

## GI complications in pediatric patients post-BMT

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### Summary:

**This retrospective study comprehensively examined hepatic and gastrointestinal complications post-bone marrow transplant (BMT) in a heterogeneous group of 132 pediatric patients that underwent 142 transplants. Hyperbilirubinemia occurred in 28% of this population with clinically evident jaundice in 16%. Acute graft-versus-host disease (GVHD) occurred in 46% of the population, with liver involvement in 39% and intestinal involvement in 60% of those with acute GVHD. Venooclusive disease (VOD) occurred in 18% of the population. A greater increase in hepatic transaminases was noted in GVHD and VOD than nonspecific liver injury. Serum bilirubin may help to differentiate between VOD and hepatic GVHD. Biliary sludging occurred in 20% of patients and was associated with increased morbidity. Common post transplant gastrointestinal complications included mucositis in 90%, vomiting in 85% and abdominal pain in 71%. TPN support post transplant was required in 91%. Diarrhea occurred in 67% with the most common identified etiologies reported as GVHD (27%), viral (6%), *Clostridium difficile* (8%) infections and unknown (28%). Typhilitis developed in 3.5%. Melena or hematochezia occurred in 11 patients (8%). However, gastrointestinal bleeding was disproportionately represented in intensive care unit admissions (5/27) and 100 day mortality (5/21). Gastrointestinal and hepatic complications represent a major cause of morbidity and mortality in pediatric BMT recipients.**

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Over the past decade, bone marrow transplantation (BMT) has gained greater acceptance for an increased number of indications. As a result, the number and variety of patients who have received or are eligible for this intervention has

grown. In order to improve care for these complicated patients, a greater recognition of the variety, severity and extent of complications that occur post-BMT requires documentation. The majority of the published data regarding these complications comes from adult studies.<sup>1–18</sup>

A paucity of information exists in the published literature regarding the incidence, range and severity of gastrointestinal (GI) complications in pediatric patients in the immediate post-BMT period.<sup>19,20</sup> The majority of the pediatric studies examined specific complications such as veno-occlusive disease (VOD), acute pancreatitis or typhilitis in fairly homogeneous patient populations.<sup>21–35</sup> The frequency of the many GI complications in this patient population have been recognized clinically but not specifically reported.

This study is the first to attempt to document the variety and incidence of hepatic, biliary, pancreatic and luminal gastrointestinal complications among pediatric bone marrow transplant recipients in the immediate post transplant period, 100 days post transplant. The specific complications, VOD and typhilitis, in this population were previously reported by our group.<sup>33,34</sup>

### Materials and methods

A retrospective health record review was completed on a historical cohort of 142 pediatric bone marrow transplants in 132 separate patients transplanted for both malignant and nonmalignant etiologies. The study population consisted of consecutive pediatric hematopoietic stem cell recipients from January 1993 to June 2000. Patients' charts were reviewed for descriptive and laboratory data related to possible hepatic, biliary, pancreatic and upper and lower gastrointestinal complications in the first 100 following transplant.

### Patient demographics and BMT details

The gender distribution was 78 male (54%) and 64 female (46%) subjects. The average age was  $8.6 \pm 5.0$  years. Ethnic distribution was 127 Caucasians, six East Indians, four South East Asians, four Native/Aboriginals and one of African descent. A total of 18 patients had a transplant for a nonmalignancy reason of which three were metabolic diseases and 15 were for hematologic diseases (nine aplastic anemia, five thalassemia and one with Kostmann syn-

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drome). Of the malignant causes, 83 were for hematologic malignancies. The three most common etiologies were ALL with variants ( $n = 46$ ), AML ( $n = 27$ ), CML ( $n = 5$ ) and five others (lymphohistiocytosis, JMML and NK cell leukemia). Solid tumors comprised 33 patients of which 16 were neuroblastomas, five were Hogkins' lymphoma, four were rhabdomyosarcoma, three Ewing's sarcoma, two Wilm's tumor, two histiocytosis and a germ cell tumor made up the remainder. CNS tumors accounted for eight patients, four of which were medulloblastomas and one each of glioblastoma, spinal astrocytoma, ependymoma and brain stem glioma.

The different modalities of BMT were autologous ( $n = 42$ ) and allogenic ( $n = 100$ ). The allogenic were divided into matched unrelated donor (MUD) ( $n = 37$ ), parental ( $n = 19$ ) and sibling ( $n = 44$ ). Patients that received TBI were all allogeneic grafts except one ( $n = 74$ ). Malignancy accounted for 68 of the 74 patients that received TBI. Leukocyte depletion or other manipulations of the donor cells was not performed.

Disease status at the time of transplant consisted of stable disease in 23 patients with hematological disease, one was experiencing progressive disease without previous remission, two others were in relapse (AML), 12 were in partial remission and 104 were considered in remission. Of note is that 14 patients previously had a BMT, four of which were at other sites prior to the study dates.

The conditioning regimens were very diverse considering the large number of different protocols used for this heterogeneous population over the 8-year data collection period. The most common induction medications used were cyclophosphamide in 63%, TBI in 52%, VP-16 in 43%, busulfan in 18%, thiotepa in 16%, carboplatin in 11% and fludarabine in 6%.

Acute graft-versus-host disease (GVHD) prophylaxis consisted of CSA in 33, MTX plus CSA in 57, MTX only in three and no GVHD prophylaxis in 49, of which 42 were autologous transplants. No prophylactic regimen was consistently given for VOD. However, four patients did receive heparin and 10 received ursodeoxycholic acid for VOD prophylaxis.

Screening for potentially hepatotoxic viruses was performed by serum antigen testing for Hepatitis B and antibody testing for Hepatitis A, B, C, HSV, VZV, CMV and EBV. Viral diarrhea was diagnosed via fecal viral culture, colonic tissue culture or latex agglutination for rotavirus. Infectious diarrhea was investigated through culture and sensitivity testing, inspection for ova and parasites, tests for *Clostridium difficile* toxin A and B, viral cultures and rotazyme tests.

VOD was diagnosed using the Seattle criteria<sup>36</sup> and GVHD was diagnosed by the international BMT criteria<sup>37,38</sup> and engraftment was considered present if the absolute neutrophil count was greater than  $500 \times 10^6/l$  for three consecutive days. Only three percutaneous liver biopsies were taken under general anesthesia for diagnostic purposes due to the high-risk nature of the procedure in this population. Tests for infectious hepatitis included serology for hepatitis A, B, C, cytomegalovirus and Epstein-Barr virus (EBV). Problematic constipation was

defined as constipation requiring laxative therapy by the attending oncologist.

#### *Inclusion/exclusion criteria*

All consecutive patients transplanted through the Alberta Children's Hospital Bone Marrow Transplant Program between January 1993 and June 2000 were included in the study. All patients were followed out to 100 days post transplant. Exclusion criteria consisted of death prior to receiving the hematopoietic stem cell transplant. No patient recorded was excluded from the study. The University of Calgary Conjoint Ethics Committee approved the study.

#### *Statistical analysis*

Descriptive analyses of the patient population characteristics used summary measures including means, medians, ranges and standard deviations. The incidences, characteristics and associations of the various complications were described and comparisons were made applying Fisher's exact test and logistic regression. Students *T*-test, Mann-Whitney *U*-test and Kruskal-Wallis tests were performed for comparison of group means with a *P*-value  $< 0.05$  as the level of a significant difference. Kaplan-Meier survival curves and hazard ratios were utilized to assess risk of death post transplantation. Stata 6.0<sup>®</sup> software was used for statistical analysis.

## **Results**

### *Hepatic complications*

Hyperbilirubinemia, diagnosed with a total serum bilirubin level of  $\geq 34 \mu\text{mol/l}$ , (1.5 times the upper limit of normal), was found in 39/142 (27.5%) of the patients. Clinically diagnosed jaundice occurred in 23/142 (16.2%) of the patients. Concomitant to this, the total bilirubin level was  $> 50 \mu\text{mol/l}$  in all cases. Identifiable causes of jaundice, in various combinations, included VOD in 15, acute GVHD in seven and biliary sludging in 12 patients. No identifiable cause was identified for five patients.

The presence of hepatocellular injury was defined as serum transaminase laboratory values, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), greater than 1.5 times the upper limit of normal with no evidence of nonhepatic causes for enzyme elevation. The highest serum laboratory value post transplant was recorded and used for analysis in all patients. A total of 15 patients displayed no evidence of hepatocellular or hepatobiliary injury as evidenced by normal values reported for AST, ALT,  $\gamma$ -glutamyl transferase (GGT), bilirubin and alkaline phosphatase (A.P.).

Three major types of hepatic complications were observed. They include VOD, acute GVHD and 'other' types of hepatocellular injury (see Table 1). The 'other' category was presumed to be medication-related raised transaminases as no episodes of infectious hepatitis (either as newly acquired infections or reactivation of dormant infections) were documented and no other causes of

**Table 1** Gastrointestinal complications and number of deaths within 100 days post transplantation listed by type of transplant received

Complication	Autologous (n = 42)	Parental (n = 19)	Sibling (n = 44)	MUD (n = 37)	Total/142 (%)
<i>Hepatic</i>					
'Other' – raised transaminases	33	13	24	22	92 (65)
GVHD – total	0	14	23	28	65 (46)
GVHD – skin	0	14	17	28	59 (42)
GVHD – liver	0	5	11	9	25 (18)
GVHD – intestine	0	11	13	15	39 (28)
VOD <sup>a</sup>	3	5	8	10	26 (18)
<i>Biliary</i>					
Biliary sludge	8	4	6	10	28 (20)
Jaundice	2	6	4	11	23 (16)
Hyperbilirubinemia	4	8	11	16	39 (28)
Acalculi cholecystitis	0	0	0	1	1 (1)
<i>Pancreatic</i>					
Pancreatitis	2	1	1	3	7 (5)
<i>Upper gastrointestinal tract</i>					
Mucositis	38	15	39	36	128 (90)
Vomiting	38	16	34	33	121 (85)
Odynophagia	12	5	5	6	28 (20)
Abdominal pain	30	11	31	29	101 (71)
<i>Lower gastrointestinal tract</i>					
Typhilitis <sup>a</sup>	2	0	1	2	5 (4)
<i>C. difficile</i> diarrhea	3	3	3	3	12 (9)
Viral diarrhea	2	4	2	2	10 (7)
Other diarrhea	21	3	8	8	40 (28)
Melena or hematochezia	0	3	3	5	11 (8)
Constipation	8	3	5	4	20 (14)
No diarrhea	16	4	18	9	47 (33)
<i>Death within 100 days</i>	4	7	3	7	21 (15)

Acute graft-versus-host disease (GVHD) of the liver, skin and intestine are reported as totals documented. GVHD and diarrhea presented clinically in combinations and so are counted more than once in this table (matched unrelated donor = MUD).

<sup>a</sup>Note: VOD and typhilitis were previously reported.<sup>32,33</sup>

hepatocellular injury were identified. Of note, 15 patients had only a raised GGT with no other abnormalities in their hepatic blood work. A greater increase in ALT and AST values was noted for both hepatic GVHD and VOD-positive patients compared to transplants in the 'other' category. No significant difference in transaminase values was found between the hepatic GVHD and VOD groups (see Table 2). Similar comparisons were made with serum bilirubin, GGT and alkaline phosphatase. Significant differences ( $P < 0.05$ ) were found between both the hepatic GVHD and VOD-positive groups and the 'other' diagnosis group for ALT, AST, serum bilirubin and GGT. AP was significantly different only between the VOD and the 'other' group. As demonstrated in Table 2 and Figure 1, mean serum bilirubin was the only laboratory value to show a significant difference between the hepatic GVHD group ( $49.1 \pm 31.1$ ) and the VOD diagnosed group ( $223.0 \pm 226.4$ ,  $P < 0.05$ ).

VOD has been previously reported in depth in this patient cohort.<sup>34</sup> As defined by the Seattle criteria,<sup>36</sup> VOD occurred in 26/142 (18.3%) of the patients. (see Table 1). There was a related mortality of 10/26 (38.5%) of which 3/26 died (11.5%) directly attributable to VOD, four to infection, one to relapse, one to chemotherapy toxicity and one to multiorgan failure. Non-VOD-related mortality

**Table 2** Means and standard deviations of the highest hepatic laboratory values recorded post transplantation for the transplants that developed hepatic graft-versus-host disease (GVHD), veno-occlusive disease (VOD) and 'other' (hepatic dysfunction without GVHD or VOD complications)

Variable	'Other' hepatic dysfunction (n = 90)	Hepatic GVHD (n = 24)	Hepatic VOD (n = 13)
ALT (IU/l)	122 ± 149	430 ± 987 <sup>a</sup>	726 ± 1061 <sup>a</sup>
AST (IU/l)	125 ± 171	311 ± 962 <sup>a</sup>	1481 ± 2572 <sup>a</sup>
GGT (IU/l)	166 ± 205	255 ± 140 <sup>a</sup>	572 ± 1147 <sup>a</sup>
Alkaline phosphatase (IU/l)	190 ± 122	202 ± 120	286 ± 290 <sup>a</sup>
Bilirubin (μmol/l)	22 ± 23	49 ± 31 <sup>a</sup>	223 ± 226 <sup>a,b</sup>

The 15 transplants that did not develop any hepatic dysfunction are not recorded in this table.

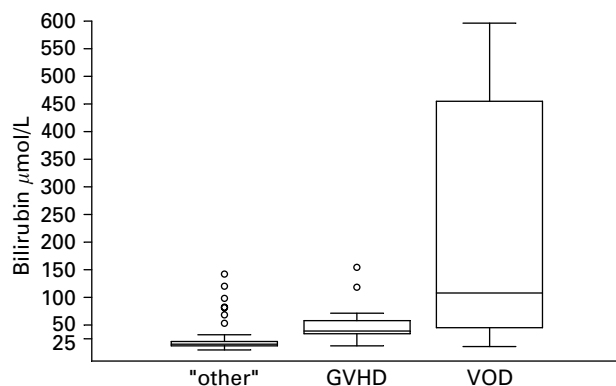
<sup>a</sup>A comparison of means between the groups found a significant difference between the 'other' group and the hepatic GVHD or the VOD group ( $P < 0.05$ ).

<sup>b</sup>A significant difference was found between the hepatic GVHD group and VOD group ( $P < 0.05$ ).

(11 patients) was due to relapse in four, infection in two, GVHD in one, chemotherapy toxicity in one, post transplant lymphoproliferative disease (PTLD) in one, multiorgan failure in one and one unknown due to loss of

follow-up. None of the four patients that received heparin prophylaxis developed VOD, but two of the 10 patients that had ursodeoxycholic acid before and during transplant did. No remarks or documentation were noted regarding the severity of VOD besides the three deaths, and no transplants had long-term sequelae from VOD at 100-day follow-up. Risk of death among those 26 diagnosed with VOD was increased 4.9 times compared to the total transplant population.<sup>34</sup> Interestingly, 13 VOD-positive patients were also diagnosed with a separate episode of hepatic GVHD occurring at least 1 week after the diagnosis of VOD. One of the three transplant patients that died of VOD complications also had GVHD.

Acute GVHD presented in 65/142 (45.8%) of the patients. This affected one or more organs, which included the liver, intestines and skin. Liver involvement occurred in 25/65 (38.5%) of these patients or 25/142 (17.6%) of the total transplant population. Manifestations of acute GVHD included raised hepatocellular transaminases, hyperbilirubinemia or both in the setting of engraftment post transplantation. Intestinal involvement (diagnosed as profuse watery diarrhea) presented in 39/65 (60.0%) of the patients that developed GVHD or 39/142 (27.5%) of the population. Investigations revealed no infectious, mal-absorptive, drug or secretory causes identified for their diarrhea. Skin involvement, in the form of typical rashes or bullae, occurred in 59/65 (90.8%) of the GVHD positive transplants or 59/142 (41.5%) overall. Most cases of GVHD, 46/65 (70.8%), had more than one organ affected. Only 6/65 (9.2%) did not affect the skin, of which 3/65



**Figure 1** Box and whisker graph of highest measured total bilirubin levels among post transplant recipients who were diagnosed with VOD, hepatic GVHD or 'other' causes of hepatic injury or dysfunction.

(4.6%) had single organ involvement. One death was attributed to severe GVHD.

Percutaneous liver biopsies under general anesthesia were performed in only three patients due to the high risk of complications. Two also had endoscopy performed for assessment for intestinal GVHD at the same time. Nonspecific findings were observed in two of the three biopsies and drug toxicity was reported in the third. No complications were reported secondary to the procedure. Indications were to identify etiologies for the patients' raised transaminases or hyperbilirubinemia.

### Biliary complications

Biliary complications assessed in this cohort were biliary sludging, acalculus cholecystitis and ascending cholangitis. Biliary sludging was a finding in 28/142 (19.7%) of the patients in this cohort. It was diagnosed on ultrasound as echogenic material found in the gallbladder. Ultrasound examination was commonly indicated for investigation into possible VOD, jaundice, right upper quadrant (RUQ) pain, serum bilirubin levels  $>34 \mu\text{mol/l}$  or raised hepatocellular transaminase laboratory values. Fisher's exact test found that biliary sludging was associated with jaundice ( $P < 0.001$ ), RUQ pain or hepatomegaly ( $P = 0.007$ ), generalized abdominal pain ( $P = 0.020$ ) and vomiting post transplant requiring antinauseant therapy ( $P = 0.014$ ). Biliary sludging was also associated with the use of TPN given in the week prior to transplant ( $P = 0.042$ ). Logistic regression with odds ratios and 95% confidence intervals confirmed these associations with biliary sludging (see Table 3). Biliary sludging did not correlate with an increase in GGT or an increase in A.P. Sludging was seen in 13/26 VOD-positive patients and in 8/24 patients positive for hepatic GVHD. No definitive cholelithiasis was documented radiologically in the population.

Acalculus cholecystitis, the only other biliary complication found in this cohort, affected 1/142 (0.7%) of the patients. This was diagnosed by clinically suspicious abdominal pain, raised conjugated bilirubin and a raised GGT in the absence of biliary sludging or gallstones on ultrasound.

There were no occurrences of ascending cholangitis documented in this cohort.

### Pancreatic disease

Acute pancreatitis was found clinically in 7/142 (4.9%) of the patients. Upon investigation, all patients developed abdominal pain associated with eating and either an

**Table 3** Fisher's exact test to compare proportions of groups with biliary sludging with other variables

Variable	Fisher's exact test P-value	Odds ratio	95% confidence intervals	Logistic regression P-value
Jaundice	$< 0.001$	7.97	3.22, 19.73	$< 0.001$
RUQ pain or hepatomegaly	0.007	3.43	1.43, 8.20	0.006
Abdominal pain	0.020	4.17	1.18, 14.68	0.026
TPN pre-transplant	0.042	2.61	1.05, 6.50	0.039
Vomiting post transplant	0.014			

Logistic regression with odds ratios and 95% confidence intervals to predict the odds of biliary sludging by each variable listed. Vomiting post transplant was predicted perfectly with logistic regression; all 28 transplants with sludging also had vomiting.

increased serum lipase or amylase level of at least 1.5 times the upper limit of normal. Of note, a raised amylase level is not very specific for pancreatitis, but it was used here as the serum marker for several years in this transplant group. No complications or mortality related to pancreatitis were documented. Finally, there was no association found between pancreatitis and any specific induction chemotherapy regimen, specifically L-asparaginase.

#### *Oral, esophageal and gastric complications*

The upper gastrointestinal tract is a common site for complications of BMT. The most common complications included mucositis, post transplant vomiting, odynophagia and generalized abdominal pain. In this study, mucositis occurred in 128/142 (90.1%) of the patients. Post transplant vomiting, likewise very common, was observed in 121/142 (85.2%) patients. Post transplant abdominal pain was also frequent, 101/142 (71.1%), in this group. Finally, odynophagia, deemed separate from the patients' mucositis, occurred in 28/142 (19.7%) of this population.

These upper gastrointestinal complications affected the patient's ability to maintain adequate oral intake. Intravenous hyperalimentation was routinely used in this cohort. Data on TPN and enteral feed usage found that 30 patients received TPN pre-transplant and one received g-tube feeds pre-transplant. Immediately post transplant, 129/142 (90.8%) of the patients required TPN nutritional support. Of these 129 patients, 14 also required nasogastric or gastrostomy tube feeding, while one required only nasogastric feedings without TPN. Only 12/142 patients (8.5%) did not require any specific interventional assistance for nutrition. Data were missing for one patient.

#### *Small and large intestine complications*

Complications of the intestine include typhilitis (neutropenic enterocolitis), *C. difficile* colitis, diarrhea of viral and other causes, melena or hematochezia, constipation and lymphoproliferative disease.

Typhilitis (neutropenic enterocolitis) was diagnosed in 5/142 (3.5%) of the transplants and was reported in detail elsewhere.<sup>33</sup> It was confirmed radiologically using a combination of abdominal roentograms, ultrasound and CT scan, depicting pneumatosis intestinalis. Two of the episodes occurred in autologous transplants and three occurred in allogeneic transplants. Four of the five patients had diarrhea, of which one was rotavirus positive, one was *C. difficile* toxin positive and two were of unknown cause (no identified infectious agent or acute GVHD). Fever was noted in four. All of these patients were successfully treated with conservative therapy and no perforations were documented.

Overall, diarrhea occurred in 95/142 (66.9%) of the patients. Causes (in various combinations) included GVHD in 39 (diagnosed clinically), viral enteritis in nine, *C. difficile* infection in 11, *C. difficile* as well as a rotaviral infection in one and etiology unknown in 40 patients.

*C. difficile* colitis occurred in 12/142 (8.5%) of the patients. Of the 12 patients, 11 had abdominal pain, one had hematochezia and one developed typhilitis

concomitant to their *C. difficile* infection. As well, two patients had a previous episode of this infection prior to transplant.

Viral enteritis causing diarrhea was diagnosed in 10/142 (7.0%) of the patients. Causative agents included rotavirus (4/10), adenovirus (4/10), astrovirus (1/10) and cytomegalovirus (1/10). Mean day of diagnosis was day +24.9±6.0 post transplant with a range of 20–40 days post transplant.

A nonspecific diarrhea, without any identifiable infectious or immunological cause, occurred in 40/142 (28.2%) of the patients. No incidents of diarrhea were reported in 47/142 (33.1%) of this transplant cohort.

Melena or hematochezia occurred in 11/142 (7.7%) of the patients. Possible causes or contributing factors to its occurrence in 9/11 included typhilitis in two cases, *C. difficile* infection in one case, viral diarrhea (CMV and adenovirus) in two cases and intestinal GVHD in four cases. Two patients showed no obvious cause of melena/hematochezia other than diarrhea. Five of the patients that developed melena or hematochezia were admitted to the intensive care unit (ICU) of which three died. Reasons for ICU admission included monitoring in two patients, complications of infection in two patients and supportive care for VOD in the last patient. Development of melena or hematochezia in the immediate post transplant period was also related to an increased risk of death in the first 100 days post transplant. Five of the 11 patients died. This is disproportionately high, as only 21 patients died less than 100 days post transplant and only eight of 27 admissions to the ICU died.

Other complications included problematic constipation in 20 patients and one patient developed gastrointestinal post transplant lymphoproliferative disease in the first 100 days post transplantation.

## **Discussion**

This study presents a broad spectrum of gastrointestinal complications in a heterogeneous pediatric cohort of post-hematopoietic stem cell transplant recipients. Some have not been previously systematically reported.

Clinically diagnosable jaundice is merely a symptom of multiple underlying processes, such as increased bilirubin production from hemolysis or decreased elimination from either biliary obstruction or hepatocellular injury. Jaundice was shown to be related to a combination of biliary sludging, GVHD and VOD in 18/23 cases. No obvious etiology was found for the remaining five. To our knowledge, the frequency of jaundice has not been previously reported in pediatric post-BMT patients.

The hepatocellular transaminases (ALT, AST), serum bilirubin and GGT were found to have higher maximum values post transplantation if either GVHD or VOD was diagnosed compared to the 'other' causes of hepatocellular injury. This information may prove useful as adjunctive data to aid in the diagnosis of these complications, but they are not specific to either. The maximum serum bilirubin level measured was the only serum laboratory value recorded that was significantly increased in the VOD-positive group compared to the GVHD-positive group.

Feasibly, caregivers could use this to help differentiate between these two diagnoses.

The incidence of VOD (18.3%) observed in this population is in the mid-range of other pediatric reports where VOD incidence varied from 1.2 to 28%.<sup>23–32</sup> This wide array of VOD instances may be due in part to the nature of retrospective data extraction, the heterogeneous backgrounds and induction protocols involved. Retrospective data extraction leads to either over-reporting or under-reporting of a complication dependent upon the extent of documentation. Additionally, different perceptions of each attending physician impact on the documented level of reporting. For example, some studies have only reported severe cases of VOD with no record of any mild or moderate cases.<sup>27</sup> This leads to speculation that milder cases were either under-reported or attributed to another diagnosis. In this study, as in previous studies,<sup>23–25,28–30</sup> the severity of individual cases was not specifically assessed with the exception of the three severe cases where the patient's death was attributable to VOD. A total of 13 VOD patients were also independently diagnosed with hepatic GVHD. In addition, some patients may have developed GVHD after VOD or a decision may have been made to change the diagnosis from VOD to GVHD due to the subsequent development of skin and/or intestinal symptoms. The increased risk of VOD among allogeneic vs autologous transplants was noted with allogeneic transplants comprising a disproportionately larger proportion of patients that developed VOD. Allogeneic BMT recipients comprised 88.5% of the VOD patients but only 70.4% of the total population. This was likely due to differences in preparative regimens and underlying diseases.

GVHD was most commonly diagnosed in conjunction with skin manifestations. A combination of skin and other organ involvement accounted for 59/65 of the reported cases. It was rare to diagnose nonskin GVHD with only single organ involvement as isolated hepatic GVHD (1/65) or intestinal tract involvement (2/65). This was likely due to the relative frequency, as well as, the ease of diagnosing skin compared to liver or intestinal manifestations of acute GVHD. After ruling out other causes of hepatic injury, hepatic GVHD was diagnosed in 18% of these patients. This was slightly lower than the previously reported 25% cited by Frisk *et al.*<sup>30</sup>

There have been no prior reports of association between biliary sludging and other morbidities in pediatric BMT recipients. Classically, it has only been noted during the investigation for VOD or identification of reasons for clinical symptoms such as RUQ pain, jaundice, raised hepatocellular transaminases or suspected cholelithiasis.<sup>19,27</sup> Otherwise, no firm associations have previously been made. This study found that biliary sludging is statistically associated with multiple morbidities. Although a statistical association does not imply causation, preventing biliary sludging may lead to a decrease in morbidities such as jaundice, RUQ pain, generalized abdominal pain or vomiting requiring antinauseant therapy. This should be investigated with a prospective study. A decrease in biliary sludging may potentially be accomplished by the use of ursodeoxycholic acid, a cholerectic agent, which is currently used in other cholestatic disorders in children and

may prove useful in the prevention of VOD in post-BMT patients.<sup>39,40</sup> However, in our population, two of the 10 patients on ursodeoxycholic acid pre-transplant developed sludging; this is a similar ratio to the overall population of 26/142.

Pancreatic disease post-HSC transplantation is not a major clinical problem in this population.<sup>1,19</sup> Earlier studies in children measured the incidence for pancreatitis and found it to be 2.1–3.5%.<sup>19,36</sup> The results obtained here are similar with 4.9% developing acute pancreatitis and was not a major contributor to morbidity or mortality in this patient population.

This is the first report to document and itemize the frequencies of upper gastrointestinal tract complications in pediatric bone marrow transplant recipients. Upper intestinal complications impaired nutritional intake and necessitate parenteral and/or enteral nutritional support, in the form of TPN, nasogastric or nasojejunal feeds. Over 90% of these patients required nutritional support.

Typhilitis (neutropenic enterocolitis), a previously reported lower intestinal complication, was uncommon in this cohort.<sup>33</sup> Our result of 3.5% was much lower than the incidences reported in children with leukemia.<sup>41,42</sup> All cases were confirmed by radiological findings. In this study other cases of suspected typhilitis may have occurred but were not documented due to lack of supporting radiological data. Two of the five episodes were associated with rotavirus or *C. difficile* infection. We recommend routine investigation for intestinal infections in suspected cases of typhilitis.

The most commonly identifiable infectious organism found in this population was *C. difficile*, which occurred in 8.5% of the patients. This is not surprising due to the frequent use of broad-spectrum antibiotics to empirically treat febrile neutropenia in these patients. Previous reports demonstrate a higher prevalence of *C. difficile* on oncology and surgical wards.<sup>43</sup> Preventative strategies, such as careful hand washing between patient contacts and the use of probiotics to prevent colonization, could benefit those in high-risk wards.<sup>43</sup> There is, however, a slight risk of developing a nosocomial infection with probiotic therapy in these highly immunosuppressed patients. Therefore, appropriate monitoring should be conducted.

Viral enteritis causing diarrhea was documented in 7% of this population. The viruses found (rotavirus, adenovirus, astrovirus and CMV) are well recognized as causes of diarrhea in BMT patients.<sup>14,17</sup> The mean day of onset was day +25. This fairly late onset may simply represent prolonged hospitalization with iatrogenic exposure, other unknown confounders or merely a chance observation. This finding requires further assessment with a larger cohort in a prospective manner.

The symptoms of melena and hematochezia may occur due to intestinal inflammation or ulceration, coagulation defects or anatomical abnormalities. We found intestinal infections, typhilitis and intestinal GVHD related to these symptoms. Morbidity and mortality associated with rectal bleeding was high, with 45% of these patients requiring admission to the intensive care. In addition, 38% of ICU deaths and 24% of deaths that occurred prior to 100 days post-BMT in this cohort involved patients with melena or

hematochezia as part of their symptoms. Since this symptom is not very common in this population (7.7%) but is associated with a disproportionately higher percentage of ICU admissions and deaths, we consider melena or hematochezia a marker for poor outcome.

To our knowledge, this is the first study to comprehensively examine the gastrointestinal complications observed in a pediatric BMT population that was transplanted for heterogeneous etiologies. The incidences of many complications described here are similar to prior reports in adult BMT recipients but were not previously documented in children. Furthermore, mild gastrointestinal complications are likely under-reported in this retrospective study. Information on the incidence, severity and manifestations of hepatic, pancreatic and luminal gastrointestinal complications of BMT provided in this report will assist caregivers in providing better care and counseling for pediatric patients with these complex medical and nutritional issues.

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