

Non-infectious complications after hematopoietic cell transplantation

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ABSTRACT

Hematopoietic cell transplantation (HCT) is a curative treatment for children with malignant and non-malignant diseases. In recent years, we have observed a significant increase in the survival of these patients, due to improved resources. In this article, we discuss non-infectious complications related to HCT, including their management, prevention, and best options of treatment.

Keywords: Hematopoietic Stem Cell Transplantation. Complications. Pediatric Patients.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a therapeutic option for children with malignant and nonmalignant diseases. Improvements in supportive care promote an increased survival, but patients still face complications, such as acute toxicities, endothelial injury, pulmonary alterations and other ones, generally secondary to conditioning regimen and immunosuppression¹.

ACUTE TOXICITIES

Nausea and vomiting

Effective antiemetic control is essential for managing chemotherapy-induced nausea and vomiting (CINV) in children undergoing conditioning for HCT. Conditioning regimens, including high-dose chemotherapy

and total body irradiation, are highly emetogenic, requiring a comprehensive strategy. Grading can be found elsewhere². Around the clock, metoclopramide and dramamine are commonly used in HCT setting.

5-HT₃ receptor antagonists (*e.g.*, ondansetron, granisetron) combined with neurokinin-1 (NK1) receptor antagonists (*e.g.*, fosaprepitant) effectively reduce acute and delayed CINV in pediatric HCT^{3,4}. American Society of Clinical Oncology guidelines recommend an NK1 antagonist, a 5-HT₃ antagonist, and dexamethasone for optimal control⁵, but the latter may increase fungal infection risk⁶.

Benzodiazepines (*e.g.*, lorazepam) help managing anticipatory nausea and anxiety-related emesis. Cannabidiol derivatives show potential in resistant CINV, though further research is needed. Chlorpromazine remains an option for breakthrough emesis unresponsive to first-line agents^{7,8}. These antiemetics generally have a favorable safety profile^{3,4,9}, but ongoing research may refine regimens and address antiemetic failures.

Mucositis

Oral mucositis is a common and, in some cases, a severe complication, occurring in up to 80% of the pediatric patients undergoing HCT, typically five to 10 days after the start of the conditioning, peaking around day 12, and resolving within two to three weeks^{10,11}. It causes pain, difficulty in nutrition, infection risk, and prolonged hospitalization. World Health Organization score can be found elsewhere, but the daily oral mucositis scale may help managing the patients (Table 1).

Table 1. Oral mucositis scale.

World Health Organization oral mucositis scale	
0	None
1	Soreness ± erythema, no ulceration
2	Erythema, ulcers; patients can swallow solid diet
3	Ulcers, extensive erythema; patients cannot swallow solid diet
4	Mucositis to the extent that oral alimentation is not possible

Source: Adapted from World Health Organization classification.

For prevention:

- Rigorous oral hygiene reduces mucositis severity. Chlorhexidine mouthwash may significantly lower the incidence of severe mucositis¹²;
- Cryotherapy induces vasoconstriction, reducing tissue exposure to chemotherapy¹³;
- Photobiomodulation or low-level laser therapy effectively reduces the severity, pain, and the duration of the mucositis¹⁴;
- Pharmacological agents are palifermin, a recombinant keratinocyte growth factor that promotes epithelial cell recovery¹⁵, and caphosol, a supersaturated calcium phosphate rinse¹⁶, but they are not available in Brazil and not routinely used.

Patients with Fanconi anemia are highly susceptible to severe mucositis due to DNA repair defects and have a specific graduation score. Lower-intensity conditioning protocols can help mitigate toxicity and improve outcomes¹⁷. Herpes simplex virus (HSV) reactivation may mimic and/or exacerbate mucositis, prolonging ulceration and increasing pain. Prophylactic acyclovir significantly reduces HSV-related lesions in HCT who have been previously infected with HSV¹⁸.

Hemorrhagic cystitis

Hemorrhagic cystitis is a frequent complication after HCT, characterized by diffuse bladder inflammation and bleeding, with sustained hematuria and lower urinary tract symptoms, in the absence of bleeding diathesis,

vaginal bleeding or urinary tract infection. Hemorrhagic cystitis may have early-onset post-HCT, typically within 48 hours of the end of the conditioning regimen, due to direct toxic effect of drug metabolites, especially acrolein, and radiotherapy on the bladder mucosa. Late-onset hemorrhagic cystitis usually starts around the time of neutrophil engraftment (weeks 2–4) up to the third month after HCT, and it is usually due to polyoma (BKV) or adenovirus infections, more often seen in allogeneic HCT with alternative donors^{19–21}. It has significant morbidity, prolonged hospitalizations, and occasional mortality.

Prophylaxis in patients receiving high doses of cyclophosphamide include hyperhydration, administration of mesna, or continuous bladder irrigation if the urinary flow is severely decreased. In the late-onset hemorrhagic cystitis, the BKV replication has a key role in exacerbating the damage of bladder mucosa through its cytopathic effect and in inducing the donor immune alloreactivity targeting the bladder mucosa. Hemorrhagic cystitis is treated with intensive intravenous hydration, forced diuresis, analgesia, spasmolytic drugs, and treatment of infections. Cidofovir inhibits adenovirus and BKV, but it has significant tubular toxicity. Then, it can be limited with the use of saline hydration²². Low-dose IV cidofovir 0.5–1.5 mg/kg, one to three times a week, without probenecid may be given²³ or 3–5 mg/kg every 7–14 days with probenecid or intravesical cidofovir at 5 mg/kg/week, left *in situ* for 1–2 hours after clamping the vesical catheter with a 50% response rate in refractory hemorrhagic cystitis²⁴. Progression of hematuria and clot retention may need cystoscopy by experienced teams, bladder irrigation, treatments to repair and regenerate the urothelial mucosa (e.g., hyperbaric oxygen therapy) and to stop bleeding (e.g., topical application of fibrin glue by cystoscopy, with an 83% response rate and most cases resolved with one or two applications²⁵. Mesenchymal stromal cells to stimulate the tissue repair and modulate inflammation and virus-specific T cells are the most innovative treatments for hemorrhagic cystitis.

A comparison between early- and late-onset hemorrhagic cystitis is presented in Table 2.

Table 2. Comparison between early- and late-onset hemorrhagic cystitis.

	Early-onset hemorrhagic cystitis	Late-onset hemorrhagic cystitis	Comments
Pathogenesis	Chemical (drugs) or actinic damage of the bladder mucosa	BK virus infection Adenovirus infection Donor alloreactivity	
Diagnosis	Macrohematuria with dysuria, increased urinary frequency, low abdominal pain	Gross hematuria, dysuria, increased urinary frequency, low abdominal pain, high load of BK/adenovirus positive in urine and/or viremia	Signs of bladder thickening and clots at ultrasound examination
Prevention	Hyperhydration, mesna (if chemo with Cy or ifosfamide), forced diuresis	Hyperhydration, mesna, forced diuresis	Routine prophylactic fluoroquinolones not recommended to prevent hemorrhagic cystitis
Therapy	Hyperhydration, mesna, forced diuresis, hyperbaric O ₂ therapy, application of fibrin glue by cystoscopy	Hyperhydration, mesna, forced diuresis, cidofovir, hyperbaric O ₂ , fibrin glue	Cidofovir at low doses three times a week or higher doses with probenecid every 7–14 days or intravesical

Source: Adapted by the authors^{19–25}.

ENDOTHELIAL INJURY

Transplant-related thrombotic microangiopathy

Transplant-related thrombotic microangiopathy (TA-TMA) is a clinical syndrome of diffuse endothelial injury, leading to microangiopathic hemolytic anemia and thrombocytopenia due to platelet aggregation, and deposition of microthrombi at the capillary level in the microcirculation, leading to severe ischemic injury of multiple organs². Prophylaxis with N-acetylcysteine and omega-3 has been described as effective in reducing the incidence of thrombotic microangiopathy¹. Vitamin D supplementation can protect endothelial cells from radiation-induced damage²⁶.

TA-TMA typically occurs in the first 100 days after transplantation¹, most frequently around day +32 to +40². It is more associated with allogeneic HCT¹, with variable incidence up to 76% of allogeneic HCT and 27% of autologous HCT²⁷. Risk factors for TA-TMA are:

- Hereditary/non-modifiable: African Americans, females, genetic variants, severe aplastic anemia, cytomegalovirus seropositivity, pre-HCT;
- Associated with HSCT: human leukocyte antigen (HLA) and ABO mismatch, use of peripheral blood stem cells, absence of antithymocyte globulin (ATG) in conditioning, myeloablative conditioning, slow metabolism of conditioning agents, unrelated HCT, and various polymorphisms;
- Post-HCT: calcineurin inhibitors, infections, acute graft-versus-host disease (GVHD), formation of autoantibodies²⁶.

The most common presentation is hypertension, thrombocytopenia, and elevated lactate dehydrogenase (LDH). Proteinuria may be present up to 10 to 14 days before the diagnosis¹. Other signs include pulmonary hypertension, headache, diarrhea, vomiting, abdominal pain, intestinal bleeding, pericardial effusion, increased transfusion requirements, anemia, thrombocytopenia, schistocytes, and decreased haptoglobin². Routine screening twice weekly until day +100 should include LDH, urine analysis, and blood pressure monitoring¹, and thereafter in the presence of GVHD or infections²⁸. Diagnosis is confirmed by biopsy of the target organ, rarely performed due to high risk involved. The Jodele criteria requires the presence of four or more of seven features: anemia, thrombocytopenia, elevated LDH, presence of schistocytes, hypertension ($\geq$ p99 or $> 140 \times 90$ mmHg if > 18 years old), elevated sC5b-9, and urinary protein/creatinine ≥ 1 mg/mg²⁸. Diagnostic criteria are demonstrated in Table 3¹.

Table 3. Diagnostic criteria for transplant-related thrombotic microangiopathy.

	Bone marrow transplant clinical trials network	International working group.	Cho et al.	Jodele et al.
Schistocyte	$> 2/\text{field}$	> 4	> 2	Positive
Lactate dehydrogenase elevation	+	+	+	+
Thrombocytopenia	-	+	+	+
Decrease in hemoglobin or increase in transfusion requirement	-	+	+	+
Negative coombs test	+	-	+	-
Decrease in haptoglobin	-	+	+	-
Renal and/or neurological dysfunction	+	-	-	Hypertension Proteinuria
Normal coagulation profile	-	-	+	-
Elevated C5b-9	-	-	-	+

Source: Adapted by the authors¹.

Other conditions that may resemble TA-TMA include sinusoidal obstruction syndrome, autoimmune hemolytic anemia, and other types of microangiopathy, such as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome¹. Factors associated with worse prognosis, with survival around 20%, include¹ proteinuria and high levels of C5b-9. Even after the resolution of the condition, there is a high risk of chronic kidney disease, hypertension, and mortality related to HCT². Treatment should be initiated immediately upon diagnosis, including control of the triggering factor (very often BK virus reactivation and GVHD), early plasmapheresis with fresh frozen plasma substitution performed daily until resolution²⁶, complement blockade, discontinuing of the use of calcineurin inhibitors, replacing them with steroids (2 mg/kg/day)¹, and, after resolution, consideration should be given to be used another immunosuppressant, such as mycophenolate mofetil, or basiliximab²⁶. Hypertension should be strictly controlled due to the risk of posterior reversible encephalopathy syndrome¹.

Due to the involvement of the renin-angiotensin system in mediating TA-TMA-associated hypertension, the use of ACE inhibitors or angiotensin receptor antagonists is preferred. However, in patients with significant

renal injury, there may be benefits from the use of calcium channel blockers²⁶. Erythropoietin may be useful in cases with significant renal injury²⁶. Rituximab may be used with the plasma exchange¹. Eculizumab, a terminal complement pathway inhibitor, increases survival from 17 to 66% one year after HCT²⁹. It should be the treatment of choice in high-risk cases (proteinuria > 2 mg/mg or organ dysfunction)¹ instead of plasma exchange or rituximab²⁶, usually administered twice a week. Another recently approved option is ravulizumab, a new C5 inhibitor that achieves complete and sustained inhibition of complement activity with an extended dosing interval and a higher binding affinity to C5 compared with eculizumab³⁰. Some studies also describe benefits with the use of defibrotide¹.

Sinusoidal obstruction syndrome

Sinusoidal obstruction syndrome (SOS), formerly known as veno-occlusive disease (VOD), is a potentially fatal liver injury due to the conditioning regimen with damage to the endothelial cells and hepatocytes and obstruction of the portal microvasculature, generally occurring between seven days after the initiation of chemotherapy and up to 21 days after its completion^{31,32}. The incidence in pediatric HCT is approximately 20%, and the main clinical manifestations include painful hepatomegaly, weight gain, thickening of the gallbladder wall, and refractory thrombocytopenia^{31–33}. As the disease progresses, ascites, cholestasis, reversal of the hepatopetal to hepatofugal flow, respiratory and renal failure may also develop, potentially leading to death. Anicteric presentations are more common in children, but a bilirubin level above 2 mg/dL at any age is a predictor of poor survival after day +100^{31,34}. Specific pediatric criteria include two or more of the five findings^{2,35}:

- Bilirubin > 2 mg/dL or an increase from baseline value for three consecutive days;
- Weight gain > 5% above baseline or any weight gain for three consecutive days despite the use of diuretics;
- Hepatomegaly (best confirmed by imaging);
- Ascites (best confirmed by imaging);
- Refractory thrombocytopenia: unexplained by other causes.

Diagnosis is clinical, and liver biopsy should be avoided due to the high risk of bleeding in patients with portal hypertension, thrombocytopenia, and coagulopathies. Imaging can help to exclude other diagnoses³⁶. Other findings that may be present include splenomegaly, gallbladder wall thickening > 6 mm, increased diameter of the portal vein, reduced diameter of the hepatic vein, and flow in the paraumbilical vein. Abdominal contrast-enhanced computerized tomography demonstrates periportal edema and gallbladder wall thickening^{36–38}. The severity criteria of the disease proposed by the European Society for Blood and Marrow Transplantation are summarized in Table 4^{37,38}.

Table 4. European Society for Blood and Marrow Transplantation sinusoidal obstruction syndrome severity criteria.

	Mild	Moderate	Serious	Very serious
Aspartate transaminase/alanine transaminase	≤ 2x	> 2 and ≤ 5		> 5x
Refractoriness to platelets	< 3 days	3–7 days		> 7 days
Bilirubin (mg/dL)	< 2	< 2	< 2	> 2
Increase in bilirubin total				Double in 48 hours
Ascites	Minimum	Moderate	Moderate	Paracentesis
Clotting	Normal	Normal	Changed	Need to reset coagulation factors
Renal function glomerular filtration rate (mL/min)	89–60	59–30	29–15	< 15
Lung function (O ₂ need)	< 2 L/min	> 2 L/min	Continuous positive airway pressure or mechanical ventilation	Continuous positive airway pressure or mechanical ventilation
Central nervous system involvement	None	None	None	Cognitive impairment

Source: Adapted by the authors^{34–36}.

If patient fulfills criteria in different categories, s/he must be classified in the most severe category. In addition, the kinetics of the evolution of cumulative symptoms within 48 hours predicts severe disease. Presence of two or more of these criteria qualifies for an upgrade to common terminology criteria for adverse events (CTCAE) level 4 (very severe SOS/VOD). Pre-existent hyperbilirubinemia is excluded due to primary disease.

Despite the high morbidity and mortality, there is no universally accepted prophylaxis. Ursodeoxycholic acid is recommended due to favorable safety profile and promising results^{32,36}. There is no strong evidence of heparin in adults³², but a 1992 study demonstrate vascular endothelial protection with the use of heparin at the dose of 100 IU/kg/day in children^{32,34,39}. Iron chelation, avoiding use of alcohol and hepatotoxic drug, if possible reduced intensity conditioning regimen and pharmacokinetics of busulfan are important^{36–38}. The interval between busulfan and cyclophosphamide must be of two days, and the interval between busulfan and melphalan must be of one day. The use of G-CSF accelerates the recovery from neutropenia, but it increases adhesion molecules (VCAM-1 and E-selectin) and can activate endothelial cells. So, routine use must be avoided³⁴. Once SOS is established, it is important to avoid fluid overload, control diuresis, and restrict fluid intake. Early treatment impacts the mortality and morbidity of the disease, with defibrotide being the only licensed medication specifically for treating SOS at a dose of 25 mg/kg/day in divided doses every 6 hours^{34,37,38}. High-dose steroid therapy alone or, preferably, in combination with defibrotide, may be an option. Methylprednisolone intravenous 500 mg/m² per dose every 12 hours for six doses, followed by a gradual reduction to 2 mg/kg/day for two days, and then tapering further⁴⁰. When ascitic fluid drainage is necessary due to respiratory failure or renal vascular compression, it should be done slowly through a peritoneal dialysis catheter or pigtail with a tap, in a closed system, and simultaneous colloid replacement to avoid hypovolemic shock⁴¹.

Capillary leak syndrome

Capillary leak syndrome (CLS) is one of the early HCT-related complications due to endothelial cell damage and activation. It is characterized by the accumulation of fluids in the extravascular space due to a diffusely increased capillary permeability, leading to positive intake balance despite furosemide administration, anasarca, hemoconcentration, hypotension⁴², and severe fluid overload⁴³. Specific diagnostic criteria, in the first 15 days after HCT, are:

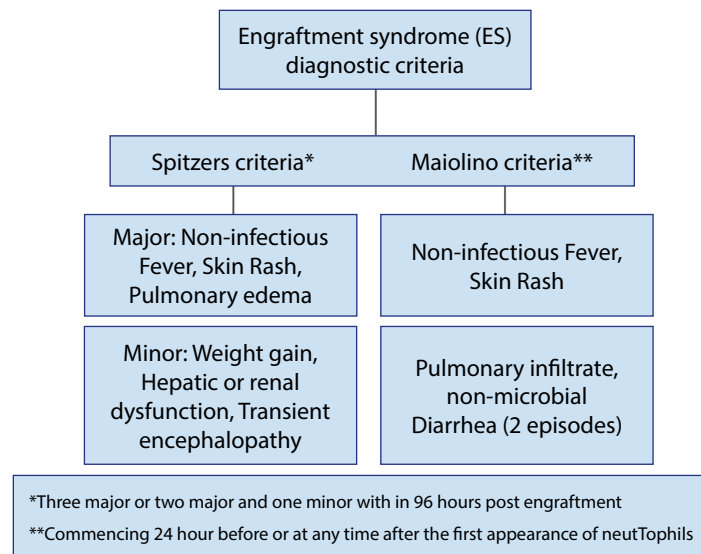
- Weight gain > 3% within 24 hours;
- Generalized edematous syndrome (ascites, pleural effusion, or pericarditis);
- Absence of response to furosemide (at least 1 mg/kg) for 24 hours.

Other features may be renal insufficiency, tachycardia, hypotension, and hypoalbuminemia⁴⁴. Specific genetic polymorphisms in the complement pathway may predispose the children to this complication⁴⁵. CLS may develop in 5% of the HCT patients, but it is more prevalent with sepsis (14%), acute GVHD (11%)⁴⁶, and with other endothelial complication⁴⁷. No specific or targeted therapy of CLS is available, only supportive care and the treatment of other vascular complications, GVHD, and infections⁴⁷.

Engraftment syndrome

Engraftment syndrome is a non-infectious complication observed in both autologous and allogeneic HCT during neutrophil recovery and is characterized by fever, diarrhea, rash, and pulmonary edema, with altered renal and hepatic function. Although in most patients it is self-limiting, it can be associated with post-transplant mortality^{48,49}. Fever is the most common symptom⁴⁸. Several diagnostic criteria have been proposed, but the Spitzer and Maiolino criteria are the most common and are represented in Fig. 1.

Specific findings are the presence of non-infectious fever (38°C), non-infectious diarrhea (two or more episodes), and maculopapular rash (≥ 25% of the body surface area), non-cardiogenic pulmonary edema,



Source: Elaborated by the authors^{48,49}.

Figure 1. Engraftment syndrome diagnostic criteria.

weight gain > 2.5% from baseline, hepatic alteration (bilirubin $\geq$ 2 mg/dL and alanine transaminase and aspartate transaminase twice normal), creatinine twice normal, and transient encephalopathy⁴⁸. The treatment is based on corticosteroids, which is started upon diagnosis, while ruling out other potential causes⁴⁸. Methylprednisolone is used at 1–1.5 mg/kg/day until the symptoms are resolved, which usually occurs in two or three days, followed by a tapering of the medication^{48,49}.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome is one of the most common neurological complications following HCT⁵⁰ with an incidence of 1–22%⁵¹. The most frequent presentation is seizure (71% of the patients), followed by headache (50%), visual symptoms (36%), and hypertension associated with typical findings on magnetic resonance imaging (white matter and bilateral vasogenic edema in the occipital and parietal lobes). Most cases are in the early post engraftment period (days +30–100)⁵¹. Risk factors for developing posterior reversible encephalopathy include hypertension, acute GVHD, and the use of calcineurin inhibitors for GVHD prophylaxis^{50–54}.

Posterior reversible encephalopathy management involves controlling blood pressure and adjusting immunosuppressive therapy. Discontinuation or modification of calcineurin inhibitors is common, although no specific management strategy has been proven superior^{55,56}. Most patients experience a complete or near-complete recovery of neurological function, although in some cases posterior reversible encephalopathy can lead to irreversible damage or contribute to mortality^{51,53,56}.

PULMONARY ALTERATIONS

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage is a non-infectious post-HCT complication, probably secondary to the rupture of the alveolar-capillary membrane secondary to the conditioning, immune-mediated events, and neutrophil infiltration during engraftment⁵⁷. The incidence of diffuse alveolar hemorrhage in the peri-engraftment period of autologous or allogeneic HCT is 2–10%^{57,58}. Risk factors include pre-HCT lung injury, prolonged thrombocytopenia, and ongoing post-HCT injury and inflammation^{57,59}. Signs and symptoms include hypoxemia and dyspnea (80–95%), cough (13–56%), hemoptysis (15–46%), and fever (2–67%)⁵⁸.

Radiographic findings may be nonspecific: early in the course of the disease, infiltrates are typically central, bilateral, and predominantly in the lower lungs. Over few days, radiographic opacities evolve to a diffuse, predominantly alveolar pattern (70%), shown on high-resolution computerized tomography as a ground-glass opacification with or without superimposed interlobular septal thickening (*i.e.*, a “crazy-paving” pattern). Many survivors of diffuse alveolar hemorrhage have complete resolution of the opacities, but half may have persistent abnormalities, and a quarter may progress to fibrosis⁵⁸. Diagnostic bronchoscopy shows return of a progressively bloodier bronchoalveolar lavage in at least three different samples from separate segmental bronchi or $\geq 20\%$ hemosiderin-laden macrophages and absence of an infectious cause^{57,58}.

Treatment involves corticosteroid therapy and supportive intensive care, correction of coagulopathies, transfusion to normal platelet values, fluid management, and protective ventilation. Some studies demonstrate benefits with aminocaproic acid, nebulized tranexamic acid, activated recombinant factor VII, and tumor necrosis factor- α blockade. Despite treatment, patients with diffuse alveolar hemorrhage have a poor prognosis, with a mortality rate of over 40–90%, with recurrent alveolar bleeding during steroid taper⁵⁸. The prognosis is better when it presents early (< 100 days) after autologous HCT (mortality $< 30\%$) compared to those with late onset or after allogeneic HCT ($> 75\%$)⁵⁷. Studies suggest that high D-dimer levels (> 500 ng/mL) are a significant risk factor for poor prognosis in diffuse alveolar hemorrhage⁵⁹. Differential diagnoses include fluid overload, pulmonary VOD, bacterial (such as *Nocardia* and *Legionella*), viral (such as SARS-CoV-2 and metapneumovirus), and fungal infections, as well as drug-induced pneumonitis and other idiopathic pneumonia syndromes⁵⁸.

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) constitutes a spectrum of disease and a rare complication that occurs within 120 days following HCT, with a mean onset time between 42 and 58 days⁶⁰. The incidence is 2 to 12%, being more common in recipients of allogeneic HCT⁶¹. The pathogenesis is multifactorial; the agents used in the conditioning regimen cause damage to the pulmonary epithelium, which can be exacerbated by the underlying disease. This injury triggers the recruitment of macrophages and T cells to the sites of injury, leading to the release of inflammatory cytokines, specifically tumor necrosis factor (TNF)- α ⁶⁰. The diagnosis is based on three main criteria: widespread alveolar injury with symptoms and signs of pneumonia; absence of active lower respiratory tract infection documented by a negative bronchoalveolar lavage; and absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiologies. Myeloablative conditioning with high-dose total body irradiation and acute GVHD are the main risk factors for the development of IPS⁶². Other risk factors include diagnosis of acute leukemia or myelodysplastic syndrome, pulmonary infection, and pre-transplant pulmonary function impairment^{60,63}. The clinical presentation is variable, but it may include fever, non-productive cough, dyspnea, tachypnea, and hypoxemia. Chest X-rays or computerized tomography scans demonstrate diffuse alveolar or interstitial infiltrates. Treatment includes supportive measures: oxygen therapy, ventilation (invasive or non-invasive—high-flow nasal, continuous positive airway pressure), empirical antimicrobials, and fluid management. Specific treatment options include corticosteroids (2 mg/kg) and etanercept (0.4 mg/kg twice weekly, total of eight doses). Only half of the patients with IPS already on mechanical ventilation respond to therapy, and overall mortality remains high, ranging from 60 to 80% within two weeks of onset^{62,63}.

OTHER COMPLICATIONS

Graft failure

Engraftment is defined as the first of three consecutive days in which the absolute neutrophil count exceeds $0.5 \times 10^9/L$, along with sustained platelet counts greater than $20 \times 10^9/L$ and hemoglobin levels above 80 g/L, without the need for transfusions². Graft failure (GF) can lead to considerable morbidity and mortality following allogeneic HCT. Frequent chimerism analysis to track successful engraftment is valuable for detecting early graft rejection and relapse. Definitions of chimeric situations are described in Table 5⁶⁴.

Table 5. Definitions of chimeric situations.

Chimerism	Definition
Full donor chimerism	> 95% or all cells are of donor cells origin.
Mixed or partial chimerism	Proportion of cells of recipient origin is detected.
Transient mixed chimerism	< 10% recipient cell detected in the first six months post allo-hematopoietic cell transplantation, and after full donor chimerism is detected.
Stable mixed chimerism	Proportion recipient cells detected post-hematopoietic cell transplantation that remain constant over time.
Progressive mixed chimerism	Recipient cells increasing over time.

Source: Adapted from Jethava et al.⁶⁴.

The incidence of GF is less than 3–5% in auto and matched allo-HCT cases, but it rises to up to 10% in haploidentical or cord blood transplant cases². The cumulative incidence of graft failure was significantly greater in non-malignant disorders compared to malignant^{65,66}. Primary graft failure is characterized by the absence of donor engraftment and is defined as never reaching an absolute neutrophil count of $\geq 0.5 \times 10^9/L$ for at least three consecutive days, without signs of disease relapse. Secondary graft failure refers to the loss of a graft that was previously functioning, accompanied by a loss of complete donor chimerism^{2,67}. The risk factors to GF are:

- After HCT: low stem cell dose, non-malignant disorders, female donor for male recipient, myeloproliferative disease, disease status at HCT, splenomegaly, iron overload;
- Immunological: HLA-mismatch, reduced intensity conditioning (RIC) regimens, major ABO incompatibility, HLA antibodies, presence of acute or chronic GVHD, adequate immunosuppressive medications;
- Infections: cytomegalovirus, HHV-6, HHV-8, parvovirus, BK virus, *Influenza*;
- Miscellaneous: use of drugs such as ganciclovir, valganciclovir, cidofovir, trimethoprim-sulfamethoxazole, allopurinol^{2,64}.

The most important strategy is to identify the underlying cause of GF as soon as possible and treat it. Initial measures should be to discontinue ongoing medications that are potentially suppressive and toxic to stem cells, treat infections, especially viral infections, and perform bone marrow aspiration to assess persistent or relapsed disease, in addition to managing GVHD by adjusting (withholding or changing) immunosuppression^{2,64,65}. A second allogeneic HCT is a viable treatment option for patients with GF, but it is associated with high non-relapse mortality. The most common conditioning regimens for second allo-HCT are fludarabine/ATG, Cy/ATG, conventional Johns Hopkins conditioning for haploidentical HCT or alemtuzumab-based haplo with fludarabine and busulfan or melphalan⁶⁸. These RIC regimens, combined with infusion of high CD34+ progenitor cells, result in consistent engraftment rates, while maintaining a low toxicity profile⁶⁵. Key considerations for performing a second allogeneic HCT in graft failure are summarized in Table 6.

Table 6. Considerations for performing a second allogeneic hematopoietic cell transplantation as treatment for graft failure.

Type of donor	No difference using the same/different donor. Consider haploidentical donors. Always avoid donors if positive donor-specific antibody.
Stem cell source	Peripheral blood or bone marrow show similar results and should be preferred to cord blood.
Conditioning regimen	Always required. Better reduced intensity conditioning.
Post-transplant immunosuppression	Required. Calcineurin inhibitor-based schemes are the most used.
T-cell depletion	For primary graft failure, it can be a good option (reduces the risk of graft-versus-host disease). Antithymocyte globulin or alemtuzumab is used to promote immunosuppression and lower graft-versus-host disease risk.

Source: Adapted by the authors^{64,65,68,71}.

Poor graft function

Poor graft function can lead to considerable morbidity and mortality following allogeneic HCT⁶⁵. It is characterized by the presence of two or three cytopenic counts (absolute neutrophil count $< 0.5 \times 10^9/L$, platelets $< 20 \times 10^9/L$, or hemoglobin $< 70 \text{ g/L}$) for at least three consecutive days after day +28, along with a transfusion requirement associated with hypoplastic or aplastic marrow and complete donor chimerism. Early (primary) poor graft function is defined as a slow or incomplete recovery of bone marrow function beyond day +28. Late (secondary) poor graft function refers to the loss of bone marrow function following initial normal recovery⁶⁹.

Approximately 5 to 27% of patients may present poor graft function and have a higher risk of infections and bleeding complications⁶⁵. Risk factors include number of CD34+ cells infused, stem cell source, stromal damage induced by conditioning regimens, donor-specific anti-HLA antibodies, ABO incompatibility, HLA mismatch, GVHD, VOD, viral infections, use of myelotoxic agents (e.g., ganciclovir), high serum ferritin level before HCT^{65,69}. For treatment, granulocyte colony stimulating factor (G-CSF) has been recommended^{2,65,66}. Recombinant human erythropoietin (rhEPO) therapy at 500 U/kg per week has been shown to improve hemoglobin levels and decrease transfusion requirements when initiated within the first month of allo-HCT with long-term survival benefits⁷⁰. Eltrombopag, an oral thrombopoietin receptor agonist (TRA), is effective in patients with prolonged isolated thrombocytopenia and those experiencing secondary failure of platelet recovery after HCT. Its response is associated with the number of megakaryocytes in the bone marrow⁷⁰. Donor lymphocyte infusion is a form of immunotherapy and could be recommended when decreasing levels of donor chimerism are observed. A thorough risk/benefit assessment is necessary as this approach is not without risk and there is a high chance of developing GVHD. It is recommended to start with a low dose, such as 1×10^6 CD3/kg, and increase it gradually^{2,64}. CD34 boost may be considered as a treatment option².

Hemophagocytic lymphohistiocytosis syndrome and macrophage activation syndrome

A variety of systemic inflammatory syndromes with distinct factors can occur associated with HCT and can evolve with graft failure⁷¹. Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is a rare, life-threatening disorder, considered a cytokine disease. Reports have suggested that abnormalities in the immune regulatory system play a central role in HLH⁷². It is a macrophage activation syndrome (MAS) that can lead to massive hyperinflammation, resulting in an exaggerated and ineffective immune response. There is activation of lymphocytes and infiltration of histiocytes in all organs, with the release of cytokines⁷³.

The high incidence of secondary HLH after HCT indicates that it may be a form of GVHD, in which there is the activation of host macrophages in response to donor cells. Some risk factors and/or trigger are: use of granulocyte colony-stimulating factor, parenteral nutrition (especially with lipid-soluble substances), infusion of CD34+ cells $< 7.66 \times 10^4/kg$ in transplants using cord blood, mismatched HCT and non-myeloablative conditioning. There are also reports of lower incidence when etoposide is used in conditioning regimens^{73–77}.

Initial symptoms can include hepatomegaly/hepatitis, splenomegaly, neurological symptoms, and pancytopenia⁷³, rash, edema, jaundice, hypoalbuminemia, and hyponatremia⁷⁸. The most important symptom is persistent fever of unknown origin⁷³. Additional immunological findings include elevated soluble interleukin (IL)-2 receptor and decreased cytotoxic NK cells⁷⁸. In MAS, high fever, hepatosplenomegaly, lymphadenopathy, cytopenias, and coagulopathy occur, with evidence of macrophage activation and bone marrow hemophagocytosis⁷⁷.

The diagnosis post-HCT requires both major criteria or one major and four minor criteria⁷⁸:

Major criteria:

- Graft failure, delay in engraftment, or secondary graft failure;
- Histopathological evidence of hemophagocytosis.

Minor criteria:

- High fever;
- Hepatosplenomegaly;
- Hyperferritinemia;
- Elevated LDH⁷⁵.

Ferritin levels above 10,000 have a sensitivity of 90% and specificity of 96% for HLH⁷⁹. The criteria associated with central nervous system dysfunction are used, such as irritability, disorientation, lethargy, headache, seizure, coma, in addition to signs of coagulopathy such as purpura, bruising, and mucosal bleeding⁷⁴.

Diagnostic tools are in Table 7. According to HLH-2004, the diagnosis is made with the presence of five or more criteria⁷⁸. In HScore, 169 points is the cutoff to diagnose secondary HLH⁷⁵.

Table 7. Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).

	HLH 2004 ⁷⁸	HScore (points) ⁷⁵
Fever	≥ 38.5°C	38.4–39.4°C (33); > 39.4°C (49)
Organomegaly	Splenomegaly	Hepatomegaly or splenomegaly (23); both (38)
Abnormalities in blood count	Cytopenias in two or more lineages	Two cell lines (24); three cell lines (34)
Abnormalities in triglycerides	≥ 265	133–354 (44); > 354 (64)
Elevation of liver enzymes	–	Aspartate aminotransferase > or = 30 (19)
Abnormalities in fibrinogen	≤ 150	< or = 250 (30)
Hyperferritinemia	≥ 500	200–600 (35); > 6,000 (50)
Alteration in NK cell activity	Low cell function	–
Elevation of cytokines/acute phase proteins	sCD25 ≥ 2,400	–
Hemophagocytosis	Bone marrow or lymph nodes	present (35)
Infection	Secondary hemophagocytic lymphohistiocytosis	Known (18)
Organ dysfunction	–	–
Diagnosis	Five criteria or more	Total above 169

Source: Elaborated by the authors^{75,76,79}.

For the diagnosis of MAS, the criteria adapted from rheumatology are used: elevated ferritin (> 684) and two or more of the criteria below^{75,80}:

- Platelet count < 181 × 10⁹/L;
- Aspartate aminotransferase > 48 U/L;
- Triglycerides > 156 mg/dL;
- Fibrinogen ≤ 360 mg/dL.

Therapeutic options include immunosuppression, immunomodulation, and cytostatic drugs⁷³. Corticosteroids are the gold standard in treatment, although half of the patients may be resistant. Dramatic responses are reported with the addition of cyclosporine at doses of 2 to 7 mg/kg/day⁷⁹. Anakinra, an IL-1 antagonist, is effective in refractory cases and relatively safe in adult patients. The dose is 1–2 mg/kg daily, increasing up to 8 mg/kg/day until a sufficient clinical response is achieved. Intravenous immunoglobulin can be effective in cases resistant to steroids and triggered by Epstein-Barr virus, as well as rituximab⁷⁹. The treatment of MAS includes control of triggering factors, and corticosteroids (high doses of intravenous pulse methylprednisolone 30 mg/kg/day for three to five days). Cyclosporine is an agent used in combination therapy (3–7 mg/kg/day) in resistant cases, as well as IVIG 2 g/kg/dose.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Zamperlini G, Martins AF, Silva BCA, Cardoso MF, Rodrigues AM, Silva TCPM, Salum ACFC, Seber A, Borges N, Gomes A. **Conception and design:** Gomes A, Seber A, Borges N. **Analysis and interpretation of data:** Gomes A, Seber A, Borges N. **Technical procedures:** Zamperlini G, Martins AF, Silva BCA, Cardoso MF, Rodrigues AM, Silva TCPM, Salum ACFC, Seber A, Borges N, Gomes A. **Statistics analysis:** Zamperlini G, Martins AF, Silva BCA, Cardoso MF, Rodrigues AM, Silva TCPM, Salum ACFC, Seber A, Borges N, Gomes A. **Manuscript writing:** Zamperlini G, Martins AF, Silva BCA, Cardoso MF, Rodrigues AM, Silva TCPM, Salum ACFC, Seber A, Borges N, Gomes A. **Final approval:** Gomes A, Seber A, Borges N.

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