Workshop summary

Allogeneic hematopoietic cell transplantation for primary immune deficiency diseases: Current status and critical needs

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Allogeneic hematopoietic cell transplantation (HCT) has been used for 40 years to ameliorate or cure primary immune deficiency (PID) diseases, including severe combined immunodeficiency (SCID) and non-SCID PID. There is a critical need for evaluation of the North American experience of different HCT approaches for these diseases to identify best practices and plan future investigative clinical trials. Our survey of incidence and prevalence of PID in North American practice sites indicates that such studies are feasible. 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 patients with SCID 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 before compromise by infection; and (4) studies of the natural history of disease in patients who do or do not receive HCT for the non-SCID diseases of Wiskott-Aldrich syndrome and chronic granulomatous disease. 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. (J Allergy Clin Immunol 2008;122:1087-96.)

Key words: *Allogeneic hematopoietic cell transplantation, primary immune deficiency, clinical trial*

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 PID diseases 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 multicenter clinical trials. An interactive partnership of immunologists and HCT physicians with a special interest in PID and experts in

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Abbreviations used

ADA:	Adenosine deaminase
BMT:	Bone marrow transplantation
CGD:	Chronic granulomatous disease
CIBMTR:	Center for International Blood and Marrow Transplant Research
CID:	Combined immunodeficiency
GVHD:	Graft-versus-host disease
HCT:	Hematopoietic (stem) cell transplantation
NK:	Natural killer
PEG-ADA:	Polyethylene glycol adenosine deaminase
PID:	Primary immune deficiency
SCID:	Severe combined immunodeficiency
TCR:	T-cell receptor
USIDNET:	United States Immunodeficiency Network
WAS:	Wiskott-Aldrich syndrome

immunology laboratory methods, clinical outcomes assessment, databases, and analysis will be critical to success as we take advantage of opportunities offered for the treatment of these rare and uniquely challenging patients.

PID diseases are rare, monogenic disorders of cellular and humoral immunity. A subgroup of PID diseases with defects in lymphocytes or granulocytes can be cured with HCT, and this subgroup was the focus of the workshop. Severe combined immunodeficiency (SCID), with more than 14 distinct genetic variants (Table I)[1,2] 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 (CIDs) are partially permissive for T-cell development because they affect later stages in T-cell development (eg, ζ chain–associated protein kinase 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 PID diseases that are correctable by means of HCT. Examples include Wiskott-Aldrich syndrome (WAS), chronic granulomatous disease (CGD), hyper-IgM syndrome, Chediak-Higashi disease, familial hemophagocytic lymphohistocytosis, X-linked lymphoproliferative disease (XLP), and others. The workshop focused on 2 conditions having substantial HCT experience: WAS and CGD. In WAS,[3] an X-linked disorder with an estimated incidence of 1:250,000 live male births, a spectrum of mutations in the WAS protein gene gives rise to phenotypes affecting all hematopoietic lineages. CGD,[4] with 1 X-linked and 3 autosomal recessive genotypes, has an estimated overall incidence of 1:250,000 births. Genes mutated in CGD affect subunits of nicotine adenine dinucleotide phosphate 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 might 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.[5] Patients with PID were among the first to receive successful HCT 40 years ago.[6,7] SCID is unique in that patients completely lacking T-cell immunity do not require immunosuppressive chemotherapy before allogeneic HCT to achieve engraftment, especially when HLA-matched related donors are available (Table II).[8-11] HLA-matched related marrow grafts are the treatment of choice for all variants of SCID; however, 75% to 80% of patients lack such a donor. Transplantation of HLA haplotype–disparate parental marrow depleted of T cells by using soybean agglutinin/sheep red blood cells, with engraftment and reconstitution of both T- and B-cell function without graft-versus-host disease (GVHD), was demonstrated in children with SCID in 1983[11] and successfully reproduced in other centers.[12-15] Other approaches for processing haplotype-disparate donor hematopoietic cells that have subsequently been developed include depletion of lymphoid cells with mAbs and $CD34^+$ selection by using either the Isolex or Miltenyi CliniMacs systems.[9-11] Outcomes of HCT for SCID have improved over the years,[16-19] and matched unrelated donors,[20] including umbilical cord blood,[21] have been used to successfully treat patients with SCID. Chemotherapy might 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.[22,23] 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 because transplantation centers have developed their own protocols based on the 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, T-cell depletion, or both. Issues of pre-HCT conditioning, choice of donor when an HLA-matched sibling is not available, and clinical condition at the time of transplantation all need to be addressed in formal multicenter studies (Table II).

KEY QUESTIONS IN HCT FOR SCID

1. How are the extent and durability of T-cell, B-cell, and natural killer (NK) cell lineage–specific reconstitution and function after HCT affected by the transplantation regimen/strategy used? Is full donor chimerism[24] needed? When no pre-HCT conditioning is used, such as in the event when an HLA-matched sibling donor is available, most recipients will have T-cell, but not B-cell, reconstitution, except for patients with intrinsically normal B cells, as in IL-7 receptor gene 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 transplantation strategies? For very young infants, can an approach be developed that does not involve conditioning to be followed, if necessary, 2 to 3 years later with a booster HCT from the same donor, possibly using conditioning?[25] Are there alternative approaches to achieving immune reconstitution that do not involve toxic chemotherapy (eg, lymphoid-depleting, myeloid-depleting, or both mAbs)?
3. What is the overall survival and long-term clinical status of patients with SCID treated with HCT in North America?

TABLE I. Human SCID genotypes

Gene defect	Defective protein, function	Percentage of SCID*	Lymphocyte profile		
			T cell†	B cell	NK cell
IL2RG (X-linked)	Common γ-chain (γc) of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	45% to 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- and B-cell 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	+/−	+/−

*Based on Buckley[1] and Cavazzana-Calvo et al[2] and unpublished estimates (J. M. Puck).
†Some patients have substantial numbers of maternally derived T cells at the time of diagnosis.

Comparison of long-term health and organ-specific function of patients with different types of SCID who have received HCT by 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 transplantation strategies for late recurrence of immune deficiency, development of autoimmune diseases,[26] or development of specific chronic infections or malignancies is essential.

4. How do the specific SCID genotypes affect transplantation 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.[2] The genotype of SCID and its effects on lymphoid development might affect transplantation outcome by contributing to graft resistance, limiting lineage specific chimerism, and causing functional deficits in specific components of the immune system (eg, humoral immunity, NK cell function, or both).
5. What is the significance of the recipient's residual T-cell immunity before HCT, as observed in patients with CID, and how does this affect 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 posttransplantation GVHD (with or without GVHD prophylaxis)?
7. If an HLA-matched related graft is unavailable, can we develop an algorithm to identify the next-best graft source and HCT regimen for patients with SCID? Such an algorithm would need to encompass the issues discussed above.
8. Patients undergoing transplantation 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. Children with SCID undergoing transplantation without receiving myeloablative conditioning maintain a state of mixed chimerism in which T cells are of donor origin, whereas 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 patients with SCID 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 polyethylene glycol adenosine deaminase (PEG-ADA) enzyme replacement therapy for the treatment of adenosine deaminase (ADA)–deficient SCID, and the current status of gene therapy applied to ADA-deficient SCID.
10. What is the role of HCT versus gene therapy for a specific gene defect, if available? Gene therapy might provide an alternative to allogeneic HCT that avoids immunologic 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 patients with X-linked SCID demonstrates potential novel toxicities that need to be better understood and reduced by further preclinical research. Unlike allogeneic HCT, in which a single approach can be used for different genotypes of SCID or other PID diseases, gene therapy will require a dedicated program for each specific genetic cause. Implementation of this concept means that the replacement of genes for IL-2Rγc chain deficiency and ADA deficiency, for example, will require separate and distinct gene constructs and more of a personalized medicine approach requiring specialized research teams.

NEWBORN SCREENING FOR SCID

Children with SCID have infections by 3 to 4 months of life and do not survive past infancy unless they receive

TABLE II. Graft sources for HCT for PID

Graft	Patient subset	Transplantation features and current challenges
HLA-matched: genotype related	SCID	No pre-HCT conditioning is needed to achieve T-cell reconstitution. B-cell reconstitution occurs in 25% to 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, nonmalignant indications. Full donor chimerism might be needed for some disorders to fully correct disease manifestations. Reduced toxicity regimens with mixed chimerism might be effective for some non-SCID PID diseases. Further study is required.
Haplocompatible related with T-cell depletion*	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 might 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 might be increased unless maternal engraftment is present and the mother is used as the donor. With immunosuppression, T-cell, but not B-cell, immunity is likely to be restored. Myeloablation might 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 transplantation-related mortality with the use of haplocompatible donors and increasing availability of unrelated donor sources makes this option less desirable.
Closely matched unrelated donor	SCID	Most HCTs from unrelated donors use myeloablative conditioning regimens, which entail risks of increased transplantation-related mortality and late effects. It remains to be determined whether 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 with matched related donors, including rate of engraftment and extent and durability of immune reconstitution. High-dose chemotherapy is required, and acute and chronic GVHD is likely. Clinical trials to assess survival, as well as other outcomes, are needed.
Unrelated cord blood	SCID	To date, data are limited. High cell dose can usually be achieved, and cells are readily available once a unit is 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% to 15%. Booster or second transplantations from the same donor are not possible. Clinical trials to assess survival, as well as other outcomes, are needed.

*T-cell depletion of the graft can be accomplished by means of selection of the soybean agglutinin–negative, sheep erythroid rosette–negative fraction[8] or by use of the Isolex or Miltenyi $CD34^+$ cell selection devices with or without negative depletion of $CD3^+$ cells.[9-11] To date, there has been no formal comparison between the different processing regimens, which results in different cell populations being infused and can have different outcomes.

immune-reconstituting treatment, such as HCT or enzyme replacement with PEG-ADA. Those given diagnoses of SCID immediately after birth before developing infections have the best chance of survival and have fewer medical complications after HCT as compared with infants with SCID who are infected before diagnosis. Viral infections are particularly devastating to infants with SCID. Better recognition of SCID before the 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 in DNA extracted from dried blood spots.[27,28] T-cell receptor excision circles 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 the feasibility of prospective, population-based screening for the 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 the clinical utility of SCID screening. Athabascan-speaking Navajo and Apache Indians have a *DCLRE1C* (Artemis) gene founder mutation that causes radiation-sensitive SCID.[29] Approximately 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 DISEASES

Supportive measures, such as lifelong prophylaxis with immunoglobulin and antimicrobial agents and aggressive management of infections, have been the traditional treatment of non-SCID PID diseases.[30-32] However, premature mortality despite such treatment has led to use of HCT, which can be curative. HCT for these disorders shares a requirement for both T-cell immunosuppression and at least some degree of myeloablation (Table II). Although the 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 bone marrow transplantation (BMT) for WAS worldwide have been preconditioned with a protocol designed to be myeloablative, consisting of busulfan, cytoxan, and anti-thymocyte globulin.[33] Despite this, a fraction (<10%) reject their first transplant, and many (20% to 30%) patients are long-term mixed chimeras. Perhaps differences in busulfan pharmacokinetics in children compared with adults are a factor.[34] Older patients with more comorbidities who have received transplants from unrelated donors have had poorer survival after HCT than younger healthier patients. A recent retrospective study in Europe revealed significant rates of late post-HCT complications in patients with WAS, including autoimmune conditions, neuropsychological impairments, and late septic deaths in patients who had received splenectomy before 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 patients with WAS who have or have not received HCT?
2. How do the specific gene mutation, age, disease manifestations, and prior treatments (eg, splenectomy) influence risk versus 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 patient with CGD'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 nonmyeloablative 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 the 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 centers, and other known HCT centers) were obtained and analyzed. An estimate of new patients seen per year is as follows: SCID (overall), 50 to 60; WAS, 20 to 30; CGD, 10 to 20; familial hemophagocytic lymphohistiocytosis, 10 to 20; and other non-SCID, 15 to 20. Nearly 750 children with SCID have undergone transplantation, and more than 500 are alive. Among 250 patients with WAS who received HCT, nearly 200 are alive; similarly, 46 of the 59 patients undergoing transplantation for CGD are alive. Today, there is a broad distribution of HCT sites that treat patients with PID diseases, well beyond the few centers in which HCT methods for PID were initially developed. Patients are evenly distributed among centers reporting 1 to 5, 6 to 10, 11 to 25, 26 to 50, and more than 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 to be performed on all patients with PID diseases after HCT. Table III represents a consensus as to the 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 might also test more frequently. Use of central laboratories, reference laboratories, or both should be considered to provide quality assurance for data generated. Key issues for multicenter clinical studies include standardization of reagents and test methods to achieve comparability, costs, and logistic barriers to establishing centralized core laboratories 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 used for molecular genetic testing, although 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 QUALITY-OF-LIFE FORMS FOR PID

Adaptation of existing testing instruments and, if necessary, development of 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 US Immunodeficiency Network (USIDNET)

TABLE III. Laboratory testing

Baseline and posttransplantation laboratory monitoring	
Time interval of evaluation: baseline; after transplantation at 3 months ± 2 weeks; 6 months ± 4 weeks; 12 months ± 4 weeks; years 2-5 after transplantation every 12 months ± 6 months; beyond 5 years after transplantation every 3 years ± 1 year after the first 5 years	
Recommended studies	
Quantitative immunoglobulins	IgG, IgA, and IgM with notation as to whether the patient is currently receiving intravenous immunoglobulin, 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, pretiters and posttiters (include time after immunization), information regarding use of intravenous immunoglobulin and if receiving intravenous immunoglobulin replacement therapy, provide timing of the pretiters and posttiters relative to intravenous immunoglobulin administration
Lymphocyte proliferation	*Mitogen*
	PHA: provide percentage of normal response = the patient's raw data cpm (or dpm) of stimulated cells divided by the lowest cpm (or dpm) of the control (normal) response established for the performing laboratory
	Other mitogens, including CD3, can be reported but are not essential.
	Antigen (if performed)
	Tetanus: provide percentage of normal response = the patient's raw data cpm (or dpm) of stimulated cells divided by the lowest cpm (or dpm) of the control (normal) response established for the performing laboratory and date of last tetanus immunization
	Candida: provide percentage of normal response = the patient's raw data cpm (or dpm) of stimulated cells divided by the lowest cpm (or dpm) of the control (normal) response established for the performing laboratory
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 percentage and absolute number should be reported: CD3, CD4, CD8, CD19 (or CD20), CD3-/CD16/56.
	Naive T cells: CD4/CD45RA/CD45RO and CD8/CD45RA/CD45RO as 3-color studies reporting $CD4^+/CD45RA^+$ and $CD8^+/CD45RA^+$ (additional markers for naive cells are not required but could be evaluated, including CD27, CD31, CD62 ligand, and CCR7)
	B-cell subset: CD19/CD27/anti-IgD as a 3-color tube (report $CD19^+/CD27^+/IgD^+$ and $CD19^+/CD27^+/IgD^-$)
Thymopoiesis	T-cell receptor excision circle 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, γ chain in naive 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: nicotine adenine dinucleotide phosphate oxidase activity

databases (see below) will be important. Data collection for diverse aspects at baseline and after HCT is provided by these databases. Existing longitudinal forms used by the CIBMTR and USIDNET have been newly revised to harmonize and optimize collection of data relevant to HCT outcomes for patients with PID diseases. A comprehensive treatment history for each patient should be obtained (Table IV). Second, age-appropriate validated instruments for determining quality of life for patients with PID diseases who have received HCT must be selected and administered. Example instruments include the Pediatric Quality of Life Inventory (both child and parent versions available for various ages), the Short Form-36, and the Foundation for Accreditation of Cellular Therapy–BMT assessment tool.

DATABASES

Two databases relevant to PID clinical studies are available. First, USIDNET, sponsored by the National Institutes of Health, is a voluntary registry of patients with PID diseases. Second, under the US Health Resources and Services Administration C. W. Bill Young Cell Transplantation Program enacted by Congress in 2005, the CIBMTR collects and maintains a standardized database of allogeneic transplantations performed in the United States. All US transplantation 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 HCTs performed for PID diseases in the United States in the future will be reported to the

TABLE IV. PID 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 diseases
Patient demographics and treatment history	Age; age and time to diagnosis; age at HCT
	Clinical status at diagnosis and at HCT
	Infections before HCT
	Major organ dysfunction before HCT
	Intravenous immunoglobulin therapy
	Antimicrobial therapy
	Immunomodulator 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
	Pretransplantation conditioning
	Posttransplantation 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, quality of life, integument, cardiovascular, respiratory, gastrointestinal, endocrine and metabolic, musculoskeletal, dentition, and psychosocial development, neurobehavioral development including neurodevelopment and neurocognition

CIBMTR. However, it is important that the data collection include valuable information on the transplant procedure and pre- and post-HCT clinical and immunologic status, so that continuous monitoring of the efficacy of HCT versus alternative forms of treatment can be performed and prospective clinical trials can be properly designed.

Harmonization of USIDNET and CIBMTR forms is both feasible and desirable. Each database uses an extensive core form that includes clinical and laboratory information and several disease-specific forms. Harmonization of forms and database procedures has been undertaken for SCID, WAS, and CGD to maximize the utility of the USIDNET and CIBMTR databases for clinical research in PID and coordinate activities with the European Stem Cell Transplantation Immunodeficiency Registry. The USIDNET and CIBMTR core and disease-specific forms were compared. Because some patients might not be entered into the USIDNET, CIBMTR, or both databases, 3 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 PID diseases. Tools to protect the patient's identity while ensuring cross-referencing between the USIDNET and CIBMTR databases will be required.

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

SCID

The cumulative experience with transplantations for SCID/CID in North America is sufficiently robust and mature to permit a comprehensive retrospective analysis and constitute a valuable resource that will provide a basis for developing prospective clinical trials. Similarly, incident cases are adequate for collaborative multicenter 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 patients with SCID 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 before the onset of infectious complications, makes newborn screening a priority. The 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 might or might 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 patients with WAS who have received HCT, evaluating their clinical status, hematologic and immunologic status, chimerism, and potential late effects of the transplantation procedure.
3. Identification of patients with WAS and X-linked thrombocytopenia 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 HCT compared with age-matched patients with CGD of similar disease 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 patients with new diagnoses of PID diseases needing HCT. Core resources for laboratory testing and databases, as described above, could be shared across multiple clinical studies. Furthermore, this group recommends that guidelines be developed for the diagnosis and management of PID before performing HCT. Guidelines for the key issues to be addressed in determining the transplantation approach for each patient with immune deficiency disease are also needed.

APPENDIX 1

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