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Diarrhea in pediatric recipients of solid organ or bone marrow transplants

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Abstract

Diarrhea is common in adults after solid organ transplantation (SOT) and bone marrow transplantation (BMT), but data in children are limited. Therefore, we aimed to determine the incidence and etiology of pediatric early-onset diarrhea in post SOT and BMT.

We reviewed children aged 6 months to 18 years who underwent liver transplantation, kidney transplantation or BMT between January 2015 and December 2019 with duration of diarrhea > 72 hours within the first 6 months after transplantation. Clinical data and diarrheal course were collected. Regression analyses were performed to define factors associated with the interested outcomes.

Among 252 transplanted patients, 168 patients (66.6%) had 289 documented episodes of diarrhea. A diagnosis of 68.2% of post-transplant diarrhea remained 'indefinite'. Enteric infection in SOT and gastrointestinal acute graft-versus-host disease (GI-aGVHD) in BMT were the commonly identified etiologies. Among 182 episodes among BMT children, skin rash was more pronounced when compared the ones with diarrhea > 7 days vs ≤ 7 days (odds ratio [OR] 13.9; 95% CI 1.8, 107.6). Males were more likely to develop GI-aGVHD as compared to females (OR 8.9). We found that GI-aGVHD was more common in the ones with skin rash and the presence of white blood cells in stool examination (OR 8.4 and 3.1, respectively). Deaths occurred in 7.7%.

Two-thirds of post-transplant children experienced at least one episode of early-onset diarrhea, of which the etiology mainly remains undefined. Various clinical factors of prolonged/chronic diarrhea and GI-aGVHD may help clinicians when managing these children.

Abbreviations: aGVHD = acute graft-versus-host disease, BMT = bone marrow transplantation, CDT = *Clostridioides difficile* toxin, CMV = cytomegalovirus, GI = gastrointestinal, GPP PCR = gastrointestinal pathogen panel polymerase chain reaction, IQR = interquartile range, KT = kidney transplantation, LT = liver transplantation, MMF = mycophenolate mofetil, SOT = solid organ transplantation, WBC = white blood cell.

Keywords: chronic diarrhea, cytomegalovirus, graft-versus-host disease, kidney transplantation, liver transplantation

1. Introduction

Diarrhea is a frequent complaint after solid organ transplantation (SOT) and bone marrow transplantation (BMT) with a broad etiologic spectrum including both infectious and non-infectious causes. Post-transplant diarrhea has been shown to increase length of hospital stay, hospital admissions, cost of the diagnostic tests,[1,2] risk of disability and negatively impact the recipient's quality of life.[2] Furthermore, post-transplant diarrhea is also associated with allograft dysfunction, graft failure, graft loss and death.[3] Most transplanted recipients share certain predisposing characteristics for the development of post-transplant diarrhea such as immunosuppressed state, exposure to various medications especially broad-spectrum antimicrobial and immunosuppressive agents.[4,5] A variety of factors may influence the rate and clinical course of post-transplant diarrhea including the type of transplanted organ, immunosuppressive regimen, duration after transplantation, and patient characteristics and underlying disease prior to transplantation.[6]

Among the SOT patients, the Spanish MITOS multicenter epidemiologic cross-sectional study reported the incidence of gastrointestinal (GI) complications in 1,788 adult SOT recipients. Diarrhea was the most frequently reported GI symptom among transplanted recipients, presenting in 27% of kidney transplantation (KT),[7] 23% of heart transplantation,[8] 20% of liver transplantation (LT),[9] and 17% of lung transplantation.[10] The causes of post-transplant diarrhea in the aforementioned studies were most often related to either infectious or drug-related effects. Less frequent etiologies were inflammatory bowel disease, post-transplant lymphoproliferative disorders.[11] Maes et al reported that diarrhea resolved in approximately 50% of KT adults either by a course of treatment for the concurrent infections such as

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Campylobacter spp. or cytomegalovirus (CMV) and/or discontinuation of diarrhea-associated drugs, especially mycophenolate mofetil (MMF). Even a smaller percentage of patients had an indefinite cause of diarrhea, most cases eventually responded well to various empirical interventions e.g., antidiarrheal agents, probiotics or lactose avoidance.[12] Another study in KT and LT recipients found that infectious etiology was detected in 75%; CMV and *Cryptosporidium parvum* were the two most frequent pathogens; and MMF was responsible for half of the cases.[13] A study of 55 SOT recipients from India showed that diarrhea was noted in 46%. Half caused by infection (69% were parasites), 29% by medications, while 22% showed an absence of identified etiology.[14]

For BMT, a retrospective study examined GI complications post BMT in 142 children. Diarrhea occurred in 67%, with the most common identified etiologies reported as gastrointestinal acute graft-versus-host disease (GI-aGVHD) in 27%, viral enteritis in 6% (e.g., rotavirus, adenovirus, astrovirus, CMV), *Clostridioides difficile* in 8%; and 28% of patients remained unknown.[15] GI-aGVHD is a unique entity in post-BMT patients which is rarely reported in SOT patients. Among post-BMT patients, differentiating between GI-aGVHD *vs.* enteric infection is always a big challenge. The decision to increase or decrease immunosuppressive agents depends on the provisional diagnosis from clinical data (such as skin rash, associated upper GI symptoms or jaundice) in conjunction with the non-invasive stool and blood tests. Endoscopy and histopathology from GI mucosal biopsy may be helpful in distinguishing various causes of diarrhea;[4,11] hence clinicians should be aware of its invasiveness, the patient's baseline coagulation abnormalities (e.g., thrombocytopenia), and the procedure-related complications.

The information on early post-transplant diarrhea has been mainly gathered from adults. Given the paucity of data in pediatric SOT (i.e., KT and LT) and BMT recipients, we therefore aimed to assess the incidence and causes of diarrhea in these patients and to evaluate various clinical factors affected on the diarrheal course and interested outcomes.

2. Materials and methods

With a systematic data collection form, we reviewed children aged 6 months to 18 years who underwent SOT or BMT at a tertiary care teaching hospital between January 2015 and December 2019. We included children with an onset of diarrhea within the first 6 months after transplantation. Each patient's medical record was searched for all episodes of diarrheal symptoms. 'Diarrhea' was defined by the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (at least 3 times in 24 hours) [16] or stool volume more than 10 mL/kg/d in small children or $>$ 200 grams/d in older children and adolescents. The study was approved by the Human Research Ethics Committee of the institution.

Patient characteristics were recorded including underlying disease and transplanted-related information. We collected the clinical data and diagnostic evaluation from each diarrheal episode with the associated symptoms and stool testing (i.e., stool examination, stool culture, stool for *Clostridioides difficile [C difficile]* toxin [CDT], and stool for gastrointestinal pathogen panel polymerase chain reaction [GPP PCR]). Endoscopic and histopathological data were also recorded, if examined.

A diagnosis of CMV GI disease required a positive histopathology from GI mucosal biopsy.[17] Lower GI-aGVHD presenting with diarrhea was defined by 1) associated typical clinical findings such as rash and/or jaundice in conjunction with a favorable response to the adjustment of immunosuppressive regimen by the responsible experienced hematologist/oncologist (if no histopathological data was available) and/or 2) the definite histopathological finding.[18]

Diarrhea-related management was recorded including the duration of nil per os and parenteral nutrition, the use of antimicrobial agents, somatostatin analog (i.e., octreotide), bile acid sequestrant, zinc supplementation, and anti-emetic drugs. We also recorded the implementation of lactose and/or cow's milk protein avoidance. Data on duration of diarrhea, hospital admission, the final diagnosis of diarrhea and causes of death were also collected.

2.1. Statistical analyses

Study variables were described as frequency and percentages, mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were compared using Chi-square test or Fisher exact test. Univariate and multivariate analyses were performed by logistic regression for the interested comparisons, including duration of diarrhea ($>$7 vs $\leq$ 7 days) in both the SOT and BMT recipients; and GVHD vs. non-GVHD in BMT recipients. All significant variables were included in the final multivariate analyses. The statistical significance was set at P value $<$ .05. The analyses were conducted by using the SPSS version 16.0 software.

3. Results

3.1. Baseline characteristics

We identified a total of 168 patients (SOT in 37.5% and BMT in 62.5%) with diarrhea in the first 6 months after the transplantation (Table 1) with no significant gender difference. The median age at transplantation was 63 months (IQR: 22,122.5). The main primary underlying disease for LT was biliary atresia, and thalassemia and leukemia for BMT. We found that the overall incidence of diarrhea after transplantation was 66% (95% CI: 60.5, 72.5). Considering the type of transplanted organ, the incidence was 72.6% in LT, 33.3% in KT, and 70.5% in BMT. Data on the incidence, total diarrheal episodes, and average episodes per patient in each type of transplantation are shown in Table 2.

3.2. Clinical data during each episode of diarrhea

From the 168 patients, we determined 289 diarrheal episodes (Table 3). Most (84.5%) had $<$ 3 episodes of diarrhea. The median onset of diarrhea was approximately 3 weeks after the transplanted date and the duration of diarrhea per episode was 9 days. When compared to SOT recipients, diarrhea occurred significantly earlier and lasted longer in BMT patients.

Most patients had watery diarrhea (82.4%). Diarrhea was associated with fever in 57.4%, abdominal pain, decreased appetite, or nausea/vomiting approximately in 10%; while 33.6% of patients had no associated symptoms. The most commonly used immunosuppressive agents at the onset of diarrhea were tacrolimus (67.5%), MMF (44.3%), and prednis-

Table 1

Demographic data of the transplanted children with diarrhea (n = 168).

Patient characteristics	Result, n (%)
Males	83 (49.4)
Transplanted organ	
Liver	53 (31.5)
Kidney	10 (6)
Bone marrow	105 (62.5)
Age, mo, median (IQR)	63 (22,122.5)
LT	18 (14.5,26)
KT	150 (126.3,197.8)
BMT	97 (47,133.5)
Underlying diseases	
LT	
Biliary atresia	41 (77.4)
Alagille syndrome	5 (9.4)
Cirrhosis	3 (5.7)
Other	4 (7.5)
KT	
End stage renal disease	4 (40)
Other	6 (60)
BMT	
Thalassemia	36 (34.3)
Severe aplastic anemia	5 (4.8)
Leukemia	29 (27.6)
Non-hematologic malignancy	21 (20.0)
Genetic disease	11 (10.5)
Other	3 (2.8)

BMT = bone marrow transplantation, KT = kidney transplantation, LT = liver transplantation.

olone (42.6%). Only 11.4% did not receive any immunosuppressive drugs at the onset of diarrhea, while approximately 75% of patients received > 1 immunosuppressive agent.

3.3. Diagnostic evaluation

The mean white blood cell (WBC) count and platelets were lowest in BMT patients (data not shown). Microscopic stool examination was performed in 63%. Stool WBC was seen in 24.4% and red blood cell in 9.8%. None had documented ova or parasites. Among the performed stool tests, GPP PCR demonstrated a higher yield as compared to others (Table 4). We further described each episode that reported positive results either from the stool culture, stool for CDT or stool for GPP PCR in Table 5. All patients with an identified organism had only one positive stool test without co-infection.

Endoscopy was performed in 25/289 episodes (8.7%), mostly done in BMT recipients (20/25). All patients who underwent endoscopy had both esophagogastroduodenoscopy and colonoscopy. Most abnormal findings from esophagogastroduodenoscopy were gastritis (56%), gastric ulcer (28%) or duodenitis (24%); and colonic ulcer (44%) or colitis (20%) from the colonoscopy. Histopathological findings showed definite CMV GI disease in 8 episodes and GI-aGVHD in the other 8 episodes (Table 4). The rest were non-specific abnormalities such as chronic gastritis, ileitis, edematous mucosa, or active colitis.

Table 3

Clinical data of the 289 diarrheal episodes.

Clinical data	n (%)
SOT	107 (37)
BMT	182 (63)
Number of episode(s) per patient	
1	88 (52.4)
2	54 (32.1)
3	16 (9.5)
>3	10 (6)
Onset of diarrhea after transplantation, days, median (IQR)	21 (5,68)
SOT	41 (14,106)
	p < .001*
BMT	3.5 (3,57)
Duration of diarrhea, days, median (IQR)	9 (5,15)
SOT	7 (5,13)
	p = .006*
BMT	10 (6,16)

BMT = bone marrow transplantation, SOT = solid organ transplantation.
* Comparing between SOT and BMT patients.

3.4. Causes of diarrhea

Overall causes of diarrhea are shown in Figure 1. Most (68.2%) episodes were 'indefinite'. Enteric infection (either bacteria or virus) was the most common cause of diarrhea post SOT, while the most commonly identified cause in BMT recipients was GI-aGVHD (20%). However, most GI-aGVHD cases were mainly diagnosed clinically with only one-third of the cases underwent endoscopy.

Among cases with enteric infection post SOT, viral infection (5 with CMV, 2 with norovirus, 2 with rotavirus, and 1 with other unidentified virus) was more commonly found than bacterial infection (5 with *Salmonella* spp. and 1 with *Campylobacter* spp.). On the other hand, bacterial infection (7 with *Salmonella* spp., 5 with *C difficile*, and 1 with *Campylobacter* spp.) was more common than viral infection (4 with CMV and 4 with norovirus) in BMT recipients. Drug-related diarrhea was noted in only 9 episodes among SOT children and 4 episodes among BMT children. Other diagnoses were cow's milk protein allergy (n = 3 in LT children), radiation enteritis and neutropenic colitis (n = 3 in BMT group).

Table 2

Incidence of diarrhea after transplantation.

Types of organ transplantation	Total N	Patients with diarrhea n (%)	Total episodes	Average episodes per patient
LT	73	53 (72.6)	94	1.77
KT	30	10 (33.3)	13	1.30
BMT	149	105 (70.5)	182	1.73
Total	252	168 (66.6)	289	1.72

BMT = bone marrow transplantation, KT = kidney transplantation, LT = liver transplantation.

Table 4

Diagnostic evaluation in post-transplant diarrhea (n = 289).

Diagnostic evaluation	n (%)
Stool examination, performed	182 (63)
Stool for parasite: positive	0 (0)
Stool culture, performed	178 (61.6)
Positive	9 (5.1)
Salmonella spp.	8
Aeromonas hydrophila	1
Stool for *Clostridoides difficile* toxin, performed	86 (29.8)
Positive	3 (3.5)
Stool for gastrointestinal pathogen panel polymerase chain reaction, performed	38 (13.1)
Positive	13 (34.2)
Salmonella spp.	6
Norovirus	4
C difficile	2
Campylobacter spp.	1
Endoscopy	25 (8.7)
Confirmed histopathological finding	
Cytomegalovirus gastrointestinal disease	8
Graft-versus-host disease	8

3.5. Diarrhea-related management

Nil per os was implemented in 19.7% (median duration of 5 days, IQR: 2, 8.5), parenteral nutrition in 38.4% (median duration of 9 days, IQR: 5, 14), added antibiotics in 76.1% (median duration of 10 days, IQR: 7, 14), and antifungal drugs in 11.4% (median duration of 14 days, IQR: 11.5, 21). Holding immunosuppressive agents was noted in 6.2% (MMF in 4.5%), while adding those drugs was documented in 23.9% (methylprednisolone 13.8%, tacrolimus 5.9%, and MMF 3.5%). Various agents were given, including octreotide (9.3%), racecadotril (16.6%), bile acid sequestrant (5.2%), zinc supplementation (30.1%), anti-emetic drugs (32.2%), and loperamide (1%). Dietary lactose and dairy avoidance were prescribed in 47.1% and 13.1%, respectively.

Table 5

Organism founded from stool tests in 25 episodes.

No. of episode	Culture	CDT	GPP PCR
1	*Salmonella* spp.	NP	NP
2	*Salmonella* spp.	NP	Negative
3	*Salmonella* spp.	NP	NP
4	*Salmonella* spp.	NP	NP
5	*Salmonella* spp.	NP	NP
6	*Aeromonas hydrophila*	NP	NP
7	Negative	Negative	*Clostridiodes difficile*
8	*Salmonella* spp.	NP	NP
9	Negative	Negative	Norovirus
10	Negative	NP	Norovirus
11	Negative	NP	Norovirus
12	Negative	NP	*Campylobacter* spp.
13	Negative	NP	*Salmonella* spp.
14	Negative	Negative	*C difficile*
15	Negative	NP	*Salmonella* spp.
16	Negative	NP	*Salmonella* spp.
17	Negative	Positive	NP
18	Negative	Negative	*Salmonella* spp.
19	Negative	Positive	Negative
20	Negative	Positive	NP
21	Negative	NP	Norovirus
22	Negative	Negative	*Salmonella* spp.
23	*Salmonella* spp.	Negative	NP
24	*Salmonella* spp.	Negative	Negative
25	Negative	Negative	*Salmonella* spp.

CDT = *Clostridiodes difficile* toxin, GPP PCR = gastrointestinal pathogen panel polymerase chain reaction; NP = not performed.

3.6. Clinical outcome

Diarrhea occurred during the transplanted admission in 73.2%, hence the median duration of hospital stay was 42 days (IQR: 28, 66). Interestingly, all 5 diarrheal episodes with *C difficile* infection occurred in post BMT children and lasted longer than 7 days (8–12 days). CMV infection was found in 9 episodes (5 in SOT and 4 in BMT), and most (7/9 episodes) also had diarrhea longer than 7 days.

The mortality rate was 7.7% (13 patients). The proposed causes of death were respiratory issue (i.e., acute respiratory distress syndrome, pneumonia) in 6 children, septicemia in 4 children, and bleeding (GI, intracranial, pulmonary) in 3 children.

3.7. Logistic regression on the potential factors and interested outcomes

Among 107 episodes in SOT recipients, episodes were divided into 2 groups in according to the duration of diarrhea: >7 days (n = 51) *vs.* ≤ 7 days (n = 58). The univariate analysis showed that decreased appetite was significantly less pronounced in diarrheal episodes > 7 days, but no factors was statistically significant in the multivariate model. Among 182 episodes in BMT children, skin rash was associated with a longer duration of diarrhea in both univariate and multivariate analyses (Table 6). Fever and the presence of immunosuppressive agents were both significant in the univariate analysis but not in the multivariate analysis.

In the BMT recipients, we performed a subgroup analysis comparing GI-aGVHD (n = 36) episodes *vs.* non GI-aGVHD (n = 146). Males were more likely to develop GI-aGVHD as compared to females (odds ratio 8.9). Independent clinical and management factors for GI-aGVHD episodes are shown in Table 7. Patients with GI-aGVHD were more likely to have skin rash, positive WBC in stool examination, be prescribed *nil per os*, methylprednisolone, and octreotide.

4. Discussion

We reported a high incidence of diarrhea both in the pediatric SOT and BMT recipients within the first 6 months after transplantation. While some episodes of the diarrhea had an unknown etiology, enteric infection was the most commonly identified cause in SOT recipients. According to our data, the etiology and clinical course of the diarrhea were different when compared SOT with BMT. Conventional stool tests such as microscopic examination, culture or CDT provided little values in the diagnostic process of diarrheal episodes.

Previous large-scale retrospective cross-sectional studies in adults reported varied incidence of diarrhea post transplantation from 17 to 46%.[7–10,17] Our LT children were mainly young children (median age of 18 months), thus these children may be more likely to suffer from unidentified self-limited enteric infection, food protein allergy or food intolerance as compared to the adult population. A study in pediatric BMT recipients

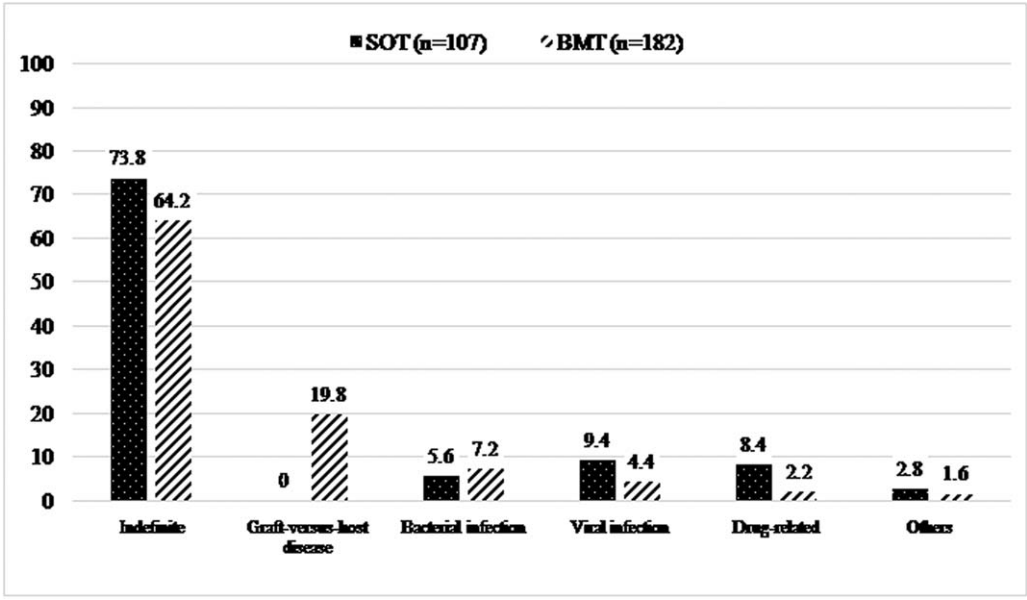

Figure 1. The final diagnosis of 289 post-transplant diarrheal episodes in both solid organ transplantation (SOT) and bone marrow transplantation (BMT) recipients.

reported a diarrhea incidence of 67%,[15] which is relatively similar to our finding. Most diarrheal episodes in this study lasted longer than 7 days (i.e., prolonged or chronic diarrhea). Children who underwent BMT developed diarrhea quicker but had a longer duration of symptom than the SOT individuals (Table 3). BMT children are more likely to receive high potency chemotherapeutic agents prior to the transplantation and possibly more potent post-transplant immunosuppressive regimen than the SOT recipients.

Even being an endemic area of parasitic infestation, we did not find ova or parasites in the basic stool examination in any studied children. Furthermore, stool culture and stool CDT demonstrated little diagnostic aid. Similar to our study, Berger et al demonstrated only 4/1072 (0.42%) HSCT adults with positive stool culture, of which all were *Campylobacter* spp.[19] Moreover, most stool cultures performed by a standard culture media may not be able to identify *Campylobacter* spp. as this organism requires a specific environment to grow. The higher yield of stool GPP PCR to detect organism's genetic substance seems promising, the finding that was similar to many previous studies.[20,21] Judicious use of stool tests to evaluate diarrhea has been shown to reduce health care cost without compromising diagnostic yield.[1]

We found that the highest percentage of an identified cause in SOT recipients was enteric infection, which was similar to the study from Pant. et al[11] CMV GI disease accounted for half of the viral infection, and salmonella in almost all with bacterial infection. Our SOT recipients generally received immunosuppressive agents targeting T lymphocyte function that potentially led to CMV reactivation. For the BMT recipients, GI-aGVHD was the most identified cause (20%). Barker et al reported GI-aGVHD in 27% of diarrhea in post BMT children.[15] However,

Table 6

Logistic regression analyses for the duration of diarrhea: subgroup as >7 vs ≤ 7 days.

	SOT (n=107)		BMT (n=182)			
	Univariate analysis		Univariate analysis		Multivariate analysis	
Clinical data	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Symptoms						
Fever	1.02 (0.48,2.18)	.96	2.35 (1.26,4.39)	.007	1.70 (0.85,3.40)	.13
Abdominal pain	0.72 (0.12,4.50)	.73	1.06 (0.45,2.51)	.90	–	–
Nausea, vomiting	0.44 (0.13,1.54)	.20	0.59 (0.22,1.61)	.31	–	–
Decrease appetite	0.12 (0.01,0.99)	.049	0.59 (0.22,1.61)	.31	–	–
Skin rash	–	–	17.0 (2.23,129)	.006	14.5 (1.87,111.9)	.01
Number of immunosuppressive drugs						
0	1.00		1.00			
1	NA	–	0.33 (0.12,0.92)	.04	0.46 (0.15,1.41)	.18
2	2.13 (0.71,6.39)	.18	0.48 (0.20,1.18)	.01	0.62 (0.24,1.60)	.32
3	–	–	0.25 (0.07,0.94)	.04	0.46 (0.11,1.92)	.29

BMT = bone marrow transplantation, SOT = solid organ transplantation.

Table 7

Logistic regression comparing between GI-aGVHD and non GI-aGVHD in bone marrow transplantation (n = 182).

	GI-aGVHD (n = 36)	Non GI-aGVHD (n = 148)	Univariate analysis		Multivariate analysis	
Clinical and management data	**N (%)**	**N (%)**	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Skin rash	11 (30.6)	10 (6.9)	5.98 (2.30,15.61)	<.001	8.41 (2.13.33.31)	.002
Presence of stool white blood cells*	14 (53.8)	23 (25.9)	3.35 (1.35,8.28)	.008	3.12 (1.15,8.49)	.03
Nil per os	25 (69.4)	21 (14.4)	13.5 (5.80,31.52)	<.001	6.17 (2.10,18.11)	.001
Antibiotics, days						
0	4 (11.1)	35 (24)	1.00		1.00	
1–7	10 (27.8)	39 (26.7)	2.24 (0.64,7.80)	.20	62.5 (1.66,2353)	.03
8–14	13 (36.1)	53 (36.3)	2.15 (0.65,7.12)	.21	2.33 (0.14,38.32)	.55
>14	9 (25)	19 (13)	4.14 (1.13,15.32)	.03	2.35 (0.10,52.81)	.59
Methylprednisolone	22 (61.1)	18 (12.3)	1.1 (4.86,25.72)	<.001	12.0 (4.26,33.72)	<.001
Octreotide	16 (44.4)	11 (7.5)	9.82 (3.99,24.12)	<.001	4.99 (1.43,17.42)	.01

GI-aGVHD = gastrointestinal acute graft-versus-host disease.
* Stool exam was performed in 26 episodes among the GI-aGVHD group and 89 episodes among the non GI-aGVHD group.

GI-aGVHD was diagnosed by histological finding in only 1/3 of the cases. Therefore, the higher percentage of GI-aGVHD may be an overrepresentation. Bacterial infection (mainly *Salmonella* spp. and *C difficile*) was more common than the viral infection among BMT children. BMT children were more likely to receive high potency chemotherapy prior to the transplantation. Therefore, they likely had a low number of neutrophils which plays an important role in anti-bacterial mechanisms. Previous studies demonstrated *Campylobacter* spp. and *C difficile* as well as CMV being the most common enteric infections.[12,14,15]

While a high rate of indefinite cause of diarrhea was noted in this study, we demonstrated a very low proportion of drug-related diarrhea as compared with other studies (12.5%–33%).[12–14] Previous reports demonstrated an indefinite diagnosis in 22%–28%.[14,15] We postulated that some of our patients may not receive extensive investigations in conjunction with an improvement of diarrhea after the initiation of various therapeutic trial(s) such as antimicrobial agents, bile acid sequestrant or dietary modification, therefore further tests may not be conducted to confirm the definite diagnosis.

In BMT recipients, skin rash is one of the hallmark features of GI-aGVHD. Skin rash has been associated with a prolonged course of diarrhea as shown in Table 6. Most GI-aGVHD patients may have undergone various time-consuming investigations and therapeutic trials before receiving an appropriate investigation (i.e., endoscopy) and definite management (i.e., appropriate type and dose of immunosuppressive agents). GVHD itself may also be more difficult to treat than other causes of post-transplant diarrhea.

We noted that males were at a higher risk for GI-aGVHD in BMT recipients than females. Previous studies in adult BMT recipients reported that the use of female donors for male recipients had a greater effect on the risk of GVHD. The authors hypothesized that females have a greater chance to receive blood transfusion or be pregnant that they may produce some autoimmunity and pass it to the transplanted recipients.[22,23] Unfortunately, we did not have the data on donor's sex. Episodes with the presence of stool WBC were also more common in the GI-aGVHD group as compared to the non-GVHD group. Stool WBC can be found as a result of GI mucosal inflammation or ulceration even most patients presented with watery stools. Therefore, microscopic stool examination may help in these regards but further studies on the specific and non-invasive tests are warranted to aid in the diagnosis of pediatric GI-aGVHD.

We acknowledged the retrospective nature of this study that may carry some missing data and cannot fully demonstrate the time-sequence analyses at a single center. Given the limited availability, our center did not always perform high-yield tests such as stool GPP PCR or endoscopy in majority of post-transplant children with diarrhea. Therefore, definite diagnosis of the causes of diarrhea may be less achieved. Management for certain conditions such as CMV reactivation or possible MMF-induced diarrhea may vary between each transplant unit (SOT *vs.* BMT) which may affect the diarrheal course. Nevertheless, we conducted a study at a tertiary care teaching hospital that performed transplantation in accordance with standard clinical guidelines. Substantial number of transplanted patients was sufficient to perform robust statistical analyses especially multiple logistic regression for clinical predictors and the interested outcomes.

5. Conclusion

Two-thirds of post-transplant children suffered from at least one episode of diarrhea within the first 6 months, of which the etiology remains undefined that may be due to suboptimal yield of non-invasive investigations. Various clinical predictors of prolonged/chronic diarrhea and GI-aGVHD may be helpful in the care of post-transplanted children.

Author contributions

Conceptualization: Jirachart Phrommas, Pornthep Tanpowpong, Songpon Getsuwan, Chatmanee Lertudomphonwanit, Songkiat Chantarogh, Usanarat Anurathapan.
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