Complications and Utility of Gastrointestinal Endoscopy Post Hematopoietic Stem Cell Transplantation: An 11 Year Experience

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ABSTRACT

Objectives: Diagnostic gastrointestinal (GI) endoscopy is used to differentiate GI graft versus host disease (GI-GvHD), which requires escalation of immunosuppressive treatment (IST), from other conditions such as viral infection, which may require reduction of IST. The aim of this study was to establish the clinical utility of GI endoscopy post hematopoietic stem cell transplant (HSCT) and the complication rate of these procedures.

Methods: This was a single-center observational retrospective cohort study. Hospital pediatric endoscopy and HSCT databases identified patients between January 2010 and December 2020. GI-GvHD was diagnosed if there were positive histological findings and clinical context. Data collected included demographics, timing of endoscopy post-HSCT, clinical utility, and complications of endoscopy. The endoscopy was deemed to be "clinically useful" if it resulted in a change of clinical management or helped to narrow down the differential diagnosis for the clinical team.

Results: Three hundred thirty-nine HSCT occurred in 320 children during the study period. Sixty-six of 339 (19%) HSCT needed an "endoscopy episode." One hundred nineteen endoscopies were performed (53 concurrent upper and lower GI endoscopies, 11 upper GI endoscopies, and 2 lower GI endoscopies). Four of 119 (3%) endoscopies had complications: septic shock (1), duodenal hematoma (1), GI bleeding (1), and colonic perforation (1). Four patients had incomplete records to assess utility of endoscopy. Fifty-seven of 62 (92%) endoscopy episodes were "clinically useful," and 41 of 62 (66%) had a change in IST.

Conclusions: The clinical utility of endoscopy is high and in the majority of cases is associated with a change in patient management. Children post-HSCT are at high risk of complications from endoscopy; this should be made clear in the process of obtaining consent for procedures.

Key Words: bone marrow transplant, pediatric, procedure, risk, safety

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What Is Known

- Graft versus host disease is associated with morbidity and mortality post-hematopoietic stem cell transplant (HSCT).
- The gold standard for diagnosis of gastrointestinal (GI) graft versus host disease is from histology review of mucosal biopsies obtained endoscopically.
- Complication rates for children undergoing diagnostic endoscopy following HSCT is higher than those who have not had a transplant.

What Is New

- This is the first UK study to publish data on pediatric GI endoscopy complication rates post-HSCT.
- This study provides pragmatic advice to gastroenterologists dealing with this niche situation and quantifies the benefits and risks of the procedure.

Graft versus host disease (GvHD) is one of the most significant complications after allogenic hematopoietic stem cell transplant (HSCT). It remains the second most common cause of mortality and can cause significant morbidity. Acute GvHD affects approximately 40% of patients who undergo allogenic HSCT. GvHD incidence depends on the type of donor and GvHD prophylaxis used (1). Chronic GvHD (chGvHD) rates in children are 20%–50% (2). GvHD occurs when immunocompetent donor T cells recognize antigens from the recipient as foreign. This adds to endothelial damage from previous treatment causing activation of antigen presenting cells, cytokine hyperproduction, and recruitment of effector T cells and natural killer cells, resulting in targeted organ damage. The organs most affected by GvHD are the skin, gastrointestinal (GI) tract, and liver (3–5).

Gastrointestinal GvHD (GI-GvHD) typically presents with nausea, vomiting, dysphagia, diarrhea, weight loss, or GI bleeding. Malabsorption, low albumin, and weight loss may be more apparent in chGvHD. These symptoms may be present in the context of other pathology or overlap with other conditions that are common in patients undergoing allogenic SCT such as chemotherapy/radiation toxicity, drugs, and infections.

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First line treatment for GI-GvHD is steroids. Increasing systemic immunosuppressive treatment (IST) significantly affects the risk of infection, particularly if there is a clinical suspicion of concomitant GvHD and infection. Confirmation of GI-GvHD diagnosis is essential prior to increasing IST. The gold standard for diagnosing GI-GvHD is based on histological findings, which requires mucosal biopsy from flexible GI endoscopy. Many clinicians may be reluctant to request this procedure as it is invasive and requires a general anesthetic in the pediatric population (6,7). The purpose of this study is to provide some real world data for clinicians battling the risk-benefit of flexible endoscopy in HSCT patients.

METHODS

This was an observational retrospective cohort study to evaluate the clinical utility and safety of flexible GI endoscopy in children following allogeneic HSCT. Our center provides regional pediatric gastroenterology care for a population of 1 million children across the South-West of England and is 1 of 16 pediatric bone marrow transplant centers in the UK. Endoscopy is performed by pediatric gastroenterologists under general anesthetic provided by pediatric anesthetists. The transplant conditioning regimen and GvHD prophylaxis follows British Society of Bone Marrow Transplantation/European Bone Marrow Transplant Organization Guidelines.

The patients were identified by crosschecking the hospital pediatric endoscopy database and HSCT database between January 1, 2010 and December 31, 2020. All children having flexible GI endoscopy following HSCT were identified and included. Demographic data, type of transplant, medication prior to and after endoscopy, results of endoscopy, and complications were retrieved from the medical records. In order to reduce bias, authors worked in pairs to review the case notes.

An endoscopy episode was a single anesthetic for one or more endoscopy procedures. The decision regarding the location of the endoscopy (upper vs lower vs upper and lower) was based on symptoms and multidisciplinary discussion. There is no nationally recognized guideline for endoscopy in this situation. An endoscopy was recorded as showing GI-GVHD if there was positive histological evidence including features such as presence of apoptosis and crypt destruction. Macroscopic findings were not used to diagnose or rule out GI-GvHD. The clinical utility of the endoscopy was defined in 2 ways. First, whether the level of IST changed post-endoscopy, that is, decreased immune suppression if no evidence of GI-GVHD was found or vice versa. Second, whether the endoscopy was felt to be of value to the team when reviewing the notes, that is, did the endoscopy appear to confirm or deny clinical suspicions of GI-GVHD. If either of these criteria were present the endoscopy was recorded as "clinically useful." Complications were defined as bleeding that required either therapeutic intervention or that resulted in an intramural hematoma, perforation, sepsis, or death.

The primary objective of this study was to define the clinical utility and safety of flexible GI endoscopy following SCT.

This was a pragmatic retrospective study based on a single-center experience therefore no power calculation was performed to inform the sample size. Descriptive statistics were calculated using nonparametric methods. This study was approved by our hospital governance team as a service evaluation using anonymized data; it therefore did not meet the criteria for an ethical board review.

RESULTS

A total of 339 HSCT occurred in 320 children during the 11-year period (Fig. 1). There was only 1 patient included in this study who underwent HSCT for an inborn error of metabolism, and the rest of the patients had malignant conditions (Table 1). The 52 children (23 girls) had a median age of 8.6 years at transplant (range 10 months to 16 years). Children had symptoms of persistent abdominal pain, nausea, vomiting, and frequent loose stool. Fifty-two of 320 children had 66 GI flexible endoscopy episodes (Fig. 2). There were a total of 119 endoscopic procedures; 64 esophagogastroduodenoscopies (OGDs), 45 sigmoidoscopies, and 10 complete colonoscopies to caecum. Fifty-three of the lower GI endoscopies had OGDs performed concurrently. Biopsies for histological examination were taken from multiple sites at all 119 procedures regardless of macroscopic appearance. Macroscopically 26 of 66 (39%) endoscopy episodes were entirely normal. Four patients had incomplete records so it was not possible to determine the clinical utility of endoscopy.

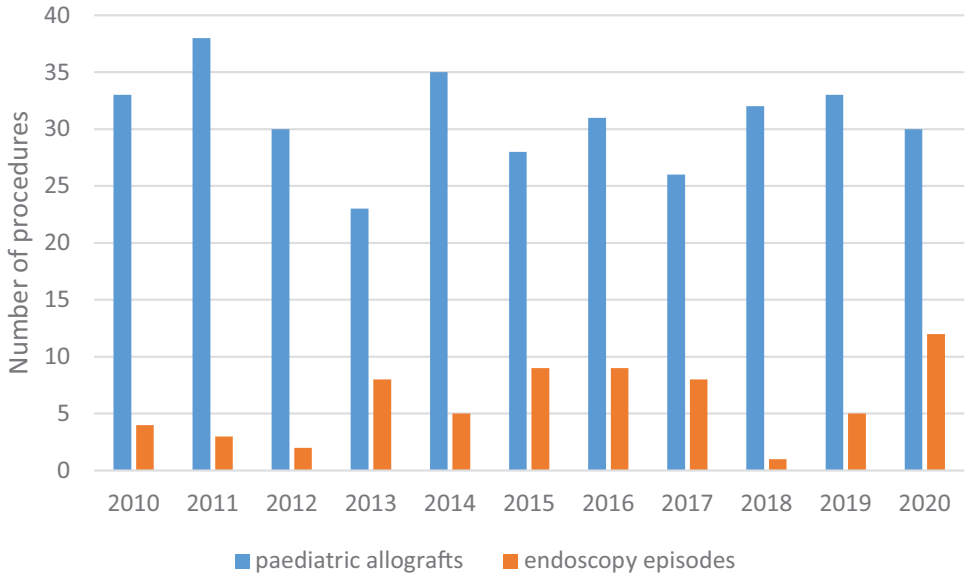

FIGURE 1. Numbers of children undergoing SCT and GI endoscopy (2010–2020). GI = gastrointestinal; SCT = stem cell transplant.

TABLE 1. Demographics of study population

Number of children	52
Median (min, max) age in years at endoscopy	8.6 (10 mo, 16 y)
Median (min, max) days posttransplant at time of endoscopy	74 (20, 726)
Diagnoses of children	
Acute lymphoblastic leukemia	23
Acute myeloid leukemia	13
Non-Hodgkin lymphoma	2
Myelodysplastic syndrome	6
Other	8
Endoscopy episodes	66
Systemic steroids at time of endoscopy episode	23
Skin GvHD at time of endoscopy episode	39
GI-GvHD positively identified on histology	33

GI-GvHD = gastrointestinal graft versus host disease.

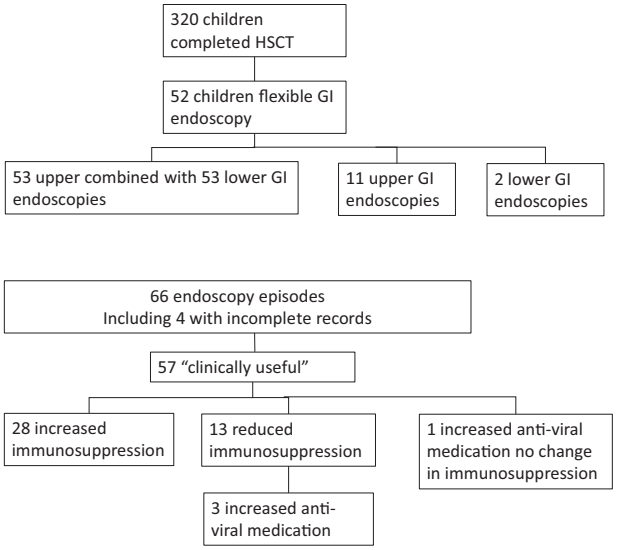

FIGURE 2. Study population, endoscopies, and outcomes.

Fifty-seven of 62 (92%) endoscopy episodes were deemed "clinically useful," perhaps more relevant and 41 of 62 (66%) had either an increase or decrease in immunosuppression. Three patients had equivocal histology results for GI-GvHD. Two patients were deemed not to have GI-GvHD and had not received immunosuppressive therapy before or after the endoscopy. One patient was treated as suspected GI-GvHD on clinical grounds; post-endoscopy the immunosuppression was continued and antibiotic therapy added in. In all 3 cases the procedures were deemed "clinically useful" by not disproving the pre-endoscopy clinical decision. Skin GvHD was already recognized in 37 patients, of whom, 23 were already receiving systemic steroids at the time of endoscopy. Four patients had antiviral treatment initiated following endoscopy.

There were 4 significant complications: 1 patient developed septic shock requiring intensive care; 1 patient developed an intramural duodenal hematoma; 1 patient had GI bleeding that required therapeutic endoscopy; and 1 patient had a colonic perforation requiring operative repair. Within 4 weeks of endoscopy, 2 patients died from multi-organ failure related to the sequela of their disease and its treatment.

Of the 53 combined procedures, 29 (55%) had GI-GvHD; the majority (20) had histological changes on both upper and lower GI endoscopy, 4 had changes only in the upper GI tract, and 5 only had changes in the lower GI tract. Ten patients had complete colonoscopy, and 9 had biopsies taken throughout the colon; at only 1 procedure were features of GI-GvHD seen on the right side of the colon that were not seen on the left.

DISCUSSION

There was a significant change in medical management, by either altering immunosuppression or starting antiviral therapy following 69% of endoscopy episodes. This clinical utility does carry a risk of complications of around 3% per endoscopy procedure.

Over the time studied there were 66 endoscopy episodes following 339 HSCT, meaning approximately 1 in 5 transplants required an endoscopy. There was clear variation year-by-year in both the number of HSCTs and the number of endoscopy episodes (Fig. 1). No clear trend is seen from the raw data and the numbers were too few to apply meaningful statistical analysis. Further multisite studies would be helpful to define if the rate of endoscopy has changed year-by-year on a national basis.

This study is limited by its retrospective design particularly as the "clinical utility" of the endoscopy was a subjective judgment and not one that was contemporaneously recorded. A further study limitation is the number of patients in whom steroid treatment of GvHD started prior to endoscopy; unfortunately, it has not been possibly to collate data to quantify the length of steroid treatment prior to procedure. This apparent delay in endoscopy reflects both the suitability of these ill patients for anesthetic GvHD affecting other organs requiring treatment and the availability of access to GI endoscopy. Despite this delay, endoscopy was still valuable to direct the direction of IST in a significant proportion of patients. Another concern of the study team was that there had been at least 6 GI histopathologists, 6 gastroenterologists, and 8 hematologists and/or transplant physicians in the 11 years studied. This will have invariably led to different management decisions over such a long time-period. Despite this, it is reassuring that endoscopy use in our center is similar to that reported elsewhere, where 18% (6), 17% (7), and 22% (8) of the transplants required endoscopy.

In considering these results, it is important to think about the broader context of flexible GI endoscopy in pediatrics. In the largest study of its kind, Attard et al recorded the frequency of complications requiring re-attendance at hospital following pediatric therapeutic (known to be higher risk than diagnostic) endoscopy procedures performed in an outpatient setting. Of 18,018 patients, only 132 (0.7%) required admission for management of any complications post-endoscopy (9). However, it is known that patients following SCT are a high-risk group even for diagnostic endoscopy. Sierra et al reviewed 1163 diagnostic upper GI endoscopies that had biopsies. The duodenal hematoma rate was significantly higher in patients post-HSCT occurring in 7% of 85 upper GI endoscopies in children post-HSCT compared to 0.09% in children that had not had HSCT (10). Duodenal hematoma has been reported in 1% (6) to 2% (11) of similar-sized series evaluating endoscopy post-HSCT. The single case of duodenal hematoma reported here is from 64 upper GI endoscopies (1.6%). GI perforation is a less frequent complication of upper and lower GI endoscopy with none reported in the large Attard et al study (9). The single case in this study from 119 procedures required laparotomy. Only one other case of perforation has been reported in children post-SCT from a series of 418 procedures but sadly for that patient it was fatal (11).

It has been attempted in previous studies to determine which biopsy sites have the highest diagnostic yield for GI-GVHD (12,13). These studies suggest that GI-GvHD is most likely to be found in biopsies from the recto-sigmoid but that upper GI tract biopsies may show GI-GVHD in a small number of cases when biopsies from the recto-sigmoid are negative (7,12,13). This study has found that if the clinicians had performed an isolated upper GI endoscopy, the GvHD diagnosis would have been missed in 17% (5/29) of cases and if performing isolated lower GI tract biopsies the diagnosis would have been missed in 14% (4/29) of cases.

CONCLUSIONS

Endoscopy is deemed to be a useful investigation by clinicians and leads to active treatment changes in at least two-thirds of children undergoing this procedure post-HSCT. Sigmoidoscopy should be combined with upper GI endoscopy to increase the yield from an endoscopy episode. Endoscopy in children post-HSCT carries around a 3% risk of complications. This patient population is particularly vulnerable to morbidity and mortality either from their disease or management pathways, so it is vital that pediatric gastroenterologists play an active role in liaising with transplant physicians to fully inform patients and their families during the consent process on the increased risk of diagnostic endoscopy.

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