohistochemistry (IHC) of biopsy material.^{37,38} However, finding viral reaction product by IHC can resolve the question of asymptomatic viral excretion vs mucosal disease (CMV and adenovirus).

Imaging of the intestine with magnetic resonance enterography, computed tomography, positron emission tomography–computed tomography, or microbubble ultrasound can provide evidence of jejunal/ileal/colon pathology.³⁹⁻⁴¹ Microbubble ultrasound displays vascular pathology in addition to measurement of mucosal thickness.⁴¹ Viral infection (especially CMV) causes diffuse transmural intestinal edema indistinguishable from GVHD. When imaging finds cecal edema, the differential diagnosis includes *C. septicum* infection (typhlitis), CMV infection, and GVHD. Imaging may also discover pneumatosis intestinalis and pneumoperitoneum in patients with either GVHD or CMV disease. Capsule endoscopy can identify abnormal-appearing mucosa, but not its cause.

Summary: patient 1. Discordance between symptoms, endoscopic findings, and “negative” mucosal histology for GVHD is common. When the burden of evidence favors a diagnosis of GVHD, treatment should be started.

Patient 2

Patient 2 developed nausea, vomiting, abdominal pain, and diarrhea at day 44 after an allograft from an HLA-matched sibling. Peak diarrheal volume was 1635 mL/d; stool studies were positive for *C. difficile* but negative for other pathogens. Endoscopy showed antral, duodenal, and rectosigmoid mucosal edema and erythema, with histologic evidence of

Table 2. Mimics of gastrointestinal and hepatic GVHD

Upper-gut GVHD	Lower-gut GVHD	Hepatic GVHD		
		Early jaundice	Cholestatic	Hepatitis
Nauseating medications	Residual effects of conditioning therapy (<day 20)	Cholangitis lenta (infection-related jaundice from IL-6, TNF-α)	Cholangitis lenta (infection-related jaundice from IL-6, TNF-α)	Hepatitis virus infection (HBV, HCV)
Residual effects of conditioning therapy (<day 20)	Viral infection (CMV > adenovirus > astrovirus, norovirus, rotavirus)	Drug-induced liver injury (DILI; http://www.dilin.org/)	Biliary obstruction (sludge, stones, tumor)	Other viral infections (adenovirus > herpesviruses)
Herpesvirus infections	Bacterial infection (<i>Clostridium difficile</i> > <i>Clostridium septicum</i>)	Residual effects of SOS	DILI	DILI
<i>Helicobacter pylori</i> infection with ulcers	Parasitic infection (<i>Giardia lamblia</i> , cryptosporidia)			Hypoxic hepatitis (SOS, respiratory failure, shock)
Increased intracranial pressure	Medication effects (Mg ⁺⁺ , MMF, brincidofovir, anticholinergics, μ-agonist opioids)			
Phlegmonous gastritis				

These disorders may also coexist with GVHD.

CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; IL-6, interleukin 6; MMF, mycophenolate mofetil; SOS, sinusoidal obstruction syndrome; TNF-α, tumor necrosis factor α.

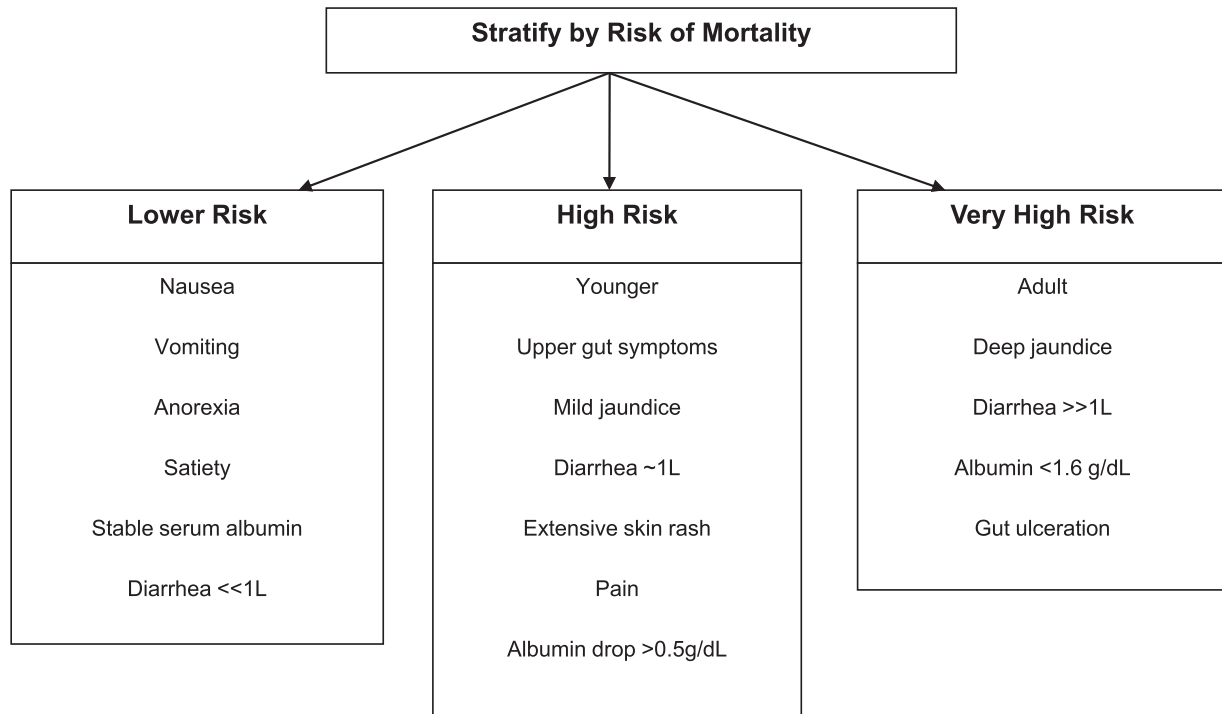


Figure 1. Triage of patients for initial treatment of acute GVHD, based on risk of GVHD-related mortality.

apoptotic crypt cells in all areas along with a neutrophilic infiltrate in the colon. Diarrhea persisted despite oral vancomycin therapy.

Discussion: patient 2. This patient illustrates difficulties that arise when Occam's razor is disposable (>1 cause of symptoms is documented). For upper-gut GVHD, ulcers caused by herpesvirus, *H. pylori*, and NSAID can confound a GVHD diagnosis. IHC for viral antigens can determine when infection plus GVHD is present rather than GVHD alone.⁴² The nauseating effect of medicines, along with lingering pathology caused by high-dose conditioning regimens, can also confound a GVHD diagnosis. In patients with diarrhea and pain, the most common combination-disease dilemmas involve GVHD plus residual conditioning therapy, or gut infection, or gut toxicity from MMF. Some clinical pearls are useful: the gut is reepithelialized by ~day 16 after high-dose myeloablative therapy, *C. difficile*-related diarrhea never exceeds 1 L/d, and there are histologic features favoring MMF toxicity.³⁴ When MMF toxicity is suspected, switching to less-toxic enteric-coated mycophenolic acid or another immune suppressive drug can be helpful.⁴³

Summary: patient 2. Diarrheal volumes >1 L plus histologic changes typical of GVHD in multiple sites indicate that GVHD is the dominant disease process. Withholding treatment of GVHD may lead to extensive mucosal necrosis.

Patient 3

Patient 3 developed fever, tachycardia, hypotension, diarrhea, abdominal pain, nausea, and vomiting at day 29. Endoscopy and mucosal histology were typical of GVHD, treated with prednisone 2 mg/kg per day. Blood cultures were positive for a gram-negative organism. Total serum bilirubin peaked at 3.4 mg/dL on day 36; liver histology showed cholestasis and normal-appearing small bile ducts. Bilirubin returned to normal by day 52.

Discussion: patient 3. Prophylaxis with ursodiol has greatly decreased the frequency of jaundice after transplant and altered the

clinical presentation of GVHD (Table 1).^{2,44} Hepatic GVHD is a mélange of 3 processes: (1) Jaundice occurring early in GVHD is related to the effect of cytokines (IL-6, TNF- α) on hepatocyte bilirubin transporters, with normal-appearing small bile ducts.^{5,45} (2) Injury to small bile ducts occurs with increases in serum bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase, usually in patients with gastrointestinal GVHD (biopsies show lymphocytic infiltration of small bile ducts with nuclear pleomorphism, epithelial cell dropout, and cholestasis in zone 3 of the liver acinus, culminating in ductopenia in severe cases).^{5,46} (3) Acute hepatitis with marked elevation of serum alanine aminotransferase, usually after day 100, is most commonly seen in allograft recipients on minimal immunosuppression or after donor lymphocyte infusion.^{47,48} The level of hyperbilirubinemia in GVHD is affected by increased loads of unconjugated bilirubin presented for conjugation (hemolysis, red blood cell transfusions) and by renal insufficiency (decreased bilirubin clearance). Liver biopsy is not useful for diagnosis of IL-6-caused cholestasis but may be essential when there are competing or simultaneous causes of liver injury (SOS or viral hepatitis or DILI).⁴⁶ In a patient with skin and gut GVHD who is not at risk for viral infection or DILI but who develops cholestatic liver injury, a clinical diagnosis can suffice. Rare cases of acute liver GVHD in the absence of skin and gut GVHD (see Table 1) must be distinguished from DILI, cholangitis lenta, and biliary obstruction. Isolated liver GVHD is more of a problem in long-term transplant survivors, as a rare cause of cirrhosis. Persistent jaundice is an independent predictor of GVHD-related mortality.^{14,19} Although anecdotal evidence suggests that some immune suppressive regimens for treatment of liver GVHD result in resolution more frequently than other regimens (pulse cyclophosphamide or extracorporeal photopheresis (ECP) or switching from one calcineurin inhibitor to another or sirolimus or oral budesonide), data from controlled trials are lacking. As with GVHD-caused gut ulceration, there appears to be a defect in epithelial regeneration of small bile ducts.

Table 3. Variables at or before the symptomatic onset of gastrointestinal GVHD that are more common in patients whose GVHD will run a more severe course

Variable	Comments
Unrelated donor (HLA mismatched > matched)	Less likely to respond to initial therapy than patients with related or cord blood donors ¹²
Diarrheal volume	Greater volume correlates with refractoriness to initial treatment with prednisone. ^{6,12}
Total serum bilirubin	Worse outcome with total serum bilirubin increase from 1 to 3 mg/dL or when jaundice is present at GVHD onset ^{12,14-17}
Serum albumin change	Abrupt fall of serum albumin ≥ 0.5 g/dL before onset of symptoms predicts grade 3 to 4 GVHD in patients who received reduced-intensity conditioning. ¹⁰
Fecal α -1 antitrypsin	Measures a luminal protein that cannot be digested by proteolytic enzymes; reflects gut protein loss ^{8,9}
Fecal calprotectin	Calcium-binding protein in neutrophils; reflects neutrophilic mucosal inflammation in inflammatory bowel disease and gut GVHD ⁹
Skin changes	More extensive skin GVHD is a predictor of severity and need for higher doses of prednisone. ^{12,18}
Endoscopic findings	Ulceration and sloughing of mucosa ^{6,19}
Mucosal histologic findings	Infiltrating neutrophils ¹⁶ Increased apoptotic cells ¹⁶ Increased eosinophils ²⁰ Low Paneth cell numbers ²¹ Crypt loss ²² Ulceration ⁶ Pericapillary hemorrhage ²³
Serum biomarkers	Increased levels with more severe GVHD: TIM3, sTNFR1, ST2, IL-6, Reg3 α ²⁴⁻²⁹
Endothelial markers	Loss of thrombomodulin expression in gut mucosal biopsies ³⁰ Increased blood levels of angiotensin-2 ³¹ Changes in circulating angiogenic factors ³²

Summary: patient 3. The mechanisms for jaundice in association with the onset of more severe GVHD are similar to those of cholangitis lenta (jaundice following infection), the effect of cytokines on hepatocyte transporters of conjugated bilirubin.

Patient 4

Patient 4, at day 57 after a reduced intensity regimen and unrelated donor graft, developed anorexia, nausea, diarrheal volumes >1600 mL/d, and a rash involving >50% of skin. Laboratory studies showed total serum bilirubin, 1.8 mg/dL; alanine aminotransferase, 212 U/L; and albumin, 2.1 g/dL. Endoscopy revealed diffuse mucosal edema in the stomach, duodenum, and rectosigmoid, with apoptotic crypt cells in all areas; stool samples and centrifugation cultures of mucosal biopsies were negative for infection.

Discussion: patient 4. A more nuanced approach to initial treatment than prednisone 2 mg/kg per day is now widely used, as not all GVHD presentations progress in the same way or have the same outcome. Some clinical, laboratory, endoscopic, histologic, and serum markers presage more severe GVHD and an increased mortality risk, and, *pari passu*, less severe GVHD with lower mortality risk (Table 3). The treatment principle is “to each according to his need.” GVHD staging/grading systems based on peak severity are inferior to an area under the curve of disease activity (AUC_{GVHD}), which is highly correlated with nonrelapse mortality.¹⁴ There is promise that plasma

biomarkers can add to prediction accuracy when compared with organ staging and other prognostic markers (Table 3); whether therapy dictated by biomarker data leads to better outcomes is an unanswered question that will be studied in the Blood and Marrow Transplant Clinical Trials Network Protocol 1202.²⁴⁻²⁷ I believe that it is possible to clearly identify patients at the extremes of outcome (ie, the readily treatable and those likely to be treatment refractory) (Figure 1). In between are those who require more than a minimalist approach to initial therapy.

For lower-risk GVHD, 2 minimalist approaches have been studied in randomized trials. Oral topical glucocorticoid (beclomethasone dipropionate [BDP], 8 mg/d) plus a 10-day course of prednisone 1 mg/kg per day was compared with placebo plus prednisone, and patients were followed for a total of 50 days.¹¹ At the 50-day end point, complete responses were seen in 69% and 52%, respectively. Note that just a 10-day prednisone dosing period was effective in half of patients in the placebo arm. A second approach compared a starting prednisone dose of 0.5 mg/kg per day with 1 mg/kg per day in patients with lower-risk GVHD, with a treatment period of 42 days, including time for prednisone taper.¹⁸ Treatment success (no secondary therapy required) was equivalent (88% vs 92%, respectively), progression to grade 3 to 4 GVHD was similar (10% vs 6%, respectively), and survival was not compromised by starting at the lower prednisone dose. There are other therapies with even less prednisone exposure that might be considered when there are contraindications to glucocorticoids (steroid psychosis or mold infection): optimization of calcineurin inhibitor dosing with intravenous formulations, use of sirolimus alone, or topical glucocorticoid therapy alone.⁴⁹ Oral BDP 8 mg/d for 28 days as the sole initial therapy resulted in complete responses in 77% of patients with lower-risk GVHD, but responses sometimes took 1 to 3 weeks to be achieved.⁴⁹ In these trials, BDP was given as gastric-release and enteric-coated pills; the equivalent adult dosage can be achieved with compounded BDP emulsion at 1 mg 4 times per day plus enteric-coated budesonide at 3 mg twice daily; pediatric doses are lower. Some topically active glucocorticoid reaches the systemic circulation as 17-beclomethasone monopropionate and budesonide, respectively; over time, adrenal insufficiency has been noted.

For high-risk GVHD, I would start prednisone 2 mg/kg per day (or the equivalent dose of intravenous methylprednisolone when vomiting and malabsorption are present) and watch carefully for signs of progression and failure of treatment in the weeks that follow. A controlled trial of prednisone plus MMF as initial treatment of GVHD did not show a benefit from MMF compared with prednisone alone.⁵⁰ A randomized Blood and Marrow Transplant Clinical Trials Network protocol will compare prednisone vs sirolimus as initial treatment. Data supporting the use of prednisone plus a second immune suppressive drug for initial treatment are lacking. Waiting for 28 days to see a clinically meaningful response risks debility and infection, and the longer a patient remains on prednisone, anorectic, jaundiced, and bed ridden, the greater the risk of death.¹⁴ Most gut GVHD treatment failures are apparent within 14 days.¹⁹ Patients in the Figure 1 high-risk classification would also be termed “high-risk GVHD” using a refined risk score studied in a large multinational cohort.¹² This refined risk score uses standard GVHD organ staging categories, with “high-risk GVHD” differentiated from “standard-risk GVHD” by number of organs involved and severity of symptoms. Failure to achieve a complete response to prednisone therapy after initial therapy for 28 days was seen in 73% and 52% of patients with “high-risk GVHD” and “standard-risk GVHD,” respectively.¹² These data suggest to me that a substantial number of patients classified as “standard-risk GVHD” had their risk treatment failure at 28 days underestimated, and buried in the classification “high-risk GVHD” are patients who

are incurable by any means. My bias is that when one layers detailed information about gut and liver injury (Table 3) over descriptive organ staging, greater precision in predicting outcomes can be achieved.

In my opinion, “gut rest” can lead to less diarrhea, but gut recovery will surely be delayed when the mucosa is deprived of luminal nutrients (polyamines and short-chain fatty acids), luminal stimuli for epithelial growth factors, and prebiotics to support the microbiome. Ingestion of polymeric food to stimulate epithelial regeneration requires minimal caloric content; parenteral nutrition may be needed to prevent negative nitrogen balance. The μ -agonist opioids have a modest effect on diarrheal volumes <500 mL/d but can result in pseudo-obstruction (“ileus”) as can anticholinergic drugs. A dose-escalation trial of octreotide in GVHD patients with diarrheal volumes >1 L/d found no dose that was effective (G.B.M., unpublished observations). How long to continue prednisone once a complete response has been noted is an unanswered question. Prednisone taper schedules designed to allow recovery of the hypothalamic-pituitary-adrenal axis serve the dual purpose of damping alloimmune damage until tolerance is achieved. However, continued prednisone treatment, even at lower doses, is a significant risk factor for mortality in patients with GVHD¹⁴; my bias is that more rapid tapering of prednisone to glucocorticoid/mineralocorticoid replacement doses is preferable to prolonged exposures in patients who respond to initial therapy with improved appetite and decreases in diarrheal volume and serum bilirubin. If flares of GVHD occur during taper, they can be treated appropriately.

For very high-risk GVHD with markers of death from GVHD at diagnosis. I know of no proven initial treatment. Few if any controlled trials of aggressive GVHD therapy stratify these patients in treatment assignments. The majority will either progress despite therapy or require continuous therapy to control symptoms before dying of infection or multiorgan failure. Controlled data are lacking on the use of desperation remedies (prednisone plus anti-T-cell therapies, anticytokines, intra-arterial glucocorticoid, ECP, lithium salts, and second allografts) for very high-risk GVHD. I recommend as initial therapy prednisone 2 mg/kg per day plus antithymocyte globulin (ATG) but admit that outcomes have been poor in almost all cases. There may be no effective treatment of extensively denuded gut mucosa and deep jaundice of GVHD.

I do not consider flares of GVHD symptoms during tapering doses or after discontinuation of immune suppressive therapy to represent treatment failure or refractory GVHD, particularly when relatively low initial doses of prednisone were given. However, repeated flares of GVHD symptoms, each requiring a return to higher-dose immune suppression, lead to a large AUC_{GVHD}, even if peak severity is not very high.¹⁴ In some patients, each flare is less intense than those preceding, and eventually tolerance is achieved.

Upon relapse of leukemia, immune suppressive medications are often discontinued and donor lymphocytes infused to achieve a graft-versus-leukemia effect. Severe GVHD that develops after donor lymphocyte infusions can lead to rapidly progressive mucosal and hepatocellular necrosis, jaundice, and multiorgan failure. There are no good therapy choices in this circumstance; both severe GVHD and relapse will lead to death.

Summary: patient 4. This case describes high-risk gut GVHD (see Table 3) whose treatment should start with prednisone 2 mg/kg per day, with close monitoring for signs of impending treatment failure in the ensuing 5 to 15 days.

Patient 4: failure of initial treatment

Patient 4 then develops melena with drop in hematocrit after 6 days of prednisone therapy, along with rise of serum bilirubin to 3.1 mg/dL and further fall in serum albumin. Magnetic resonance enterography

shows diffuse mucosal edema involving the jejunum, ileum, and right colon.

Discussion: patient 4. How soon can failure of initial treatment be declared and by what means? One prospective trial declared treatment failure after 5 days of prednisone 2 mg/kg per day; mortality among early treatment failures was 49% compared with 27% among early responders.⁵¹ Other studies have designated a 28-day treatment period to determine responses, but failure of response is often obvious long before 28 days of therapy.¹⁹ Our analysis of 116 consecutive patients with more severe gut GVHD (stage 3–4) identified 4 variables during the first 14 days of initial therapy that predicted mortality: adult age, failure of initial doses of prednisone to control symptoms, jaundice, and gastrointestinal bleeding.¹⁹ Continuing prednisone therapy alone in the face of these variables, hoping for a response, often leads to disabled, bed-bound patients at the 28-day time point.

The best responses to secondary therapy are in patients whose initial therapy was with lower initial doses of prednisone.¹⁸ These patients often respond to higher-dose prednisone, and do not suffer higher mortality rates.¹⁸ There are 4 categories of therapy that are in wide use for prednisone-refractory GVHD, but none achieves $>30\%$ to 50% sustained responses or $>20\%$ survival: anti-T-cell antibodies (ATG, alemtuzumab); additional T-cell suppressive drugs (MMF, mycophenolic acid, or sirolimus); anticytokine biological agents (TNF- α , IL-6); and a variety of other therapies (pulse cyclophosphamide, ECP, psoralen plus ultraviolet light therapy, Janus kinase inhibitors, autologous transplants, allogeneic transplants from different donors).^{1,52-54} When treatment failures after 5 days of prednisone 2 mg/kg per day were randomized to secondary treatment with prednisone 5 mg/kg per day with or without ATG, outcomes were similar (33% vs 24% complete responses, respectively).⁵¹ Any secondary therapy has to be accompanied by drastic reductions in prednisone exposure, as mounting losses of lean body mass and bone density are themselves major contributors to death independent of infection risk.

Summary: patient 4. The failure of initial prednisone doses to control gut symptoms, along with development of jaundice and bleeding, is a harbinger of GVHD-related death that can be recognized within days to weeks. The more difficult decisions are in patients who reach day 28 of therapy still requiring prednisone 1 to 2 mg/kg per day to control symptoms, leading to a large AUC_{GVHD} and a high mortality risk.

Patient 5

Patient 5 developed acute gut GVHD on day 52 following a reduced-intensity regimen and allograft, characterized by nausea, anorexia, peak diarrhea volumes of 750 mL/d, and peak total serum bilirubin of 3.6 mg/dL. Although symptoms improved on prednisone 2 mg/kg per day, several attempts at reducing prednisone doses were greeted by recurrent symptoms, leading to treatment with ATG on day 110. Despite the resulting leukopenia, diarrhea and anorexia persisted, and endoscopy revealed persistent ulceration in the duodenum and colon. At day 180, symptoms were little improved, and performance score was declining steadily.

Discussion: patient 5. A paradox of current transplant care is that advances in viral and fungal control have created a situation where patients with treatment-refractory GVHD now suffer longer, lingering deaths. In the past, patients on high-dose immunosuppression for persistent GVHD often died of infection within weeks. Defining with certainty the futility of further therapy is impossible, but knowing that there were no survivors among adult patients with severe gut GVHD who were unresponsive to prednisone, jaundiced, with gastrointestinal bleeding leads to end-of-life discussions and hospice care.¹⁹ It is more difficult to gauge the outcome of patients with less severe GVHD that

requires never-ending therapy. I find that calculation of the Acute GVHD Activity Index at points in time to day 100 can provide an estimate of nonrelapse mortality, useful in counseling individual patients.¹⁴

Summary: patient 5. This patient's course illustrates 2 points: first, that peak diarrheal volumes and level of jaundice (GVHD stages) are not as useful in prognosis as persistent need for immune suppression, and second, the difficulty in defining futility of GVHD treatment.

Conclusions

A GVHD treatment strategy based on predicted outcomes encompasses minimalist immune suppression for low-risk GVHD and higher doses for more severe GVHD. The pathophysiology of gut and liver GVHD is plagued by unknowns: the target antigens in epithelial crypt cells and small bile ducts, the mechanisms by which GVHD damages endothelium and opens the zonula occludens in gut mucosa, and the reasons why epithelial hyperplasia fails to repair denuded mucosa and damaged bile ducts. If severe gut and bile duct damage from GVHD is incurable, the focus must be on prevention based on a deeper understanding of pathobiology and explanations for the unexpected appearance of severe GVHD in patients not currently thought to be at risk.⁵⁵ A preemptive treatment approach, based on falling serum albumin and plasma biomarkers before clinical symptoms, deserves study. However, my skeptical self thinks

that biological determinism will trump preemptive therapy. Gastrointestinal and hepatobiliary problems in long-term survivors are beyond the scope of this article, but I have reviewed them recently.^{3,56,57}

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Authorship

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