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Report

# 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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A B S T R A C T

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-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.



## 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

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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