Long-term follow-up after pediatric hematopoietic stem cell transplantation

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ABSTRACT

This article, part of the Pediatric Group consensus of the Brazilian Society of Bone Marrow Transplantation, addresses lifelong follow-up in pediatric hematopoietic stem cell transplant survivors. With the growing number of long-term survivors, specialized monitoring is essential, especially for high-risk groups such as infants, recipients of total body irradiation, and those with inherited bone marrow failure syndromes. The consensus outlines surveillance strategies for detecting and managing late complications, including chronic graft-*versus*-host disease and secondary effects. Multidisciplinary recommendations aim to optimize early intervention and quality of life, establishing a standardized follow-up framework for pediatric transplant care in Brazil.

Keywords: Follow-Up Studies. Cancer Survivors. Long Term Adverse Effects. Pediatrics.

INTRODUCTION

As the number of long-term transplant survivors continues to grow, comprehensive lifelong follow-up is crucial. These patients, especially those with specific considerations such as infants, individuals who received total body irradiation or have inherited bone marrow failure syndromes, face elevated risks of late complications. Therefore, dedicated long-term monitoring is essential for early detection and management of potential issues, including chronic graft-versus-host disease and other late effects.

Period	Category	Exam / Evaluation	Frequency
180 days	Laboratory	Complete blood count	At each visit
		Renal function	At each visit
		Liver function	At each visit
		Lipid profile, blood glucose, fasting insulin, HbA1c	Every 6 months
		Ferritin	Every 6 months
		Microalbuminuria	Every 6 months
		Vitamin D	Every 6 months
		Immunoglobulin levels	Every 6 months
		Thyroid evaluation	Every 6 months
	Imaging	Echocardiogram and ECG	Every 6 months
		Spirometry	Every 6 months
	Specialist	Dental evaluation	Every 6 months
		Pediatric endocrinologist	Referral
		Vaccination schedule (and check immune response later)	To be initiated and evaluated
360 days	Laboratory	Complete blood count	At each visit
		Renal function	At each visit
		Liver function	At each visit
		Lipid profile, blood glucose, fasting insulin, HbA1c	Annually
		IGF-1 / Somatomedin C	Annually
		Gonadal evaluation (FSH, LH, testosterone, estrogen)	Annually
		Ferritin	Annually
		Microalbuminuria	Annually
		Vitamin D	Once
		Thyroid evaluation	Annually
		Serologies (HIV, HTLV, syphilis, Chagas, hepatitis B/C, etc.)	Once
	Imaging	X-ray for bone age	Annually
		Pelvic ultrasound	Annually
		Thyroid ultrasound	Annually
		Echocardiogram and ECG	Annually
		Spirometry	Once
		Bone densitometry	Then annually
	Specialist	Dental evaluation	Then annually
		Ophthalmologist	Annually
		Pediatric cognitive assessment	Annually

This schedule is a general suggestion. Each case should be individualized according to clinical condition and patient needs, with adjustments in exam frequency as appropriate.

Parameter/test	Frequency	Notes	Recommendations
Ocular complications post-hematopoietic stem cell transplantation[1–4]			
Ophthalmological assessment	Annual or earlier in the presence of symptoms	Risk factors: TBI and corticosteroid therapy IOP monitoring important in patients receiving any form of glucocorticoid Risk of premature cataracts for TBI recipients—treatment is surgical, typically indicated in bilateral cases	Question about eye concerns
Oral and dental complications post-hematopoietic stem cell transplantation[5–10]			
Dental evaluation	6 and 12 months old. Then annually	Earlier and more frequent evaluation to be considered in high-risk patients (refractory chronic GVHD, cranial/neck radiation, Fanconi anemia, Diamond-Blackfan anemia) Perform oral and radiological assessment for tooth development	Screen for chronic GVHD, high-risk habits (smoking, vape, tobacco)
Bone complications post-hematopoietic stem cell transplantation[8–10]			
DEXA	Annual DXA scans recommended for all hematopoietic stem cell transplantation recipients with follow-up frequency determined by results	DXA provides dual benefit: bone mass assessment and body composition analysis (fat and lean mass)	Screen for hormonal factors that may impair bone health (hypogonadism/ growth hormone deficiency) Implement lifestyle interventions: adequate nutrition, appropriate physical activity, and controlled sun exposure when permitted Ensure sufficient calcium and vitamin D intake Bisphosphonate therapy for severe cases—endocrinologist-guided treatment
Infectious complications post-hematopoietic stem cell transplantation[8,10,11]			
Pneumocystis jirovecii	Mandatory prophylaxis for ≥ six months post-transplantation or until immunosuppression discontinuation		
Varicella-zoster and herpes simplex virus	Duration: first year post-hematopoietic stem cell transplantation or until eight months after immunosuppression (IS) cessation (whichever is later)		
Encapsulated bacteria	Chronic GVHD: long-term chemoprophylaxis recommended due to unreliable vaccine protection. First-line: trimethoprim-sulfamethoxazole. Alternative: oral penicillin V (if trimethoprim-sulfamethoxazole intolerance). Supplemental medication required for *Pneumocystis jirovecii* pneumonia prophylaxis when using penicillin	For at least six months after discontinuation of all IS medications. Post-hematopoietic stem cell transplantation asplenic patients with chronic GVHD: prophylaxis until six months after IS or until 6 years old or two years after splenectomy (whichever occurs last) Post-hematopoietic stem cell transplantation asplenic patients without chronic GVHD: one year after transplantation or until 6 years old or two years after splenectomy (whichever occurs last) Sickle cell anemia: daily prophylactic penicillin for two years post-hematopoietic stem cell transplantation OR until 10 years old (whichever is longer); antibody titers should be assessed following post-transplant revaccination
CMV	Prophylaxis	Letermovir: effective for CMV-seropositive recipients (R+) until D+100 post-transplant. May extend to D+200 in selected cases	
Fungal infections	Prophylaxis	Duration: fluconazole until D+75 post-hematopoietic stem cell transplantation GVHD cases: prophylaxis recommended when immunosuppression includes corticosteroids (≥ 0.3 mg/kg/ day prednisone equivalent)	

Gastrointestinal and hepatic complications post-hematopoietic stem cell transplantation[9,10,12–15]		
Recommendations		Ask about gastrointestinal symptoms of GVHD at follow-up visits
		Monitor liver function by checking total bilirubin, alkaline phosphatase, and alanine aminotransferase (ALT) every one or two months during the first-year post-transplant, then annually for allo-hematopoietic stem cell transplantation recipients without liver disorder risk factors. Also evaluate ferritin levels to assess for possible iron overload
		Patients with pre-transplant indicators of hepatitis B (testing positive for HBsAg or anti-HBc) or those receiving stem cell from hepatitis B-infected donors face a risk of developing fulminant hepatitis B post-transplant if antiviral prophylaxis is not administered. These patients should receive prophylactic antiviral treatment
		Hepatitis C infected patients: consider diagnosis of fulminant immune-rebound hepatitis, particularly during IS tapering. When clinically indicated, implement treatment with antiviral drugs. Patients with chronic hepatitis B and C should receive follow-up care with a hepatologist
		HBsAg testing or viral load quantification (polymerase chain reaction) for hepatitis B and C should be performed at least one year after transplantation
Post-transplant diarrhea		Evaluation criteria: duration, volume, blood presence, fever, concurrent symptoms
		Differential diagnosis: GVHD, medication effects (especially magnesium supplementation), viral infections (varicella zoster, herpes simplex, CMV, adenovirus, rotavirus, norovirus and others), enteric pathogens (bacterial pathogens, giardiasis, cryptosporidiosis)
		Pancreatic abnormalities, though uncommon, should be considered in patients presenting with steatorrhea and weight loss. Evaluation for pancreatic insufficiency is essential, which may result from GVHD or medication toxicity, particularly tacrolimus
Iron overload[16–18]		
Diagnosis		Serum ferritin: indirect marker of iron overload; influenced by inflammation and infection. Monitor every three to six months during the first year and/or during treatment
		Transferrin saturation: assesses iron binding capacity. Monitory every three to six months during the first year and/or during treatment
		T2-MRI (liver/heart)*: most sensitive technique to detect iron deposits in organs. If ferritin > 1,000 ng/mL, annual after engraftment
		Liver biopsy confirms excessive iron deposits in cases of uncertain diagnosis, rarely used
Treatment	**Phlebotomy**	Most effective in patients with adequate hemoglobin levels (≥ 10 g/dL) and stable engraftment. It can be performed every 20–30 days. The volume per session ranges from 4 to 7 mL/kg, depending on patient tolerance, with a maximum limit of 400 mL
	Iron chelators	Deferoxamine (SQ, IM, or IV): 1,000–2,000 mg SQ daily; 500–1,000 mg IM daily; 40–50 mg/kg IV daily
		Deferiprone oral tablets (with or without food): 75 mg/kg (typically 25 mg/kg three times daily
		Deferasirox (oral tablets): Exjade (20 mg/kg daily, dissolved in liquids) or Jadenu (14 mg/kg daily). Both on an empty stomach or with a light meal (Jadenu)
Neurological complications[7,9,10,19–25]		
Recommendations		Perform childhood cognitive developmental milestones ≥ annually. Some children, especially those given TBI before the transplant, may have learning disabilities (particularly in mathematics and abstract thinking)
		Neurocognitive testing and educational/vocational progress assessment in pediatric survivors
		Neurological examination should be performed in all bone marrow transplant patients
		Audiologic evaluation: within first year post-hematopoietic stem cell transplantation
		Clinical assessment for peripheral nervous system and central nervous system dysfunction, especially in patients with GVHD

Endocrinological complications post-hematopoietic stem cell transplantation[5,8–10,26,27]			
Growth hormone deficiency	Risk factors	Young age at diagnosis/treatment, radiotherapy: cranial ≥ 18 Gy (especially > 30 Gy) or TBI, hypothalamic-pituitary tumors or surgery near sellar region and medications: prolonged glucocorticoids, TKI, isotretinoin, hedgehog inhibitors	
	Clinical monitoring	Assess weight, height, body mass index, growth velocity at every visit; evaluate pubertal stage (Tanner) at every visit; check body proportions annually if patient received spinal irradiation	
	Initial workup (for growth deficit/ decreased velocity)	Bone age, thyroid function (TSH, free T4), IGF-1, growth hormone stimulation test	
	Growth hormone deficiency diagnostic criteria	Clinical: reduced growth velocity (< -2 SD/1 year or < -1.5 SD/2 years); laboratory: normal thyroid function, low IGF-1, inadequate growth hormone response to stimulation; radiological: normal magnetic resonance imaging or decreased pituitary; additional: other pituitary deficiencies and/ or history of cranial radiotherapy, two growth hormone stimulation tests showing growth hormone peak < 5 ng/mL (only one test needed for radiotherapy patients)	
	Treatment	Should be carried out under the guidance of a pediatric endocrinologist. Initiate after one year from the end of oncological treatment. Daily subcutaneous recombinant growth hormone (rGH). Confirm absence of active disease, or stable disease. Consider safety, risks, and benefits: risk of recurrence of the underlying disease (low and inherent to the disease) and second malignant neoplasm (decreases with time and is associated with radiotherapy use). Monitor growth and adverse events	
Thyroid alterations	Annually: physical examination, thyroid function tests, and thyroid ultrasound	In case of alterations, request for hypothyroidism: anti-thyroperoxidase and anti-thyroglobulin; hyperthyroidism: anti-thyroperoxidase, anti-thyroglobulin, and TSH receptor antibody (TRAb) levels	Treatment of post-radiotherapy hypothyroidism and papillary carcinoma is similar to that of the general population.
Gonadal dysfunction	Monitor Tanner stages at each visit, in females: track menarche/menstrual cycles; measure FSH/LH and conduct pelvic ultrasonography (uterine volume, estrogenic activity) for ages > 12–13; in males: measure LH, FSH, and total testosterone for ages > 13–14. Pediatric endocrinology follow-up essential for hormone replacement based on height/bone age. For thrombosis-risk females, prioritize transdermal hormone replacement		
Fertility	Low fertility rates in post-transplant adolescents. Refer patients wanting pregnancy to fertility specialists. In adolescents: assess sexual activity, address difficulties, emphasize contraception despite fertility uncertainties		
Adrenal insufficiency	Evaluate HPA axis function (ACTH, cortisol) in patients on prolonged corticosteroids, assess recovery to determine if physiological doses can be discontinued, provide written instructions to affected patients to double medication during fever, trauma, or surgical procedures		
Obesity and metabolic syndrome	Monitor annually: body mass index, blood pressure, and abdominal circumference, as well as glucoses, basal insulin, lipid profile, and glycated hemoglobin levels. Follow-up with endocrinologist and pediatric cardiologist according to clinical and/or laboratory alterations		
Vitamin supplementation	Recommended for one year or until immunosuppression discontinuation (iron-free)		
	Vitamin D	Replacement: levels 20–30 ng/mL: < 1 year (400 IU/day), 1–8 years (600 IU/day), 9–18 years (800 IU/ day), levels < 20ng/mL: 1–12 months (1,000–2000 IU/day for eight weeks), 1–18 years (1,000–5,000 IU/day or 50,000 mcg/week)	
		Check 25OH vitamin D after three months; repeat treatment if < 30 ng/mL	
Magnesium	Replacement necessary for all patients using IS (cyclosporine and tacrolimus)		

Post-hematopoietic stem cell transplantation pulmonary complications[10,26,28,29]	
Recommendations	Pulmonary function test screening protocol: perform every three months in first year post-hematopoietic stem cell transplantation, every six months in second year, then annually for five years (or until final adult height in pediatric patients). For children under 6 years old unable to perform standard pulmonary function tests, consider alternative screening methods including pulse oximetry, multiple breath washout testing, or parametric mapping by computed tomography
	Computed tomography chest imaging: at onset of pulmonary symptoms or if abnormal pulmonary function test
	Preventive measures: discourage smoking/vaping and recommend pneumococcal vaccination
	For chronic GVHD patients: pulmonary function tests at diagnosis and quarterly until IS ends
	Children who have received TBI have an increased risk of developing restrictive lung disease later in life, 5–20 years after hematopoietic stem cell transplantation: perform pulmonary function test annually on an ongoing basis
	Clinical assessment for respiratory symptoms at every visit

Cardiovascular complications post-hematopoietic stem cell transplantation[10,30–32]	
Recommendations	Blood pressure measurement at all consultations
	Prevention through lifestyle modifications: tobacco avoidance, exercise, diet, weight management
	Post-hematopoietic stem cell transplantation: regular electrocardiogram and echocardiography (three, six, 12 months, then annually)
	GVHD patients: more frequent monitoring (every three months), due to the increased risk of dysrhythmias, endothelial injury, and pericardial effusion
	Metabolic syndrome increases cardiovascular risk. Assessment and control of obesity, hypertension and disorders of glycemia, cholesterol and triglycerides
	Regular ferritin level checks with intervention if elevated and cardiac magnetic resonance imaging for specific cases

Post-hematopoietic stem cell transplantation revaccination[10,33-38]	
Patient immunity	Hematopoietic stem cell transplantation patients (autologous/allogeneic) lose previous immunity and require complete revaccination
Vaccine response	Returns to near-normal two or three years post-hematopoietic stem cell transplantation; patients have lower response rates due to incomplete immune reconstitution, immunosuppression, GVHD
Vaccination access	Special vaccines available at CRIEs (reference centers); some vaccines only available privately
Vaccination restart timing	Inactivated vaccines can be used as early as three months post-hematopoietic stem cell transplantation, as immunogenic vaccines show substantial response rates at this timepoint
Household contact vaccination	CRIEs provide influenza, varicella and MMR vaccines for susceptible household members. Oral polio vaccine is contraindicated for household members. Inactivated polio vaccine should be used instead when polio protection is needed
Chronic GVHD considerations	Patients require additional doses due to inadequate immune response: fourth dose of hepatitis B vaccine, fourth dose of 13- or 15-valent pneumococcal vaccine, second dose of influenza vaccine (regardless of age)
Check these links for more information	https://www.hematolog.app/imunizacao/
	https://www.gov.br/saude/pt-br/vacinacao/informes-tecnicos/informe-tecnico-vacina-covid-xbb/view
	https://sbim.org.br/images/calendarios/calend-sbim-crianca.pdf
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Psychological[10,39–41]	
Professional support	Ensure access to psychologists specialized in hematopoietic stem cell transplantation patients
Pre-transplant preparation	Implement routine psychological consultations before procedure
Address common issues	Target anxiety, post-traumatic stress disorder, depression, fatigue, and sleep disturbances
Focus on positive psychology	Promote optimism, gratitude, hope, and perseverance
Special attention to young adults	Provide additional support for employment and social reintegration
Regular monitoring	Review symptoms, distress, medications, and physical activity at each follow-up (minimum: D+100, D+180, D+365, then annually)
Standardized screening	Use mental health questionnaires regularly
Medication adherence	Discuss and provide educational support
Lifestyle guidance	Set goals for healthy diet, activity, and weight management
Caregiver support	Monitor psychological adjustment of spouse/caregiver and family functioning
Reintegration assistance	Help with return-to-work/school programs; provide healthcare education for adolescents and young adults patients
Holistic approach:	Encourage adequate sleep and age-appropriate preventive measures

Renal complications[10,42–49]	
Chronic kidney disease	eGFR ≤ 60 mL/min/1.73 m² calculated from serum creatinine for at least three months or more
	Risk factors: previous AKI/hypertension, baseline dysfunction, GVHD, older age, allogeneic transplant, myeloablative conditioning, nephrotoxic drugs, specific infections, and diagnosis
	General screening: UA, rUPCR, BUN and creatinine levels every three months in the first year and ≥ yearly thereafter. Shorter interval if abnormal values or complications
Transplant-associated thrombotic microangiopathy	After D+100 weekly screening if severe GVHD or infections
	Screening presence ≥ three of the following: anemia, thrombocytopenia, elevated LDH, proteinuria (≥ 1 mg/mg rUPCR), schistocytes, refractory HTN requires additional testing
	High-risk TA-TMA: any of following: elevated sC5b9, rUPCR ≥ 1 mg/mg, organ dysfunction (except KDIGO stage I), LDH ≥ 2x ULN, concurrent GVHD 2-4, or infections
Nephrotic syndrome	Proteinuria (≥ 2g) or albuminuria > 3.5 g/24 h; edema; hypoalbuminemia; hypercholesterolemia; lipiduria
Hypertension	Lifestyle changes and antihypertensive therapy to reduce risks of cardiovascular and CKD
Secondary malignancies[9,10,26,50,51]	
Increased risk	Skin cancers, solid tumors, myelodysplastic syndromes, leukemias, and post-transplant lymphoproliferative disorder
Recommendations	Skin exam with the complete physical examinations and clinical history
	Pap smears and mammogram (women aged 25 or eight-years post-radiotherapy, whichever occurs later, but no later than age 40) and education to reinforce self-breast exams. Prostate exam and prostate-specific antigen (men > 45 years). Occult blood in stool (> 40 years) and colonoscopy (baseline at age 50, in absence of a family history, and as clinically indicated thereafter)
	Oral exam by the dentist at six-month intervals
	Regular thyroid ultrasound; fine needle aspiration in case of suspicious nodule (patients at risk: after TBI or local radiation)
	Complete blood counts, thyroid function, and other tests as applicable
	Patients with inherited bone marrow failure syndromes have a higher risk of solid cancers. Fanconi anemia survivors with mutations in BRCA2 (FANCD1) or PALB2 (FANCN) require screening for specific solid cancers (including leukemias, brain tumors, and childhood-onset solid tumors)
	Consider meningioma screening in patients who received central nervous system radiotherapy
	All patients should use sun blocking creams or sunscreens (> 30 sun protection factor) when outdoors to prevent skin cancers and to prevent activation of chronic GVHD
	Encourage to avoid high-risk behaviors, unhealthy diet (*e.g.*, tobacco and vaping, passive tobacco exposure, alcohol abuse, high fat/low fiber diet)
Post-transplant proliferative disorder[51–61]	
Risk factor	Main risk factors: EBV status and T-cell immunosuppression; highest risk: pediatric patients with negative EBV status; risk-increasing agents: ATG, anti-CD52 (alemtuzumab); risk-reducing agent: post-transplant cyclophosphamide
Classification	Plasmacytic hyperplasia, infectious mononucleosis-like, florid follicular hyperplasia, polymorphic, monomorphic (B-cell or T-/NK-cell types), and classical Hodgkin lymphoma post-transplant proliferative disorder
Diagnostic evaluation	Positron emission tomography/computed tomography: highly sensitive for identifying active disease and guiding biopsy sites
	Magnetic resonance imaging: preferred for central nervous system involvement assessment
	Ultrasound: useful for detecting abdominal masses or lymphadenopathy
Treatment strategies	Reduction of immunosuppression: first-line approach in stable patients
	Rituximab (anti-CD20): effective in EBV-driven B-cell post-transplant proliferative disorder. Dose: 375 mg/m² intravenously weekly for four doses
	Chemotherapy: indicated for aggressive or refractory cases
	EBV-specific cytotoxic T cells: emerging therapy with promising outcomes
	Antiviral therapy: Limited role but may be combined with other treatments

TBI: total body irradiation; IOP: intraocular pressure; GVHD: graft *versus* host disease; DXA: dual-energy X-ray absorptiometry/bone densitometry; *for more information on diagnosis, treatment, and monitoring, refer to the chapter on infectious complications; CMV: cytomegalovirus; SQ: subcutaneous; IM: intramuscular; IV: intravenous; Gy: gray; TKI: tyrosine kinase inhibitors; TSH: thyroid-stimulating hormone; IGF-1: insulin-like growth factor 1; SD: standard deviation; FSH: follicle-stimulating hormone; LH: luteinizing hormone; HPA: hypothalamic-pituitary-adrenal; ACTH: adrenocorticotropic hormone; CRIE: Reference Center for Special Immunobiologicals; MMR: measles, mumps and rubella; eGFR: estimated glomerular filtration rate; AKI: acute kidney injury; UA: urine analysis; rUPCR: urine protein-to-creatinine ratio; BUN: blood urea nitrogen; LDH: lactate dehydrogenase test; TA-TMA: transplant-associated thrombotic microangiopathy; sC5b-9 is not available in most Brazilian centers; sC5b9: soluble complement C5 fraction b-9; KDIGO: Kidney Disease: Improving Global Outcomes; ULN: upper limit of normal; HTN: hypertension; CKD: chronic kidney disease.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All dataset are presented/analysed in the text.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Pelegrina PRD, Gouveia RV, Macedo AV, Vieira AK, Landi GGF, Lopes J, Menezes Neto OA, Ferreira RS, Miachon AAS, Tavares R, Bonfim C. **Conception and design:** Pelegrina PRD, Gouveia RV, Macedo AV, Vieira AK, Landi GGF, Lopes J, Menezes Neto OA, Ferreira RS, Miachon AAS, Tavares R, Bonfim C. **Analysis and interpretation of data:** Pelegrina PRD, Gouveia RV, Macedo AV, Vieira AK, Landi GGF, Lopes J, Menezes Neto OA, Ferreira RS, Miachon AAS, Tavares R, Bonfim C. **Manuscript writing:** Pelegrina PRD, Gouveia RV, Macedo AV, Vieira AK, Landi GGF, Lopes J, Menezes Neto OA, Ferreira RS, Miachon AAS, Tavares R, Bonfim C. **Final approval:** Pelegrina PRD.

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