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Allogeneic Hematopoietic Cell Transplantation for Primary Immune Deficiency Diseases Current Status and Critical Needs

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) has been employed for 40 years to ameliorate or cure primary immune deficiency (PID) diseases, including severe combined immune deficiency (SCID) and non-SCID PID. There is a critical need for evaluation of the North American experience of different HCT approaches for these diseases, in order to identify best practices and plan future investigative clinical trials. A conference of experts in HCT treatment of PID has recommended: (1) a comprehensive cross-sectional and retrospective analysis of HCT survivors with SCID; (2) a prospective study of SCID patients receiving HCT, with comparable baseline and follow-up testing across participating centers; (3) a pilot study of newborn screening for SCID to identify affected infants prior to compromise by infection; and (4) for the non-SCID diseases, Wiskott-Aldrich syndrome and Chronic Granulomatous Disease, studies of the natural history of disease in patients who do or do not receive HCT. To accomplish these goals, collaboration by a consortium of institutions in North America is proposed. Participation of immunologists and HCT physicians having interest in PID and experts in laboratory methods, clinical outcomes assessment, databases and analysis will be required for the success of these studies.

Keywords

Allogeneic hematopoietic cell transplantation; primary immunodeficiency; clinical trial

Introduction

The objectives of this 1.5 day workshop were to review the current North American experience in hematopoietic cell transplantation (HCT) for primary immune deficiency (PID) diseases, identify critical needs, and propose and prioritize future clinical studies. Because individual PIDs are rare, no single institution is capable of determining optimal treatment approaches. A comparative evaluation of the current treatments with regard to risks, benefits and key outcomes is needed to serve as a basis for future research, including prospective multi-center clinical trials. An interactive partnership of immunologists and HCT physicians with a special interest in PID and experts in immunology laboratory methods, clinical outcomes assessment, databases and analysis will be critical to success as we take advantage of opportunities offered for treatment of these rare and uniquely challenging patients.

PIDs are rare, monogenic disorders of cellular and humoral immunity. A subgroup of PIDs with defects in lymphocytes or granulocytes can be cured by HCT, and this subgroup was the focus of the workshop. Severe Combined Immunodeficiency (SCID), with over 14 distinct genetic variants (Table 1) and an estimated incidence of 1/50,000 to 1/100,000 births, includes a spectrum of genetic disorders of the immune system that render affected patients incapable of mounting antigen-specific T or B cell immune responses against exogenous pathogens.[1] The related "Combined Immunodeficiencies" (CID) are partially permissive for T-cell development, because they affect later stages in T-cell development (e.g., ZAP-70 deficiency), or are due to hypomorphic mutations. Without treatment to

provide effective lymphocyte immunity, children afflicted with SCID rarely survive the first year of life.

There are also several non-SCID PIDs that are correctable by HCT. Examples include Wiskott-Aldrich Syndrome (WAS), Chronic Granulomatous Disease (CGD), Hyper IgM Syndrome, Chediak-Higashi Disease (CHD), Familial Hemophagocytic Lymphohistocytosis (HLH), X-linked Lymphoproliferative Disease (XLP), and others. The workshop focused on two conditions having substantial HCT experience, WAS and CGD. In WAS,[2] an X-linked disorder with an estimated incidence of 1/250,000 live male births, a spectrum of mutations in the Wiskott-Aldrich Syndrome Protein (*WASP*) gene gives rise to phenotypes affecting all hematopoietic lineages. CGD,[3] with one X-linked and three autosomal recessive genotypes, has an estimated overall incidence of 1/250,000 births. Genes mutated in CGD affect subunits of NADPH oxidase complex, which catalyzes the “respiratory burst” in all myeloid cells. Thus, affected individuals are at risk for severe and persistent infections. X-linked CGD may have a worse prognosis, and complete defects are more severe than partial defects.

Allogeneic HCT as curative therapy for SCID

Allogeneic HCT can ameliorate or cure patients with life-threatening PID.[4] Patients with PID were among the first to receive successful HCT 40 years ago.[5,6] SCID is unique in that patients completely lacking T cell immunity do not require immunosuppressive chemotherapy prior to allogeneic HCT to achieve engraftment, especially when HLA matched, related donors are available (Table 2). HLA-matched related marrow grafts are the treatment of choice for all variants of SCID, however, 75-80% of patients lack such a donor. Transplant of HLA haplotype disparate parental marrow depleted of T-cells using soy bean agglutinin (SBA) / sheep red blood cells (SRBC), with engraftment and reconstitution of both T and B cell function without GVHD, was demonstrated in children with SCID in 1983[7] and successfully reproduced in other centers.[8-11] Other approaches for processing haplotype disparate donor hematopoietic cells, which have subsequently been developed include depletion of lymphoid cells with monoclonal antibodies and CD34 positive selection using either the Isolex or Miltenyi CliniMacs systems.[12-14] Outcomes of HCT for SCID have improved over the years,[15-18] and matched unrelated donors[19] including umbilical cord blood[20] have been used to successfully treat patients with SCID. Chemotherapy may be needed to ensure engraftment when alternative donors are used, raising concerns about both short term toxicity and long term effects on growth and development in these highly susceptible infants.[21,22] Also, most children with SCID present with severe infections that raise the risk of treatment with high dose chemotherapy.

HCT treatment for SCID is not uniform, as transplant centers have developed their own protocols based on training and experience of local HCT clinicians. Without a consensus on the optimal approaches, the choice of donor when an HLA matched sibling is unavailable is influenced by the center’s preferences and access to technologies for stem cell enrichment and/or T cell depletion. Issues of pre-HCT conditioning, choice of donor when an HLA matched sibling is not available, and clinical condition at the time of transplant all need to be addressed in formal multi-center studies (Table 2).

Key questions in HCT for SCID

1. How are the extent and durability of T, B and NK cell lineage-specific reconstitution and function post-HCT affected by the transplant regimen/strategy utilized? Is full donor chimerism[23] needed? When no pre-HCT conditioning is used, for example, in the event an HLA-matched sibling donor is available, most recipients will have T, but not B cell reconstitution, except for patients with

intrinsically normal B cells, as in interleukin-7 receptor (IL7R) defects. In contrast, when myeloablative chemotherapy is used multilineage engraftment is likely, even with an alternative donor, although this raises questions regarding early and late toxic effects.

2. To minimize toxic effects, yet achieve full and durable immune reconstitution, what are the best transplant strategies? For very young infants, can an approach be developed that doesn't involve conditioning, to be followed if necessary two to three years later with a booster HCT from the same donor, possibly using conditioning?[24] Are there alternative approaches to achieving immune reconstitution that do not involve toxic chemotherapy, e.g. lymphoid- and/or myeloid-depleting monoclonal antibodies?

3. What is the overall survival and long-term clinical status of patients with SCID treated by HCT in North America? Comparison of long term health and organ-specific function of patients with different types of SCID who have received HCT using different approaches is needed. Evaluation of long term outcome should include neuropsychological maturation and function and the growth and function of drug sensitive organs such as the lungs, teeth, liver, brain, and kidneys. In addition, assessment of long term risks associated with specific transplant strategies for late recurrence of immune deficiency, development of autoimmune diseases[25] or development of specific chronic infections or malignancies is essential.

4. How do the specific SCID genotypes affect transplant outcomes including engraftment, sustained thymopoiesis, and the function of B cell and NK cell populations? The genotype and phenotype of the child with SCID likely plays a critical role in HCT outcome and should influence the particular approach.[26] The genotype of SCID and its effects on lymphoid development may affect transplant outcome by contributing to graft resistance, limiting lineage specific chimerism, and causing functional deficits in specific components of the immune system (e.g, humoral immunity, and/or NK cell function).

5. What is the significance of the recipient's residual T-cell immunity prior to HCT, as observed in patients with CID, and how does this impact selection of an optimal donor, conditioning regimen, and graft manipulation?

6. When the donor graft is T-cell depleted, what is the relation of the method used, source of cells and extent of T-cell depletion on post-transplant GVHD (with or without GVHD prophylaxis)?

7. If an HLA-matched related graft is unavailable, can we develop an algorithm to identify next-best graft source and HCT regimen for patients with SCID? Such an algorithm would need to encompass the issues discussed above.

8. Patients transplanted for SCID, particularly those who have received HLA-haplotype disparate T-cell depleted grafts, constitute a unique clinical model for examining interactions between donor and host cells that shape the immune repertoire and contribute to tolerance. SCID children transplanted without receiving myeloablative conditioning maintain a state of mixed chimerism in which T-cells are of donor origin while other hematopoietic elements, including antigen-presenting cells of myeloid lineages and in some patients also B cells are of host type. How does this ultimately affect durable immune reconstitution and can the large number of surviving SCID patients be studied to answer these questions?

9. For long term SCID survivors who received treatments other than transplantation, a similar retrospective analysis and comprehensive evaluation of lymphoid populations and their function is also urgently needed. Examples include the use of

PEG-ADA enzyme replacement therapy for the treatment of ADA deficient SCID, and the current status of gene therapy applied to ADA deficient SCID.

10. What is the role of HCT vs. gene therapy for a specific gene defect, if available? Gene therapy may provide an alternative to allogeneic HCT that avoids immunological complications because it is an autologous HCT. Clear-cut successes for gene therapy of ADA-deficient SCID and X-linked SCID demonstrate proof of efficacy, but complications from insertional oncogenesis in 25% of XSCID patients demonstrates potential novel toxicities that need to be better understood and reduced by further preclinical research. Unlike allogeneic HCT where a single approach may be used for different genotypes of SCID or other PID, gene therapy will require a dedicated program for each specific genetic etiology. Implementation of their concept means that the replacement of genes for IL-2Rγc chain deficiency and adenosine deaminase deficiency, for example, will require separate and distinct gene constructs, more of a personalized medicine approach requiring specialized research teams.

Newborn screening for SCID

Children with SCID develop infections by 3 to 4 months of life and do not survive past infancy unless they receive immune-reconstituting treatment, such as HCT or enzyme replacement with PEG-ADA. Those diagnosed with SCID immediately after birth, before developing infections, have the best chance of survival and have fewer medical complications after HCT as compared to SCID infants who are infected prior to diagnosis. Viral infections are particularly devastating to infants with SCID. To better recognize SCID before onset of infections, however, requires universal screening of newborns. An assay for T cell lymphocytopenia has been developed that is based on quantitating T-cell receptor excision circles (TRECs) in DNA extracted from dried blood spots.[27,28] TRECs are present in newly formed T cells, but essentially absent in the blood of infants with SCID, in whom T cell maturation is impaired.

Pilot clinical trials are needed to establish feasibility of prospective, population-based screening for diagnosis of SCID. A successful newborn screening program requires a sensitive and specific test, but also must have mechanisms for following up abnormal results, promptly arriving at a definitive diagnosis and providing effective treatment. The State of Wisconsin is currently conducting one such trial, but a trial in a population with a high incidence of SCID would be the most efficient means to demonstrate clinical utility of SCID screening. Athabascan-speaking Navajo and Apache Indians have a *DCLRE1C (Artemis)* gene founder mutation that causes radiation sensitive SCID.[29] Around 1/2000 Navajo births is affected with SCID, an incidence at least 20-fold higher than that of the general population. Thus, there would be a high likelihood of finding SCID in a trial of limited size among Navajo Indians. Outreach and referral for HCT are in place, making the Navajo Reservation a promising setting for a clinical trial of SCID newborn screening.

Allogeneic HCT as curative therapy for non-SCID PID

Supportive measures, such as life-long prophylaxis with immunoglobulin and antimicrobials and aggressive management of infections, have been the traditional treatment of non-SCID PIDs.[30-32] However, premature mortality despite such treatment has led to utilization of HCT, which can be curative. HCT for these disorders share a requirement for both T cell immunosuppression and at least some degree of myeloablation (Table 2). Although risks of HCT with other than HLA-matched related donors are high, recent advances in HCT technology have improved this mode of treatment, even as the long term morbidities have become increasingly clear. For example, most patients undergoing BMT for WAS

worldwide have been pre-conditioned with a protocol designed to be myeloablative, consisting of busulfan, cytoxan and ATG.[33] Despite this, a fraction (less than 10%) reject their first transplant, and many (20-30%) patients are long term mixed chimeras. Perhaps differences in busulfan pharmacokinetics in children as compared to adults are a factor.[34] Older patients with more co-morbidities, who have received transplants from unrelated donors, have had poorer survival post HCT than younger, healthier patients. A recent retrospective study in Europe revealed significant rates of late post-HCT complications in WAS patients, including autoimmune conditions, neuropsychological impairments and late septic deaths in patients who had received splenectomy prior to HCT[35] No similar studies have been performed in North America. For CGD, only a minority of patients, most of whom are children with life-threatening infections, currently receive HCT.[36-38]

Key questions in HCT for non-SCID, represented by WAS and CGD

1. How does immune function compare for age-matched WAS patients who have or have not received HCT?
2. How do the specific gene mutation, age, disease manifestations and prior treatments (such as splenectomy) influence risk vs. benefit of HCT for WAS?
3. Does attaining full donor lymphoid and myeloid chimerism reduce the risk of post-HCT autoimmune and inflammatory complications for WAS?
4. What degree of donor chimerism in the myeloid compartment is required for clinical cure of CGD?
5. For CGD, does the burden of infectious and inflammatory manifestations relate to the biochemical consequences of the underlying genotype?
6. Based on an individual CGD patient's biochemical profile and clinical course, is it possible to develop guidelines as to those patients most likely to benefit from HCT?
7. Do the recent advances in HCT regimens, such as high resolution HLA matching for unrelated donor selection,[39] and the newer reduced-intensity and non-myeloablative conditioning regimens[40] offer possible advantages for patients with PID? Future investigations in the context of clinical trials are needed.

Feasibility – survey of current North American practice base

To assess feasibility of prospective studies, and to ascertain previous experience with HCT in SCID and non-SCID disorders, the group surveyed the number and type of PID cases diagnosed and treated per year in the United States and Canada. Responses from 34 sites (including Center for International Blood and Marrow Transplant Research (CIBMTR) centers, Pediatric Blood and Marrow Transplant Consortium (PBMTC) centers, and other known HCT centers) were obtained and analyzed. An estimate of new patients seen per year is as follows: SCID (overall), 50-60; WAS: 20-30; CGD: 10-20; HLH: 10-20; other non-SCID: 15-20. Nearly 750 children with SCID have been transplanted, and over 500 are alive. Among 250 patients with WAS who received HCT, nearly 200 are alive; similarly, 46 of the 59 patients transplanted for CGD are alive. Today, there is a broad distribution of HCT sites that treat patients with PID, well beyond the few centers where HCT methods for PID were initially developed. Patients are evenly distributed among centers reporting 1-5, 6-10, 11-25, 26-50, and >50 patients per center, for the SCID and non-SCID groups combined. Therefore, for studies to be comprehensive and meaningful, a broad collaboration encompassing both large and small centers will be needed.

Laboratory evaluations core

The group proposed a common set of laboratory studies be performed on all PID patients post HCT. Table 3 represents a consensus as to minimum testing recommended and time intervals for this testing such that all participating centers will be able to monitor their patients. It is recognized that some centers will do additional testing and may also test more frequently. Use of central laboratories and/or reference laboratories should be considered to provide quality assurance for data generated. Key issues for multi-center clinical studies include standardization of reagents and test methods to achieve comparability, costs and logistical barriers to establishing centralized core labs, and funding for laboratory testing.

Regarding the minimum level of evaluation needed to establish a diagnosis of PID before HCT, the above plus mutation diagnosis of specific disease genes was considered essential. Core or reference laboratories could be utilized for molecular genetic testing, though these tests are currently clinically indicated for genetic counseling and in some instances tailoring the specific HCT.

Long term follow-up core, including need to validate QOL forms for PID

Adaptation of existing testing instruments and if necessary, developing new ones for gathering information from individuals with SCID and non-SCID PIDs treated with HCT in prospective and retrospective studies will permit assessment of the long-term benefits and complications and quality of life. Two approaches will be key. First, enrollment of study subjects in the CIBMTR and the US Immunodeficiency Network (USIDNET) databases (see below) will be important. Data collection for diverse aspects at baseline and post-HCT is provided by these databases. Existing longitudinal forms used by the CIBMTR and the USIDNET have been newly revised to harmonize and optimize collection of data relevant to HCT outcomes for PID patients. A comprehensive treatment history for each patient should be obtained (Table 4). Second, age-appropriate validated instruments for determining the quality of life for PID patients who have received HCT must be selected and administered. Example instruments include the Pediatric Quality of Life (QOL) Inventory (both child and parent versions available for various ages), the SF-36, and the Foundation for Accreditation of Cellular Therapy (FACT) - BMT assessment tool.

Databases

Two databases relevant to PID clinical studies are available. First, the USIDNET, sponsored by the NIH, is a voluntary registry of patients diagnosed with PID. Second, under the U. S. Health Resources and Services Administration (HRSA) C. W. Bill Young Cell Transplantation Program enacted by Congress in 2005, the CIBMTR collects and maintains a standardized database of allogeneic transplants performed in the U.S. All U.S. transplant centers are required to provide outcomes data to the new national Stem Cell Therapeutic Outcomes Database. Centers in other countries are also encouraged to participate. Thus, all allogeneic HCT performed for PID in the U.S. in future will be reported to the CIBMTR. However, it is important that the data collection include valuable information on the transplant procedure and pre- and post-HCT clinical and immunological status, so that continuous monitoring of the efficacy of HCT vs. alternative forms of treatment can be performed, and prospective clinical trials properly designed.

Harmonization of USIDNET and CIBMTR forms is both feasible and desirable. Each database utilizes an extensive core form that includes clinical and laboratory information, and several disease-specific forms. To maximize utility of the USIDNET and CIBMTR databases for clinical research in PID, and coordinate activities with the European Stem Cell Transplantation Immunodeficiency Registry (SCETIDE) registry, harmonization of forms

and database procedures has been undertaken for SCID, WAS and CGD. The USIDNET and CIBMTR core and disease-specific forms were compared. Because some patients may not be entered into USIDNET and/or to CIBMTR databases, three simple forms were proposed: a pre-HCT form, an HCT form, and a post-HCT follow-up form. These could also be used for patients who receive alternative treatments, such as PEG-ADA or gene therapy. This approach will be extended to other PIDs. Tools to protect the patient's identity while ensuring cross-reference between the USIDNET and CIBMTR databases will be required.

Summary, conclusions and recommendations

SCID

The cumulative experience with transplants for SCID/CID in North America is sufficiently robust and mature to permit a comprehensive retrospective analysis and constitute a valuable resource which will provide a basis for developing prospective clinical trials. Similarly, incident cases are adequate for collaborative multi-center prospective studies. To compare in a meaningful way the extent and durability of recovery of cellular and humoral immunity resulting from different HCT approaches, similar lineage-specific chimerism and immunologic testing for all patients will be required. The following studies are proposed.

1. A comprehensive cross-sectional and retrospective analysis of SCID HCT survivors in North America to define immune reconstitution, late effects and quality of life in long term survivors.
2. A prospective study of SCID patients who receive HCT, including baseline and follow up testing, to compare patient outcomes across multiple participating centers.
3. Recognizing the value of earlier diagnosis of SCID, allowing HCT to be performed prior to onset of infectious complications, makes newborn screening a priority. Effectiveness of newborn screening for SCID should be sought through pilot programs; as soon as evidence-based SCID screening is available it should be included in the public health programs of all states.

Non-SCID

Starting with WAS and CGD as examples of non-SCID PIDs that may or may not be treated with HCT, recommendations for study are as follows.

1. A descriptive cross sectional study of HCT outcomes for WAS in North America.
2. A long term retrospective follow-up study of WAS patients who have received HCT, evaluating their clinical status, hematologic and immunologic status, chimerism, and potential late effects of the transplantation procedure.
3. Identification of WAS and X-linked thrombocytopenia (XLT) patients who have not received HCT, updating the description of their clinical, hematologic and immunologic functional status as they have been followed over time.
4. For CGD, an understanding of the natural history of the disease in the current era is needed along with a retrospective review of outcomes of HCT performed for CGD since 2000.
5. A prospective longitudinal study of patients with CGD who receive an HCT compared to age-matched patients with CGD of similar severity who were managed medically.

Collaborative studies by a consortium of institutions in North America is the only way to accomplish the investigations of long term survivors and newly diagnosed patients with PID

needing HCT. Core resources for laboratory testing and databases, as described above, could be shared across multiple clinical studies. Further, this group recommends that guidelines be developed for diagnosis and management of PID prior to performing HCT. Guidelines for the key issues to be addressed in determining the transplant approach for each individual patient with immune deficiency disease are also needed.

Acknowledgments

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Abbreviations used

ADA	Adenosine deaminase
BMT	Bone marrow transplant
CD	Cluster of differentiation
CGD	Chronic granulomatous disease
CHD	Chediak-Higashi disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CID	Combined immune deficiency
DCLR	DNA cross-link repair (gene)
E-rosette	(Sheep) erythroid rosette
FACT	Foundation for Accreditation of Cellular Therapy
FOX	Forkhead box
GVHD	Graft-versus-host disease
HCT	Hematopoietic (stem) cell transplant
HLA	Human leukocyte antigen
HLH	Familial hemophagocytic lymphohistiocytosis
HRSA	US Health Resources and Services Administration
Ig	Immunoglobulin
ILR	Interleukin receptor
IVIG	Intravenous immunoglobulins
JAK	Janus kinase
LCK	Leukocyte-specific protein tyrosine kinase
LIG	(Deoxyribonucleic acid) ligase
MUD	Matched unrelated donor
NADPH	Nicotine adenine dinucleotide phosphate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NK	Natural killer (cell)
PBMTC	Pediatric Blood and Marrow Transplant Consortium
PEG-ADA	Polyethylene glycol adenosine deaminase
PHA	Phytohemagglutinin
QOL	Quality of life
RAG	Recombinase activating gene
SBA	Soy bean agglutinin

SCETIDE	European Stem Cell Transplantation Immunodeficiency Registry
SCID	Severe combined immune deficiency
SRBC	Sheep red blood cell(s)
TCR	T-cell receptor
TREC	T-cell receptor excision circles
USIDNET	United States Immunodeficiency Network
WAS	Wiskott-Aldrich syndrome
WASP	Wiskott-Aldrich syndrome protein
XLP	X-linked lymphoproliferative disease
XLT	X-linked thrombocytopenia
XSCID	X-linked SCID
ZAP	Zeta-chain-associated protein kinase

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Table 1

Human SCID genotypes

Gene Defect	Defective Protein, Function	% of SCID[a]	Lymphoctye Profile		
			T[b]	B	NK
IL2RG (X-linked)	Common γ-chain (γc) of receptors for IL-2, 4, 7, 9, 15, 21	45-50%	−	+	−
ADA	Adenosine deaminase	16%	−	−/+	−
IL7R	α chain of IL-7 receptor	9%	−	+	+
JAK3	Janus kinase 3 activated by γc	6%	−	+	−
DCLRE1C	Artemis, T and B cell antigen receptor rearrangement	<5%	−	−	+
RAG1/2	T and B cell antigen receptor rearrangement	<5%	−	−	+
LIG4	DNA ligase IV antigen receptor rejoining	rare	−	+	+
CD45	Protein tyrosine phosphatase receptor (PTPRC), required for T, B activation by antigen	rare	−/low	+	+/low
TCRD, TCRE, TCRZ	CD3 δ, ε, and ζ deficiency with impaired T cell development	rare	−/low	+	+
LCK	Lymphocyte tyrosine kinase p56lck, T cell development and activation	rare	−/low	+	+
FOXN1	Forkhead box N1, thymus and hair follicle development (ortholog of nude mouse)	rare	−/low	+	+
Currently unknown	Unknown, including reticular dysgenesis and congenital anomaly syndromes with SCID	~10%	−/low	+/−	+/−

[a] Based on Buckley,[1] Cavazzana-Calvo et al.[26] and unpublished estimates (J. Puck).

[b] Some patients have substantial numbers of maternally derived T cells at time of diagnosis.

Table 2

Graft sources for HCT for PID

Graft	Patient subset	Transplant Features and Current Challenges
HLA-matched: genotypic related	SCID	No pre-HCT conditioning is needed to achieve T cell reconstitution. B cell reconstitution occurs in 25-30% of cases depending in part on genotype; other factors are probably also important but not well defined.
	Non-SCID	Immunosuppression and myeloablation are generally required, similar to HCT for non-PID, non-malignant indications. Full donor chimerism may be needed for some disorders to fully correct disease manifestations. Reduced toxicity regimens with mixed chimerism may be effective for some non-SCID PID. Further study is required.
Haplocompatible related with T cell depletion[a]	SCID: B+NK−	Without pre-HCT chemotherapy, donor T-cell engraftment is easily achieved, but donor B cells are unlikely to engraft and post-HCT B cell function may remain abnormal. Myeloablative chemotherapy increases the likelihood of both T and B cell reconstitution, but entails risks of short and long term sequelae especially in young infants and those presenting with severe infections. A haplocompatible related (parental) donor is readily available.
	SCID: B+/− NK+	Without pre-HCT immunosuppression, graft rejection may be increased unless maternal engraftment is present and the mother is used as the donor. With immunosuppression, T but not B cell immunity is likely to be restored. Myeloablation may yield more durable donor T-cell engraftment and an improved rate of donor B cell engraftment, but entails risks of short and long term sequelae especially in young infants and those presenting with severe infections.
	Non-SCID	Immunosuppression and myeloablative chemotherapy are required. Higher transplant related mortality with the use of haplocompatible donors and increasing availability of unrelated donor sources makes this option less desirable.
Closely matched unrelated donor (MUD)	SCID	Most HCT from unrelated donors use myeloablative conditioning regimens, which entail risks of increased transplant related mortality and late effects. It remains to be determined if fully allele matched unrelated donor HCT can be successful without any conditioning. However, GVHD is a greater risk than with matched related donors and the search process can take weeks to months.
	Non-SCID	High resolution allele matched unrelated donors appear to compare favorably to matched related donors, including rate of engraftment and extent and durability of immune reconstitution. High dose chemotherapy is required and acute and chronic GVHD likely. Clinical trials to assess survival as well as other outcomes are needed.
Unrelated cord blood (CB)	SCID	To date data are limited. High cell dose can usually be achieved and cells are readily available once a unit isx identified. High dose chemotherapy conditioning is usually given. Further studies are needed to define optimal conditioning regimens.
	Non-SCID	High dose chemotherapy is required. Risk of graft failure/rejection is 10-15%. Booster or second transplants from the same donor are not possible. Clinical trials to assess survival as well as other outcomes are needed.

[a]T-cell depletion of the graft may be accomplished by selection of the soy bean agglutinin (SBA) negative, sheep erythroid (E) - rosette negative fraction,[7] or by use of the Isolex or Miltenyi CD34+ cell selection devices with or without negative depletion of CD3+ cells.[12-14] To date, there has been no formal comparison between the different processing regimens, which result in different cell populations being infused and may have different outcomes.

Table 3

Laboratory testing

Baseline and Post-Transplant Laboratory Monitoring	
Time interval of evaluation: baseline; post-transplant at 3 months ± 2 weeks; 6 months ± 4 weeks; 12 months ± 4 weeks; years 2-5 post-transplant every 12 months ± 6 months; beyond five years post-transplantation every 3 years ± 1 year after the first five years.	
Recommended Studies	
Quantitative immunoglobulins	IgG, IgA, IgM with notation as to whether the patient is currently on IVIG and if so the dose and date of last administration
Isoagglutinins	Anti-A and anti-B titers (include patient and donor blood type)
Immunization	Provide vaccine used, pre and post (include time following immunization) titers, information regarding use of IVIG and if on IVIG replacement therapy, provide timing of the pre and post titers relative to IVIG administration
Lymphocyte proliferation	**Mitogen** **PHA:** provide percent of normal response = the patient raw data cpm (or dpm) of stimulated cells divided by the lowest cpm (or dpm) of the control (normal) response established for the performing lab **Other mitogens** including CD3 can be reported but are not essential
	Antigen (if performed) **Tetanus:** provide percent of normal response = the patient raw data cpm (or dpm) of stimulated cells divided by the lowest cpm (or dpm) of the control (normal) response established for the performing lab and date of last tetanus immunization **Candida:** provide percent of normal response = the patient raw data cpm (or dpm) of stimulated cells divided by the lowest cpm (or dpm) of the control (normal) response established for the performing lab
Flow cytometry	Testing for T cell and B cell surface antigens to be performed as follows; recommended to be performed centrally
	Surface antigens: The following should be evaluated at each interval and both percent and absolute number should be reported: CD3, CD4, CD8, CD19 (or CD20), CD3-/CD16/56
	Naïve T cells: CD4/CD45RA/CD45RO and CD8/CD45RA/CD45RO as three color studies reporting CD4+/CD45RA+ and CD8+/CD45RA+ (additional markers for naïve cells are not required but could be evaluated including CD27, CD31, CD62L and CCR7)
	B cell subset: CD19/CD27/anti-IgD as a three color tube (report CD19+/CD27+/IgD+ and CD19+/CD27+/IgD−)
Thymopoiesis	**TREC analysis:** Guthrie card blood spot method will be performed centrally.
Chimerism	T cell, B cell and myeloid chimerism should be performed at 12 months and the method used should also be reported.
Genotyping	All patients not previously genotyped should have a genetic diagnosis established.
Disease-specific assay	The following examples are provided **For SCID or CID:** Expression of disease-specific proteins in different lineages and at various developmental stages (eg, gamma chain in naïve vs. memory B cells in patients with mixed chimerism) Expression of MHC II molecules in different lineages (for Bare Lymphocyte Syndrome) **For WAS:** WAS protein levels **For CGD:** NADPH oxidase activity

Table 4

PIDD HCT clinical studies assessments

Clinical Studies Variables	
Genetic and phenotypic immune defect	Genetic variant and phenotype of SCID and other CID, WAS, CGD, or other PID
Patient demographics and treatment history	Age; age and time to diagnosis; age at HCT Clinical status at diagnosis and at HCT Infections prior to HCT Major organ dysfunction prior to HCT Intravenous IgG (IVIG) therapy Anti-microbial therapy Immuno-modulator therapy Transfusions Surgical procedures Autoimmune conditions **If SCID or CID, other therapy received:** PEG ADA for ADA deficient SCID Gene therapy for ADA deficient or X-linked SCID Fetal liver / thymus transplants
HCT regimen	Donor type HLA-matched; 1-2 allele disparate; haplotype disparate Sibling Related or unrelated adult Unrelated cord blood Transplant modification Unmodified marrow T-cell depleted – limited / extensive Pre-transplant conditioning Post-transplant prophylaxis against GVHD Prophylaxis and treatments of infection (including isolation) Decade in which treatment was instituted
Outcome-clinical	Clinical evidence of hematopoietic and immune reconstitution Acute and chronic GVHD Autoimmune disorders and inflammatory complications Neoplastic diseases Status including health, growth and development, QOL, the integument, cardiovascular, respiratory, gastrointestinal, endocrine and metabolic, musculoskeletal, dentition, and psychosocial development, neurobehavioral development including neurodevelopment and neurocognition