ORIGINAL ARTICLE

AG-2022-21
doi.org/10.1590/S0004-2803.202204000-83

Hematopoietic stem cell transplantation and Crohn's disease: position paper from the Transplantation Committee of the Brazilian Group for the Study of Inflammatory Bowel Diseases (GEDIIB)

Milton Artur **RUIZ**[1], Rogério Serafim **PARRA**[2], Gilmara Pandolfo **ZABOT**[3], Adriana Ribas **ANDRADE**[4], Lilian **PIRON-RUIZ**[1], Ana Marcela Rojas **FONSECA-HIAL**[5], Eloisa Moreira **MARTIN**[6], Tainara Souza **PINHO**[1], Luiz Gustavo de **QUADROS**[1], Roberto Luiz **KAISER JUNIOR**[1] and José Miguel Luz **PARENTE**[7]

Received: 4 February 2022
Accepted: 1 June 2022

ABSTRACT – Crohn's disease (CD) is a relapse-remitting inflammatory bowel disease that can affect any part of the digestive system. This heterogeneous disease has multiple factors that contribute to an abnormal immune response to intestinal microorganisms. Treatment is based on the use of anti-inflammatories, corticosteroids, immunosuppressants and biologic biologic agents either alone or in combination. Surgical treatment is usual and, ten years after diagnosis, more than 80% of patients report having undergone surgical procedures related to the disease. Unfortunately, none of the treatments described offer a cure, and many cases become refractory or without therapeutic options. In this scenario, hematopoietic stem cell transplantation has been suggested because clinical remission was obtained in patients who had CD associated with malignant hematological diseases and an alternative since the first reports in 2010. In this report, the Transplantation Committee of the Brazilian Group for the Study of Inflammatory Bowel Diseases reviews the history and results of the procedure in patients with CD, detailing and discussing the various relevant points that permeate hematopoietic stem cell transplantation and cell therapy in this disease.

Keywords – Crohn's disease; inflammatory bowel diseases; stem cell transplantation; hematopoietic stem cell transplantation.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) of a multifactor pathogenesis and progressive nature that can affect any part of the gastrointestinal (GI) tract[1, 2]. The etiology of CD remains unknown, but genetic, epigenetic, and environmental factors affect the immune response to intestinal microorganisms[3-5]. IBD is characterized by periods of activity and remission, and its global prevalence has been increasing since 2000 and now affects 12 to 38 per every 100,000 individuals in Brazil[6-8]. CD significantly impacts the quality of life and productivity, resulting in social and economic implications[9-12].

CD can affect individuals of any age but most often presents in patients younger than 30 years, although the incidence in older individuals has increased[13]. The transmural behavior of CD results in an inflammatory, fibrostenotic, or penetrating phenotype, with progressive bowel damage and disability[14]. According to population data, about 50% of adults with CD will experience some intestinal complication within 20 years after diagnosis. Almost half will need surgery within ten years. The risk of postoperative recurrence can reach 45–55% in 10 years[1, 15]. It is essential to remember that surgery is not curative, and patients still require ongoing pharmacologic therapy due to disease recurrence[16]. Only 10% of patients will have sustained clinical remission in the long term[17].

Treatment for CD

Treatment for patients with CD depends on disease severity, patient risk stratification, patient preference, and clinical factors, including age at onset, the extent of the disease, and complications. The treatment repertoire includes steroids, immunomodulators, monoclonal antibody therapies, and surgery[1, 18-21].

Medical treatment for CD has changed substantially over the past two decades. Biological drugs, including tumor necrosis factor blockers (anti-TNF) and novel biologics, such as anti-integrins

Declared conflict of interest of all authors: Parra RS has received fees for serving as a speaker and/or an advisory board member for AbbVie, Ferring Pharmaceuticals, Janssen, and Takeda. Zabot GP has received fees for serving as a speaker and/or an advisory board member for AbbVie, Takeda, and Janssen. Andrade AR has received fees for serving as a speaker and/or an advisory board member for AbbVie, Janssen, and Takeda.
Disclosure of funding: no funding received
[1] Associação Portuguesa Beneficência, São José do Rio Preto, SP, Brasil. [2] Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Departamento de Cirurgia e Anatomia, Ribeirão Preto, SP, Brasil. [3] Hospital Moinhos de Vento, Porto Alegre, RS, Brasil. [4] Hospital São Rafael, Salvador, BA, Brasil. [5] Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo, SP, Brasil. [6] Hospital do Servidor Público Estadual de São Paulo,São Paulo, SP Brasil. [7] Universidade Federal do Piauí, Departamento de Clínica Médica, Gastroenterologia, Teresina, PI, Brasil. Corresponding author: Milton Artur Ruiz. E-mail: milruiz@yahoo.com.br

and anti-interleukins, have revolutionized treatment for CD[2], promoting the control of intestinal inflammation and, consequently, preventing or at least delaying progressive intestinal damage[22, 23]. The target is deep remission, defined as both symptomatic and endoscopic remission. In addition, Transmural and mucosal healing (respectively assessed by cross-sectional imaging techniques and histology) have also been associated with deep remission[1].

Despite the effectiveness of biological drugs, between 10 and 40% of patients with IBD have no primary response[23]. Moreover, among the patients who initially respond to anti-TNF therapy, up to 50% of patients may experience secondary loss of response in the first year of treatment, leading to the need for the intensification or interruption of this therapy[23]. Treatment-refractory CD results in digestive tract damage that manifests as strictures, short bowel syndrome, and the need for a stoma. These aspects are associated with reducing the quality of life, recurrent hospitalizations, and increased mortality[24, 25].

Surgical treatment is indicated for a perianal CD to control infectious complications combined with medical therapy to prevent luminal activity and treat complications, such as abscesses, strictures, fistulas, colorectal dysplasia, or cancer[19]. Moreover, patients who have an inadequate response to multiple biologic treatment classes and nonadherent individuals should be considered for surgery[14].

There is no curative treatment for CD, and therapeutic options are lacking for patients with advanced or long-term illness or undergone various surgical approaches and multiple drug treatments. Due to the high morbidity and mortality rates in these refractory patients, require novel therapeutic options like hematopoietic stem cell transplantation (HSCT) has been shown to reboot the immune system[26-28].

HSCT and CD

In 1993, Drako reported the first HSCT in a patient with CD who developed non-Hodgkin's lymphoma. As a result, the remission of both diseases occurred and remained many years after the procedure[29]. Numerous autologous and allogeneic transplants have since been performed in patients with CD and coincidental hematological or malignant conditions, achieving clinical remissions and demonstrating encouraging results for both diseases (TABLE 1).

These results paved the way for autologous HSCT in patients with CD. Reports the first cases described in 2003[43-45] followed by several case series addressing various aspects related to the toxicity of the procedure and immunological recovery. Burt et al. described the control of the disease in 24 CD patients in a 5-year follow-up. The previous treatment of these patients was discontinued after autologous HSCT[46].

Only one randomized controlled trial has been completed to date – the Autologous Stem Cell International Crohn's Disease (ASTIC) trial[47]. Forty-five patients with active disease and impaired quality of life despite having tried at least one immunosuppressive and two biological treatments were eligible. The patients were divided into two groups: mobilization and HSCT versus mobilization alone, followed by conventional therapy. The trial failed to meet its primary endpoint of a clinical and endoscopic 'cure' after 1 year (freedom from the disease in imaging and endoscopic analyses), Crohn's Disease Activity Index (CDAI) <150 and no endoscopic or radiological evidence of intestinal inflammation in patients who performed HSCT[47]. A secondary analysis considering traditional endpoints in CD clinical trials showed superior results in the autologous HSCT group for clinical and endoscopic endpoints, although associated with a high occurrence of adverse events[25].

The long-term outcome after HSCT is reported in a single-center cohort of 29 CD patients in Barcelona refractory to at least two biological therapies. One patient died due to systemic cytomegalovirus (CMV) infection, and another one required an urgent colectomy for colitis with CMV and Epstein-Barr virus (EBV). Drug-free clinical and endoscopic remission [CDAI <150, Simple Endoscopic Score for Crohn's Disease (SES-CD) <7] was found in 61% at 1 year, 52% at 2 years, 47% at 3 years, 39% at 4 years and 15% at 5 years. HSCT appeared to be effective at controlling refractory CD: 68% experienced complete remission or significant improvement in symptoms in a median follow-up period of 41 months; 27% required no medical therapy at any point post-HSCT. Treatment-free survival at 1 year was 54%[48].

Hernanz et al.[49] published a single-center experience in Madrid with seven patients who received HSCT due to refractory CD. Three (43%) patients had clinical and endoscopic remission, 1 (14%) patient showed clinical improvement without remission and the disease remained active in 3 (43%) patients, with the need to restart treatment at the assessment of the initial response to HSCT (after 6 months). Symptoms recurred in five of the 7 (71%) patients, all of whom had to restart medical treatment after an average of 13.8 months (range: 3–30 months). Only one patient required surgery after HSCT. At the end of follow-up after a mean of 48 months (range: 17–78 months), 5 (71%) of the seven patients were in clinical remission with or without treatment[49].

Considering the studies described above, CD is the third most common indication for HSCT in autoimmune disease after multiple sclerosis and systemic sclerosis[50]. These studies are summarized in TABLE 2.

Objectives

This report is a review and position paper from the Transplantation Committee of the Brazilian Group of Inflammatory Bowel Diseases (GEDIIB) and aims to update and discuss the current state of HSCT in the treatment of CD.

Questions and points to highlights regarding HSCT in CD

After an initial presentation on CD and HSCT, the GEDIIB Transplantation Committee developed relevant questions and points to be discussed on the topic to achieve the objectives proposed in this report.

What are the background and experimental justification for the use of HSCT in the treatment of CD?

HSCT in the treatment of CD is based on experimental studies that justify the procedure in the treatment of autoimmune diseases[64,65]. Syngeneic cells derived from bone marrow marked with green fluorescence protein occupied 37.6% and 4.25% of the colon epithelium on the 28th and 56th day after bone marrow transplantation. Moreover, significant amounts of mucosal and submucosal interstitial cells were derived from the bone marrow. These data indicate the participation of infused cells in tissue regeneration[66].

Stem cells and endothelial progenitor cells contribute to tissue regeneration through neo-angiogenesis or neo-vasculogenesis in ischemia-related or inflammatory diseases. Epithelial repair occurs with the recruitment of cells to the damaged digestive tract in the large intestine, which facilitates mucosal repair in moderate to severe colitis[67]. In non-myeloablative HSCT, an increase in

TABLE 1. Summary of Hematopoietic Stem Cell Transplants in Patients with Crohn's Disease and Coincidental Diseases.

Reference	HSCT type	#of pts	Indication	Outcome
Drakos 1993[29]	Autologous	1	NHL	Remission of both diseases at 6 months
Castro 1996[30]	Autologous	1	Breast cancer	Remission of both diseases at 7 years
Talbot 1998[31]	Allogeneic	1	AL	Remission of both diseases >8 years
Lopez-Cubero 1998[32]	Allogeneic	1 5	AML CML	CD Remission between 4,5 to 15 years and one patient relapsed CD 1,5 years after HSCT
Kashyap 1998[33]	Autologous	1	LNH	Remission both disease >7 years
Musso 2000[34]	Autologous	1	HL	Remission of both diseases for >3years
Soderhölm 2002[35]	Autologous	1	AML	Remission of both diseases for >5 years
Ditschowski 2003[36]	Allogeneic 7 CD pts 4 UC pts	1 9 1	AML CML Secondary MDS	10 pts alive without IBD symptoms after 34 months. One patient with mild persistent symptoms of Crohn's disease early after transplant
Anumakonda[37]	Autologous	1	NHL	Relapsed CD after 8 years HSCT
Nishimoto 2013[38]	Allogeneic	1	AML	Remission of both diseases for 20 months
Hu 2014[39]	Allogeneic	1	MDS	Remission of both diseases for 25 months
Rabian 2016[40]	Allogeneic	9 7 1 1	AL MDS/MPL NHL MM	59% Overall survival for 48 months. Status: ND
Zhang 2020[41]	Allogeneic	1	MDS	Death, 125 d. after HSCT with pulmonary mucormycosis

HSCT: hematopoietic stem cell transplantation; pts: patients; NHL: non-Hodgkin lymphoma; AL: acute leukemia; AML: acute myeloid leukemia; CD: Crohn's disease; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome, MPL: myeloproliferative syndrome; MM: multiple myeloma; Nd: not described. #number; >up. Adapted from Ruiz MA et al.[42].

TABLE 2. Summary of case series, prospective clinical trials and randomized studies on autologous HSCT in patients with CD.

Reference	#pts	Mobilization	Conditioning	Outcome
Burt 2003[45]*	2	CY 2g/m²	CY 200 mg/kg hATG 90 mg/kg	Remission for 1 year – no histologic remission
Kreisel 2003[43]	1	CY 4g/m²	CY 200 mg/kg	Relapsed 9 m after mobilization. Clinical remission for 9 months - no histologic remission
Craig 2003[44]*	4	CY 2g/m²	CY 200 mg/kg hATG 90 mg/kg	CDAI remission at 11 months - no endoscopic remission
Scimè 2004[51]	1	CY 2g/m²	CY 200 mg/kg	ND
Oyama 2005[52]**	12	CY 2g/m²	CY 200 mg/kg hATG 90 mg/kg	11/12 CDAI <150 clinical remission for mean of 18.5 months – endoscopic remission rare
Cassinotti 2008[53]*	4	CY 1.5/m²	CY 200 mg/kg rATG 7.5 mg/kg	3/4 (75%) clinical (CDAI <150) and endoscopic remission at mean of 16.5 months
Burt 2010[46]*	24	CY 2 g/m²	CY 200 mg/kg hATG 90 mg/kg or rATG 6.0 mg/kg	CDAI <150 in 91%, 63%, 57%, 39% and 19% at 1, 2, 3, 4, and 5 years, respectively - no histologic remission
Clerici 2011[54]*	6	CY 1.5/m²	CY 200 mg/kg rATG 7.5 mg/kg	CDAI and endoscopic remission in 5/6 at 1 year. TNFα, IL-10 decreased at 1 year
Hommes 2011[55]**	3	CY 4g/m²	CY 200 mg/kg hATG 90 mg/kg	1 patient mobilized only - relapsed after 2 years 2 of 3 underwent HSCT – relapsed at 6 and 12 months
Kountouras 2011[56]*	1	CY 4g/m²	CY 200 mg/kg rATG 10 mg/kg	Clinical, endoscopic, histologic remission for 31 months
Hasselblatt 2012[57]**	12	CY 4g/m²	CY 200 mg/kg	12 mobilized, 9 underwent HSCT – 5/9 clinical end endoscopic remission at 6 months, 7/9 relapsed by 12 months
Kriván 2014[58]*	1	CY 2 g/m²	CY 200 mg/kg hATG 30 mg/kg	Relapsed at 1 year
Snowden 2014[59]*	6	CY 4g/m²	CY 200 mg/kg rATG 7.5 mg/kg	Median time to relapse: 10 months
Hawkey 2015[47]***	45	CY 4g/m²	CY 200 mg/kg rATG 6.5 mg/kg	Complex end point CDAI <150, no immune drugs, no endoscopic or radiologic disease – not significant compared to control
Ruiz 2015[60]	1	CY 2g/m²	CY 200 mg/kg rATG 6.5 mg/kg	Clinical, endoscopic, histologic remission for 7 years
Lopez-Garcia 2017[61]**	35	CY 4g/m²	CY 200 mg/kg rATG 6.5 mg/kg	CDAI <150 and SES <7 in 61%, 52%, 47%, 39%, 15% at 1, 2, 3, 4, and 5 years, respectively
Lindsay 2017[25]**	40	CY 4g/m²	CY 200 mg/kg rATG 6.5 mg/kg	CDAI <150 (steroid free) at 1 year in 38%
Ruiz 20107[28]**	14	CY 2g/m²	CY 200 mg/kg rATG 6.5 mg/kg	13/14 in remission CDAI <150 at 30 days
Ruiz 2017[62]*	1	CY 2g/m²	CY 200 mg/kg rATG 6.5 mg/kg	Clinical remission at 1 year, no endoscopic remission
Hernanz 2019[49]*	7	CY 4g/m²	CY 200 mg/kg rATG (ND)	5/7 (71%) relapsed after mean of 13.8 months
Ruiz 2020[63]**	50	CY 2g/m²	Cy200 mg/kg rATG 6.5 mg/kg	CDAI <150 in 97%, 80%, 65%, 38% and 20% at 1, 2, 3, 4, and 5 years, respectively

CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CY: cyclophosphamide; hATG: horse anti-thymocyte globulin; HSCT: hematopoietic stem cell transplantation; ND: not done or not reported; pts: patients; SES: simple endoscopic score; TNF: tumor necrosis factor. *Case series; **prospective clinical trials; ***randomized studies. Adapted from Ruiz, MA et al.[42].

survival, remission of clinical activity and a significant reduction in the histological severity score occur 35 days after the procedure[26]. Genetically marked cells are detected in the submucosa of the damaged colon epithelium, along with tissue regeneration induced by probable vasculogenesis and/or the differentiation of the transplanted stem cells into endothelial cells and increased microcirculation at the injured site[68].

A Brazilian study mimicked what happens in autologous non-myeloablative HSCT, lending support to previously described data in addition to concluding the benefits of the procedure when using isolated cyclophosphamide as well as superiority in the group in which hematopoietic stem cell infusion was also performed after the conditioning regimen[69].

What are the clinical justifications for the use of HSCT in the treatment of CD?

The rationale behind HSCT is based on the concept of immunoablation using high-dose chemotherapy, with subsequent regeneration of naive T-lymphocytes derived from re-infused hematopoietic progenitor cells (HPCs)[70]. The consideration of HSCT in patients with CD should be based on five pillars: the correct diagnosis of CD, evidence of inflammatory activity, severe disease, inadequate response to medical therapies and contraindication or patient refusal regarding surgery[26]. The proper selection and best moment for HSCT to avoid advanced disabling disease exerts an influence on results and quality of life.

The definition of an inadequate response to each drug class is mandatory and displayed in TABLE 3. For corticosteroids, a refractory patient is one with an inability to withdraw from methylprednisolone (1 mg/kg) after four to 6 weeks without relapse or having a relapse within 1 year after completing a course of corticosteroids[1]. For immunosuppressants, azathioprine should be used at doses of 1.5 to 2.5 mg/kg/day, mercaptopurine at 0.75 to 1.5 mg/kg/day and intramuscular methotrexate at 25 mg/week. Failure to achieve steroid-free remission after 16 weeks of therapy with these immunosuppressants should be considered an inadequate response[1]. Regarding biological drugs, the response should be evaluated at week 12 to 14 for TNF inhibitors[1], week eight for ustekinumab[71] and week 14 for vedolizumab (after an additional administration of 300 mg of vedolizumab from week 10 in non-responders)[72]. In patients not responding to induction therapy with a biological agent and those losing response without signs of intolerance, treatment should be intensified to the highest approved dose, possibly guided by therapeutic trough levels and the potential presence of anti-drug antibodies. The confirmation of therapeutic drug levels is necessary before patients are considered resistant to anti-TNF therapy. If a response is not obtained after intensification or the response is insufficient, the first option should be switching to another biological class not previously used[1]. If several biological drugs, immunosuppressants and corticosteroids have failed, the patient could be a candidate for HSCT[26].

TABLE 3. Definitions criteria for inadequate or loss of response to drugs in CD treatment[1,73].

Drug	Criteria
Corticosteroids	Inability to withdraw from methylprednisolone (1 mg/kg) after 4–6 weeks without relapse or having relapse within 1 year of completing course of corticosteroids.
Methylprednisolone 1 mg/kg	
Immunosuppressors	
Azathioprine (2.0–2.5 mg/kg/day) or 6-mercaptopurine (0.75–1.5 mg/kg/day)	Failure to achieve steroid-free remission after 16 weeks of therapy.
Biologic Therapy	
TNF inhibitors	at week 12 to 14.
Ustekinumab	at week 8.
Vedolizumab	at week 14, after additional administration of 300 mg of vedolizumab from week 10 in non-responders.

CD: Crohn's disease; TNF: tumor necrosis factor.

What are the indications for HSCT in the treatment of CD?

Clinical active disease should be proved by endoscopic exams (diseased tissue should be accessible endoscopically for objective histological study), biomarkers and/or cross-section exams(TABLE 4). Patients with severe disease, with more than one exacerbation/year despite optimized treatment, with the failure of two biological drugs including one TNF blocker (preference for infliximab) and contraindication to surgery[26], specially when there is an increased risk of developing short bowel syndrome; colonic/perianal refractory CD when the patient does not give consent for the creation of a stoma; or patient refusal for surgery with a previous Form of Assignment Agreement. These criteria are described in TABLE 4.

TABLE 4. Inclusion criteria for autologous HSCT in patients with CD.

CD confirmed diagnosis	By clinical, endoscopic methods (endoscopy/colonoscopy/enteroscopy), histology, laboratorial (inflammatory markers) and cross-sectional imaging (CT or MRI enterography, bowel ultrasound).
Clinically active disease	CDAI >150.
	HBI >8.
	CCSI >15.
Endoscopic active disease	Ileal or ileocolonic disease: SES-CD ≥7 or CDEIS ≥9.
	For jejunoileal disease: Lewis ≥790.
	CECDAI >9.2.
	Esophageal, gastroduodenal disease: visual aspect of ulcers.
Refractory disease (at least 1 relapse/year)	Refractory or intolerant to immunosuppressors: azathioprine, 6-mercaptopurine and/or methotrexate or cyclosporine.
	Refractory or intolerant to at least two biologic therapies (anti-TNF therapy, anti-integrin or anti-IL12/IL23), one of which is TNF blocker (infliximab or adalimumab); all with optimized dose.
Surgery criteria	Candidate for whom surgery is considered not appropriate or has been declined.
	Refusal to accept proposed mutilating surgery.

CD: Crohn's disease; HSCT: hematopoietic stem cell transplantation; CDAI: Crohn's Disease Activity Index; HBI: Harvey-Bradshaw Index; CCSI: Craig Crohn's Severity Index; SES-CD: Simplified Endoscopic Score for Crohn's Disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; CECDAI: Capsule Endoscopy Crohn's Disease Activity Index.

The ASTIC trial reported 50% mucosal healing one year after HSCT in a population of refractory patients to all available therapeutic options[47]. Moreover, in the largest single-center cohort study published to date, HSCT achieved drug-free endoscopic remission in 60% of patients at the one year of follow-up. Although these data are uncontrolled, they enable viewing the outcome of HSCT in the context of reports of novel biological therapies[74].

What are the contra-indications of HSCT in the treatment of CD?

In the majority of the studies, patients were excluded if they had organ failure or other severe comorbidities, active infection, increased infectious risk as hepatitis B and C virus, HIV, human T-lymphotropic virus (HTLV), American trypanosomiasis (Chagas disease), *Treponema pallidum,* latent tuberculosis, malnutrition (body mass index ≤18 kg/m^2 and serum albumin ≤20 g/L) or if they were pregnant or unwilling to use contraception during the study. An infection-orientated medical history and determination of CMV, EBV, herpes simplex virus (HSV), varicella zoster virus (VZV) and *Toxoplasma gondii* serology are also important[26]. All patients should be tested for SARS-CoV-2 and the test results should be negative before starting HSCT. Many centers also include a pre-transplant dental assessment, although divergent opinions are found regarding the benefits of such an evaluation. Finally, fertility issues need to be discussed with patients in the reproductive period of life, with the consideration of semen cryopreservation in males and reproductive medicine consultation in females. The prospect of premature menopause also requires counseling and plans for hormone replacement therapy, when appropriate[26].

Pre-existing hematologic malignancies are not a contraindication for HSTC[40]. On the other hand, non-hematologic malignant neoplasms are considered absolute contraindications if less than five years since the diagnosis.

In patients with predicted risk for pulmonary complications, a post-transplantation diffusing capacity of the lungs for carbon monoxide <50% and Tiffeneau index (FEV_1/FVC ratio) <60% are proposed as relative contraindications for HSCT[26]. Many transplant centers do not proceed HSCT in patients with a left ventricular ejection fraction (LVEF) <45%, making it necessary to perform electrocardiography and transthoracic echocardiography to assess this factor. Pre-transplant laboratory exams are recommended for the assessment of impaired kidney or liver function, low serum ferritin and anemia of any cause, which are considered risk factors for various unfavorable transplant outcomes. A full blood count and protein electrophoresis may be used to guide the decision to perform a bone marrow examination prior to HSCT. Hematinics and coagulation should be checked routinely and vitamin deficiencies should be corrected[26]. TABLE 5 presents the exclusion criteria for HSCT in patients with CD.

What are cautions should be exercised when performing HSCT during coronavirus 19 (COVID-19) pandemic?

Since the end of 2019, the world has been affected by the coronavirus 19 (COVID 19), which is responsible for a systemic infection denominated severe acute respiratory coronavirus 2 (SARS-COV-2)[75,76]. Managing IBD during the COVID-19 pandemic has been a challenge for clinicians and their patients[77]. Due to the characteristics of the global pandemic, it is necessary to know about the virus, its mechanism of action, the impact it could have on patients with IBD and the measures to be taken regarding patients

TABLE 5. Exclusion criteria for autologous HSCT in patients with CD.

Comorbidities	Renal: creatinine clearance <40 mL/min (measured or estimated).
	Cardiac: clinical evidence of refractory congestive heart failure, left ventricular ejection fraction <45% by multigated radionuclide angiography or cardiac echo; uncontrolled ventricular arrhythmia; pericardial effusion with hemodynamic consequences evaluated by experienced echocardiographer.
	Hepatic: AST >2 times upper limit of normal.
	Concurrent neoplasms.
	Bone marrow insufficiency defined as neutropenia with absolute neutrophil count $<1 \times 10^9$/L or thrombocytopenia with a platelet count $<50 \times 10^9$/L or anemia with hemoglobin <80 g/L.
	Uncontrolled hypertension, defined as resting systolic blood pressure ≥140 mmHg and/or resting diastolic pressure ≥90 mmHg despite at least 2 anti-hypertensive agents.
	Uncontrolled acute or chronic infection with HCV, HBV, HIV, HTLV – 1 or 2, hepatitis viruses, Chagas Disease, SARS-CoV-2 or any other infection.
	Other chronic diseases causing significant organ failure, including established cirrhosis with evidence of impaired synthetic function in biochemical testing and known respiratory disease causing resting arterial oxygen tension < 8 kPa or CO_2 tension >6.7 kPa. FEV_1/FVC <50%.
Past history	Active or latent mycobacterial infection.
	Prior exposure to HBV, HCV or HIV 1+2.
Increased risk of infection	Positive or indeterminate serology: CMV, toxoplasmosis, HSV, SARS-COV2.
	Evidence of enteric or systemic infection.
Disease profile	No evidence of active CD in CDAI, HBI or CCSI or endoscopic screening.
	Inability to assess endoscopic active disease due to strictures.
	Evidence of intra-abdominal sepsis on abdominal MRI.
	Undrained perianal fistulae (patients with previous perianal disease or perianal disease adequately drained with seton in situ are eligible).
	Presence of undrained perianal sepsis on screening pelvic MRI.
Others	Participants currently pregnant, breastfeeding or planning pregnancy within duration of study. Current pregnancy confirmed with pregnancy test at screening assessment.
	Unwilling to use adequate contraception (if appropriate) for at least 12 months after last dose of study drug.
	Contraindication to use of CY, fludarabine, G-CSF or rATG.
	Psychiatric comorbidity.

CD: Crohn's disease. HSCT: hematopoietic stem cell transplantation; AST: aspartate transaminase; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HTLV: human T-cell leukemia-lymphoma virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CO_2: carbon dioxide; kPa: kilopascal; FEV_1/FVC: forced expiration/forced vital capacity in first second; CMV: cytomegalovirus; HSV: herpes simplex virus; CDAI: Crohn's Disease Activity Index; HBI: Harvey-Bradshaw index; CCSI: Craig Crohn's Severity Index; MRI: magnetic resonance image; CY: cyclophosphamide; G-CSF: granulocyte colony-stimulating factor; rATG: rabbit antithymocyte globulin.

already submitted to or candidates for HSCT. Although patients with IBD do not appear to be at increased risk for COVID-19, the potential impact of immunosuppressive therapies on patients with CD infected with SARS-CoV2 is a call for concern among clinicians and patients[77].

Understanding the outcomes and immunologic characteristics of cellular therapy recipients with SARS-CoV-2 is crucial to performing such therapies, including HSCT, in the COVID era[78]. It was previously reported that autologous HSCT has favorable clinical outcomes for patients with COVID-19 without active malignancy[78]. The answer to these questions is pending, but there is no evidence or reports of increased risk for COVID-19 in patients with CD or those undergoing biological treatments[79].

All patients should be tested for SARS-CoV-2 and the test results should be negative before the start of conditioning regardless of the presence of upper respiratory symptoms. If a transplant candidate is diagnosed with COVID-19, postponement for at least three months is advisable, in accordance with European Centre for Disease Prevention and Control, among others. However, this is not always possible due to the risk of progression of the underlying disease. In patients with high-risk disease, autologous HSCT should be deferred until the patient is asymptomatic and has two negative virus polymerase chain reaction (PCR) swabs taken at least 24 hours apart. Postponement should be for a minimum of 14 days (preferably 21 days) and a new PCR is recommended before the start of conditioning. In patients with low-risk disease, a three-month postponement of HSCT is recommended[80]. TABLE 6 shows the EBMT recommendations for COVID-19 and HSCT[26].

Another aspect that must be borne in mind is post-acute COVID-19 syndrome and the possibility of flareups of pre-existing diseases or the emergence of autoimmune diseases[82,83]. In a series of 50 patients with CD who underwent HSCT, four were infected by COVID-19. One of the patients presented tense skeletal muscle manifestations, hypothyroidism (anti-thyroid peroxidase positive) and the relapse of CD (clinical and colonoscopic appearance) six months after autologous HSCT[84].

What are the best assessments for autologous HSCT in CD?

Autologous HSCT is considered a potentially curative procedure in various hematological malignancies and autoimmune diseases[62]. After defining the patient's eligibility for HSCT, the therapeutic plan must be established. The heterogeneity of CD, nuances of each case, special and particular situations, such as implanted colostomy bag, fistulas and perianal disease, must be analyzed by the bone marrow transplantation (BMT) team. Patients must receive clarifications regarding the steps of the procedure, central venous catheter (CVC) implantation, the selection of the venous catheter as well as prolonged hospitalization due to mobilization and conditioning phases.

The mobilization period must be explained. The patient should also be aware of the need to have access to hematopoietic progenitor stem cells (HPSCs) and what role these cells play in the conditioning period. The patient should be aware of the leukapheresis procedure, in which the extraction and separation of HPSCs expanded in the peripheral blood occurs in sessions of 3 to 5 hours. Although, the procedure is usually safe, problems such as hypotension, paresthesia, hypovolemia or electrolyte disorders, such as hypocalcemia or CVC-related disorders, may occur and are properly addressed and resolved[85]. Moreover, the aim of the mobilization period with HPSC extraction is to be a support for the period of aplasia and absolute neutropenia that occurs after the administration of the conditioning drugs. At the end of the administration of the drugs, the HPSCs are reinfused. This is the first day of HSCT. The conditioning period, the function of the drugs that cause immunosuppression and transient myeloablation in the subsequent days in addition to organic toxicities must be explained, along with palliative measures and prophylaxis that will be taken to minimize adverse effects during HSCT[86]. In addition to being aware, the patient must agree to sign a specific statement of informed consent regarding all HSCT events.

A psychological assessment is recommended, as the overall hospitalization period is long (around 25 days). The patient must be aware of the risks of the procedure as well as current results of national and international studies in the scientific literature[86]. Although ambulatory or outpatient autologous transplants can be performed with other diseases, we do not recommend this approach for patients with CD. The main risks in the early mobilization and conditioning phases are related to the dose and include febrile neutropenia, fluid and electrolyte imbalances, gut toxicity, anemia and the complications of an indwelling venous catheter, specially infection.

What is the best mobilization regimen for autologous HSCT in patients with CD?

Mobilization is the process to maximize HPSCs are released from the bone marrow into the blood to be collected and infused later to reduce the period of neutropenia after the conditioning

TABLE 6. Recommendations of European Society for Blood and Marrow Transplantation regarding COVID-19 and HSCT recipients.

Scenario	Low-disease risk	High-disease risk	Notes
Confirmed diagnosis	Deferred for 3 months	Deferred, until asymptomatic and 3 negative PCRs at least one week apart	
Symptoms of URTI	Testing with multiplex respiratory viral PCR, consider deferral	Testing with multiplex respiratory viral PCR, consider deferral	COVID-19 testing on case-by-case basis per local guidelines
Close contact with case of COVID-19	PCR test for COVID-19, deferred for 14–21 days	PCR test for COVID-19, deferral based on clinical judgment	Follow local guidelines for isolation and testing for COVID-19
Travel to high-risk areas** or close contact with person travelling from high-risk areas**	Deferred for 14–21 days	Deferral based on clinical judgment	Follow local guidelines for isolation and testing for COVID-19

*Adapted from reference[81]; **As defined by healthcare authorities. COVID-19: coronavirus-19; EBMT: The European Society for Blood and Marrow Transplantation; PCR: polymerase chain reaction; URTI: upper respiratory tract infection.

regimen. It is the first phase of an Autologous HSCT[87]. HPSCs may be collected from the peripheral blood or bone marrow. The peripheral blood is the most frequently used source in patients with CD. Peripheral blood stem cells (PBSCs) are capable of self-renewal and give rise to progenitor cells, which are multipotent cells that differentiate and proliferate into the mature cells of the blood and immune system. PBSC mobilization practices vary significantly among institutions. Effective mobilization regimens involve growth factor alone or a combination of chemotherapy and growth factor. More recently, plerixafor has been incorporated with either approach for poor mobilizers. Many institutions have developed algorithms to improve stem cell mobilization success rates and cost effectiveness. However, an optimal stem cell mobilization regimen has not yet been defined. Recommendations are found in a comprehensive review from the American Society of Blood and Marrow Transplantation[88].

The cytokine growth factors used are granulocyte colony-stimulating factor (G-CSF [filgrastim]) or granulocyte-macrophage colony-stimulating factor (GM-CSF [sarmosgastrim]). Among chemotherapeutic drugs, the most widely described are cyclophosphamide, etoposide and cytarabine. The relative increase in autologous colony-forming unit cells collected by apheresis using G-CSF or chemotherapy alone is tenfold more than that found in the steady state. When G-CSF and chemotherapy are combined, this number increases to 1000-fold more[89].

In a study involving refractory autoimmune diseases, 15 patients with systemic sclerosis (SS), 11 with multiple sclerosis (MS) and nine with other autoimmune diseases were analyzed. There was no inclusion of patients with CD. Mobilization was combined with cyclophosphamide (CY) plus G-CSF. The dose of CY was 4 g/m^2 in 16 patients and 2 g/m^2 in 17. The dose of G-CSF was 5 to 10 ug/kg /day, started on the sixth day after CY administration and maintained until the completion of PBSC collection. In 71% of cases, one apheresis session was enough to reach the minimum collection target of 2.0 x 10^6 CD34+/kg. The final results of the collections of patients with SS, MS and other autoimmune diseases were 12.2, 8.0 and 8.2, respectively. There was no significant difference among patients regarding the dose of CY[90].

The mobilization protocols described in literature for CD used doses of CY ranging from 1.5 g/m^2[53,54] to 4 g/m^2[47,48,91]. G-CSF is used in all studies at the usual doses described above. Evaluating these data, patients with CD were found to be good mobilizers and cases of difficulty collecting cells are sparse[92].

In rare cases, the isolated use of G-CSF is described. This is due to the fear that the drug may trigger flareups or manifestations in patients with autoimmune diseases. Four out of 100 patients who were enrolled in protocols of high-dose immunosuppression with peripheral blood stem cell rescue for MS experienced neurologic worsening while receiving recombinant human granulocyte colony-stimulating factor, with flareup of the disease[93]. Moreover, approximately 60% of patients using G-CSF had myalgias and bone pain, which may impact its use as monotherapy.

The best mobilization approach indicated in the literature for CD is the combined use of CY and G-CSF. This approach is less toxic and practice has shown a better response in patients with CD compared to hematologic patients. Absolute neutropenia occurs from 1 to 4 days and transfusion requirements are commonly restricted to red blood cell concentrate[90]. Hyperhydration, alkalinization of the urine and mesna are prescribed to prevent hemorrhagic cystitis. Moreover, G-CSF 5 to 10 mcg/kg/day subcutaneously commencing five days after the last cyclophosphamide infusion and ending the day before the last leukapheresis is extremely important to obtain a large number of cells (see below). Monitoring of the full blood count for anemia, neutropenia and thrombocytopenia and CD34+ count is mandatory. Patients should preferably undergo leukapheresis as soon as CD34+ blood levels exceed 10/mL. This is expected to occur on 10th day of mobilization[48,94]. A target CD34+ level between 4 and 5 x 10^6 cells/kg seems to be the most reasonable based on available data and several studies estimate 3.5 x 10^6 as the goal for patients with CD.

What is the procedure for obtaining a good cell product for HSCT in CD?

The mobilization period in autologous HSCT ends with obtaining PBSCs in the apheresis session. The collected graft material must be cryopreserved to maintain the integrity and effectiveness of the cells for subsequent use. Freezing must be carried out in a progressive, programmed manner and the most widely used cryoprotectant is dimethyl sulfoxide (DMSO)[48]. When added to the graft material, this solvent has the property of stabilizing the cryopreserved cell membranes in addition to preventing the formation of intracellular ice crystals during the freezing process. The final concentration of DMSO in the graft product is between 5 and 10%. Cryopreservation occurs in an ultra-freezer at a temperature of -76ºC and the product remains in storage until the time of thawing and reinfusion in the patient, which is Day Zero of the transplant.

The aim of separating the HPCs from the graft product is to maximize the results of autologous HSCT by the enrichment method via positive or negative selection. Physical, immunological and pharmacological methods are employed. Cell Pro CEPRATE was once the most widely used method, even in autologous HSCT for CD, which employed columns and CD34+ monoclonal antibodies. The method was discontinued and there is no evidence of clinical benefits in patients with CD who underwent autologous HSCT. The graft product only freezes as described above without any type of manipulation or positive or negative selection with monoclonal antibodies before being reinfused.

What is the best conditioning regimen for HSCT in patients with CD?

The conditioning regimen is the critical aspect of HSCT and is divided into three categories: myeloablative (MA), reduced intensive dose (RIC) or non-myeloablative (NMA). This division is based on the dose and effects of the associated drugs, duration of cytopenia and transfusion requirements necessary to support the patient in the aplasia phase that takes place after conditioning. The MA regimen causes irreversible cytopenia and HPC infusion is mandatory, otherwise hematological recovery will not occur. In RIC, cytopenia may or may not be irreversible, the duration is variable and hematological recovery may or may not occur with HPC infusion after the conditioning regimen. The non-myeloablative regimen causes minimal cytopenia and hematological recovery will occur regardless of HPC infusion. However, infusion is recommended for the purposes of safety as well as reductions in the neutropenia period and risk of infection[95].

In CD, the most commonly used conditioning regimen has been CY 200 mg/kg with anti-T-cell serotherapy in accordance with EBMT guidelines[26]. The choice of anti-T-cell serotherapy (ATG) depends on availability but has most commonly been

polyclonal rabbit-derived (rATG) (from various pharmaceutical suppliers), although horse-derived ATG (hATG) (again from various pharmaceutical suppliers) and other serotherapies, including monoclonal antibodies, such as alemtuzumab, have been used in other autoimmune diseases in accordance with EBMT guidelines. Caution should be exercised with ATG. Febrile reactions are commonly seen as a first-dose effect, with cytokine release. Such reactions are usually easily controlled with steroids and antihistamines, but anaphylaxis can occur in rare cases. The staff involved in ATG administration should be aware of this risk and have appropriate treatment on hand.

As a suggestion for the total dose of the conditioning regimen with CY 200 mg/kg and rATG 6.5 mg/kg used in Brazilian patients, the conditioning regimen should be carried out under constant monitoring at the BMT unit. Twenty-four hours before the onset of conditioning, the patient should be hydrated and CY should be administered daily in fractional doses, interspersed with the use of uromitexan. After the administration of rATG, the patient should receive methylprednisolone at a dose between 200 and 500 mg and prophylaxis with analgesics and antipyretics. The staff must be prepared for an adverse reaction, such as anaphylactic shock. rATG should be administered in small doses in the first few days, which is increased until the total dose predicted for the medicine is reached. The interval between administrations should not be less than six hours. A study described no undesirable effects when using rATG or CY[96].

EBMT guidelines have previously specified a conditioning regimen with fludarabine (150 mg/m^2), CY (120 mg/kg) and anti-T-cell serotherapy (such as rATG) for pediatric patients. Although not previously used in CD, this regimen was incorporated into the current UK 'ASTIC-lite' trial protocol (available via clinicaltrials.gov) for adults to assess its safety and efficacy. However, outside of this trial, the CY 200 mg/kg + rATG regimen (dose range: 5 to 7.5 mg/kg) is used, but anti-thymocyte globulin (ATG) may involve infusion-related reactions that should be adequately managed with steroids and antihistamines. Although ATG is usually given with high doses of methylprednisolone, there remains the potential for fever and other reactions following cessation of the corticosteroids (potential serum sickness), which may require additional doses. Slow tapering of steroids over the first seven to ten days after ATG is recommended while appropriate vigilance for infection is maintained. The hyperhydration required for CY administration combined with the fluid retention associated with high-dose steroids and ATG may lead to fluid overload and particular attention to fluid and electrolyte imbalance is required from the onset of the conditioning. Patients should be monitored once or twice daily with weight measurements as well as fluid balance and stool chart recordings. There is currently no consensus on the conditioning regimen, but it should be as least toxic as possible while ensuring effective, lasting immunosuppression after HSCT.

What care should be taken for patients with CD during autologous HSCT under special conditions?

Patients with ostomy

In a candidate for HSCT with temporary or definitive ostomy, a careful evaluation is required by a specialized team dedicated to the care of ostomized patients[97]. Ileostomy complications, such as abscess, stenosis, allergy, edema, irritative or mechanical trauma, hemorrhage, dermatitis, necrosis, folliculitis, parastomal herniation, prolapse, retraction and parastomal varices, can occur soon after or many years after the procedure. According to Leong et al.[56], the incidence of stomal complications after 20 years of follow-up in patients with CD was 59%; the most common complications were skin problems (34%), intestinal obstruction (23%), retraction (17%) and parastomal herniation of the oblique muscles (16%)[62]. In a cross-sectional study, patients with CD and a stoma had high rates of psychological comorbidity and low quality of life scores. A negative illness perception appeared to explain some of the findings, but most patients were not receiving psychological help. Thus, psychological care is indicated for many of these patients and further research is needed[98]. Complications in HSCT ostomized patients haven't been referred. However, an ostomy is not a contraindication for HSCT[97].

Clostridium difficile

In cases of suspected relapse or progression of the disease, it is important to exclude secondary *Clostridium difficile* infection (CDI). The diagnosis is usually based on a clinical history of recent antimicrobial usage and diarrhea or abdominal distention in combination with laboratory tests. The recommended first step is screening with a glutamate dehydrogenase enzyme immunoassay (GDH-EIA) or the nucleic acid amplification test (NAATs)[99]. Samples determined to be negative in the first step can be considered negative for CDI, whereas those with positive results should be confirmed with toxins A and B in the feces. Treatment in these patients with a higher risk of other complications includes oral vancomycin combined or not with intravenous metronidazole[100,101].

Fever of unknown origin

A high suspicion of CMV, EBV or other viral reactivations is recommended in cases of fever of an unknown origin or other infective complications. If the patient presents with fever of an unknown origin, culture screening must be performed with blood from the central venous catheter or peripheral vein, as determined by each BMT unit[102].

Sepsis

Active treatment of infection should follow institutional protocols.

Perianal disease

Pelvic magnetic resonance imaging (MRI) is mandatory in patients with fistulizing perianal CD. Surgical drainage of abscesses should be performed before the onset of the procedure. Extensive drainage of abscesses and/or seton placement should be performed to prevent worsening of the disease or septic complications during the transplant period[23]. An area of ongoing investigation is the local application of autologous or allogeneic mesenchymal stem cells. These are non-hematopoietic multipotent cells with anti-inflammatory and immunomodulatory properties, the use of which may successfully treat refractory patients and seems to be a promising, safe alternative to achieving fistula healing in Crohn's disease with no known systemic effects[103].

Enterocutaneous fistula

The lifetime risk of developing enterocutaneous fistulas in patients with CD ranges from 20 to 40% and the cumulative risk

is 12 to 24% after 10 and 20 years, respectively[104]. Management is complex and requires a multidisciplinary approach. Despite the advent of anti-TNF drugs, the majority of patients still need surgical management[105]. A cohort study from the GETAID IBD society in France concluded that anti-TNF therapy may be effective in up to one-third of patients, especially in the absence of stenosis and complex fistula[106]. Studies with human gut xenograft mouse models are in development[107].

What are the indications for allogeneic HSCT in CD?

Allogeneic HSCT is performed with related donors (usually siblings or, more recently, haploidentical donors, such as parents, siblings or cousins) or unrelated donors (bone marrow donors registry). The sources of the cells are bone marrow, peripheral blood or cord blood. The procedure poses a higher risk of complications, such as infections and graft-versus-host-disease (GVHD), compared to autologous transplants, with mortality rates that can reach as high as 15% in patients undergoing HSCT. TABLE 2 shows several reports of patients with CD and concomitant malignant hematological diseases who were submitted to allogeneic HSCT. We found patients with acute and chronic myeloid leukemias, acute lymphoid leukemias and myelodysplasia with prolonged remissions in transplanted neoplastic disease as well as CD[31,32,36,38,39,41].

A recent 5-year evaluation was published of nine patients (four males and five females) with refractory CD submitted to allogeneic HSCT[108]. Three of the patients had full-match sibling donors and six received double umbilical cord blood (UCB) (5 6/6 and 1 5/6 HLA match). The conditioning regimen consisted of cyclophosphamide, fludarabine and alemtuzumab and prolonged immunosuppression after HSCT with tacrolimus[108]. The three full-match donor transplants presented CD3+ ranging from 13% to 30% 6 months after HSCT. Only one of the patients completed the 5-year assessment without symptoms of CD or GVHD, remaining in remission (clinical, magnetic resonance, endoscopic and histological analyses) and free of medications.

At 5 years, the stable mixed chimera persisted in 4.3% of donor CD3+ T cells. The other two patients were not followed up but reported having no symptoms after 5 years. There were descriptions of chronic GVHD and renal failure in one of the cases due to the use of calcineurin inhibitors. The interpretation of the results in these three patients is that mixed chimerism produces remission in CD.

Among the six patients who underwent allogeneic UCB HSCT, one died of infection by disseminated adenovirus, a fact that forced the suspension of the recruitment of patients. In the other five patients, there was no description of GVHD and none had a CD3+ or CD33+ donor graft after 6 months. Without a donor graft, calcineurin inhibitors were also discontinued at six months. As a result, the patients were free of any immunosuppressive drugs and CD, with no clinical, radiographic, endoscopic or histological evidence of disease. UCB results indicate that a donor graft is not necessary to achieve CD remission.

What would explain the effectiveness of the allogeneic UCB HSCT in which the graft failed?

The author speculates and indicates several hypotheses: 1: the conditioning regimen and six months of maintenance tacrolimus may, by itself, be sufficient for long-term remission; 2: transient donor graft versus autoimmunity before disappearance in 6 months after HPC infusion; 3: allogeneic UCB HSCT provides non-hematopoietic cells, as mesenchymal stromal cells would facilitate a durable remission.

Despite this new information, there are no criteria for the indication of allogeneic HSCT for CD due to the risks described to date.

What are the perspectives for using stem cell therapy (SCT) in perianal CD?

Mesenchymal stem cells or mesenchymal stromal cells (MSCs) have been suggested as a treatment option for CD[109]. MSCs are found throughout the body: one out of every 10,000 nucleated cells in bone marrow, adipose tissue, placental tissue, synovial tissue in joints and UCB[110]. MSCs have identifying properties, such as adhesion to plastic in cultures, the ability to differentiate in vitro into chondrocytes, osteoblasts and adipocytes in addition to expressing antigens CD105, CD73, and CD90. These cells do not express CD45, CD34, CD14, CD11b, CD79a, CD19 or HLA DR[111-114]. Studies describing use of SCT in systemic therapy or as localized therapy in complex perianal fistulas are found in the literature[115-118].

Despite the encouraging results, several logistical, regulatory and feasibility problems for the use of MSCs with the procedure remain a challenge, such as the standardization of the source, dosage, number of doses, interval between doses, cell purity, mechanisms of action, interaction of the MSC with the microenvironment, biodistribution, ability to reach the compromised tissue and interaction with the microbiota in addition to obtaining a license for the production and handling of MSCs[119-121].

What are the recommendations upon discharge and for follow up after HSCT?

After discharge, patients must be closely followed-up by gastroenterologists and hematologists, with clinical activity measured by the CDAI, Harvey-Bradshaw Index and patient-reported outcomes as well as laboratory parameters (complete blood count, liver function, C-reactive protein, kidney function and electrolytes, beta2 microglobulin, D vitamin and fecal calprotectin) assessed weekly during the first 30 days after HSCT, then at 90 days, 180 days and one year, followed by annually until the end of follow-up (5 years).

Recommendations for infectious prophylaxis have been described. Colonoscopy and/or MRI were performed at week 26 after transplant as well as after one, 2 and 4 years of follow-up or at any time when CD relapse was suspected. Patients should be assessed for quality of life (Inflammatory Bowel Disease Questionnaire, Short Form 36 or other) every 6 months after transplantation.

Monitoring of either CMV-associated pp65 antigen or PCR for virus-associated DNA fragments (or both) and EBV monitoring is strongly recommended for 90 days after transplant. The first year after treatment includes an early visit at 1 month. Considering the severe course of the disease before autologous HSCT, the persistence or recurrence of endoscopic lesions should lead to the re-introduction of specific therapies. In the suspicion of relapse, confounding factors such as *Clostridium difficile* and viral infections must be excluded. In confirmed cases of recurrence, we recommend treatment with highly effective therapy for CD, such as the combination of immunosuppressants and a TNF inhibitor in patients with endoscopically or radiologically active disease according to the current ECCO guidelines[26].

What about vaccination before and after HSCT?

Prior to HSCT, patients should receive vaccines indicated for immunocompetent persons based on age, vaccination and exposure history. After HSCT, one dose of inactivated influenza vaccine should be administered annually to persons aged ≥6 months starting 6 months after HSCT or starting 4 months after HSCT if there is a community outbreak of influenza defined by the local health department. Three doses of 13-valent pneumococcal conjugate vaccine (PCV13) should be administered starting three to 6 months after HSCT. One dose of pneumococcal polysaccharide vaccine-23 (PPSV23) should be given 12 months after HSCT, provided the patient does not have GVHD. For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HSCT. Three doses of *Haemophilus influenzae* type b vaccine should be administered 6 to 12 months after HSCT. Two doses of quadrivalent meningococcal conjugate vaccine (MCV4) should be administered six to 12 months after HSCT to persons aged 11 to 18 years, with a booster dose given at age 16 to 18 years for those who received the initial post-HSCT dose of vaccine at age 11 to 15 years. Three doses of tetanus/diphtheria-containing vaccines should be administered 6 months after HSCT. Administration of three doses of diphtheria toxoid-tetanus toxoid-acellular pertussis (DTaP) should be considered. Alternatively, a dose of Tdap vaccine should be administered followed by either two doses of diphtheria toxoid combined with tetanus toxoid (DT) or two doses of diphtheria toxoid (Td) vaccine. Three doses of hepatitis B (HepB) vaccine should be administered 6 to 12 months after HSCT. If a post-vaccination antibody against hepatitis B virus surface antigen (anti-HBs) concentration of ≥ 10 mIU/mL is not attained, a second three-dose series of HepB vaccine should be administered. Three doses of inactivated poliovirus (IPV) vaccine should be administered 6 to 12 months after HSCT. Consider the administration of three doses of quadrivalent human papillomavirus (HPV) vaccine 6 to 12 months after HSCT for female patients aged 11 to 26 years and HPV4 vaccine for males aged 11 to 26 years. Do not administer live vaccines to HSCT patients with active GVHD or ongoing immunosuppression. A two-dose series of combined measles, mumps and rubella (MMR) vaccine should be administered to measles-seronegative persons 24 months after HSCT in patients with neither chronic GVHD nor ongoing immunosuppression and 8 to 11 months (or earlier if there is a measles outbreak) after the last dose of immune globulin intravenous (IGIV). A two-dose series of varicella vaccine (VAR) should be administered 24 months after HSCT to varicella-seronegative patients with neither GVHD nor ongoing immunosuppression and 8 to 11 months after the last dose of IGIV[122,123].

What is the risks and safety for CD patients undergoing autologous HSCT ?

HSCT in CD is currently considered a safe procedure when performed in transplant centers with expertise in autoimmune diseases. However, despite advances, HSCT presents morbidity, especially during the aplasia phase, where severe neutropenia commonly increases the risk of infections[124].

Febrile neutropenia is a crucial complication and occurs in 80% of autologous transplants when performed to treat neoplastic diseases. The mortality rate in these cases is around 10%[124].

Currently, the Autologous HSCT mortality rate is less than 1%[125], the risk of HSCT Autologous starts with the implantation of the Central Venous Catheter in manipulation and the extended stay, in addition to the need for hospitalization to perform the procedure.

Adverse events are frequent and can affect various body sectors due to the toxicity of the chemoimmunosuppression used in the mobilization and conditioning phase of the transplant. In patients with malignant hematological neoplastic diseases, infection is considered a cause of death in approximately 8% of patients when undergoing autologous transplantation[126].

Late risks of HSCT Autologous, in addition to disease recurrence, are endocrinopathies, reproductive failure, secondary autoimmune disease, infections, and viral reactivations, and rarely secondary neoplasms and post-transplant lymphoproliferative disorder restricted to allogeneic transplants[127-129].

What outcomes and endpoints need to be observed in patients with CD undergoing HSCT?

The criteria for assessing the evolution of patients after HSCT are summarized in this section. There is a need to assess overall survival and mortality related to the procedure, which today are practically 100% and zero, respectively, due to advances in care, prophylaxis and the proper handling of patients, but these aspects should be included in the objective follow-up of patients. Other criteria refer more specifically to aspects related to disease activity scores, whether or not to use medications associated with colonoscopy results and images that provide evidence of disease-free remission. Other data that should be valued are patient-reported outcomes and the use of quality-of-life questionnaires, such as the Inflammatory Bowel Disease Questionnaire, Short Form 36 and others). These parameters are described in TABLE 7.

What is the current status of HSCT procedures for CD in Brazil?

In its 2018 resolution on medical activity, the Brazilian Code of Medical Ethics (CEM) helps us understand the current status of HSCT procedures in the treatment of CD in the country[132]. Some fundamental principles are set out in Item XXIV, such as respecting national ethical standards whenever physicians participate in research involving human beings or animals and the protection of the vulnerability of the research subjects.

Article 32, stipulates physicians must not fail to use all available scientifically recognized means of health promotion and prevention, diagnosis, and treatment of diseases in favor of the patient.

Article 100, stipulates that approval of a protocol for research involving human beings is required under current legislation. Art. 101 stipulates that, prior to conducting research involving human beings, a statement of informed consent from the patient or legal representative is required after due explanations about the nature and consequences of the research. Art. 102 states that a therapy cannot be used when its use is not authorized in the country. The sole paragraph of Article 102 states that the use of experimental therapy is permitted when accepted by government health organizations and consent is obtained from the patient or legal representative after adequate clarifications regarding the situation and possible consequences. It should be noted that there is no Brazilian legislation for compassionate treatments. HSCT in its various modalities and from different cell sources is an established procedure and duly standardized in the country[119].

The National Health Agency has a list of diseases for which it recommends HSCT as a mandatory treatment for all Brazilians through the Public Healthcare System. Individuals with private health insurance should have the costs of the procedure covered. Aplastic anemia is the only autoimmune disease that appears on

TABLE 7. Outcome evaluations suggested for CD after HSCT.

Clinical response	Decrease of at least 50% in PRO2 (abdominal pain and stool frequency)[124,125].
Clinical remission	CDAI <150[126]. HBI <5[127]. PRO2 (abdominal pain ≤1 and stool frequency ≤3)[73].
Endoscopic remission	Endoscopic remission (SES-CD ≤2 points or CDEIS <3) and lack of ulcerations (i.e., any ulcerations, including aphthous ulcers)[73,128].
Disease Free Remission 1 (DFR1)	Disease Free Remission, Type 1: CDAI <150, without CD-related medications, without endoscopic evidence of disease and MRI or CT without evidence of disease.
Disease Free Remission 2 (DFR2)	Disease Free Remission type 2: CDAI <150, without CD-related medications, without endoscopic evidence of disease, without MRI or CT evidence of disease and without histological evidence of disease.
Transmural healing	Magnetic Resonance Index of Activity score below 7[129,135].
Health-related quality of life	IBDQ[130,136]: bowel-related symptoms, systemic function, social function, emotional status. Response: increase ≥16 points. Remission ≥210 points. SF 36: vitality, mental health, emotional aspects, general health, social aspects, physical limitations, pain, functional capacity.
Disability	IBD Disability Index[131,137]. Comprises following domains: mobility, self-care, major daily life activities, gastrointestinal-related problems, mental health and interaction with environment. No disability: 0–20.
Overall survival	Percentage of HSCT survival in patients with CD.
Clinical relapse-free survival after HSCT	Time between HSCT and disease flareup.
Transplant-related mortality	Mortality directly related to HSCT.

CD: Crohn's disease; HSCT: Hematopoietic stem cell transplantation; PRO2: item patient-reported outcomes; CDAI: Crohn's Disease Activity Index; HBI: Harvey-Bradshaw Index; SES-CD: Simple endoscopic score for Crohn's disease; CDEIS: Crohn's Disease Endoscopic Index of Severity; MRI: magnetic resonance imaging; CT: computed tomography; IBDQ: Inflammatory Bowel Disease Questionnaire; SF36: Short Form 36; IBD: irritable bowel disease.

this list. For others, such as Crohn's disease, HSCT is considered experimental treatment according to the Federal Council of Medicine[138]; it must be carried out according to an experimental research protocol and follow the rules of the National Research Ethics Council. Autologous HSCT is performed for Crohn's disease in several countries and is currently recommended by the *Sociedade Brasileira de Transplante de Medula Óssea* (SBTMO [Brazilian Society of Bone Marrow Transplantation]) for refractory patients to immunosuppressants and biological agents or in the absence of a therapeutic option[50,63,133,134,139,140].

Conclusion: Positioning of the GEDIIB Transplantation Committee

This report summarizes criteria and indications for autologous HSCT in CD and the positioning of the GEDIIB Transplantation Committee, which include:

1) patients refractory to immunosuppressants and at least two biological agents, preferably one of them an anti-TNF;
2) the persistence of disease activity proven by endoscopy, colonoscopy, enteroscopy or magnetic resonance enterography;
3) extensive disease for which an imminent surgical procedure exposes the patient to the risk of short bowel syndrome or refractory colonic/perianal disease in which coloproctectomy with a definitive stoma implant is not accepted by the patient;
4) autologous non-myeloablative HSCT without any graft manipulation of cells;
5) HSCT must be performed at a BMT center by a multidisciplinary team with expertise in CD;
6) Absolute contraindications are active infection and recent malignant neoplasms except for hematologic neoplasms for which treatment needs to be HSCT;
7) All risks cited in contraindications must be individualized and discussed by a multidisciplinary team with each patient;
8) Randomized studies are needed in selected patients, whether or not to use prolonged immunosuppression and management for patients who relapsed after HSCT.

ACKNOWLEDGMENTS

The authors thank Fátima Lombardi, executive manager of Brazilian Group for the Study of Inflammatory Bowel Diseases (GEDIIB), and Camila de Jesus Souza for the support. In addition, the authors thank all members of the GEDIIB Transplantation Committee for their participation in the discussions and meetings of the committee.

Authors' contribution

All authors contributed to the literature review and interpretation of the data. Ruiz MA, Parra RS, Zabot GP, Andrade AR and Fonseca-Hial AMR, wrote and critically revised the manuscript. Quadros LG, Parente JML, and Kaiser Junior RL contributed to the critical revision of the manuscript. All authors granted final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Orcid

Milton Artur Ruiz: 0003-0000-2212-4883.
Rogério Serafim Parra: 0000-0002-5566-9284.
Gilmara Pandolfo Zabot: 0000-0002-1253-4945.
Adriana Ribas Andrade: 0000-0001-6012-2155.
Lilian Piron-Ruiz: 0000-0002-3602-5897.
Ana Marcela Rojas Fonseca-Hial: 0000-0002-6683-3836.
Eloisa Moreira Martin: 0000-0001-6104-9690.
Tainara Souza Pinho: 0000-0003-3531-079X.
Luiz Gustavo de Quadros: 0000-0001-9586-8109.
Roberto Luiz Kaiser Junior: 0000-0003-1952-1255.
José Miguel Luz Parente: 0000-0003-4563-2784.

Ruiz MA, Parra RS, Zabot GP, Andrade AR, Piron-Ruiz L, Fonseca-Hial AMR, Martin EM, Pinho TS, Quadros LG, Kaiser Junior RL, Parente JML. Transplante de células tronco hematopoiéticas e doença de Crohn: posição do Comitê de Transplantes do Grupo Brasileiro para estudo das doenças inflamatórias do intestino (GEDIIB). Arq Gastroenterol. 2022;59(4):462-77.

RESUMO – A doença de Crohn (DC) é uma doença inflamatória intestinal (DII) recidivante recorrente que pode afetar qualquer parte do sistema digestivo. É doença heterogênea e possui múltiplos fatores que contribuem para uma resposta imune anormal aos microrganismos intestinais. O tratamento baseia-se no uso de anti-inflamatórios, corticosteroides e imunossupressores e imunobiológicos que são utilizados isoladamente ou em combinação. O tratamento cirúrgico é frequente e 10 anos após o diagnóstico, mais de 50% dos pacientes relatam terem sido submetidos a procedimentos cirúrgicos relacionados à doença. Infelizmente, nenhum dos tratamentos descritos oferece cura, e inúmeros casos tornam-se refratários ou sem opções terapêuticas. Nesse cenário, o transplante de células-tronco hematopoéticas (TCTH) em decorrência da remissão clínica de pacientes que apresentavam DC associada a doenças hematológicas malignas, passou a ser alternativa desde os primeiros resultados em 2010. Neste relato, a Comissão de Transplantes do Grupo Brasileiro de Estudo das Doenças Inflamatórias Intestinais revisa a história e os resultados do procedimento em pacientes com DC, detalhando e discutindo os diversos pontos relevantes que permeiam o TCTH e a terapia celular no tratamento da moléstia.

Palavras-chave – Doença de Crohn; doenças inflamatórias intestinais; transplante de células-tronco; transplante de células-tronco hematopoiéticas; transplante autólogo.

REFERENCES

1. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2020;14:4-22.
2. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, et al. Crohn's disease. Nat Rev Dis Primers. 2020;6:1-19.
3. Loftus EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504-17.
4. Stange EF, Schroeder BO. Microbiota and mucosal defense in IBD: an update. Expert Rev Gastroenterol Hepatol. 2019;13:963-76.
5. de Souza HSP, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol. 2016;13:13-27.
6. Windsor JW, Kaplan GG. Evolving Epidemiology of IBD. Curr Gastroenterol Rep. 2019;21:40.
7. Victoria CR, Sassak LY, Nunes HR de C. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern São Paulo State, Brazil. Arq Gastroenterol. 2009;46:20-5.
8. Parente JML, Coy CSR, Campelo V, Parente MPPD, Costa LA, da Silva RM, et al. Inflammatory bowel disease in an underdeveloped region of Northeastern Brazil. World J Gastroenterol. 2015;21:1197-206.
9. Parra RS, Chebli JMF, Amarante HMBS, Flores C, Parente JML, Ramos O, et al. Quality of life, work productivity impairment and healthcare resources in inflammatory bowel diseases in Brazil. World J Gastroenterol. 2019;25:5862-82.
10. de Sá Brito Fróes R, da Luz Moreira A, Carneiro AJ de V, Moreira JPL, Luiz RR, de Barros Moreira AMH, et al. Prevalence, Indirect Costs, and Risk Factors for Work Disability in Patients with Crohn 's Disease at a Tertiary Care Center in Rio de Janeiro. Dig Dis Sci. 2021;66:2925-34.
11. Zaltman C, Parra RS, Sassaki LY, Santana GO, Ferrari M de LA, Miszputen SJ, et al. Real-world disease activity and sociodemographic, clinical and treatment characteristics of moderate-to-severe inflammatory bowel disease in Brazil. World J Gastroenterol. 2021;27:208-23.
12. Vilela EG, Rocha HC, Moraes AC, Santana GO, Parente JM, Sassaki LY, et al. Inflammatory bowel disease care in Brazil : How it is performed , obstacles and demands from the physician's perspective . Arq Gastroenterol. 2020;57:416-27.
13. Tran V, Limketkai BN, Sauk JS. IBD in the Elderly: Management Challenges and Therapeutic Considerations. Curr Gastroenterol Rep. 2019;21:60.
14. Lightner AL, Vogel JD, Carmichael JC, Keller DS, Shah SA, Mahadevan U, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease. Dis Colon Rectum. 2020;63:1028-52.
15. Peyrin-Biroulet L, Loftus EV, Colombel J-F, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105:289-97.
16. Vuitton L, Peyrin-Biroulet L. Pharmacological Prevention of Postoperative Recurrence in Crohn's Disease. Drugs. 2020;80:385-99.
17. Freeman HJ. Natural history and long-term clinical course of Crohn's disease. World J Gastroenterol. 2014;20:31-6.
18. Cushing K, Higgins PDR. Management of Crohn Disease: A Review. JAMA. 2021;325:69-80.
19. Adamina M, Bonovas S, Raine T, Spinelli A, Warusavitarne J, Armuzzi A, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment. J Crohns Colitis. 2020;14:155-68.
20. Atreya R, Neurath MF, Siegmund B. Personalizing Treatment in IBD: Hype or Reality in 2020? Can We Predict Response to Anti-TNF? Front Med (Lausanne). 2020;7:517.
21. Sulz MC, Burri E, Michetti P, Rogler G, Peyrin-Biroulet L, Seibold F, et al. Treatment Algorithms for Crohn's Disease. Digestion. 2020;101 (Suppl 1): 43-57.
22. Fiorino G, Bonifacio C, Allocca M, Danese S. Impact of therapies on bowel damage in Crohn's disease. United European Gastroenterol J. 2020;8:410-7.
23. Vulliemoz M, Brand S, Juillerat P, Mottet C, Ben-Horin S, Michetti P, et al. TNF-Alpha Blockers in Inflammatory Bowel Diseases: Practical Recommendations and a User's Guide: An Update. Digestion. 2020;101 (Suppl 1):16-26.
24. Brierley CK, Castilla-Llorente C, Labopin M, Badoglio M, Rovira M, Ricart E, et al. Autologous Haematopoietic Stem Cell Transplantation for Crohn's Disease: A Retrospective Survey of Long-term Outcomes From the European Society for Blood and Marrow Transplantation. J Crohns Colitis. 2018;12:1097-103.
25. Lindsay JO, Allez M, Clark M, Labopin M, Ricart E, Rogler G, et al. Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial. Lancet Gastroenterol Hepatol. 2017;2: 399-406.

26. Snowden JA, Panés J, Alexander T, Allez M, Ardizzone S, Dierickx D, et al. Autologous Haematopoietic Stem Cell Transplantation (AHSCT) in Severe Crohn's Disease: A Review on Behalf of ECCO and EBMT. J Crohns Colitis. 2018;12:476-88.
27. Ruiz MA, Kaiser Junior RL, Piron-Ruiz L, Peña-Arciniegas T, Saran PS, De Quadros LG. Hematopoietic stem cell transplantation for Crohn's disease: Gaps, doubts and perspectives. World J Stem Cells. 2018;10:134-7.
28. Ruiz MA, Kaiser RL, de Quadros LG, Piron-Ruiz L, Peña-Arciniegas T, Faria MAG, et al. Low toxicity and favorable clinical and quality of life impact after non-myeloablative autologous hematopoietic stem cell transplant in Crohn's disease. BMC Res Notes. 2017;10:495.
29. Drakos PE, Nagler A, Or R. Case of Crohn's disease in bone marrow transplantation. Am J Hematol. 1993;43:157-8.
30. Castro J, Bentch H SL. Prolonged clinical remission in patients with inflammatory bowel disease(IBD) after high dose chemotherapy(HDC)and autologous blood stem cell transplantation. Blood. 1996;88(Suppl):133A.
31. Talbot DC, Montes A, Teh WL, Nandi A PRL. Remission of Crohn's disease following allogeneic bone marrow transplant for acute leukaemia. Hosp Med. 1998;59:580-1.
32. Lopez–Cubero SO, Sullivan KM, McDonald GB. Course of Crohn's disease after allogeneic marrow transplantation. Gastroenterology. 1998;114:433-40.
33. Kashyap, Forman SJ. Autologous bone marrow transplantation for non-Hodgkin's lymphoma resulting in long-term remission of coincidental Crohn's disease. Br J Haematol. 1998;103:651-2.
34. Musso M, Porretto F, Crescimanno a, Bondì F, Polizzi V, Scalone R. Crohn's disease complicated by relapsed extranodal Hodgkin's lymphoma: prolonged complete remission after unmanipulated PBPC autotransplantation. Bone Marrow Transplant. 2000;26:921-3.
35. Soderholm JD, Malm C, Juliusson G, Sjodahl R. Long-term endoscopic remission of crohn disease after autologous stem cell transplantation for acute myeloid leukaemia. Scand J Gastroenterol. 2002;37:613-6.
36. Ditschkowski M, Einsele H, Schwerdtfeger R, Bunjes D, Trenschel R, Beelen DW, et al. Improvement of inflammatory bowel disease after allogeneic stem-cell transplantation. Transplantation. 2003;75:1745-7.
37. Anumakonda V, Hayee C-FG. Remission and relapse of Crohn's disease following autologous haematopoietic stem cell transplantation for non-Hodgkin's lymphoma. Gut. 2007;56:1323-4.
38. Nishimoto M, Nakamae H, Watanabe K, Koh H, Nakane T, Ohsawa M, et al. Successful treatment of both acute leukemia and active crohn's disease after allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning with fludarabine and busulfan: A case report. Transplant Proc. 2013;45:2854-7.
39. Hu C, Lv L, Liu D, Huo J. Treatment of Crohn's disease complicated with myelodysplastic syndrome via allogeneic hematopoietic stem cell transplantation: Case report and literature review. Clin J Gastroenterol. 2014;7:299-304.
40. Rabian F, Porcher R, Sicre de Fontbrune F, Lioure B, Laplace A, Nguyen S, et al. Influence of Previous Inflammatory Bowel Disease on the Outcome of Allogeneic Hematopoietic Stem Cell Transplantation: A Matched-Pair Analysis. Bone Marrow Transplant. 2016;22:1721-4.
41. Zhang Y, Lou L, Shi X, Lu S, Zhang L, Huang X, et al. Allogeneic hematopoietic stem cell transplantation for Crohn disease complicated with myelodysplastic syndrome. MEDICINE. 2020;10:6-9.
42. Ruiz, MA et al. Stem cell transplantation an alternative to treat Crohn's disease – Chapter 53 in Burt,RK, Farge D, Ruiz MA, Saccardi R, Snowden JA. Stem cell transplantation and cellular therapies for autoimmune diseases (2021), CRC Press / Taylor and Francis group. LLC, Boca Raton, FL, USA. In the press.
43. Kreisel W, Potthoff K, Bertz H, Schmitt-Graeff A, Ruf G, Rasenack J, et al. Complete remission of Crohn's disease after high-dose cyclophosphamide and autologous stem cell transplantation. Bone Marrow Transplant. 2003;32:337-40.
44. Craig RM, Traynor A, Oyama Y, Burt RK. Hematopoietic stem cell transplantation for severe Crohn's disease. Bone Marrow Transplant. 2003;32 (Suppl 1):S57-59.
45. Burt RK, Traynor A, Oyama Y, Craig R. High-dose immune suppression and autologous hematopoietic stem cell transplantation in refractory Crohn disease. Blood. 20031;101:2064-6.
46. Burt RK, Craig RM, Milanetti F, Quigley K, Gozdziak P, Bucha J, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. Blood. 2010;116:6123-32.
47. Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, et al. Autologous Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. JAMA. 2015;314:2524-34.
48. López-García A, Rovira M, Jauregui-Amezaga A, Marín P, Berastegui R, Salas A, et al. Autologous Haematopoietic Stem Cell Transplantation for Refractory Crohn's Disease: Efficacy in a Single-Centre Cohort. J Crohns Colitis. 2017;11:1161-8.
49. Hernanz N, Sierra M, Volpato N, Núñez-Gómez L, Mesonero F, Herrera-Puente P, et al. Autologous haematopoietic stem cell transplantation in refractory Crohn's disease: Experience in our centre. Gastroenterol Hepatol. 2019;42:16-22.
50. Oliveira MC, Elias JB, Moraes DA de, Simões BP, Rodrigues M, Ribeiro AAF, et al. A review of hematopoietic stem cell transplantation for autoimmune diseases: multiple sclerosis, systemic sclerosis and Crohn's disease. Position paper of the Brazilian Society of Bone Marrow Transplantation. Hematol Transfus Cell Ther. 2021;43:65-86.
51. Scimé R, Cavallaro AM, Tringali S, Santoro. Complete Clinical Remission after High- Dose Immune Suppression and Autologous Hematopoietic Stem Cell Transplantation in Severe Crohn ' s Disease Refractory to Immuno- suppressive and Immu- nomodulator Therapy. Inflamm Bowel Dis. 2004;10:892-4.
52. Oyama Y, Craig RM, Traynor AE, Quigley K, Statkute L, Halverson A, et al. Autologous Hematopoietic Stem Cell Transplantation for Crohn's Disease : High Risk for a High Reward. Gastroenterology. 2005;11:778-9.
53. Cassinotti a, Annaloro C, Ardizzone S, Onida F, Della Volpe a, Clerici M, et al. Autologous haematopoietic stem cell transplantation without CD34+ cell selection in refractory Crohn's disease. Gut. 2008;57:211-7.
54. Clerici M, Cassinotti A, Onida F, Trabattoni D, Annaloro C, Della Volpe A, et al. Immunomodulatory effects of unselected haematopoietic stem cells autotransplantation in refractory Crohn's disease. Dig Liver Dis. 2011;43:946-52.
55. Hommes DW, Duijvestein M, Zelinkova Z, Stokkers PCF, Ley MH, Stoker J, et al. Long-term follow-up of autologous hematopoietic stem cell transplantation for severe refractory Crohn's disease. J Crohns Colitis. 2011;5:543-9.
56. Kountouras J, Sakellari I, Tsarouchas G, Tsiaousi E, Michael S, Zavos C, et al. Autologous haematopoietic stem cell transplantation in a patient with refractory Crohn's disease. J Crohns Colitis. 2011;5:275-6.
57. Hasselblatt P, Drognitz K, Potthoff K, Bertz H, Kruis W, Schmidt C, et al. Remission of refractory Crohn's disease by high-dose cyclophosphamide and autologous peripheral blood stem cell transplantation. Aliment Pharmacol Ther. 2012;36:725-35.
58. Krivan G, Doloresz S, Krisztian K, Gabor B CK. Successful autologous hematopoietic stem cell transplantation in severe, therapy-resistant childhood-onset Crohn's disease. Report on the first case in Hungary. Orvosi Hetilap. 2014;155:789-92.
59. Snowden J a, Ansari A, Sachchithanantham S, Jackson G, Thompson N, Lobo A, et al. Autologous stem cell transplantation (asct) in severe, resistant crohn's disease: long-term follow-up of UK patients treated on compassionate basis. QJM. 2014;107:871-7.
60. Ruiz MA, Kaiser Junior RL, Gouvêa Faria MA, de Quadros LG. Remission of refractory Crohn 's disease after autologous hematopoietic stem cell transplantation. Rev Bras Hematol Hemoter. 2015;37:136-9.
61. López-García A, Rovira M, Jauregui-Amezaga A, Marín P, Barastegui R, Salas A, et al. Hematopoietic, Autologous Cell, Stem For, Transplantation Crohn, Refractory Cohort, Single-centre Cohort. J Crohns Colitis. 2017;11:116:116.
62. Ruiz, MA, Kaiser Junior, RL, De Quadros LG,Caseiro GHX, Oliveira AF, Peña-Arciniegas, T, Piron-Ruiz L. Hematopoietic stem cell transplantation in a severe refractory Crohn's disease patient with intestinal stoma : a case report. Int Med Case Rep J. 2017;10:353-9.
63. Ruiz MA, Junior RLK, Piron-Ruiz L, Saran PS, Castiglioni L, de Quadros LG, et al. Medical, ethical, and legal aspects of hematopoietic stem cell transplantation for Crohn's disease in Brazil. World J Stem Cells. 2020;12:1113-23.
64. Ikehara S. Bone marrow transplantation for autoimmune diseases. Acta Haematol. 1998;99:116-32.
65. Cominelli F, Arseneau KO, Rodriguez-Palacios A, Pizarro TT. Uncovering Pathogenic Mechanisms of Inflammatory Bowel Disease Using Mouse Models of Crohn's Disease-Like Ileitis: What is the Right Model? Cell Mol Gastroenterol Hepatol. 2017;4:19-32.
66. Komori M, Tsuji S, Tsujii M, Murata H, Iijima H, Yasumaru M, et al. Involvement of bone marrow-derived cells in healing of experimental colitis in rats. Wound Repair Regen. 2005;13:109-18.
67. Ismail AM, Abdou SM, Aty HA, Kamhawy AH, Elhinedy M, Elwageh M, et al. Autologous transplantation of CD34(+) bone marrow derived mononuclear cells in management of non-reconstructable critical lower limb ischemia. Cytotechnology. 2016;68:771-81.
68. Khalil PN, Weiler V, Nelson PJ, Khalil MN, Moosmann S, Mutschler WE, et al. Nonmyeloablative stem cell therapy enhances microcirculation and tissue regeneration in murine inflammatory bowel disease. Gastroenterology. 2007;132:944-54.
69. Godoi DF, Cardoso CR, Ferraz DB, Provinciatto PR, Cunha FQ, Silva JS, et al. Hematopoietic SCT modulates gut inflammation in experimental inflammatory bowel disease. Bone Marrow Transplant. 2010;45:1562-71.
70. Farge D, Labopin M, Tyndall A, Fassas A, Mancardi GL, Van Laar J, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. Haematologica. 2010;95:284-92.

71. Rutgeerts P, Gasink C, Chan D, Lang Y, Pollack P, Colombel J-F, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. Gastroenterology. 2018;155:1045-58.
72. Peyrin-Biroulet L, Danese S, Argollo M, Pouillon L, Peppas S, Gonzalez-Lorenzo M, et al. Loss of Response to Vedolizumab and Ability of Dose Intensification to Restore Response in Patients With Crohn's Disease or Ulcerative Colitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;17:838-846.e2.
73. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160:1570-83.
74. Corraliza AM, Ricart E, López-García A, Carme Masamunt M, Veny M, Esteller M, et al. Differences in Peripheral and Tissue Immune Cell Populations Following Haematopoietic Stem Cell Transplantation in Crohn's Disease Patients. J Crohns Colitis. 2019;13:634-47.
75. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.
76. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323:1061-9.
77. Chebli JMF, Queiroz NSF, Damião AOMC, Chebli LA, Costa MH de M, Parra RS. How to manage inflammatory bowel disease during the COVID-19 pandemic: A guide for the practicing clinician. World J Gastroenterol. 2021;27:1022-42.
78. Shah GL, DeWolf S, Lee YJ, Tamari R, Dahi PB, Lavery JA, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. J Clin Invest. 2020;130:6656-67.
79. Aziz M, Fatima R, Haghbin H, Lee-Smith W, Nawras A. The Incidence and Outcomes of COVID-19 in IBD Patients: A Rapid Review and Meta-analysis. Inflamm Bowel Dis. 2020;26:e132-3.
80. Ljungman P, Mikulska M, de la Camara R, Basak GW, Chabannon C, Corbacioglu S, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplant. 2020;55:2071-6.
81. Dholaria B, Savani BN. How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat? Br J Haematol. 2020;189:239-40.
82. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. Curr Opin Rheumatol. 2021;33:155-62.
83. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020;16:413-4.
84. Piron-Ruiz L SARS -COV-2 in Crohn's disease patients submitted to Autologous HSCT. 2021 personnel communication.
85. Kindwall-Keller T. Peripheral stem cell collection: from leukocyte growth factor to removal of catheter. J Clin Apher. 2014;29:199-205.
86. Christopeit M, Schmidt-Hieber M, Sprute R, Buchheidt D, Hentrich M, Karthaus M, et al. Prophylaxis, diagnosis and therapy of infections in patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation. 2020 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol. 2021;100:321-36.
87. Devine H, Tierney DK, Schmit-Pokorny K, McDermott K. Mobilization of hematopoietic stem cells for use in autologous transplantation. Clin J Oncol Nurs. 2010;14:212-22.
88. Duong HK, Savani BN, Copelan E, Devine S, Costa LJ, Wingard JR, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2014;20:1262-73.
89. Burt RK, Deeg HJ, Santos GW. On Call In. Bone Marrow Transplantation. Landes Company and Chapman & Hall; 1996. (69-75; vol. Chapter 3.2).
90. Blank N, Lisenko K, Pavel P, Bruckner T, Ho AD, Wuchter P. Low-dose cyclophosphamide effectively mobilizes peripheral blood stem cells in patients with autoimmune disease. Eur J Haematol. 2016;97:78-82.
91. Jauregui-Amezaga A, Rovira M, Marín P, Salas A, Pinó-Donnay S, Feu F, et al. Improving safety of autologous haematopoietic stem cell transplantation in patients with Crohn's disease. Gut. 2016;65:1456-62.
92. Ruiz MA, Kaiser RL, Piron-Ruiz L-, Peña-Arciniegas T, Castiglioni L, Saran PS, et al. Crohn's disease patients effectively mobilized peripheral blood stem cells to perform autologous haematopoietic stem cell transplantation. bioRxiv. 2018;348763.
93. Openshaw H, Stuve O, Antel JP, Nash R, Lund BT, Weiner LP, et al. Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. Neurology. 2000;54:2147-50.
94. Perez-Simon JA, Diez-Campelo M, Martino R, Sureda A, Caballero D, Canizo C, et al. Impact of CD34+ cell dose on the outcome of patients undergoing reduced-intensity-conditioning allogeneic peripheral blood stem cell transplantation. Blood. 2003;102:1108-13.
95. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15:1628-33.
96. Piron-Ruiz L. Care in Conditioning Patients with Crohn's Disease. 2021 personal communication.
97. Berti-Hearn L, Elliott B. Ileostomy Care: A Guide for Home Care Clinicians. Home Healthc Now. 2019;37:136-44.
98. Knowles SR, Wilson J, Wilkinson A, Connell W, Salzberg M, Castle D, et al. Psychological well-being and quality of life in Crohn's disease patients with an ostomy: a preliminary investigation. J Wound Ostomy Continence Nurs. 2013;40:623-9.
99. Del Prete R, Ronga L, Addati G, Magrone R, Abbasciano A, Decimo M, et al. Clostridium difficile. A review on an emerging infection. Clin Ter. 2019;170:e41–7.
100. Zhang K, Beckett P, Abouanaser S, Stankus V, Lee C, Smieja M. Prolonged oral vancomycin for secondary prophylaxis of relapsing Clostridium difficile infection. BMC Infect Dis. 2019;19:51.
101. D'Aoust J, Battat R, Bessissow T. Management of inflammatory bowel disease with Clostridium difficile infection. World J Gastroenterol. 2017;23:4986-5003.
102. Heinz WJ, Buchheidt D, Christopeit M, von Lilienfeld-Toal M, Cornely OA, Einsele H, et al. Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol. 2017;96:1775-92.
103. Bermejo F, Guerra I, Algaba A, López-Sanromán A. Pharmacological Approach to the Management of Crohn's Disease Patients with Perianal Disease. Drugs. 2018;78:1-18.
104. Hawkey CJ, Hommes DW. Is Stem Cell Therapy Ready for Prime Time in Treatment of Inflammatory Bowel Diseases? Gastroenterology. 2017;152:389-97.e2.
105. Yzet C, Le Mouel JP, Hakim S, Brazier F, Fumery M. P608 Endoscopic treatment of enterocutaneous fistulas in Crohn's disease patient. J Crohns Colitis. 2020;14(Suppl 1):S508-S508.
106. Amiot A, Setakhr V, Seksik P, Allez M, Treton X, De Vos M, et al. Long-term outcome of enterocutaneous fistula in patients with Crohn's disease treated with anti-TNF therapy: a cohort study from the GETAID. Am J Gastroenterol. 2014;109:1443-9.
107. Bruckner RS, Marsiano N, Nissim-Eliraz E, Nir E, Leutenegger M, Gottier C, et al. P034 Validation of a novel xenograft mouse model for intestinal fistulas. J Crohns Colitis. 2018;12 (Suppl 1):S109-10.
108. Burt RK, Craig R, Yun L, Halverson A, Quigley K, Arnautovic I, et al. A pilot feasibility study of non-myeloablative allogeneic hematopoietic stem cell transplantation for refractory Crohn Disease. Bone Marrow Transplant. 2020;9-12.
109. Zhang J, Lv S, Liu X, Song B, Shi L. Umbilical Cord Mesenchymal Stem Cell Treatment for Crohn's Disease: A Randomized Controlled Clinical Trial. Gut Liver. 2018;12:73-8.
110. Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. Cell Commun Signal. 2011;9:12.
111. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8:315-7.
112. Voswinkel J, Francois S, Gorin N-C, Chapel A. Gastro-intestinal autoimmunity: preclinical experiences and successful therapy of fistulizing bowel diseases and gut Graft versus host disease by mesenchymal stromal cells. Immunol Res. 2013;56:241-8.
113. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007;110:3499-506.
114. Satija NK, Singh VK, Verma YK, Gupta P, Sharma S, Afrin F, et al. Mesenchymal stem cell-based therapy: a new paradigm in regenerative medicine. J Cell Mol Med. 2009;13:4385-402.
115. Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. Gastroenterology. 2018;154:1334-42.e4.
116. García-Olmo D, García-Arranz M, García LG, Cuellar ES, Blanco IF, Prianes LA, et al. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy. Int J Colorectal Dis. 2003;18:451-4.
117. Liang J, Zhang H, Wang D, Feng X, Wang H, Hua B, et al. Allogeneic mesenchymal stem cell transplantation in seven patients with refractory inflammatory bowel disease. Gut. 2012;61:468-9.

118. Duijvestein M, Vos ACW, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW, et al. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. Gut. 2010;59:1662-9.
119. Galipeau J, Sensébé L. Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. Cell Stem Cell. 2018;22:824-33.
120. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018;14:493-507.
121. Carvello M, Lightner A, Yamamoto T, Kotze PG, Spinelli A. Mesenchymal Stem Cells for Perianal Crohn's Disease. Cells. 2019;8:764.
122. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:e44-100.
123. Conrad A, Alcazer V, Valour F, Ader F, Lyon HEMINF Study Group. Vaccination post-allogeneic hematopoietic stem cell transplantation: what is feasible? Expert Rev Vaccines. 2018;17:299-309.
124. Signorelli J, Zimmer A, Liewer S, Shostrom VK, Freifeld A. Incidence of Febrile Neutropenia in Autologous Hematopoietic Stem Cell Transplant (HSCT) Recipients on levofloxacin prophylaxis. Transpl Infect Dis. 2020;22:e13225. doi: 10.1111/tid.13225.
125. Balassa K, Danby R, Rocha V. Haematopoietic stem cell transplants: principles and indications. Br J Hosp Med (Lond). 2019;80:33-9. doi: 10.12968/hmed.2019.80.1.33.
126. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JA, Boeckh MJ; Center for International Blood and Marrow Research; National Marrow Donor program; European Blood and MarrowTransplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143-238. doi: 10.1016/j.bbmt.2009.06.019.
127. Majhail NS. Long-term complications after hematopoietic cell transplantation. Hematol Oncol Stem Cell Ther. 2017;10:220-7. doi: 10.1016/j.hemonc.2017.05.009.
128. Burns LJ. Late effects after autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(Suppl 1):21-4. doi: 10.1016/j.bbmt.2008.10.009.
129. Pegoraro F, Favre C. Post-transplantation lymphoproliferative disorder after haematopoietic stem cell transplantation. Ann Hematol. 2021;100:865-78. doi: 10.1007/s00277-021-04433-y.
130. Bojic D, Bodger K, Travis S. Patient Reported Outcome Measures (PROMs) in Inflammatory Bowel Disease: New Data. J Crohns Colitis. 2017;11(Suppl 2):S576-S585.
131. Feagan B, Sandborn WJ, Rutgeerts P, Levesque BG, Khanna R, Huang B, et al. Performance of Crohn's disease Clinical Trial Endpoints based upon Different Cutoffs for Patient Reported Outcomes or Endoscopic Activity: Analysis of EXTEND Data. Inflamm Bowel Dis. 2018;24:932-42.
132. Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70:439-44.
133. Harvey RF, Bradshaw JM. A simple index of Cronh's disease activity. The Lancet. 1980;315:514.
134. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60:505-12.
135. Buisson A, Pereira B, Goutte M, Reymond M, Allimant C, Obritin-Guilhen H, et al. Magnetic resonance index of activity (MaRIA) and Clermont score are highly and equally effective MRI indices in detecting mucosal healing in Crohn's disease. Dig Liver Dis. 2017;49:1211-7.
136. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989;96:804-10.
137. Gower-Rousseau C, Sarter H, Savoye G, Tavernier N, Fumery M, Sandborn WJ, et al. Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. Gut. 2017;66:588-96.
138. Conselho Federal de Medicina, 2019. Código de Ética Médica: Resolução CFM no 2.217, de 27 de setembro de 2018, modificada pelas Resoluções CFM no 2.222/2018 e 2.226/2019 / Conselho Federal de Medicina.
139. Transplante de Células tronco Hematopoéticas – TCTH. Diário Oficial da União – seção 1, 18 de novembro de 2004, pág 43-47.
140. Oliveira MC, Ruiz MA, Moraes D, Dias JE, Piron-Ruiz L, et al. HSCT for Autoimmune diseases. BMTCT. 2021;2:127-30.