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REVIEW ARTICLE

Gastroenterology

Intestinal involvement in graft versus host disease in children: An overview by the ESPGHAN Gastroenterology Committee

Marina Vincent[1] | **Amit Assa**[2] | **Osvaldo Borrelli**[3] | **Matjaž Homan**[4] | **Javier Martin-de-Carpi**[5] | **Zrinjka Misak**[6] | **Maria Giovanna Puoti**[7] | **Isabelle Scheers**[8] | **Sara Sila**[6] | **Caterina Strisciuglio**[9] | **Christos Tzivinikos**[10] | **Jernej Dolinsek**[11] | **Emmanuel Mas**[12]

Correspondence

Emmanuel Mas, Service de Gastroentérologie, Hépatologie, Nutrition, Diabétologie et Maladies Héréditaires du Métabolisme, 330, Ave de Grande-Bretagne, TSA 70034, 31059 Toulouse cedex 9, France.
Email: mas.e@chu-toulouse.fr

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Abstract

Graft versus host disease (GVHD) is a complication that frequently occurs after haematopoietic stem cell transplantation and concerns many children in paediatric haematology-oncology and bone marrow transplantation departments. It can affect various organs, with the skin, gastrointestinal tract and liver being the most commonly involved. To confirm intestinal GVHD and to rule out differential diagnoses endoscopy is frequently needed. Currently, there are no specific consensus recommendations concerning the best method for endoscopic exploration and medical management of this disease in children, with limited studies available, including a low number of patients. Sigmoidoscopy could be initially proposed under sedation. If sigmoidoscopy is normal or if a general anaesthesia is required, colonoscopy and upper endoscopy should be planned, avoiding duodenal biopsy because of the risk of duodenal haematoma. Regarding therapeutic options, corticosteroids are the first-line treatment for GVHD. Ruxolitinib, a Janus kinase inhibitor, is indicated for children aged 12 years and older with acute or chronic GVHD who have an inadequate response to corticosteroids or other systemic therapies. Nutritional support has a key role in the management of intestinal GVHD and should be considered to guarantee the best possible evolution of intestinal GVHD.

KEYWORDS

endoscopy, haematopoietic stem cell transplantation, intestine

1 | INTRODUCTION

Graft versus host disease (GVHD) is a multisystemic disease that frequently occurs after allogenic haematopoietic stem cell transplantation (HSCT). It results from recognition by the donor's T cells of the recipient's cells, which leads to an immune reaction and damages of the target tissues for acute-GVHD (aGVHD).[1] The pathophysiology of chronic-GVHD (cGVHD) is more complex, involving inflammation, cell-mediated and humoral immunity and fibrosis.[2]

For affiliations refer to page 253.

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HSCT consists of two steps: a conditioning phase and stem cell transplantation. Conditioning (myeloablative or non-ablative) provides the immunosuppression required for graft acceptance; it is based on chemotherapy and sometimes total body irradiation. Three types of haematopoietic stem cells can be transplanted: from bone marrow (BM), peripheral blood (PB) and cord blood (CB).[3]

1.1 | Incidence

Between 2004 and 2017, 41.0 ± 3.6% of children and young adults who received an unrelated donor stem cell transplant for acute leukaemia developed Grades II–IV aGVHD.[4] The incidence was higher in older patients (13–21 years, $n = 70$) than in younger ones (2–12 years, $n = 118$), 55.7 ± 5.9% and 32.2 ± 4.3%, respectively. There was no significant difference in cumulative incidence of cGVHD between adolescents/young adult patients and younger children (26.5 ± 5.9% vs. 20.2 ± 4.0%).

1.2 | Risk factors

In 55 children, multivariate analysis revealed that significant risk factors of cGVHD were previous aGVHD, malignant disease, recipient age (>10 years), and a female donor to male recipient.[5] When aGVHD was excluded, malignant disease and older recipient age remained risk factors.

Multivariate analysis of children with cGVHD ($n = 51$) and late aGVHD ($n = 60$) revealed that risk factors of cGVHD were Grades II–IV aGVHD, PB grafts and recipient age ≥12 years.[6] The risk was reduced by a GVHD prophylaxis regimen using a calcineurin inhibitor and mycophenolate mofetil rather than a calcineurin inhibitor and methotrexate. Only a history of Grades II–IV aGVHD and PB grafts were significantly associated with an increased risk of late aGVHD.

Children who underwent CB ($n = 113$) had a lower incidence of aGVHD and cGVHD than recipients of BM ($n = 2052$) transplant, from human leucocyte antigen-identical siblings.[7]

1.3 | Affected locations

GVHD can involve the skin, the liver, and the upper and lower intestinal tract.[8]

In cGVHD children, gastrointestinal (GI) tract (GIT) was involved in 39%, while the skin was in 62%, and the liver in 27%.[1] Another study with 173 cGVHD children reported 28% liver and 24% GI involvement.[9]

GI involvement in GVHD is frequently present and raises the problem of optimal diagnostic approach, in particular, the place of endoscopy to improve the diagnostic yield. Indeed, GI symptoms can be attributed to other diagnoses, and these patients also present operative risks, such as duodenal haematoma[10] or high anaesthetic risks; thus, endoscopy indication should be carefully assessed.

The aim of this article is to determine, with a literature review, which type of endoscopic approaches could be the most effective and the least dangerous, what are the current therapeutic strategies, and the best nutritional management.

What is Known

- Grading of acute and chronic graft versus host disease (GVHD) is based on organ involvement.
- Intestinal GVHD in children is confirmed by upper and lower gastrointestinal endoscopies if symptoms persist.
- Corticosteroids are the first-line treatment for acute GVHD.
- Parenteral nutrition is often proposed at diagnosis.

What is New

- Rectosigmoidoscopy could be the initial endoscopic assessment.
- Ruxolitinib can be considered as second-line treatment for children ≥12 years.
- Enteral nutrition is recommended, if possible, for nutritional support in children diagnosed with intestinal GVHD.

2 | GVHD SCORE AND GRADING

The classification of GVHD as acute or chronic was previously based on the time of onset of symptoms (aGVHD before Day 100 of HSCT), while it is now based on the type of symptoms (Table 1).[8] Late aGVHD is defined by the same manifestations as aGVHD, but starting after Day 100 of HSCT.

2.1 | Clinical scores of aGVHD

The first step includes the evaluation of each organ from Stages 0 to 4 (Table 2).[7] Subsequently, the severity of GVHD is classified from Grades I to IV depending on the severity and the number of involved organs. Several scores are available in the literature (Table 3). In the 1970s, the Glucksberg classification staged the involvement of skin, lower GIT, and liver,

each one on a scale from 0 (absent) to 4 (severe) points, to create a final overall grade of I (mild) to IV (life-threatening). The International Bone Marrow Transplant Registry (IBMTR) aGVHD classification is an alternative based on similar raw organ staging and resulted in a final grade of A–D (Table 3); it provides a slightly more accurate prediction of mortality. In 2016, the Mount Sinai Acute GVHD International Consortium (MAGIC) revisited these criteria, and is considered the most updated and detailed to diagnose and score the severity of aGVHD, especially for the clear establishment of clinically significant upper GIT symptoms and Stage 4 skin and GIT involvement.[8]

2.2 | Clinical scores of cGVHD

In 2014, the National Institute of Health (NIH) revised and adapted to children the grading score for cGVHD, which included involvement of GIT and/or liver. Intestinal cGVHD grading depends on the child weight loss.[1]

TABLE 1 Symptoms of acute and chronic GVHD.

Acute GVHD		Chronic GVHD	
Skin	Maculopapular rash	Skin	Lichen planus or skin manifestations of scleroderma
Upper GIT tract	Persistent nausea and/or vomiting	GIT tract	Dryness of the oral mucosa
Lower GIT tract	Abdominal pain		Weight loss
	Watery diarrhoea		Ulcerations/fibrosis of the GIT
	Bloody diarrhoea		
	Ileus		
Liver	Elevated bilirubin	Liver	Elevated bilirubin

Abbreviations: GIT, gastrointestinal tract; GVHD, graft versus host disease.

The grade of liver damage is determined in the same way for aGVHD and cGVHD, using the total bilirubin level (Supporting Information S1: Table 1).[11]

3 | CLINICAL FINDINGS

GVHD involves the upper GIT in 24%–60% of patients; the most common symptoms are anorexia with weight loss, nausea >3 days, vomiting >2 episodes/day lasting at least 2 days and dyspepsia.[12] Lower GIT involvement presents with symptoms such as diarrhoea, abdominal pain, functional ileus up to obstruction and gut bleeding. Staging of lower GIT involvement is based on the precise measurement of daily stool volume and documentation of the presence of rectal bleeding or severe abdominal pain. The most severe stage is characterized by severe abdominal pain, ileus and/or bloody stools (Table 2).[12]

Liver involvement is less common, but has a poor prognosis, based on total serum bilirubin levels.[13] The diagnosis must be cautious because hyperbilirubinemia may result from other causes such as chemotherapy toxicity or parenteral nutrition (PN)-associated liver disease, and transaminase increase without hyperbilirubinemia could be explained by many other causes.[12]

4 | ENDOSCOPIC ASSESSMENT

4.1 | Macroscopic findings

A retrospective study compared the macroscopic and pathological findings of 175 adults after HSCT. These patients had both endoscopic and histological assessment, at least 20 days post-allogeneic HSCT, and they did not have any identified infectious disease. The macroscopic criteria for diagnosing and grading

TABLE 2 GVHD severity stages of involved organs.

Stage	Skin	Liver	Upper GIT	Lower GIT
0	No active rash	Total bilirubin <34 µmol/L	No/intermittent nausea, vomiting or anorexia	Stool volume <10 mL/kg/day or <4 episodes/day of diarrhoea
1	Maculopapular rash <25% BSA	Total bilirubin 35–51 µmol/L	Persistent nausea, vomiting or anorexia	Stool volume <20 mL/kg/day or <6 episodes/day of diarrhoea
2	Maculopapular rash 25%–50% BSA	Total bilirubin 52–102 µmol/L		Stool volume <30 mL/kg/day or <10 episodes/day of diarrhoea
3	Maculopapular rash >50% BSA	Total bilirubin 103-255 µmol/l		Stool volume >30 mL/kg/day or >10 episodes/day of diarrhoea
4	Generalized erythroderma + bullous formation and desquamation >5% BSA	Total bilirubin >255 µmol/L		Severe abdominal pain with or without ileus or grossly bloody stool

Abbreviations: BSA, body surface area; GIT, gastrointestinal tract; GVHD, graft versus host disease.

TABLE 3 aGVHD scores.

aGVHD grading	Glucksberg	Modified Glucksberg	MAGIC	IBMTR	IBMTR grading
0	No organ involvement: absence of GVHD				0
I	Skin: stages 1 or 2, no GIT/liver involvement, no PS decrease	Skin: stages 1 or 2, no GIT/liver involvement		Skin: stage 1, no GIT/liver involvement	A
II	Skin: stages 1 or 2, GIT/liver: stages 1 or 2, mild PS decrease	Skin: stage 3 and/or liver: stage 1 and/or GIT: stage 1		Skin: stage 2 and/or liver: stage 1 or 2 and/or GIT: stage 1 or 2	B
III	Skin and/or liver and/or GIT: stages 2, 3 or 4 and marked PS decrease	Liver: stages 2 or 3 and/or GIT: stages 2, 3 or 4	Liver: stages 2 or 3 and/or GIT: stages 2, 3	Skin: stage 3 and/or liver: stage 3 and/or GIT: stage 3	C
IV	Skin and/or liver and/or GIT: stages 2 or 3 or 4 and Karnofsky <30%	Skin: stage 4 and/or Liver: stage 4	Skin: stage 4 and/or liver: stage 4 and/or GIT: stage 4		D

Abbreviations: aGVHD, acute graft versus host disease; GIT, gastrointestinal tract; IBMTR, International Blood and Marrow Transplant Research; MAGIC, Mount Sinai Acute GVHD International Consortium; PS, performance status.

GI-GVHD were based on the Freiburg Criteria (Supporting Information S1: Table 2).[14] The authors demonstrated that using the modified 'Freiburg Criteria' for ileo-colonoscopy, macroscopic changes had both high sensitivity (89.2%) and specificity (79.4%) for diagnosing aGVHD, and they could promote rapid decision-making.

4.2 | Endoscopic explorations

Endoscopy is frequently needed to confirm GI-GVHD and to rule out infectious diseases.[15] The treatment could be changed according to the biopsy results.[16] There is no recommendation regarding the best endoscopic evaluation for GI-GVHD diagnosis in children. Studies are retrospective and include small samples (Table 4).[15–23] They reported that the use of rectosigmoidoscopy was reliable, with a good sensitivity,[23] often superior to upper GIT endoscopy,[15,17,19] and a negative predictive value (NPV) similar to upper GIT endoscopy.[18,19] Sensitivity for different sites of upper GIT (stomach, duodenum and oesophagus) was different in each study.[15,17–19,21,22] If upper GIT endoscopy is performed in addition to rectosigmoidoscopy, the sensitivity is equal to that of upper GIT endoscopy and total colonoscopy.[17] The aforementioned studies suggest that lower endoscopy is as efficient as upper endoscopy. Moreover, in some studies, rectosigmoidoscopy provides the same diagnostic yield as colonoscopy, and it does not require a general anaesthesia. However, a study reported a better diagnostic yield with right colonoscopy than rectosigmoidoscopy alone.[22] If the macroscopic results of the colonoscopy are in favour of GI-GVHD, upper GIT endoscopy could be done at the same time.

Complications reported: duodenal haematomas (4 in 198 patients, one combined with pancreatitis, and 1 in 79 patients respectively),[10,15,16] duodenal bleeding (8 in 198 patients)[15] with perforation (1 in 13 patients),[19] and one patient died after splenic flexure perforation.[15]

Adult studies had larger cohorts. Lower endoscopy was more sensitive than upper GIT endoscopy (50% vs 39%), with sigmoid (48%) and rectum (45%) more affected than duodenum (38%) and stomach (27%).[24] Another study confirmed that rectosigmoid biopsies had the highest sensitivity, specificity, positive predictive value (PPV) and NPV for GI-GVHD diagnosis, 95.6%, 100%, 100% and 84%, respectively (sensitivity of gastric and duodenal biopsies was 72.5% and 79.2% respectively; NPV of gastric and duodenal biopsies was 45.6% and 52.5% respectively).[25] Moreover, upper endoscopy had a poorer diagnostic yield (44% if lower GIT symptoms and 27% if upper GIT symptoms, 50% if upper and lower symptoms) than lower endoscopy (50% if lower GIT symptoms and 53% in mixed

TABLE 4 Endoscopic studies in children with acute GI-GVHD.

First author	Year of publication	Number of patients	RS Se	UE Se	Colonoscopy Se	RS NPV	UE NPV	Additional conclusions
Khan et al.[15]	2006	191	38%	31%				4 duodenal haematomas in 198 UE
Gassas et al.[16]	2016	79						1 duodenal haematoma; positive biopsy for GVHD = 62%; higher therapeutic change for positive biopsies
Mårtensson et al.[17]	2018	44	85%	83%	97%			RS + UE 97.4% Colonoscopy + UE 100%
Sultan et al.[18]	2012	48	77%	77% (86% gastric, 50% duodenum)		61%	61%	Se and NPV of gastric biopsies were 85% and 63%, and for duodenal biopsies they were 50% and 57%, respectively
Lee et al.[19]	2016	15	87%	78% (22% oesophagus, 30% gastric, 80% duodenum)	87%	61%	50%	No difference colonoscopy and RS
Crowell et al.[20]	2013	20				67%		PPV of RS: 100%. Colonic GVHD in 90% of the time in liver disease.
Faraci et al.[21]	2022	26		57%				Se for lower endoscopy (colonoscopy or RS): 81.8%
Slae et al.[22]	2021	16			63%			Infections (± GVHD) = 42%; specific right-side findings = 38%
Nydegger et al.[23]	2007	26	64% rectum, 60% sigmoid	66% duodenum, 75% stomach, 17% oesophagus	33% right colon	64%		No usefulness of total colonoscopy; moderate discordance between gastric and duodenal biopsies

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; RS, rectosigmoidoscopy; Se, sensitivity; UE, upper endoscopy.

symptoms). The 15 sigmoidoscopies (vs. 28 colonoscopies) had often led to a diagnosis of GI-GVHD: 5/6 (83%) for mixed GI symptoms and 5/9 (55%) for lower symptoms.[26]

Taking into consideration all these studies, sigmoidoscopy could be initially proposed under sedation. If sigmoidoscopy is normal or if a general anaesthesia is required, colonoscopy and upper endoscopy should be planed, avoiding duodenal biopsy.

5 | HISTOLOGY

Histologically, the diagnosis of GI-GVHD is based on the presence of apoptosis, especially in areas of mucosal regeneration, that is, the intestinal crypts, the deeper antral glands and the neck of the gastric body glands. It is also possible to observe crypt loss, inflammation and abscesses. The Lerner grade reports the rate of apoptotic cells per section and thus gives the grade of histological activity from 0 (no alteration) to 5 (severe histological activity) (Supporting Information S1: Table 3).[1]

Criteria for the histological diagnosis and grading of GI-GVHD are well established for most of the GIT, but not for the oesophagus. In the oesophagus, histological features of aGVHD were found, ranging from vacuolar degeneration and single-cell apoptosis to the formation of clefts and mucosa denudation in advanced cases. These findings correlated with GI-GVHD involving the stomach and duodenum.[27] Another study reported that 79.1% of oesophageal biopsies had inflammatory findings such as erosions (25%), cleavage between the chorion and squamous epithelium (37.5%), lichenoid inflammatory infiltrate (41.7%), apoptotic cells (54.1%) and epithelial vacuolation (54.1%). Erosions and epithelial cleavages were more often associated with a worse outcome.[28] It has also been demonstrated that one of the endoscopic features that can be found in GI-GVHD is duodenal villous atrophy.[29]

The histology of liver GVHD shows apoptosis of cholangiocytes, hepatocytes, bile duct damage, cholestasis, fibrosis, lobular or portal inflammation with hepatitis lesions. It is also possible to find a ductopenia or on the contrary, a ductular proliferation.[1]

6 | TREATMENT

6.1 | Prophylaxis

Consensus GvHD prophylaxis regimens usually include a calcineurin inhibitor in combination with either methotrexate or mycophenolate, depending on GVHD risk (type of donor and disease). Other medications may include anti-thymocyte globulin and, less commonly, sirolimus or steroids.[30]

The decision on treatment is based on clinical signs. Endoscopy and biopsies are recommended, but they should not delay treatment initiation.

6.2 | First-line treatment in aGVHD

Systemic treatment is initiated for Grades II–IV aGVHD, while topical steroids are sufficient for Grade I, decreasing infections. The starting dose of methylprednisolone is 2 mg/kg/d, or 2-2.5 mg/kg/d prednisone. Nonabsorbable oral steroids, like budesonide (9 mg/day) or oral beclomethasone (1.3–2.0 mg, four times daily), can be given in addition to systemic corticosteroids.[31] Grade II aGVHD with isolated skin or upper GI manifestations can be treated with lower doses, such as 1 mg/kg/day methylprednisolone or prednisone.[31] The addition of immunosuppressants (mycophenolate mofetil, anti-T-cell globulin, infliximab or anti-IL2 antibody) besides steroids increases survival by 14%.[31]

Corticosteroid-resistant aGVHD (or refractory) means that there is progression after 3–5 days or no improvement after 5–7 days of treatment with 2 mg/kg/day of corticosteroids. Around one third of paediatric patients require a second-line immunosuppressive treatment.[32]

6.3 | Second-line treatment in aGVHD

There is no consensus on second-line treatment for GI-GVHD. According to the recommendations of the European Society for Blood and Marrow Transplantation, second-line treatments include immunosuppressive drugs (mycophenolate mofetil, methotrexate and sirolimus), biologics (alemtuzumab, basiliximab, daclizumab, vedolizumab, Janus kinase [JAK] inhibitors), cell therapy including mesenchymal stromal cells (MSCs), extracorporeal photopheresis, faecal microbiota transplantation, pentostatin and anti-thymocyte serum.[30]

Over 158 corticosteroid-resistant children with Grades II–IV aGvHD after HSCT, 81 required a second-line therapy; MSC therapy was used in 47%, and infliximab in 30%. In 12 patients, second-line therapy consisted of a combination of two or three of the following agents: infliximab, vedolizumab, basiliximab, MSC, etanercept, tacrolimus and/or ruxolitinib. Forty patients required an additional line of therapy (third or more).[33]

The studies concerning these second-line treatments are of a low level of evidence, except for the REACH 2 study. REACH 2 was a phase 3, randomized, multicentre study (117 centres in 22 countries) comparing the administration of ruxolitinib (a JAK inhibitor) with the best available alternative therapy (BAT) in patients over 12 years of age with Grades II–IV aGVHD

who were corticosteroid-dependent or resistant. The ruxolitinib arm included 154 patients and the BAT arm 155 patients. The overall and complete response rates at Days 28 and 56 were significantly higher in the ruxolitinib group than in the BAT group (62.3% vs. 39.4% and 39.6% vs. 21.9%, respectively, $p < 0.001$).[34]

Vedolizumab is a monoclonal antibody blocking α4β7 integrin, interfering with the homing of T cells to the GIT endothelium. A study assessed vedolizumab in 13 children with aGVHD. Ten patients were treated for corticosteroid-resistant aGVHD, six of them for severe aGVHD (Stage 3 or 4). Staging of aGVHD after the first dose of vedolizumab showed improvement in 9 out of 13 patients. On Day 56, six patients had a complete response and four patients had a partial response. The median follow-up was 13 months; eight patients had complete recovery (obtained between 15 and 170 days), two had persistent chronic colitis, and three patients died.[32]

6.4 | cGVHD treatment

6.4.1 | First-line treatment in cGVHD

According to NIH criteria, decision to start treatment is based on symptom type and severity.[30] First-line treatment is steroids (1 mg/kg/day orally).[31]

6.4.2 | Second-line treatment in cGVHD

The REACH 3 study was a randomized, open-label Phase 3 trial comparing ruxolitinib 10mg × 2 daily with investigator-selected therapy. There were 329 children over 12 years of age with chronic moderate to severe corticosteroid-dependent or resistant aGVHD. There was a greater overall response at week 24 in the ruxolitinib group vs the control group (49.7% vs. 25.6%, $p < 0.001$). There was also a longer median failure-free survival in the ruxolitinib group than in the control group (>18.6 months vs. 5.7 months; hazard ratio: 0.37; $p < 0.001$) and higher clinical response (24.2% vs. 11.0%; odds ratio: 2.62; $p = 0.001$).[35]

REACH 2 and 3 studies resulted in a positive opinion in March 2022 for early access approval of ruxolitinib for the treatment of ≥12-year-old patients with acute or chronic GVHD who have an inadequate response to corticosteroids or other systemic therapies.

Addition of other agents (azathioprine, cyclosporin, thalidomide, mycophenolate mofetil, or hydroxychloroquine) to prednisone in randomized trials failed to show a clinically meaningful benefit. In severe cGVHD, the primary addition of another immunosuppressant is a valuable option. Ruxolitinib is recommended in adults with steroid-refractory cGVHD; belumosudil and ibrutinib are potential therapeutic options.[31] There are no clear recommandations for children.

6.4.3 | Supportive treatment

Chronic pain related to GI-GVHD is often difficult to treat, causing a significant decrease in quality of life. Nonsteroidal anti-inflammatory drugs are contraindicated because of the risk of intestinal bleeding and hepatic toxicity. Long term use of ketamine has proven its effectiveness for cancer pain, and it has been safely used for cGVHD pain for a 5-year-old child.[36] Patients should be closely monitored for excessive sedation, liver toxicity, haematuria, hypertension, tachycardia or psycho-mimetic effects and slow weaning.

Intestinal haemorrhage, perforation and stricture with bowel obstruction can also occur in severe GI-GVHD. Bowel obstruction is a possible complication related to cGVHD and despite immunosuppression, it may require surgery.[37,38]

6.5 | Nutritional management

Nutrition is essential for the management of children with GVHD (Supporting Information S1: Figure 1).[39] However, currently, no consensus exists for the nutritional management of these patients.

Adequate enteral nutrition (EN) is linked to a lower incidence of both overall GVHD and acute GI-GVHD compared to PN. This benefit is attributed to EN's ability to preserve mucosal integrity, regulate the immune response to intensive chemo/radiotherapy, and support the GI environment, including gut microflora.[40]

Once GI-GVHD developed, EN use showed beneficial results. In a retrospective study, children who underwent HSCT and developed GI-GVHD were placed on a stepwise upgrade diet, including PN and EN in addition to medical treatment. Over 105 patients who underwent HSCT, 7 developed Grades III–IV acute GI-GVHD (5 Grade III and 2 Grade IV). PN was initiated in all seven patients after the diagnosis of GI-GVHD combined with minimal EN (1–2 mL/kg/day standard paediatric enteral formula/special meat soup). A special diet protocol including five steps was provided. In each step new solid foods were introduced along with EN. GI-GVHD improved with this type of nutritional support and medical treatment in all seven patients, with no change in body weight. Full oral intake was achieved in 10–30 days. The authors proposed that stepwise diet management with EN contributes to rapid improvement of the digestive tract and may accelerate the recovery period of Grades III and IV acute GI-GVHD.[41]

These findings were confirmed in adult studies.[42,43] Furthermore, they reported that EN might reduce PN-related complications (infection, venous thrombosis and metabolic disturbances),[42] and patients with EN had slower decrease in BMI as compared to the PN group and maintained more stable levels of albumin.[43]

To conclude, based on available evidence, EN is the best option both for prevention and supportive treatments of GI-GVHD.

7 | PROGNOSIS

The Minnesota score is a new risk score for GVHD.[44] It more accurately predicts response to corticosteroid therapy, survival, and mortality than other scores. Minnesota high risk (MHR) patients had a lower complete or partial response than standard risk (MSR) patients at day 14 of corticosteroid initiation; graft-related mortality at 6 months was significantly higher in MHR patients.[45] Another study with patients who underwent allogeneic HSCT described significant risk factors for mortality: corticosteroid resistance, age >18 years, increased total serum bilirubin and overt GI bleeding.[3]

Compared to children, older age had a significantly higher hazard of death and CB graft recipients had a significantly lower chance to reach corticosteroid-resistant aGVHD remission than BM or PBSC graft recipients. Mortality rate in aGVHD patients requiring second-line treatment was 47% (38/81). Respiratory insufficiency (infectious and noninfectious), multiorgan failure from aGVHD and treatment related toxicity (inlcuding sepsis) were the most frequent causes of death (35/38).[33]

8 | CONCLUSION

The current review of the literature confirms that lower endoscopy is as efficient as upper endoscopy for lower or mixed GI symptoms, and avoids the risk of duodenal haematoma; moreover, recto-sigmoidoscopy is as effective as colonoscopy for GI-GVHD diagnosis, and does not require a general anaesthesia. As the combination of upper and lower GIT endoscopy could improve the diagnostic performance rate, it can be proposed in a second step. First-line treatment is based on steroids and enteral nutritional support. In unresponsive children above 12 years of age, second-line treatments, such as ruxolitinib, are available.

AFFILIATIONS

[1]Department of Paediatric, University Hospital Center, Limoges, France

[2]The Juliet Keidan Institute of Paediatric Gastroenterology and Nutrition, Shaare Zedek Medical Centre, The Hebrew University, Jerusalem, Israel

[3]Division of Neurogastroenterology & Motility, Department of Paediatric Gastroenterology, Great Ormond Street Hospital, London, UK

[4]Department of Gastroenterology, Hepatology and Nutrition, University Children's Hospital, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[5]Department of Paediatric Gastroenterology, Hepatology and Nutrition, Hospital Sant Joan de Déu, Barcelona, Spain

[6]Referral Centre for Paediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, Medical School, University of Zagreb, Zagreb, Croatia

[7]Department of Paediatric Gastroenterology and Hepatology, Santobono-Pausilipon Hospital, Naples, Italy

[8]Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium

[9]Department of Woman, Child and General and Specialist Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

[10]Paediatric Gastroenterology Department, Al Jalila Children's Specialty Hospital, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

[11]Department of Pediatrics, University Medical Centre Maribor, and Department of Pediatrics, Medical Faculty, University of Maribor, Maribor, Slovenia

[12]Service de Gastroentérologie, Hépatologie, Nutrition et Maladies Héréditaires du Métabolisme, Hôpital des Enfants, and IRSD, Université de Toulouse, INSERM, INRAE, ENVT, UPS, Toulouse, France

CONFLICT OF INTEREST STATEMENT

Osvaldo Borrell received the last 3 years' consultation and lectures fees from Danone, Nutricia and Mead Johnson. Javier Martin-de-Carpi received the last 3 years' consultation and lecture fees from Abbott, AbbVie, Adacyte, Janssen, Nestle and Norgine. Zrinjka Misak received the last 3 years' consultation and lectures fees from Milsing, Sandoz and Hipp. Christos Tzivinikos received the last 3 years' payments/honorariums for lectures/consultation from Sanofi, Takeda, Nestle, Nutricia and AbbVie; Research Grants support IS from the Fondation contre le Cancer and FNRS. The remaining authors declare no conflicts of interest.

ORCID

Emmanuel Mas https://orcid.org/0000-0001-5425-7352

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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