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EARLY COMPLICATIONS IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Carla Nolasco Monteiro Breviglieri[1,2], Natalia Maria Tavares Ferreira Borges[3,4], Gabriele Zamperlini Netto[1,5], Alessandra Araujo Gomes[1,6]

1. Instituto de Tratamento do Câncer Infantil (ITACI) – Instituto da Criança – Hospital das Clínicas da Universidade de São Paulo, São Paulo-SP
2. Hospital Samaritano, São Paulo-SP
3. Hospital São Rafael, Salvador-BA
4. Hospital Martagão Gesteira, Salvador-BA
5. Hospital Israelita Albert Einstein, São Paulo-SP
6. Hospital Sírio-Libanês, São Paulo-SP

Correspondence to: Alessandra Araujo Gomes (ale_a_gomes@hotmail.com)

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has the potential to cure a significant proportion of patients with malignant and nonmalignant diseases. The high doses of chemotherapy and/or radiotherapy included in conditioning regimens affect all organs and tissues, producing several early and late complications.

The most common early effects are nausea, vomiting and mucositis. Other early complications, less frequent, but cause of morbidity and mortality are hemorrhagic cystitis, sinusoidal obstruction syndrome, thrombotic microangiopathy, capillary leak syndrome, engraftment syndrome, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome.

NAUSEA/VOMITING

The conditioning regimens used in HSCT are known to have a high emetogenic risk. Nausea and vomiting are some of the most feared adverse effects of chemotherapy and radiotherapy. Studies show that administering prophylactic regimens concordant with published guidelines significantly reduces and controls symptoms for patients receiving moderately or highly emetogenic treatment. Focused on the prevention, guidelines recommend a combination of aprepitant, dexamethasone and a serotonin antagonist in pediatric patients.[2,4]

Emetogenic potential of intravenous antineoplastic agents

Probability of vomiting	Agent
High	Busulfan IV ≥0,8mg/kg/dose Cyclophosphamide IV (≥ 1200mg/m²/dose) Melphalan IV Carmustine Carboplatin IV ≥175mg/m²/dose Cisplatin IV ≥12mg/m²/dose Cytarabine IV ≥3g/m²/day Methotrexate IV ≥12g/m²/dose Thiotepa ≥300mg/m²
Moderate	Cyclophosphamide IV (1000mg/m²/dose) Cytarabine IV 75mg/m²/dose Methotrexate IV 5g/m²/dose Ifosfamide
Low	Cyclophsphamide IV 500mg/m²/dose Mitoxantrone IV ≤33mg/m²/dose Etoposide Methotrexate IV ≤90mg/m2/dose Procarbazine PO
Minimal	Fludarabine Vincristine IV ≤1,5mg/m²/dose

*Adapted from Sing EPC et al4 and EBMT Handbook[2]

MUCOSITIS

Mucositis is characterized by mucosal damage ranging from mild inflammation to extensive ulceration, which may affect the oral cavity and other parts of the gastrointestinal tract. It is seen in 75-99% of patients who had combined total body irradiation and chemotherapy. It peaks between day 6 and 12 and resolution coincides with engraftment. Oral mucositis causes disturbances in feeding, swallowing, and speaking, along with the possibility of secondary severe infection. Basic oral care consists of a pre-transplant oral/dental examination aimed at decreasing the oral infectious and inflammatory burden, and routine mouth care with bland rinses and soft toothbrush. Cryotherapy prevents oral mucositis in protocols containing high dose melphalan. Oral mucositis is often so severe that patients require parenteral narcotics for relief of pain and total parenteral nutrition.[2,5,6] Oral mucositis grading scales are below:

WHO SCORE	
GRADE 0	No objective findings, function irrelevante
GRADE 1	Erythema plus pain, function irrelevante
GRADE 2	Ulceration, ability to eat solids
GRADE 3	Ulceration, ability to eat liquids
GRADE 4	Ulceration, nothing by mouth

WHO 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 alimentation is not possible

*Adapted from WHO classification

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis is characterized by diffuse bladder inflammation and bleeding, with sustained hematuria and lower urinary tract symptoms, in the abscence of other conditions such as vaginal bleeding, bleeding diathesis, or urinary tract infection. It has significant morbidity, prolonged hospitalization and occasional mortality. Symptoms vary from microscopic to macroscopic hematuria with clots, urinary obstruction, and renal and/or bladder damage, and dysuria.[1,3,7,8]

GRADING SYSTEM FOR HEMORRHAGIC CYSTITIS	
GRADE I	Microscopic hematúria
GRADE II	Macroscopic hematúria
GRADE III	Macroscopic hematuria with small clots
GRADE IV	Gross hematúria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

*Adapted from Decker DB et al[7]

Etiology:

1) Chemotherapy: alkylating agentes (especially cyclophosphamide and ifosfamide): the main metabolite, acrolein, can precipitate in the bladder, causing mucosal edema, ulceration, epithelial necrosis and submucosal fibrosis;

2) Infectious: adenovírus, cytomegalovirus, BK vírus – cytopathic effect on bladder mucosa, causing inflammation;

3) Radiotherapy: causes chronic fibrosis, endarteritis and mucosal desquamation.

Prevention:

The three main approaches for prophylaxis of cyclophosphamide-induced hemorrhagic cystitis include mesna, hyperhydration with forced diuresis, and continuous bladder irrigation.

Treatment:

Intensive intravenous hydration, forced diuresis, analgesia, spasmolytic drugs, treatment of infections. Progression of hematuria and possibly clot retention often necessitate bladder irrigation. In more aggressive cases, it is possible to use cystoscopy, clot evacuation, and fulguration1,3,7,8.

Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), also called hepatic veno-occlusive disease (VOD), remains a complication after HSCT and belongs to a group of systemic endothelial diseases. Toxic metabolites generated by the conditioning regimen damage the sinusoidal endothelial cells and hapatocytes in zone 3 of the hepatic acinus. The first events are loss of fenestrae in endothelial cells, formation of gaps, and rouding up or swelling. Red blood cell, leukocytes and debris penetrate into the space of Disse and dissect off the sinusoidal lining. The venous lumen narrows and sinusoidal venous outflow is reduced, resulting in post-sinusoidal hypertension9-11. Risk factors are below:

Transplant-related factors	Unrelated donor HLA-mismatched donor Non T-cell-depleted transplant Myeloablative-conditioning regimen Oral or high-dose busulfan-based regimen High-dose TBI-based regimen Second HSCT
Patient and disease-related general factors	Older age Karnofsky score below 90% Metabolic syndrome Female receiving norethisterone Advanced disease (beyond second CR or relapse/refractory) Thalassemia Genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype)
Hepatic-related	Transaminases >2.5 upper limit of normal Serum bilirubin >1.5 upper limit of normal Cirrhosis Active viral hepatites Abdominal or hepatic irradiation Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin Hepatotoxic drugs Iron overload
Specific pediatric risk factors	Osteopetrosis Hemophagocytic lymphohistiocitosis Griscelli syndrome X-linked lymphoproliferative disease Neuroblastoma Hemoglobinopathies Infants (age <1-2 years)

*Adapted from Mohty M et al10 and Corbacioglu S et al[11]

Clinical manifestations are weight gain, fluid retention with ascites and anasarca, painful hepatomegaly, jaundice, consumption of platelets (it is usually one of the earliest signs in children) and multi-organ dysfunction in severe cases with pleural effusion, renal failure and encephalopathy9-11. Differences between children and adults are below:

CRITERIA	CHILDREN	ADULTS
INCIDENCE	Approximately 20% Up to 60% in high-risk patients	Approximately 10%
RISK FACTORS	Additional pediatric factors: -Infants - Pediatric/genetic diseases with incidences above average	Established risk factors
CLINICAL PRESENTATION	Late-onset in 20% Anicteric in 30% Hyperbilirubinemia, if present: -Is frequently pre-existent -Occurs late during SOS -Is typical of severe SOS	Late-onset is rare Anicteric is rare
NEED FOR PROPER ASSESSMENT OF ASCITES AND HEPATOMEGALY	High incidence of disease-related hepatomegaly and ascites pre-HSCT	
TREATMENT	Defibrotide for severe SOS with multi-organ dysfunction/failure was associated with better results in children	
PREVENTION	Defibrotide demonstrated efficacy for prevention in children in a randomized prospective trial	

*Adapted from Corbacioglu S et al[11]

The diagnostic criteria recently published by European Society for Blood and Marrow Transplantation (EBMT) are below:

EBTM diagnostic criteria for hepatic SOS in children
-No limitation for time onset of SOS
The presence of two or more of the following:
-Unexplained consumptive and transfusion-refractory thrombocytopenia
-Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain >5% above baseline value
-Hepatomegaly (best if confirmed by imaging) above baseline value
-Ascites (best if confirmed by imaging) above baseline value
-Rising bilirubin from a baseline value on 3 consecutive days or bilirubin >2mg/dL within 72h

*Adapted from Corbacioglu S et al[11]

Diagnostic imaging is complementary. Ultrasonography (US) is more available, and as a bedside tool. Computed tomography and magnetic resonance imaging can substitute for or complement US. The most common findings are hepatomegaly, ascites, hepatic artery resistive index, velocity of portal venous flow, increased periportal echogenicity and increased hepatic echotexture, and gallbladder wall thickening. Doppler US assesses hepatic and portal vascular flow, pressure abnormalities and hepatic arterial early acceleration indices. Portal venous flow reversal (hepatofugal flow) are not consistently present or are a late finding, and might therefore be useful for the assessment of severity rather than early diagnosis.[11]

Severe SOS resulting in multi-organ dysfunciton/failure, EBMT criteria for grading the severity is below:

CRITERIA	MILD (1)	MODERATE (2)	SEVERE (3)	VERY SEVERE (4)
Liver function test	<2x normal	>2 and <5x normal	>5	>5
Persistent refractory thrombocytopenia	<3 days	3-7 days	>7 days	>7 days
Bilirubin (mg/dL)	<2	<2	>2	>2
Ascites	Minimal	Moderate	Necessity for paracentesis	Necessity for paracentesis
Bilirubin kinetics				Doubling within 48h
Coagulation	Normal	Normal	Impaired coagulation	Impaired coagulation
Renal function (mL/min)	89-60	59-30	29-15	<15 (renal failure)
Pulmonary function (oxygen requirement)	<2L/min	>2L/min	Invasive pulmonar ventilation (including CPAP)	
Central nervous system	Normal	Normal	Normal	New onset cognitive impairment

*Adapted from Corbacioglu S et al[11]

Prophylaxis for SOS includes reducing iron overload, use reduced intensity conditioning regimen if possible, busulfan pharmacokinetic monitoring, avoid acute fluid overload. For those patients receiving a busulfan(Bu)-cyclophosphamide(Cy) regimen, studies show that the order of application of Cy and Bu as impact on lower incidence of SOS. Ursodeoxycholic acid reduces hydrophobic bile acids, which can be toxic to hepatic parenchymal cells, and randomized trials demonstrate a reduced risk of SOS in transplant patients. Heparin is not suggested for prophylaxis in adults, but some studies showed a significant reduction in SOS in children.[12-15]

The treatment includes supportive care (restriction of fluids, diuretics, and renal replacement in severe cases) and use of Defibrotide (6.25mg/kg/dose, 4 times a day). Corticosteroids can be used in some cases where Defibrotide is not available or in combination with Defibrotide in severe cases. The initial dose is 500mg/m2/dose every 12 hours for six doses and gradual reduction.[12,16]

Implementation of the new criteria for diagnosis and assessment of the severity of SOS allowed earlier identification of patients in need of intervention for the better treatment of SOS.

Transplant-Related Thrombotic Microangiopathy

Transplant-related thrombotic microangiopathy (TA-TAM) is a side effect that usually occurs in the first

100 days after hematopoietic stem cell transplantation (HSCT), with undetermined incidence and more frequently reported in allogeneic bone marrow transplantation.[17] TA-TAM corresponds to a clinical syndrome resulting from endothelial injury, with platelet activation and microthrombi deposition at the capillary level, which may lead to consequent ischemic injury of several organs and microangiopathic hemolytic anemia. It presents a wide variety of severity levels, and there may be mild self-limited conditions up to multiple organ dysfunction with mortality up to 80%.

The pathogenesis of TA-TAM is not fully understood yet, however, it is known that endothelial injury plays a central role in its origin. During an early period of HSCT, several factors may lead to a hypercoagulable states in the endothelium due to collagen exposure and tissue factor activation, such as, conditioning regimen, use of colony growth factors, HLA incompatibility, long period of immobility and infections. This scenario leads to a second phase, which causes further endothelial injury and starts platelet aggregation, abnormal activation of the complement and thrombus formation in microvessels. At this time, the use of calcineurin inhibitors, especially when associated with mTOR inhibitors, in addition to GVHD and infectious conditions are the main responsible for the endothelial injury[17]. Abnormal activation of the classical and alternative complement pathway causes endothelial damage, propagating its dysfunction.[18,19]

The kidney is the main target organ, also accompanied by gastrointestinal tract, heart, lungs and central nervous system. The main signs include increased creatinine serum level, proteinuria and hypertension, nonspecific conditions that also can happen in patients without TA-TAM. Impaired renal function may not be present, but its absence should not exclude the diagnosis. Signs of pulmonary hypertension, headache, diarrhea, vomiting, abdominal pain, gastrointestinal bleeding and pericardial effusions may be the predominant symptoms, and therefore they should be highly suspicious18.

The most common and early clinical manifestations seen in TA-TAM are hypertension, thrombocytopenia, and increased lactate dehydrogenase serum level (LDH). Proteinuria may be also present about 10-14 days before the diagnosis of microangiopathy. Thus, patients who present risk factors should be routinely screened twice weekly LDH dosage, weekly urinalysis, and a careful follow-up of blood pressure assessment, especially in the first 100 days post- HSCT. [20,21,22]

Hypertension is a common post- HSCT side effect, however, when its levels are upper than expected while using calcineurin or steroid therapy, usually requiring >2 antihypertensive medications, it should increase clinical suspicion for TA-TMA and be further investigated.

The diagnosis is confirmed by biopsy of the target organ, but due to the complexity and performing risks, such evidence is hardly feasible.[1] Therefore, TA-TAM is confirmed by using diagnostic criteria. There is a wide variety, according to the authors, in the parameters to be evaluated, which makes it difficult to evaluate its incidence. The four most used currently are described below:

	BMT-CTN	IWG	Cho et al	Jodele et al
Schistocytes	>2 Per field	> 4%	>2 Per field	Present
Elevated LDH	+	+	+	+
Thrombocytopenia	-	+	+	+
Decreased Hb or increased red cell transfusion	-	+	+	+
Negative coombs test	+	-	+	-
Decreased haptoglobin	-	+	+	-
Renal and/or neurologic dysfunction	+	-	-	Hypertension or proteinuria
Normal coagulation studies	-	-	+	-
Elevated soluble C5b-9	-	-	-	+
Abbreviations: BMT-CTN =Bone Marrow Transplant Clinical Trials Network; Hb =hemoglobin; IWG =International Working Group; LDH =lactate dehydrogenase; TA-TMA = transplant-associated thrombotic microangiopathy; '+'= required; ' – ' =not specified				

*Adapted from Khosla J et al[18]

It is important to rule out others conditions that can be similar to TA-TAM, as sinusoidal obstruction syndrome, autoimmune hemolytic anemia and other types of microangiopathy, like thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)[20].

The factors associated with worst severity in TA-TAM are the presence of proteinuria and evidence of activation of the complement terminal pathway (increased dosage of C5b-9) showing survival rates under 20% when two factors are present, however, the last mentioned is not performed in Brazil[21,23]. Another easy to be performed parameter, which can help predict prognosis, is the TAM index based on the relation of LDH (in U/L) by platelet count (in x109/L), which when ≥ 100 is associated with lower survival[20,24].

Since fast start of therapy leads to better survival rates and long-term outcomes, regular screening and early diagnosis are important. Initial treatment is based on reducing the factors that can induce TA-TAM, and should be promptly performed by treating infections and GVHD, in addition to discontinuation of calcineurin inhibitors. However, the change of immunosuppressors in the presence of GVHD should be done with precaution, since its reactivation can lead to worsening of the microangiopathy scenario. In addition, hypertension should be strictly controlled by the risk of posterior reversible encephalopathy syndrome (PRES).

The benefit of plasmapheresis is controversial, being described only in small cohorts[25]. Most studies describe low survival rates despite the initial response to it26. If performed, its early onset seems to be associated with better survival, especially when there is still no target organ injury[25,27]. Initially, daily sessions should be performed for at least 2 weeks, with subsequent gradual pause according to clinical and laboratory response. Rituximab can be used alone or in association with plasmapheresis and is especially effective in the presence of antibodies.

The use of eculizumab, an inhibitor of the complement terminal pathway, is associated with better results and survival[28,29] and should by choice be used in all high-risk cases (proteinuria >2mg/mg or target organ injury – C5b-9 dosage not performed in Brazil). In the disease displayed by gastrointestinal bleeding, doses of eculizumab with shorter pauses (up to alternate days vs weekly) should be used29. Attention should be given to a higher risk of encapsulated bacteria infections related to its use, and antimicrobial prophylaxis should be established. In general, the discontinuation of eculizumab use after induction and maintenance phases is not associated with reactivation of the disease.

Several reports have been made regarding the benefit of the use of defibrotide in the treatment of TA-TAM20.

Currently, prophylaxis with N-acetylcysteine and omega[3] has been described as effective in reducing the incidence of TA-TAM with the rates in the pediatric high-risk population falling from 28.2% to 4.5%30.

CAPILLARY LEAK SYNDROME

Capillary leak syndrome is characterized by the loss of intravascular fluids into interstitial spaces and is triggered by a combination of inflammation and endothelial damage. Patients presents sudden weight gain, generalized edemas (ascites, pleural effusion, pericarditis) unresponsive to diuretic treatment, and hypotension eventually leading to cardiovascular shock with respiratory and pre-renal insufficiency. It is mainly observed in children, although true incidence is unknown (some series: 5%)[1,3,31].

Diagnostic criteria include: early after HSCT (days +10 to 11), unexplained weight gain >3% in 24h, positive intake balance despite furosemide evaluated 24h after its administration. (livro EBMT)

Treatment: withdraw growth factors and supportive care (colloids, catecholamines, plasma). Corticosteroids can be used. Intravenous immunoglobulin (IVIG) and Bevacizumab (anti-VEGF) have been used in some cases with good response[1,3,31].

ENGRAFTMENT SYNDROME

Engraftment syndrome (ES) includes a range of signs and symptoms occurring close to granulocyte recovery after stem cell transplantation is performed. ES is classically observed after autologous HSCT, although it has also been described after allo-transplantation. Several names can be given to this syndrome, as capillary leak syndrome, autoaggression syndrome (after autotransplants), aseptic shock syndrome and autologous GVHD. There is not a consent regarding the definition of ES, which makes it difficult to dictate the incidence and risk factors. There are also conflicting data regarding an association between ES, NRM and survival32-34.

The pathophysiology of ES is poorly understood although it probably involves release of pro-inflammatory cytokines, consequence of degranulation and oxidative metabolism, and systemic endothelial damage that may ultimately result in multi-organ failure[35]. In some cases, the concomitant administration of G-CSF, which is highly toxic to endothelial tissue, contributes to its development[1].

Diagnosis criteria for ES typically includes fever from non-infectious etiologies and features of systemic vascular leak. The two most used diagnostic criteria were described according to Spitzer and Maiolino and are listed below.

	Spitzer	Maiolino
Requirements	3 major or 2 major + 1 minor within 4 days of the engraftment	major + 1 minor within 1 day from presence of neutrophils
Major criteria	- Temperature ≥ 38.3 °C with undefined infectious etiology - Erythrodermatous rash compromising 25% of body surface area and not caused by a medication - Non-cardigenic pulmonary edema, expressed by diffuse pulmonary infiltrate, expected with this diagnosis, and hypoxia	- Non-infectious fever
Minor criteria	- Hepatic impairment with either bilirubin 2 mg/dL or transaminase serum levels twice baseline - Renal insufficiency (serum creatinine twice baseline - Weight gain 2.5% of baseline body weight - Transient encephalopathy unexplainable by other causes	- Skin rash - Pulmonary infiltrates - Diarrhea starting 24 hours before or at any time after the first rise of neutrophils

Regardless of the criteria used to diagnose ES, it is important to distinguish ES from other complications including acute GVHD, and radiation and drug-related toxicities and infections. Whether the ES cytokine cascade contributes to the initiation of GVHD after allotransplantation or is an early manifestation of ES is unclear[36].

ES may be self-limited and require no therapy. In several cases with clinically significant manifestations of vascular leak, in the absence of other etiology, treatment with corticosteroid 1 mg/kg/day as a starting dose is usually enough. ES is highly responsive to corticosteroid and treatment is given only as long as symptoms persist, which typically occurs within 2 to 3 days, followed by progressive lowering[36,37].

DIFFUSE ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage (DAH) is probably a consequence of damage to the alveolar capillary basement membrane[3]. It is a non-infectious complication that occurs in up to 5% of patients post-HSCT and carries a high mortality (60-100%). Clinical presentation is hypoxemia, dyspnea, diffuse opacities on chest radiography, and progressively bloodier bronchoalveolar lavage on bronchoscopy. Alveolar hemorrhage results from loss of integrity in the alveolar-capillary basement membrane, and accumulation of red blood cells in the alveolar space. Lung injury from conditioning regimens, total body irradiation, occult infections, and other comorbidities such as graft versus host disease, TMA, and cytokine

release and inflammation are risk factors. Management includes supportive measures (intensive care, ventilation, optimization of fluid and electrolyte balance, correction of coagulation and prophylactic antibiotics), transfusion of blood products, corticoids. Some studies demonstrate benefits with aminocaproic acid, nebulized tranexamic acid, recombinant activated fator VII[3,38].

IDIOPATHIC PNEUMONIA SYNDROME

Idiopathic pneumonia syndrome (IPS) is a rare complication following HSCT, defined by diffuse alveolar injury in the abscence of active lower respiratory tract infection, cardiac or renal dysfunction, and iatrogenic fluid overload. The incidence ranges from 2% to 15% in the first 120 days after HSCT. Some risk factors are full intensity conditioning, TBI, older age at transplant, acute GVHD, diagnosis of acute leukemia or myelodysplastic syndrome. Clinical presentation is variable but includes fever, non-productive cough, dyspnea, tachypnea and hypoxemia. X-rays or CT scans demonstrates diffuse alveolar or interstitial infiltrates. The pathogenesis is multifactorial, with endothelial cell activation and injury for toxic effect of conditioning regimens, leading to release of inflammatory cytokines, specifically TNF-alfa. The treatment includes supportive measures: oxygen therapy, ventilation (invasive or not – high-flow nasal, CPAP), empiric antimicrobials and control of fluids. Specific treatment options are corticosteroids, and Etanercept (an TNF-alfa binding protein). Despite the advances, the mortality from IPS remains high at 59-80% at 2 weeks of evoluition[3,39].

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