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Recommendations for Screening and Management of Late Effects in Patients with Severe Combined Immunodeficiency after Allogenic Hematopoietic Cell Transplantation: A Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT

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Abstract

Severe combined immunodeficiency (SCID) is effectively treated with hematopoietic cell transplantation (HCT), with overall survival approaching 90% in contemporary reports. However, survivors are at risk for developing late complications because of the variable durability of high-

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quality immune function, underlying genotype of SCID, comorbidities due to infections in the pretransplantation and post-transplantation periods, and use of conditioning before transplantation. An international group of transplantation experts was convened in 2016 to review the current knowledge of late effects seen in SCID patients after HCT and to develop recommendations for screening and monitoring for late effects. This report provides recommendations for screening and management of pediatric and adult SCID patients treated with HCT.

Keywords

Long-term follow-up guidelines; Severe combined immune deficiency; Bone marrow transplantation

INTRODUCTION

To consider late effects after hematopoietic cell transplantation (HCT) in pediatrics, including severe combined immunodeficiency (SCID), the Pediatric Blood and Marrow Transplant Consortium sponsored a conference of experts in May 2016. Key aims of the meeting were to assess current knowledge regarding late effects for patients diagnosed and treated for SCID and to address the lack of standardized guidelines for proactive monitoring and screening after HCT. Pediatric Blood and Marrow Transplant Consortium leaders engaged key experts from the Primary Immune Deficiency Treatment Consortium (PIDTC), a collaboration of 44 centers in North America [1], and the European Society for Immune Deficiencies/European Society for Blood and Marrow Transplantation Inborn Errors Working Party to address this need. In our recent review of the published experience for survival and late effects seen after HCT for SCID [2], we documented the need for long-term data collection and analysis from these patients to improve outcomes. The goal of the present report is to review current practices for monitoring and assessment in pediatric HCT survivors and identify the unique needs of such patients with SCID. We provide recommendations for longitudinal evaluation that can be incorporated into protocols by those conducting clinical trials and carried out by a broad range of providers, including general pediatricians, general internists, pediatric and adult immunologists, HCT physicians, and survivorship programs.

CURRENT RECOMMENDATIONS AFTER PEDIATRIC HCT AND UNIQUE NEEDS FOR SCID

Current recommendations for evaluation of late effects after HCT for all transplantation survivors were published as an international consensus statement that identified organ system–specific areas of risk and additional areas of higher medical risk, such as chronic graft-versus-host disease (cGVHD) [3]. Recommendations for evaluations starting as early as 6 months after HCT were made for all patients, regardless of age at HCT or indication for transplantation. For pediatric HCT survivors in particular, a critical need for long-term follow-up guidelines was identified and additional organ system–specific recommendations were made [4]. Further, it was noted that over one-third of pediatric HCT procedures were performed for nonmalignant indications. Such patients have specific needs unique to their

underlying disease that differ from those of patients who receive HCT for malignancy [4]. The nonmalignant indications included patients with primary immunodeficiency (PID), such as SCID.

SCID has been treated with HCT for 50 years and is the most common diagnostic indication for HCT for pediatric PID. Newborn screening for SCID is now performed in nearly all states in the United States and has been introduced into other countries worldwide. The revised incidence of SCID is 1 of 58,000 in the United States, higher than the original estimate of 1 of 100,000 [5,6]. Significantly higher incidence rates occur in many population subgroups with high consanguinity and founder mutations [7–10]. Given this new epidemiologic data and widespread newborn screening, there will be an even larger population of children with SCID who undergo transplantation during infancy and surviving to adulthood [11]. The average overall survival for SCID patients treated in early infancy is >90% at 3 years after transplantation [12–16]. However, this can vary substantially depending on multiple factors, including age, infection status at the time of transplantation, type and degree of HLA matching of the donor and recipient, graft source and manipulation before transplantation, graft-versus-host disease (GVHD) prophylaxis, type and dose of conditioning utilized (if any), and underlying SCID genotype [17].

In addition to survival, for all pediatric patients after HCT, other important aspects to monitor include the degree of immune reconstitution, complications of chemotherapy-based conditioning and immunosuppressive agents given in infancy, growth and development, and quality of life. It has been reported that pediatric survivors of HCT for a broad range of indications, including SCID, may have persistent abnormalities in immune function [18]. Also, pediatric patients have been reported to have increased risk for neurocognitive dysfunction, physical disability, and issues associated with poor health-related quality of life after transplantation [19]. However, a single-center follow-up study of SCID patients who underwent transplantation but did not receive pretransplantation chemo-ablation or post-transplantation GVHD prophylactic immunosuppressive agents did not find many of these issues [14]. For SCID patients, preparative regimens vary from none to serologic or pharmacologic immune suppression alone to full ablative chemotherapy regimens. Although late outcomes are expected to vary depending on regimen used, further studies are needed. Furthermore, detailed examination of specific genotypes is likely to reveal the need for tailored treatment approaches for particular genotypes as well as monitoring and management of persistent medical and quality-of-life issues [20].

Here, we report consensus recommendations for SCID patients surviving after HCT and address special concerns unique to these patients and other PID survivors. This guidance builds upon previous recommendations of the PIDTC for the management of patients with PID before, during, and after HCT [21].

IMMUNE FUNCTION AND INFECTION RISK

Establishing the durability and quality of immune reconstitution after HCT for SCID should be a major focus of post-HCT evaluations. Immune reconstitution can vary significantly based on the SCID genotype, the type of graft used, and whether and how much

conditioning therapy was employed. To support survival beyond the first year of life, T cell reconstitution is the most urgently needed aspect of immune recovery; however, B and natural killer (NK) cell function are also important for long-term infection control. Robust immune reconstitution is crucial for early and long-term survival and for avoiding late morbidity/mortality through protection from opportunistic and other serious infections and autoimmunity. In a study of survivors with a median follow-up of 11 years after HCT for SCID, cGVHD, autoimmunity, and/or poor nutrition were factors associated with increased risk of late post-HCT mortality [22]. Assessing lineage-specific chimerism and immune reconstitution in a comprehensive and systematic manner over time is crucial, even if the patient is well and without signs of infection, to allow detection of possible declines developing gradually. If deterioration in lymphocyte number or function can be detected early, intervention can be made before clinical complications develop. The PIDTC has published recommendations for specific needs of the SCID patient in testing immune reconstitution [21,23], including a panel of evaluations focused on the T, B, and NK lymphoid components (Table 1). Testing is recommended to start no later than 3 months after HCT and to continue lifelong.

T Cells

For evaluation of T cells, flow cytometry of CD3, CD4, and CD8 with concomitant testing for CD4-specific and CD8-specific memory (CD45RO), naïve (CD45RA), and/or recent thymic emigrants (CD45RA/CD31) can be followed over time to detect trends that may indicate graft loss or dysfunction. In addition, T cell receptor excision circles counts assayed consistently in the same laboratory over time are also a useful marker for measuring thymic output [24]. The presence of naïve T cells, particularly recent thymic emigrants, is indicative of engrafted T cell precursors developing via normal thymic-directed maturation, rather than simply the presence of peripherally expanded T cells, which have a memory phenotype. T cell spectratyping is useful to assess diversity of the T cell repertoire [24]; this an important part of the immune evaluation since a skewed repertoire may be associated with higher risk of autoimmunity, infection, or other clinical sequelae of poor immune function. Lymphocyte proliferation with phytohemagglutinin (PHA) is an assessment of T cell function, but proliferative responsiveness to antigens such as tetanus or candida or direct CD3 stimulation are more stringent assays. Measurement of lineage-specific chimerism, including T, B, and myeloid cells, is also recommended for all SCID patients. It is important to note that patients who received HCT for leaky SCID, who had the ability to make some dysfunctional T cells before HCT, have a greater potential for autologous T cell re-emergence in the setting of graft failure, making standard flow cytometry an inadequate assessment of T cell reconstitution in these patients. Also, patients with B-negative SCID have been noted in several studies to have more challenges with declining T cell counts and function over time [12,17]. Prophylaxis against *Pneumocystis jirovecii* should be continued in patients 2 years or more after transplantation if CD4 counts remain under 200 cells/uL, poor T cell function (PHA proliferation <50% of the lower limit of normal for the lab) is noted, or chronic immunosuppressive therapy is being given [25]. In addition, sufficient T cell reconstitution should be attained before the administration of live vaccines (see below).

B Cells

The likelihood of humoral immune reconstitution is impacted by the genotype of the patient and use of conditioning. Patients with IL2RG (the genetic etiology of x-linked SCID) and JAK3 SCID typically have B cells at the time of diagnosis, but without engraftment of donor B cells, these intrinsically abnormal B cells are unlikely to produce sufficient antigen-specific immunoglobulin to avoid antibody replacement [16,26,27]. In contrast, in children with other forms of SCID, such as IL7R, CD3, and adenosine deaminase (ADA) deficiency, immunoglobulin replacement may not be necessary even without B cell engraftment providing they have sufficient T cell reconstitution [16]. In all forms of SCID, several studies have demonstrated that the use of either myeloablative or reduced-intensity chemotherapy–based conditioning is associated with an improved ability to achieve B cell engraftment and immunoglobulin independence; therefore, serial testing for B cell recovery and normal function is recommended. Because B cell engraftment is generally associated with an ability to achieve independence from immunoglobulin replacement, measurement of B cell lineage chimerism is advisable. In addition to flow cytometric assessment of CD19 and/or CD20, quantification of total immunoglobulins (IgA, IgM, and IgE, recognizing that IgG levels reflect immunoglobulin infusions) is recommended. When B cell recovery is noted, it may be useful to test for normal maturation of B cells via flow cytometry for switched memory B cells ($CD19^+/CD27^+/IgD^-$) [16].

Independence from immunoglobulin replacement is another goal of successful HCT for SCID. The ability to discontinue immunoglobulin replacement must be carefully evaluated in SCID patients after HCT. Because B cell number alone is insufficient, functional studies can help determine the likelihood of success of a trial off immunoglobulin replacement. Normal or near-normal serum IgM and/or IgA levels are an important early indicator of functional B cells, and presence of IgM isohemagglutinins to the A and B blood group antigens in a titer of ≥1:8 indicate intact specific antibody production. One or both tests can reassure physicians as they consider a trial off immunoglobulin replacement. Although prevaccination and postvaccination titers for typhoid and rabies have also been used to assess B cell–independent and B cell–dependent responses, respectively, in antibody-deficient patients on immunoglobulin replacement, further study is needed to assess the utility and safety of these vaccines to determine whether SCID patients can trial off intravenous immunoglobulin replacement after HCT.

Trials off immunoglobulin should ideally be timed for spring and/or early summer to decrease risk of contracting viral illnesses and to allow time to assess vaccine responses outside of the fall-winter virus season. After immunoglobulin replacement is stopped for at least 3 months, immunizations can be initiated. There is no specific level of IgG that dictates whether immunoglobulin replacement is required. This is an area of limited available data for review and there is need for additional prospective evaluation to determine the clinical relevance of IgG levels, vaccine responses, patient age, and infection risk when considering trials off immunoglobulin replacement.

Immunizations

Post-transplantation immunizations with inactivated or recombinant vaccines should be started after patients have successfully discontinued immunoglobulin replacement for a minimum of 3 months. Table 2 is a summary of current recommendations regarding timing and intervals for administration of specific vaccines for patients who have received HCT. Measurement of prevaccination and postvaccination titers ensures that vaccines are inducing a protective response. Prevaccination titers should be obtained no sooner than 3 months after stopping immunoglobulin replacement. Responses to vaccines should be measured 4 to 6 weeks after the vaccine is given [28–31]. After a positive response to recombinant or inactivated vaccines has been documented, and also after adequate T cell immunity has been documented, live viral vaccines may be considered. Some experts recommend demonstration of minimal levels of CD4 counts for age and function based on proliferation to PHA and antigens, but further study is needed to validate this approach [28,29,32]. As post-transplantation guidelines for vaccination are updated regularly, clinicians should use the most current guidelines to assist in choosing how best to proceed with vaccination of children with SCID after transplantation. Finally, because postvaccination antibody titers have been noted to decline over time for patients after HCT as compared to normal individuals, antibody titers should be periodically evaluated [32].

Long-Term Immunoglobulin Replacement

Some patients require long-term immunoglobulin replacement, which can be administered via the intravenous or subcutaneous route [33]. In patients who are unable to achieve protective levels of antibodies in response to vaccines, immunoglobulin replacement therapy should be reinstituted and continued with appropriate dosing and administration interval to achieve minimum IgG trough levels of 800 mg/dL for patients on i.v. therapy and 1000 mg/dL for patients on s.c. therapy [34]. These recommendations are based on patients with immune deficiencies who are unable to produce immune globulins, and exact levels needed after transplantation for patients with SCID require further study. It should also be noted that the IgG level needed to control infection can vary between patients. Cases of late-onset bronchiectasis attributed to recurrent infections have been noted in post-transplantation SCID patients maintained on immunoglobulin therapy with low IgG trough levels (personal communication, R. Buckley and J. Puck). IL2RG and JAK3 patients are at particularly higher risk for poor humoral immune reconstitution, with continued need for immunoglobulin replacement; therefore, clinicians should maintain a higher index of suspicion for humoral dysfunction after HCT in this group [16,26,27].

N K Cells

NK cells, which may be cytotoxic against viruses, malignant cells, and HLA-mismatched donor cells, are also absent in several forms of SCID, including IL2RG, JAK3, and ADA SCID. Although a recent report demonstrated that a lack of NK cell reconstitution did not have clinical consequences for IL2RG (n = 12) and JAK3 (n = 6) SCID patients after HCT [35], further study is needed. NK cell populations ($CD3^{-}/CD56^{+}$ and/or $CD3^{-}/CD16^{+}/CD56^{+}$) can be followed by lymphocyte flow cytometry panels.

GVHD

GVHD has a negative impact on immune function because of effects on the thymus and spleen in addition to the immunosuppressive therapies needed to control this complication. Patients with cGVHD should have care consistent with local standards and published guidelines [36]. Many patients with cGVHD need ongoing prophylactic antimicrobials until symptoms have fully resolved and they are off immune suppression for an extended period.

Specific Recommendations

- Immune reconstitution should be evaluated serially over time, starting no later than 3 months after transplantation and continued life-long in cooperation with a clinical immunologist and HCT transplantation specialist. Late deterioration of immune function, with frequent infections and/or declining number and diversity of T cells or inadequate total or specific antibody protection, may occur and may require intervention with further cellular therapy.
- Minimal recommended testing should include assessment of T, B, and NK cell numbers, naïve ($CD4^+CD45RA^+$) T cells, T cell receptor excision circles, T cell function via proliferation, and B cell function via immunoglobulin levels and isohemagglutinin titers, as well as lineage-specific engraftment.
- *Pneumocystis jirovecii* prophylaxis should be continued until immunosuppressive therapies are stopped and there is evidence of T cell recovery. Some experts recommend CD4 >200 cells/uL and demonstration of PHA >50% of the lower limit of normal for the laboratory, but more study is needed.
- When there is evidence of the ability to discontinue immunoglobulin replacement, prevaccination titers should be measured no sooner than 3 months after the last immunoglobulin infusion. Immunization of patients should then start with conjugated/inactivated vaccines, followed by assessment for adequate antibody responses after completion of the primary series of vaccinations. When adequate titers to conjugated/inactivated vaccines have been noted, clinicians can consider administering live vaccinations. For all SCID patients off intravenous immunoglobulin replacement and successfully immunized, periodic screening of antibody titers to conjugated/inactivated and live viruses should also be performed.
- Live vaccines should not be given to patients with cGVHD, poor T cell reconstitution, or continued need for immunoglobulin replacement.
- Patients who do not recover B cell function should continue immunoglobulin replacement without interruption.

NONIMMUNE ORGAN SYSTEM LATE EFFECTS

In addition to poor immune reconstitution manifesting with opportunistic infections, autoimmune disease, persistent cGVHD, and poor growth with need for nutritional support have been associated with increased mortality for patients with SCID after HCT [22].

Effects of pretransplantation conditioning on organ function, particularly focused on monitoring the lungs, liver, central nervous system, and endocrine organs, is extremely important. For newborns and very young infants diagnosed by newborn screening or family history, the toxic effects of conditioning may be even greater [37]. Other late effects secondary to the use of alkylator-based conditioning regimens are similar to those seen in non-SCID HCT recipients [3]. Sterility is another major potential side effect of conditioning and should be prospectively investigated. Recommendations for screening and support of late effects are summarized in Table 3.

DNA repair defects (Artemis, DNA Ligase IV, DNA-PKcs, Cernunnos-XLF deficiency, and Nijmegen breakage syndrome) affect lymphocytes and cause SCID by preventing antigen-receptor rearrangement, and they also affect nonimmune tissues, leading to abnormalities in a variety of organ systems, including variable degrees of microcephaly and neurocognitive impairment. Moreover, DNA repair defects cause increased sensitivity to ionizing radiation and alkylator-based conditioning, leading to exaggerated toxicity seen exclusively in radiosensitive (RS) SCID patients [38]. Artemis-deficient SCID recipients of radiation or alkylating chemotherapy have decreased survival and, among survivors, significantly reduced height as well as increased frequency of dental anomalies, endocrine abnormalities, exocrine pancreatic insufficiency, and pulmonary fibrosis [39,40].

In certain SCID genotypes, particularly ADA deficiency and reticular dysgenesis (RD), multisystem disease is a consequence of effects of mutations on cells other than lymphocytes. In some patients with IL2RG and JAK3, and to a lesser degree IL7R SCID, several groups have described severe warts after HCT, secondary to human papillomavirus infection [14,22,41]. Use of the human papillomavirus vaccine, while recommended for all patients, may be particularly important in these genotypes of SCID. Neurocognitive impairment [42] and hearing impairment [43], both before and after HCT, have been described in patients with ADA-deficient SCID and RD [44].

Specific Recommendations

- All patients should have, at a minimum, annual monitoring of weight and height, with more frequent monitoring for those with continued need for nutritional support or those who demonstrate evidence of slowed growth or falling percentiles on growth curves
- All patients should have routine developmental screening after age-appropriate pediatric guidelines, with a low threshold for referral for supportive therapies
- Because infants and children with SCID are at risk for neurocognitive and psychiatric impairments, due to combinations of underlying genetic defects, sequelae of infections and conditioning regimens, chronic illness, prolonged hospitalization, isolation from other children, and significant family stresses, all patients should have neurocognitive testing when they are capable of participation and this should be repeated every other year or as needed thereafter with a low threshold for referral for supportive therapies

- In all patients, assessment of psychosocial impact on the patient and caregiver utilizing health related quality of life assessment tools validated for patient age and/or parent proxy response is recommended during the first year after HCT and annually thereafter with prompt referral of the patient and/or family for mental health professional counseling if concerns are identified.
- Thyroid dysfunction is a common complication in those who receive alkylator-based conditioning; therefore, annual monitoring of T4/thyroid-stimulating hormone with en-docrinology referral as needed is recommended.
- Assessment of gonadal function and longitudinal follow-up for evidence of sterility or impaired fertility are important for those who receive pretransplantation conditioning or who have underlying genotypes, eg, RS-SCID that may put them at risk. Further prospective studies are needed to better define this risk as it relates to underlying genotype
- Pulmonary dysfunction is common; lung disease/bronchiectasis related to infections may exist before HCT or can occur after alkylator-based conditioning, and there is also risk of developing chronic lung disease while on inadequate immunoglobulin replacement. Therefore, annual spirometry is recommended when the patient is old enough to participate. Additional evaluation including full pulmonary function testing with diffusion capacity and chest computed tomography/magnetic resonance imaging rather than less sensitive plain chest (including lateral) radiography should be considered based on clinical presentation and with attention to avoiding unnecessary radiation exposure in RS-SCID genotypes
- Abnormal hearing is of special concern not only in patients with ADA SCID or RD, but also in individuals who received prolonged doses of aminoglycosides for treatment of infections, and assessments should be made at least annually; early audiology referral for any concern is recommended
- Patients with Artemis associated SCID who received alkylator-based conditioning are at increased risk for short stature and can also have growth hormone abnormalities; therefore, close following of growth with early endocrinology referral is recommended. This may also be true for patients with other forms of RS-SCID and careful monitoring is recommended
- Patients with Artemis associated SCID who received alkylators are at increased risk for dental abnormalities and close monitoring with a dentist is recommended; every effort should be made to preserve primary teeth as secondary teeth may not develop. Similarly, patients with other forms of RS-SCID, careful dental follow-up is recommended
- Patients with IL2RG, JAK3, or IL7R SCID genotypes should have dermatology consultation for treatment of warts if they develop

GENETIC COUNSELING

Data from the recent PIDTC prospective natural history study of SCID indicates that most babies with SCID can be assigned a molecular diagnosis [45]. Knowledge of the specific gene defect may be important in decisions about whether conditioning is needed, and if so, what type and dose, as well as whether gene therapy may be an option. A molecular diagnosis also allows for appropriate risk stratification after transplantation. However, the initiation of definitive therapy should not be delayed by the search for a genotype. In patients with a T-B-NK− phenotype, rapid assessment for ADA deficiency can allow initiation of enzyme replacement therapy and consideration of gene therapy. In patients with T-B + NK-SCID, assessment for IL2RG can allow consideration for gene therapy. Finally, genetic testing in T-B-NK+ SCID to rule out RS-SCID is an important consideration before initiation of alkylator-based conditioning regimens. In older patients who have already had a transplantation and present for long-term follow-up, the use of a skin biopsy or other nonblood tissue (eg, hair follicle), or blood or other samples from parents can be used to isolate DNA to establish a gene diagnosis. In addition to allowing for appropriate care of the post-transplantation patient, a gene diagnosis permits genetic counseling and prenatal testing for SCID patients of child-bearing age and their parents and at-risk relatives.

Specific Recommendations

- Patients and families should have a molecular diagnosis sought, using the most advanced and rapid technology available; this does not preclude moving forward with allogeneic HCT when an appropriate donor is identified
- Genetic information may be shared in the acute setting of HCT for a SCID-affected child, but genetic counseling for family members must also be offered in follow-up settings when parents are better able to process this information
- SCID patients who have undergone HCT and approaching childbearing age, as well as their relatives who may be considering having a child, should be offered genetic testing and counseling

RECOMMENDATIONS FOR FOLLOW-UP SUMMARY DOCUMENT/ROADMAP TEMPLATE

Recommendations for providers caring for patients with SCID who have been treated with HCT are summarized in the accompanying document (Figure 1). We suggest this tool be used to facilitate the comprehensive care of patients as they transition through the various phases of their life-long medical care, from the acute post-HCT period, to long-term pediatric care, and to adult providers.

CONCLUSIONS

Most patients diagnosed with SCID and treated with HCT now survive well into adulthood. As we have outlined here, there is clearly a need for continued surveillance of overall health for these survivors, with attention directed to the long-term effects of pretransplantation conditioning as well as immunologic health throughout life. There is an increased risk of

chronic lung disease because of respiratory infections both before and after transplantation (particularly for those continuing immunoglobulin replacement), as well as toxicities from conditioning used for HCT. Patients treated with alkylator-based therapies may have distinct needs, especially those with RS-SCID genotypes.

These guidelines are aimed to facilitate the standardization of longitudinal care for SCID patients treated with allogeneic HCT, from the time of diagnosis through treatment and adulthood. We hope this guidance will be useful in both clinical care and the design of clinical trials. There is a critical need for research of long-term outcomes after HCT for SCID, particularly for those beyond 2 to 5 years after treatment, to confirm and refine these recommendations. In addition, the long-term follow-up needs for patients treated with gene therapy is not yet known, but will also need study as gene therapy moves from smaller proof of concept clinical trials to broader use in certain SCID genotypes. Finally, we recommend programs be developed to facilitate the transition of patient care in SCID and other PID from pediatric to adult providers.

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Patient name:_____
Patient DOB:_____
Genetic cause of SCID: __IL2RG __RAG1/RAG2 __ARTEMIS/DCLRE1C __ADA __IL7R __CD3 __CD45 __JAK3 __Other:_____
Date of HCT:_____
Type of HCT: __MRD (Sibling) __MMRD (Haplo) __ MUD BMT __MUD PBSC __UCB
Type of conditioning: __None __Biologics without other chemotherapy:_____
Reduced intensity:_____
Myleoablative:_____
Chronic GVHD: __no __yes, organs affected:_____
On Immunoglobulin replacement: __no __yes, product and dose: _____
Other medications:_____

Key health screenings with specific time points noted

System	Last tested/next due	Result	Interventions/notes
IMMUNE SYSTEM			
CD3			
CD4			
CD8			
CD4/CD45RO			
CD4/CD45RA/CD62L or CD31			
TREC			
Spectratyping			
PHA			
Tetanus proliferation			
Candida proliferation			
CD3 proliferation			
B cells: CD19/CD20			
IgG			
IgA			
IgM			
IgE			
Tetanus titer			
Pneumococcal titers			
NK Cells: CD3-/CD56 and/or CD16			
Whole blood chimerism			
T chimerism			
B chimerism			
Myeloid (CD33 or CD14&/or15) chimerism			
GROWTH			
Height (percentile)			
Weight (percentile)			
DEVELOPMENTAL ASSESSMENT			
HEARING SCREEN			
NEUROCOGNITIVE TESTING			
HRQOL ASSESSMENT			
ENDOCRINE			
TSH			
AM Cortisol			
Growth hormone			
Gonadal hormone assessment			
DENTAL EXAM			
DERMATOLOGIC EXAM			
PULMONARY: PFT/Spirometry			
CARDIOVASCULAR			
Blood pressure			
HEPATIC: LFT's			
OTHER INVESTIGATIONS			

Figure 1.
Patient summary/care transition document template.

Table 1

Interval for Immunologic Studies after Transplantation in SCID Patients (Recommended)

Study	Baseline	3 Mo. (± 2 Wk)	6 Mo. (± 4 Wk)	12 Mo (± 4 Wk)	Annually for 2 to 5 Yr (± 6 mo.)	>5 to 11 Yr, Every 3 Yr (± 1 yr)	After 11 Yr Every 5 Yr (± 1 yr)
T cell flow cytometry							
CD3, CD4, CD8, CD4/CD45RA, CD4/CD45RO, CD8/CD45RA, CD8/CD45RO	X	X	X	X	X	X	X
TRECS or CD4/CD45RA/CD31 (CD31 optional)		X	X	X	X	X	X
Spectratyping		X	X	X	X	X	X
Proliferation to PHA	X		X	X	X	X	X
Proliferation to tetanus			X	X	X	X	X
Proliferation to candida			X	X	X	X	X
Proliferation to anti-CD3			X	X	X	X	X
B cell flow cytometry							
CD20 or CD19	X	X	X	X	X	X	X
Switched Memory B cell testing *			X	X	X	X	x
CD19/CD27+/IgD−							
IgG †, IgA, IgM, IgE	X	X	X	X	X	X	x
Isohemagglutinins ‡			X	(X)	(X)	(X)	(X)
NK cell flow cytometry							
CD3−/CD16 +/or C56	X	X	X	X	X	X	X
Chimerism (T, B, myeloid)		X	X	X	X	X	X

Trec indicates T cell receptor excision circles.

*Testing should be deferred until CD19 or CD20 noted to present in those previously treated with rituximab or equivalent.

†Make note if patient on/off intravenous immunoglobulin replacement at time of testing.

‡Stop testing when present (optional).

Table 2

Recommended Vaccines for Post-Transplantation Administration in SCID Patients after Evidence of B Cell Reconstitution Is Demonstrated (See Text)

Vaccine	Minimum Age	No. of Doses and Interval between Doses	Comments
Inactivated influenza	6 mo	Two doses in first year are administered for patients aged 6 mo–8 yr; once annually after the first year of administration	NA
Pneumococcal conjugate	2 mo	Three doses given at least 4–8 weeks apart; if cGVHD give fourth dose at 12 mo after HCT	NA
Pneumococcal polysaccharide	2 yr	One dose if no cGVHD	NA
Tetanus, diphtheria, pertussis	2 mo	Three doses if < 7 yr old, given at least 4 wk apart	If >7 yr old, Tdap may be given ×1, followed by DT × 2 doses or Td × 2 doses
Haemophilus influenzae b conjugate	2 mo	Three doses; if first dose given under 1 yr of age then second dose may be given after 4 wk; otherwise, 8 wk between doses	NA
Polio-inactivated	2 mo	Three doses with at least 4 wk between each dose	NA
Hepatitis B	NA	Three doses; at least 4 wk between first and second dose; at least 8 wk between second and third dose AND 16 weeks between first and third dose	If anti-HBs Ab <10mIU/mL after all 3 doses; a second 3-vaccine series should be given
Meningococcal conjugate (ACWY serotypes)	11–18 yr	Two doses at least 8 wk apart	Booster should be given at 16–18 yr old if first dose given between 11–15 yr of age; administration of meningococcal B vaccine after HCT in SCID has not yet been studied
Human papillomavirus	9–26 yr	Three doses; 4–8 wk between first and second dose; 6 mo between first and third dose	NA
Measles, mumps, rubella	12 mo	Two doses: first dose given when deemed clinically safe; second dose at 4–6 yr OR Two doses separated by at least 4 wk if >4 yr at time of first dose	Patients should have adequate T cell immunity (see text), be without cGVHD, not on immunosuppression, and without immunoglobulin replacement for 8–11 mo
Varicella	12 mo	Two doses: first dose given when deemed clinically safe; second dose at 4–6 yr. OR Two doses separated by at least 4 wk if >4 yr at time of first dose	Patients should have adequate T cell immunity (see text), be without cGVHD, not on immunosuppression and without immunoglobulin replacement for 8–11 mo
Yellow fever	Check national reference	Check national reference	Patients should have adequate T cell immunity (see text), be without cGVHD, not on immunosuppression and without immunoglobulin replacement for 8–11 mo; consideration if travelling to an endemic area cannot be avoided; safety data are limited
Rotavirus	NA	Do not administer	NA
Zoster	NA	Do not administer	NA
BCG	NA	Do not administer	NA
Oral polio vaccine	NA	Do not administer	NA

Vaccine	Minimum Age	No. of Doses and Interval between Doses	Comments
Cholera	NA	Do not administer	NA
Intranasal influenza vaccine	NA	Do not administer	NA
Oral typhoid vaccine	NA	Do not administer	NA

Adapted from Rubin et al., 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host [29] and Ljungman et al., Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT and Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, United States, 2017.

NA indicates not applicable.

Table 3

Long-Term Follow-Up after HCT by Organ System in SCID Patients

Tissue/Organ System	Late Complications	Risk Factors	Monitoring Tests	Monitoring/Treatment Recommendations after HCT for All SCID Patients	Monitoring/Treatment Recommendations after HCT for High-Risk SCID Patients
Immune system	Loss of/decreased quality of immune reconstitution; infections; PTLD; autoimmunity	B-SCID genotypes have higher risk of poor immune reconstitution; varied use of conditioning; HLA disparity is associated with poorer immune reconstitution; T cell depletion is associated with delayed T cell reconstitution; cGVHD; prolonged iatrogenic immunosuppression; asplenia; implanted venous access devices; use of B cell directed monoclonal antibodies (example, rituximab)	See Table 1. CMV testing including serology and/or PCR; EBV PCR	See Table 1. Vaccinations should be used to test quality of immunoglobulin production with pre- and postimmunization titers, postimmunization titers should be drawn at least 4 wks after immunization and followed periodically thereafter. **Prophylaxis** PJP prophylaxis should be continued for at least 6 mo or until completion of immune-suppressive therapy and/or evidence of T cell function (CD4 >200 and PHA >50% control) **Vaccines** Immunization should be initiated with inactivated vaccines with assessment of pre- and postvaccination titers to determine level of protection and immune function; influenza vaccine should be given annually for all HCT recipients >6 mo of age; live vaccines (varicella, MMR) to be given when inactivated vaccine responses demonstrated and off systemic immunosuppression with demonstration of adequate recovery of functional T cells; all patients able to receive	**cGVHD**: encapsulated organism and PJP prophylaxis for duration of immunosuppressive therapy **cGVHD**: defer live vaccinations **Hypogammaglobulinema**: patients with evidence of poor B cell reconstitution (as defined in text) should be treated with immunoglobulin replacement either i.v. or s.c.at dose equivalents of 400–600 mg/kg/dose when given every 28 d (125–150 mg/kg/dose when given weekly as in most subcutaneous therapy); dose should be titrated in cooperation with a clinical immunologist **IL2RG/JAK3 patients:** administration of HPV vaccine should be strongly encouraged

Tissue/Organ System	Late Complications	Risk Factors	Monitoring Tests	Monitoring/Treatment Recommendations after HCT for All SCID Patients	Monitoring/Treatment Recommendations after HCT for High-Risk SCID Patients
				vaccines should receive catch- up immunization per most current consensus guidelines for immunization after HCT (Table 2)	
Growth	Failure to thrive; growth delay	Busulfan/alkylators in RS SCID genotypes	Monitoring of height and weight; growth velocity	Annual assessment of weight with percentile comparison and referral for nutritional support as needed; annual assessment of growth with bone age as needed; bone age and referral to endocrinology for poor growth; GH therapy may reveal hypothyroid status	
Developmental	Developmental delay; ADHD; mental retardation	ADA SCID; busulfan/alkylators		Developmental milestone assessment every 3 mo for the first 2 yr of life; annually thereafter with monitoring of school performance; prompt referral for supportive interventions (PT, OT, speech); neurocognitive assessment every other yr	
Neurologic	Calcineurin neurotoxicity; sensorineural deafness	AK2 genotype; ADA genotype		Annual clinical evaluation of neurologic symptoms; neuro-imaging as guided by symptoms	Hearing assessment for AK2, ADA patients
Psychosocial	Depression; anxiety; fatigue; caregiver adjustment difficulties	Cyclophosphamide	HR-QOL testing; psychological evaluation for patient and caregiver/family member	Clinical assessment throughout recovery period; annually thereafter, with professional mental health counseling if concerns identified; HR-QOL periodically in the first yr after HCT; annually thereafter using assessment tools validated for patient	High risk at time of transition from immediately after HCT to long-term follow-up

Tissue/Organ System	Late Complications	Risk Factors	Monitoring Tests	Monitoring/Treatment Recommendations after HCT for All SCID Patients	Monitoring/Treatment Recommendations after HCT for High-Risk SCID Patients
				age and/or parent proxy response; encourage development of robust social support networks; regularly assess level of care-giver psychosocial adjustment/family functioning	
Endocrine	Hypothyroidism; hypoadrenalism; gonadal dysfunction	Busulfan; cyclophosphamide; chronic steroid use; busulfan/ alkylators in RS SCID genotypes	Thyroid function tests; AM cortisol, and adrenal axis testing	Test thyroid function annually; if TSH abnormal with normal T4 then reassess in 2 mo and refer for endocrinology evaluation; adrenal axis testing at the time of steroid cessation	If chronic steroid use: (1) slow terminal tapering of corticosteroids and (2) stress dose steroids during acute illness until AM cortisol normalizes
Oral/dental	Sicca syndrome; caries; enamel dysplasia; abnormal development of dentition	GVHD; busulfan/alkylators in RS SCID genotypes	Dental assessment	Annual clinical dental assessment starting at 1 yr of age or at 6 mo after transplantation, whichever is later; counseling to avoid tobacco exposure, decrease sugared beverage intake, and avoid oral piercings	cGVHD: heightened awareness of potential for intraoral malignancy; RS-SCID: Increased risk of dental anomalies
Muco-cutaneous/dermatologic	Warts; alopecia; nail dystrophy; sweat impairment; skin depigmentation; sclerosis; vaginal mucosal abnormalities (ulcerated mucosa, fissures, narrowing of introitus, scarring, obliteration); skin malignancy	IL-2RG/JAK3 SCID; busulfan; cGVHD		Routine self-examination of skin; counsel patients to limit sun exposure/use sunscreen; clinical assessment annually; annual gynecologic exam as age appropriate with provider aware of after transplantation status and risks	Prompt dermatology evaluation and treatment of warts, particularly in IL2RG/JAK3 SCID genotypes
Ocular	Cataracts; Sicca syndrome; CMV retinitis	Corticosteroids; GVHD	Ophthalmologic exam	Clinical exam starting at 24 mo after HCT and annually thereafter	Evaluation for CMV retinitis in patients at increased risk of CMV reactivation
Respiratory	Idiopathic pneumonia syndrome; bronchiolitis obliterans syndrome; cryptogenic organizing pneumonia; bronchiectasis	GVHD; busulfan exposure; lung disease before transplantation	Spirometry; PFTs; radiologic assessments (CT/ CXR)	Clinical examination at 6 mo and 1 yr after HCT ; annually thereafter; counseling	cGVHD: variable recommendation for earlier/ more frequent clinical/PFT assessment

Tissue/Organ System	Late Complications	Risk Factors	Monitoring Tests	Monitoring/Treatment Recommendations after HCT for All SCID Patients	Monitoring/Treatment Recommendations after HCT for High-Risk SCID Patients
				to avoid tobacco exposure, including secondhand exposure; spirometry/PFT annually starting at 5 yr of age, more frequently for those with symptoms/signs of lung compromise; radiologic assessment as indicated by clinical course; use of MRI preferred over chest CT for patients with RS SCID; pulmonology consultation with changes >15% on PFT	
Cardiovascular	Hypertension; dyslipidemias	Calcineurin inhibitor exposure	Blood pressure; fasting lipids; fasting glucose	Routine clinical assessment of CVS risk factors per general health maintenance at 1 yr; annually thereafter; counseling regarding heart healthy lifestyle (regular exercise, healthy weight, no smoking); hypertension management per routine health guidelines (also has implications for renal health)	
Liver	GVHD; hepatocellular cancer	Busulfan exposure; young age at transplantation; hepatitis B or C positive	LFTs	LFTs every 3–6 mo after HCT in the first year; then annually at minimum; consider liver biopsy if considering immunosuppression for GVHD without any symptoms other than hepatic involvement	Annual hepatocellular cancer screening if hepatitis B/C +, obese, and/or with low platelet count; liver transplantation has been performed in rare cases of severe progressive GVHD
Renal	Chronic renal disease; bladder dysfunction	Young age at HCT; drug exposures (calcineurin inhibitors, amphotericin, aminoglycosides); hypertension; Infection history (CMV, BK)	BUN; serum creatinine; urine protein	BUN, serum creatinine, urine protein at 6 and 12 mo after HCT, then annually at minimum; nephrology consultation, additional studies (ultrasound/ biopsy) as dictated by	More frequent assessment for those on chronic calcineurin inhibitors

Tissue/Organ System	Late Complications	Risk Factors	Monitoring Tests	Monitoring/Treatment Recommendations after HCT for All SCID Patients	Monitoring/Treatment Recommendations after HCT for High-Risk SCID Patients
				lab results and clinical course; ACEi/ARB if albumin: creatinine ratio >300 mg/kg ×1 or persistent ratio >30 mg/kg on 3 occasions and patient has hypertension	
Musculoskeletal	Myopathy; fasciitis/scleroderma; polymyositis	Chronic steroid use; cGVHD	Assessment of ability to stand from sitting; ROM assessment		At each clinic visit for patients on chronic steroids or with GVHD
Bone health	Osteopenia; osteonecrosis/avascular necrosis	Chronic steroid use; calcineurin Inhibitors	DEXA; MRI to evaluate patients with joint symptoms	DEXA as early as clinically possible 1 yr after transplantation, yearly if Z score <1; calcium/vitamin D supplementation; recommend weight-bearing exercise **unless** there is concern for osteonecrosis	Referral to orthopedics if osteonecrosis on MRI
Reproductive health/fertility	Hypogonadism; sexual dysfunction; sterility/ impaired fertility	Busulfan (females > males)	FSH, LH, testosterone; psychological evaluation; genetic counseling	Clinical and endocrine gonadal assessment/ Tanner staging of boys and girls at 12 mos after transplantation; endocrine re-assessment if girls do not experience puberty by 12–13 yrs; boys as needed; testosterone/ estradiol, FSH, LH, inhibin B yearly from age 10 yr; ask age-appropriate patients about sexual function annually, discuss contraception in all patients; consider referral to reproductive specialists for those considering pregnancy or with difficulty related to conception; all patients should receive genetic counseling regarding risk of transmission of SCID to offspring	

Tissue/Organ System	Late Complications	Risk Factors	Monitoring Tests	Monitoring/Treatment Recommendations after HCT for All SCID Patients	Monitoring/Treatment Recommendations after HCT for High-Risk SCID Patients
Secondary malignancy	Solid tumors; lymphoproliferative disorders	Myeloablative busulfan/ cyclophosphamide; T cell depletion; HLA disparity; GVHD	HPV vaccine; EBV PCR	Counsel regarding risks of secondary malignancy; encourage self-examination, avoidance of high-risk behaviors (smoking); general population recommendations for cancer screening	
General health				Provision of survivorship plan; referral to pediatric and adult providers including hematopoietic stem cell physicians and clinical immunologists experienced in monitoring SCID patients after HCT	

PTLD, post-transplantation lymphoproliferative disorder; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PJP, Pneumocystis jirovecii pneumonia; MMR, measles mumps and rubella; GH, growth hormone; ADHD, attention deficit hyperactivity disorder; PT, physical therapy; OT, occupational therapy; HR-QOL, health-related quality of life; TSH, thyroid-stimulating hormone; PFT, pulmonary function testing; CT, computerized tomography scan; CXR, chest x-ray; MRI, magnetic resonance imaging; LFT, liver function test; BUN, blood urea nitrogen; ACEi, angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ROM, range of motion; DEXA, dual-energy X-ray absorptiometry; FSH, follicle stimulating hormone; LH, luteinizing hormone; HPV, human papilloma virus.

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