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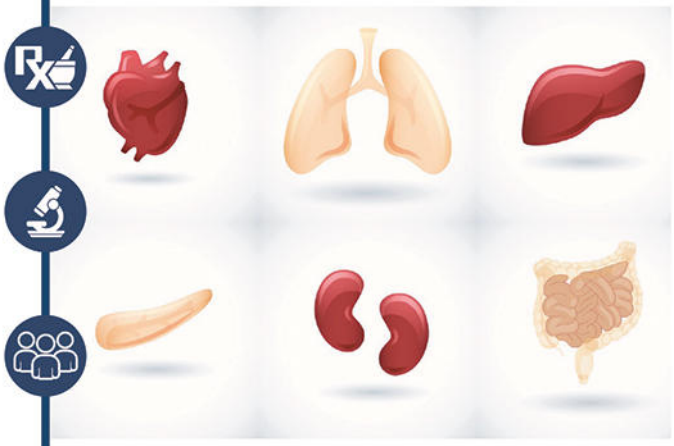

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Clinical relevance of endoscopy with histopathological assessment in children with suspected gastrointestinal graft-versus-host disease

Thomas Mårtensson[1] | Karin Mellgren[2] | Jacek Toporski[3] | Johan Arvidson[4] | Attila Szakos[5] | Thomas H. Casswall[1] | Britt Gustafsson[1]

[1]Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden

[2]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]Department of Pediatrics, Skåne University Hospital, Lund, Sweden

[4]Department of Women´s and Children´s Health, Uppsala University Children's Hospital, Uppsala, Sweden

[5]Department of Clinical Pathology and Cytology, Karolinska University Hospital, Stockholm, Sweden

Correspondence
Thomas Mårtensson, MD, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Novum, Blickagången 6A, S-141 57 Huddinge, Sweden.
Email: thomas.martensson@ki.se

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Abstract

Endoscopy with histopathological assessment is an established practice to confirm gastrointestinal graft-versus-host disease (GI-GVHD). However, the clinical relevance of this approach in children is incompletely evaluated. In a retrospective cohort study, we investigated the frequency of treatment changes in response to histopathological findings in all children (<18 years) in Sweden who underwent endoscopy for suspected GI-GVHD (2000-2013) after receiving hematopoietic stem cell transplantation. Sixty-eight children with ninety-one endoscopic occasions were enrolled. At the time of endoscopy, anti-GI-GVHD treatment was ongoing in 71% (65/91). In 18% (12/65) with ongoing treatment, no histopathological evidence of GI-GVHD or another cause to justify anti-GI-GVHD treatment was found. In 48% (44/91), endoscopy with histopathological assessment led to changes in the treatment regimen. Re-endoscopy was more frequent among those with treatment changes, versus unchanged treatment, 39% (17/44) and 13% (6/47), respectively (P = .007). Histopathological findings generating treatment changes were as follows: GI-GVHD in 68% (30/44), normal histology in 25% (11/44), and an alternative diagnosis in 7% (3/44). In conclusion, this study supports that endoscopy with histopathological assessment should be considered in all children with suspected GI-GVHD.

KEYWORDS

children, endoscopy, gastrointestinal graft-versus-host disease, hematopoietic stem cell transplantation, histopathology, treatment change

1 | INTRODUCTION

Graft-versus-host disease affecting the gastrointestinal tract (GI-GVHD) is an important success-limiting factor in allogeneic hematopoietic stem cell transplantation (HSCT).[1-3] Despite the potentially protective influence of age below 18 years, acute GI-GVHD (aGI-GVHD) stages III-IV still carries a 2-year mortality risk of 45%-55% in children following HSCT.[1,2]

Symptoms associated with GI-GVHD are non-specific, and so endoscopy with histopathological verification is recommended.[4-7]

Thomas H. Casswall and Britt Gustafsson Shared last authorship.

However, endoscopy with biopsy sampling from the gastrointestinal tract in children requires general anesthesia in most cases,[8,9] contributing to the medical risk and resource burden of the procedure.[10-12]

Only one previous pediatric study has evaluated the clinical importance of histopathological assessments of gastrointestinal biopsies in children with clinically suspected GI-GVHD.[13] In that study, treatment changes were defined as *initiating* or *escalating* anti-GI-GVHD treatment but did not include *dose reduction* or *withdrawal* of treatment. However, *dose reduction* or *withdrawal* of anti-GI-GVHD drugs is of particular interest, since one- to two-thirds of children undergoing endoscopy for clinically suspected GI-GVHD are already on anti-GI-GVHD treatment at the time of the endoscopy.[13,14] Furthermore, the potentially harmful effects of anti-GI-GVHD drugs[15-18] underscore the importance of evaluating the coherence between pre-endoscopy initiation of anti-GI-GVHD treatment and histopathology-based confirmation of the GI-GVHD diagnosis.

The present study was based on the hypotheses that a) endoscopy with histopathological assessment, performed to confirm suspected pediatric GI-GVHD, has a substantial impact on the pharmacological treatment regimen, and that b) histopathology-guided adjustment of the treatment influences prognosis. To test these hypotheses, the primary objective of the study was to evaluate the frequency of treatment changes in response to histopathology findings. The secondary objectives were as follows: (a) to evaluate whether histopathological findings of GI-GVHD are identified in the endoscopic biopsies of children who have anti-GI-GVHD treatment initiated based on clinical symptoms prior to endoscopy, and (b) to compare the 2-year post-HSCT survival rate in individuals with and without treatment changes, based on the histopathology reports.

2 | PATIENTS AND METHODS

2.1 | Design and inclusion criteria

This was a retrospective cohort study, including all pediatric HSCT centers in Sweden (Gothenburg, Lund, Stockholm, Uppsala). Participants were identified via hospital record databases, local registers of HSCT-treated children, and pathology databases. The inclusion criteria were as follows: (a) HSCT performed during 2000-2012, (b) age below 18 years at the time of the transplantation, (c) gastrointestinal endoscopy with biopsy sampling performed within the first year following HSCT, due to clinically suspected GI-GVHD, and (d) available histopathology reports.

2.2 | Outcome parameters

2.2.1 | Primary outcome parameter

Frequency of treatment changes: *initiation*, *dose escalation*, *dose reduction* or *withdrawal* of anti-GI-GVHD treatment, and *other changes* to medication triggered by the histopathological findings.

2.2.2 | Secondary outcome parameters

(a) Agreement between initiation of anti-GI-GVHD treatment (at least one day before endoscopy), and confirmed histopathology-based GI-GVHD diagnosis, and (b) 2-year post-HSCT survival rate in individuals with and without treatment changes based on histopathology reports.

2.3 | Endoscopic occasion

Endoscopic occasion was defined as any single diagnostic endoscopy procedure, regardless if solely upper or lower endoscopy was performed or if the occasion included combined upper and lower procedures.

2.4 | Data sources and subgroups

The study was based on data from histopathology reports and hospital records. Data collected from the hospital records included clinical background information, symptom-based GI-GVHD severity stage, changes in drug treatment prompted by histopathological findings, survival, cause of death, and result from cytomegalovirus (CMV) screening (whole blood, quantitative real-time PCR). If information regarding treatment change was lacking in the medical records, classification as treatment change was only done if the change was made in agreement with the histopathology report and was made subsequent to, but within 14 days of the histopathology report being issued.

The study population was divided dichotomously according to whether participants had a treatment change or not, guided by their histopathology report following endoscopy.

2.5 | Histopathology reports and number of biopsied regions of the GI tract

All endoscopic occasions with a histopathology report indicating a suggestion of GI-GVHD were classified as GI-GVHD. Thus, phrases in the histopathology reports, such as “possible,” “slight,” and “minimal”, were judged as GI-GVHD.

The GI tract was divided into different regions to define the extent of the endoscopic procedures, using an approach described previously.[14]

2.6 | Symptom-based diagnosis and staging of GI-GVHD

In the present study, clinical GVHD classification criteria and clinical severity staging have been performed in accordance with the *National Institutes of Health (NIH) 2014* criteria for chronic GI-GVHD

(cGI-GVHD)[19] and the *Mount Sinai aGVHD International Consortium* (MAGIC) criteria for aGI-GVHD.[4] Thus, classification of cGI-GVHD based on the previous definition (onset of symptoms >100 days post-HSCT), but without diagnostic signs of cGI-GVHD, was re-classified as aGI-GVHD. Furthermore, for aGI-GVHD, the *MAGIC* staging groups for clinical disease severity[4] were merged into two: stages I-II and stages III-IV. For individuals re-classified from cGI-GVHD to aGI-GVHD, mild cGI-GVHD was re-staged as aGI-GVHD "stages I-II"; moderate to severe cGI-GVHD was re-staged as aGI-GVHD "stages III-IV".

2.7 | Survival

Death within 24 months post-HSCT was assessed from the first endoscopy date and forward. Survival analysis was performed comparing the group with treatment changes versus the group without treatment changes.

2.8 | Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethics Committee, Stockholm, Sweden.

2.9 | Statistics

Endoscopic occasion has been the main unit for analyses performed in this study. In individuals who underwent more than one endoscopic occasion, each was considered to be independent in the analyses.

Variables were summarized as frequencies and percentages, means with standard deviations (SD), and medians with interquartile ranges (IQR), as appropriate. Fisher's exact test was used to compare categorical data between different subgroups of the study population. For numerical data, the corresponding method was *t* test for normally distributed data, and Mann-Whitney *U* test for non-normally distributed data. In both cases, calculations were performed with exclusion of missing data. For the comparison of survival rate between the treatment change and unchanged treatment group, a stratified proportional cox regression analysis was performed. In that analysis, patients with recurrent events (ie, more than one endoscopy performed) the first endoscopic occasion contributed to the survival function until the time point of the next endoscopy but was censored thereafter. Data analysis was performed using R version 3.4.4, and statistical significance was defined as $P < .05$.

3 | RESULTS

A total of 68 children with 91 endoscopic occasions fulfilled the inclusion criteria and had data available on treatment changes influenced by histopathology reports (Figure 1). Twenty-three procedures were re-endoscopies. The study population included 61.8% boys (42/68) and 38.2% girls (26/68), and the mean age at the time of HSCT was 9.0 (SD 5.5) years. A malignant blood disease was the cause of HSCT in 75.0% (51/68), the most common being acute lymphoblastic leukemia (21/51) (Table 1). The median duration from HSCT to endoscopy was 81 days (IQR 37-153). Pre-endoscopically, none fulfilled the criteria of cGI-GVHD. Thus, all individuals had symptom-based aGI-GVHD at the time of the endoscopy. Anti-GI-GVHD treatment was ongoing at the time of the endoscopic occasion in 71.4% (65/91) and consisted of systemic steroids in 59/65 (90.8%) (Table 2). The median number of days with the treatment before endoscopy was 13 (IQR 4.75-34.0).

3.1 | Histopathology-based diagnoses

Immunohistochemical staining for CMV was performed as a part of the histopathological assessment in 84.6% (77/91) of the endoscopies. The median number of biopsied regions per endoscopic occasion was 6.0 (IQR 3.0-10.0).

Including normal and non-specific histological findings, 98 histopathological diagnoses were established among the 91 endoscopic occasions performed. GI-GVHD was the most frequently observed diagnosis, seen in 57.1% (52/91), followed by normal or non-specific findings in 37.4% (34/91), and an alternative diagnosis in 13.2% (12/91). In seven endoscopic occasions, histopathological assessments detected GI-GVHD and a concomitant alternative diagnosis. In five of them, GI-GVHD was detected together with positive immunohistochemical staining of CMV, in one together with esophagitis, and finally in one together with reactive gastritis (Table 3).

In the 23 re-endoscopies, the histopathological assessment revealed a GI-GVHD diagnosis in 52.2% (12/23), normal findings in 39.1% (9/23), and an alternative diagnosis in 8.7% (2/23) (CMV in one re-endoscopy and esophagitis in one). The corresponding figures for the first endoscopic occasion among those with serial endoscopies were as follows: GI-GVHD in 68.7%, normal findings in 25.0%, and an alternative diagnosis in 6.3%. These results did not differ significantly compared to histopathology findings from the subsequent re-endoscopies.

3.2 | Start of anti-GI-GVHD treatment pre-endoscopically, and confirmed histopathology-based GI-GVHD diagnosis

At the time of endoscopy, anti-GI-GVHD treatment was ongoing in 71.4% (65/91), and not ongoing in 28.6% (26/91). Based on the results from the histopathology reports, a total of 63.1% (41/65) with ongoing, and 42.3% (11/26) without anti-GI-GVHD treatment at the time of the endoscopy were diagnosed with GI-GVHD ($P = .100$). Furthermore, another twelve endoscopic occasions with ongoing anti-GI-GVHD treatment at the time of endoscopy, but without histopathological evidence of GI-GVHD, had symptoms or signs of extraintestinal GVHD, most often severe skin-GVHD (8/12). In the

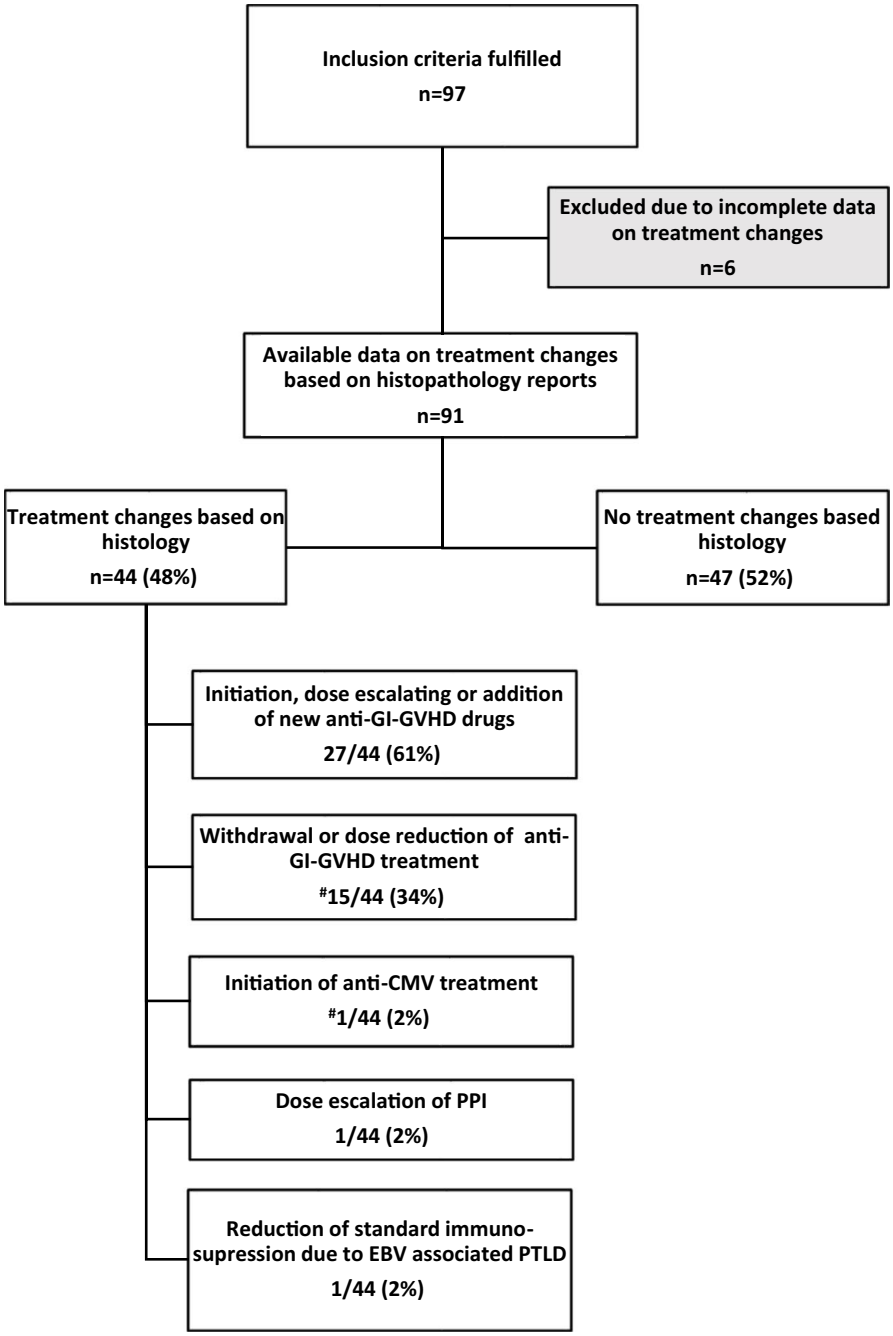

FIGURE 1 Study flowchart, from inclusion to changes in pharmacological treatment based on histopathology reports. #One endoscopic occasion resulted in simultaneous withdrawal of anti-GI-GVHD drugs and initiation of anti-CMV treatment. (GI-GVHD, gastrointestinal graft-versus-host disease; PPI, proton pump inhibitor; PTLD, post-transplant lymphoproliferative disorder)

remaining 18.5% (12/65) with ongoing anti-GI-GVHD treatment at the time of endoscopy, no histological evidence of the GI-GVHD diagnosis or other clinical causes justifying treatment with anti-GVHD drugs were found. The median (IQR) number of biopsied regions of the GI tract in these 12 endoscopic occasions was 6.5 (IQR 3.7-8.0).

3.3 | Treatment changes based on histopathology reports

Overall, histopathology-based treatment changes occurred after 44/91 (48.3%) of the endoscopic occasions (Figure 1). In one, a dual treatment change was initiated after endoscopy, that is, withdrawal of anti-GI-GVHD drugs and initiation of anti-CMV treatment.

Re-endoscopies were followed by a treatment change in 73.9% (17/23). Furthermore, re-endoscopies were statistically significantly more frequent in the treatment change group compared with the unchanged treatment group (P = .007) (Table 2).

In the treatment change group and unchanged treatment group, respectively, frequencies of histopathology-based GI-GVHD diagnosis were 30/44 (68.2%) and 22/47 (46.8%). The corresponding figures for normal histology were 11/44 (25.0%) and 23/47 (48.9%), respectively. Finally, an alternative diangosis was made in 3/44 (6.8%) in the treatment change group and in 9/47 (19.1%) in the unchanged treatment group.

TABLE 1 Baseline HSCT data of 68 children with gastrointestinal endoscopy performed for clinically suspected gastrointestinal GVHD

	Treatment change[a] n = 27 (%)	Unchanged treatment[a] n = 41 (%)	*P*
Gender			.612
Boys	18 (66.7)	24 (58.5)	
Girls	9 (33.3)	17 (41.5)	
Age (y) at HSCT			.370
Mean (SD)	9.9 (5.6)	8.7 (5.5)	
Underlying diagnosis for HSCT			.849
Blood malignancies	20 (74.1)	31 (75.6)	
Benign blood diseases	1 (3.7)	1 (2.4)	
Immunodeficiency diseases	4 (14.8)	4 (9.7)	
Miscellaneous	2 (7.4)	5 (12.2)	
Stem cell source			.419
Bone marrow	15 (55.6)	26 (63.4)	
Peripheral blood stem cells	7 (25.9)	12 (29.3)	
Umbilical cord blood	5 (18.5)	3 (7.3)	
Donor type[b]			.543
Unrelated	12 (54.5)	26 (68.4)	
Haploidentical	5 (22.7)	6 (15.8)	
Sibling	5 (22.7)	6 (15.8)	
HLA antigen compatibility[b]			.548
Match	12 (54.5)	26 (68.4)	
≥ one antigen mismatch	7 (31.8)	10 (26.3)	
Missing data	3 (13.6)	2 (5.3)	
Conditioning regimen			.338
Myeloablative	23 (85.2)	31 (75.6)	
Reduced intensity	3 (11.1)	9 (22.0)	
Missing data	1 (3.7)	1 (2.4)	
Irradiation in the conditioning regimen			.273
Yes	9 (33.3)	9 (22.0)	
No	17 (63.0)	32 (78.0)	
Missing data	1 (3.7)	0	
Stem cell dose			.138
≤4.0 × 10^6 CD34+ cells/kg BW	9 (33.3)	6 (14.6)	
>4.0 × 10^6 CD 34+ cells/kg BW	15 (55.6)	26 (63.4)	
Missing data	3 (11.1)	9 (22.0)	
GVHD prophylaxis			.443
Cyclosporine and Methotrexate	8 (29.6)	20 (48.8)	
Tacrolimus ± other ISD	10 (37.0)	12 (29.3)	
Mycophenolate mofetil ± other ISD	4 (14.8)	5 (12.2)	
Cyclosporine and Prednisolone	3 (11.1)	2 (4.9)	
Miscellaneous	2 (7.4)	1 (2.4)	
Missing data	0	1 (2.4)	

Abbreviations: BW, body weight; GVHD, graft-versus-host disease; ISD, immunosuppressive drugs; SD, standard deviation.

[a]Based on histopathology reports.

[b]Cord blood transplantations excluded.

TABLE 2 Clinical background data of 91 endoscopic occasions performed in 68 children for suspected GI-GVHD

	Treatment change[a] n = 44 (%)	Unchanged treatment[a] n = 47 (%)	*P*
Endoscopy timing—days post-HSCT			.809
Median (IQR)	81 (37-151)	76 (35-156)	
Days from onset of symptoms to endoscopy			.963
1-7 d	13 (29.5)	14 (29.8)	
8-30 d	20 (45.5)	20 (42.6)	
>30 d	10 (22.7)	12 (25.5)	
Missing data	1 (2.3)	1 (2.1)	
Symptoms at time of endoscopy			
Diarrhea	39 (88.6)	37 (78.7)	.263
with grossly bloody stool	12 (27.3)	4 (8.5)	**.027**
Nausea or vomiting	27 (61.4)	29 (61.7)	1.000
Abdominal pain	23 (52.3)	23 (48.9)	.835
Weight loss	8 (18.2)	13 (27.7)	.327
Solely non-diarrheal GI symptoms	5 (11.4)	10 (21.3)	.263
Ongoing anti-GI-GVHD treatment at time of endoscopy			
Yes	34 (77.3)	31 (66.0)	.336
Median number of treatment days (IQR)	11.0 (4.0-47.0)	15.0 (7.0-30.0)	.745
Type of treatment[b]			
Prednisolone or other systemic steroids	29 (85.3)	30 (96.8)	.200
Budesonide	9 (26.5)	6 (19.3)	.565
Miscellaneous	11 (32.3)	4 (12.9)	.081
Severity of GI-GVHD symptoms[c]			.519
aGI-GVHD stages I-II	27 (61.4)	32 (68.1)	
aGI-GVHD stages III-IV	17 (38.6)	15 (31.9)	
Number of biopsied regions of the GI tract			.350
Median (IQR)	6.0 (3.5-8.0)	6.0 (4.0-11.2)	
Re-endoscopies			**.007**
Number	17 (38.6)	6 (12.8)	
Donor lymphocyte infusion			.730
Yes	5 (11.9)	4 (8.5)	
Missing data	2 (4.5)	0	
IV antibiotics during ≥3 consecutive days[d]			.294
Yes	23 (52.3)	30 (63.8)	
CMV-PCR in whole blood[e]			.084
<2000/mL	33 (75.0)	41 (87.2)	
≥2000/mL	10 (22.7)	4 (8.5)	
Missing data	1 (2.3)	2 (4.3)	

Abbreviations: aGI-GVHD, acute graft-versus-host disease in the gastrointestinal tract; IQR, interquartile range; IV: intravenous.

[a]Based on histopathology reports.

[b]Based on the total number with ongoing anti-GI-GVHD treatment in each group.

[c]At the time of endoscopy.

[d]Within 21 d preceding the endoscopy.

[e]Highest value within 21 d before the endoscopy. If analyzed in serum or plasma, conversion into units for whole blood was performed by a factor of 0.18 log.[31]

TABLE 3 Histopathological diagnoses based on biopsies collected during 91 pediatric endoscopic occasions performed for clinically suspected gastrointestinal GVHD

Histopathological diagnosis	n = 98[a]	%
GI-GVHD *(all)*	**52**	53.1
Acute GI-GVHD	*49*	
Chronic GI-GVHD	*3*	
Alternative diagnosis (all)	**12**	12.2
CMV	*6*	
PTLD (EBV associated)	*2*	
Esophagitis	*2*	
Aphthous colitis	*1*	
Reactive (chemical) gastritis	*1*	
Normal or non-specific findings	**34**	34.7

Abbreviations: EBV, Epstein-Barr virus; GI-GVHD, graft-versus-host disease in the gastrointestinal tract; PTLD, post-transplant lymphoproliferative disorder.

[a]Simultaneous detection of GI-GVHD and an alternative diagnosis in 7 endoscopic occasions (5/8 CMV, 1/8 esophagitis, 1/8 reactive gastritis).

3.3.1 | GI-GVHD

In 27 out of 30 endoscopic occasions with a treatment change due to histopathology-based GI-GVHD diagnosis, treatment adjustment consisted of *initiation*, *dose escalation*, or *addition of a second- or third-line* anti-GI-GVHD drug. In the remaining three endoscopic occasions with GI-GVHD, all with ongoing anti-GI-GVHD treatment at the time of the endoscopy, the histopathological pattern was less severe than expected, and thus, anti-GI-GVHD treatment was reduced. These three endoscopic occasions, together with 12 with ongoing anti-GI-GVHD treatment at the time of the endoscopy, but with either normal histopathological findings (11/12) or CMV enteritis (1/12), represent all cases with withdrawal or dose reduction of anti-GI-GVHD treatment (Figure 1).

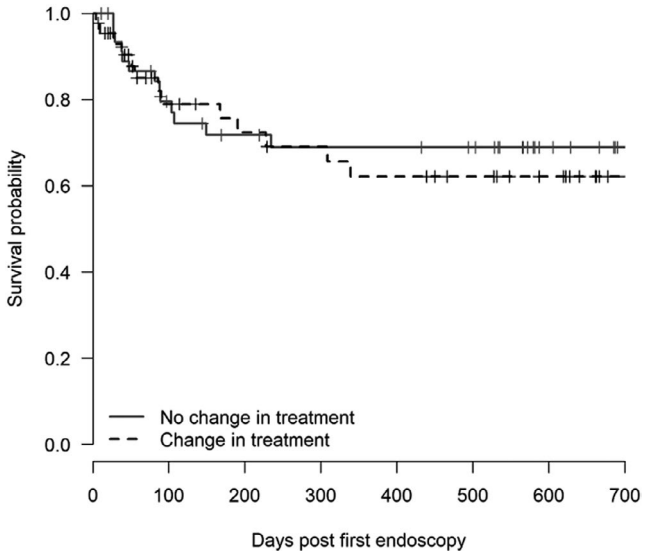

FIGURE 2 Probability of survival based on 91 endoscopic occasions—*treatment change* versus *unchanged treatment*, guided by histopathology reports (Hazard ratio 1.28, 95% CI 0.60-2.70, *P* = .524)

3.3.2 | CMV

Histopathological assessments detected six cases with positive immunohistochemical staining for CMV (Table 3). In one, the result was interpreted as CMV enteritis and anti-CMV treatment was started (Figure 1). In the remaining five, anti-CMV treatment was already ongoing (n = 3), or the finding was interpreted as of "subordinate importance" (n = 2).

3.3.3 | Post-transplant lymphoproliferative disorder (PTLD)

Histopathological assessment after two endoscopic occasions identified PTLD with positive EBER in situ hybridization staining (Epstein-Barr virus-encoded RNAs) (Table 3), one of which was not suspected at the time of the endoscopy. That child, therefore, had a reduction of the standard immunosuppression (Figure 1). In the other child, the disease was known at the time of the endoscopy, but not the involvement of the GI tract. Thus, in the latter, anti-PTLD treatment was ongoing at the time of the endoscopy.

3.3.4 | Esophagitis

Esophagitis was identified after two endoscopic occasions, and in both cases treatment with a proton pump inhibitor was ongoing at the time of the endoscopy (Table 3). However, a dose escalation was initiated in one individual, based on the histopathological report (Figure 1).

3.4 | Risk factors for mortality in the treatment change versus unchanged treatment group

Grossly bloody diarrhea was more frequently present at the time of endoscopy in the treatment change group than in the unchanged treatment group, 27. 3% (12/44) versus 8.5% (4/47), respectively (*P* = .027) (Table 2). However, no significant differences were observed regarding other prognostic factors, such as symptom-based disease severity score, lower GI tract symptoms, HLA antigen mismatch, use of unrelated donors, or duration of anti-GI-GVHD treatment (Tables 1 and 2).

3.5 | Survival

The 2-year post-HSCT overall survival for the entire study population was 61.7% (42/68). In a subgroup analysis of the probability of

TABLE 4 Causes of death within 2 y post-HSCT in 26 children with endoscopy performed for suspected gastrointestinal GVHD

Causes of death	All n = 26 (%)	Treatment change[a] n = 13 (%)	Unchanged treatment[a] n = 13 (%)
Infection	10 (38.5)	6 (46.1)	4 (30.8)
PTLD (EBV associated)	2 (7.7)	0	2 (15.4)
GVHD *(All)*	7 (26.9)		
GI-GVHD		3 (23.1)	1 (7.7)
Liver-GVHD		1 (7.7)	2 (15.4)
Relapse	7 (26.9)	3 (23.1)	4 (30.8)

Abbreviations: EBV, Epstein-Barr virus; GI-GVHD, graft-versus-host disease in the gastrointestinal tract; PTLD, post-transplant lymphoproliferative disorder.

[a]Based on histopathology reports and related to the last endoscopic occasion, if serial endoscopies were performed.

survival, no difference was observed between individuals with a treatment change based on the histopathology reports, compared with those with unchanged treatment ($P = .524$) (Figure 2). Finally, in the analysis of causes of death, no differences were observed in relapse and non-relapse mortality between the treatment change and the unchanged treatment group (Table 4).

4 | DISCUSSION

In the present study, nearly half of the endoscopic occasions were followed by a change in the pharmacological treatment regimen, defined as *initiating*, *dose escalating*, *dose reduction* or *withdrawal* of anti-GI-GVHD drugs, as well as *other* changes in medication. To our knowledge, only one previous study has examined this area, identifying a treatment change in every third child.[13] However, that study only included *initiating* or *escalating* anti-GI-GVHD treatment in their definition of treatment change.

Although all endoscopies in our study were performed for suspected GI-GVHD, an alternative histopathological diagnosis was observed in 13%. Similar and even higher frequencies of histopathological detection of alternative diagnoses from biopsies collected from children with clinically suspected GI-GVHD have been reported previously.[13,20-22] Furthermore, coexisting histopathological diagnoses were noticed in 8% of the endoscopic occasions in our study. Thus, endoscopy with subsequent histopathological assessment of biopsies appears important in detecting coexisting pathology and differential diagnoses to the GI-GVHD diagnosis.

It is recommended that endoscopy in children should be performed under general anesthesia, or under deep sedation where anesthesia is unavailable, either in an operating theater or endoscopic procedure room.[8,9] The time needed to plan and conduct endoscopy in children may well interfere with the process of accurately verifying the GI-GVHD diagnosis before starting treatment.[23] In our study, this effect may explain our observation that the majority (71%) were already receiving anti-GI-GVHD treatment at the time of the endoscopy.

Previous studies have identified the extent of the endoscopy in the GI tract as an important factor for histopathological detection of GI-GVHD.[14,21,24] In the present study, the median number of biopsied regions of the GI tract was six, which is a relatively high figure in comparison to others.[13,20,21,25] Thus, it is less likely that our study would have missed focally spread GVHD lesions.

In our study, one in five with ongoing anti-GI-GVHD treatment at the time of endoscopy had no histopathological evidence of GI-GVHD or other clinical causes to justify anti-GVHD treatment. We do not believe that this result represents endoscopically undetected GI-GVHD, since the number of biopsied regions of the GI tract in these endoscopic occasions did not differ from the remaining study population. On the contrary, we consider anti-GI-GVHD treatment as potentially unnecessary in these cases, introducing avoidable exposure to a risk of harmful effects related to the anti-GI-GVHD drugs.[15-18]

In the present study, re-endoscopies were statistically significantly more frequent in the treatment change group compared with the unchanged treatment group. In an adult patient study by Martínez et al,[26] including serial endoscopies performed for suspected GI-GVHD, treatment changes were observed after 77% of the re-endoscopies. The corresponding figure in our study was 74%. However, in contrast to Martínez et al, we could not explain this observation in relation to differences in histopathological findings between the first and subsequent endoscopies.

The overall survival rate in the present study is in line with that previously reported in a corresponding cohort.[27] However, no previous pediatric study has compared the probability of survival between those with treatment changes versus unchanged treatment, based on histopathological assessments. We observed a similar overall 2-year survival in these subgroups. This finding was unexpected since the treatment change group represented all individuals in the study cohort exposed to over- or undertreatment with anti-GI-GVHD agents during the pre-endoscopically period. Furthermore, the treatment change group was more frequently affected by the negative prognostic factor, grossly bloody diarrhea[1,28] as compared to the unchanged treatment group. Taken together, the treatment change group possibly represents the subgroup of our study

population with the less optimal survival outlook following HSCT. Although our study does not allow us to investigate causality, the observed similarity in survival between the treatment change group and the unchanged treatment group may indicate that histopathology-guided treatment change favors survival in children with clinically suspected GI-GVHD.

The results of the present study might have been influenced by its retrospective design. Furthermore, we cannot exclude the possibility that our results were affected by interobserver disagreement in histopathological diagnosis of GI-GVHD,[29,30] as the study had a multicenter design with different pathologists performing the assessments at different centers. Therefore, further studies are needed to clarify whether decisions to change treatment would have been the same if it was based on a histopathological assessment with a consistently and uniform definition used for the GI-GVHD diagnosis.

In conclusion, this study supports that endoscopy with histopathological assessment should be considered in all children with suspected GI-GVHD.

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CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

Thomas Mårtensson has been the principal responsible person for the planning and implementation of the study, for the writing process, and the collection of clinical data for patients from Stockholm. Karin Mellgren has been responsible for the identification and collection of clinical data for patients who have undergone HSCT in Gothenburg and has also been involved in the planning and implementation of the study, as well as the writing process. Jacek Toporski has been responsible for the identification and collection of clinical data for HSCT-treated children in Lund and has also been involved in the planning and implementation of the study, as well as the writing process. Johan Arvidson has been responsible for the identification and collection of clinical data for patients who have undergone HSCT in Uppsala and has also been involved in the planning and implementation of the study, as well as the writing process. Atilla Szakos has been involved in planning and implementing of the study and has been involved in the writing process. Thomas H. Casswall has been involved in the planning and implementation of the study, as well as the writing process, and has also been involved in the collection of clinical data for patients who have undergone HSCT in Uppsala. Britt Gustafsson has been involved in the planning and implementing of the study, as well as the writing process. She has also been involved in the collection of clinical data for patients who have undergone HSCT in Uppsala.

ORCID

Thomas Mårtensson https://orcid.org/0000-0002-4074-2653

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