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Improving cellular therapy for primary immune deficiency diseases: Recognition, diagnosis, and management

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*See Appendix E1 in this article's Online Repository at www.jacionline.org for a list of expert opinion and workshop participants.

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Abstract

More than 20 North American academic centers account for the majority of hematopoietic stem cell transplantation (HCT) procedures for primary immunodeficiency diseases (PIDs), with smaller numbers performed at additional sites. Given the importance of a timely diagnosis of these rare diseases and the diversity of practice sites, there is a need for guidance as to best practices in management of patients with PIDs before, during, and in follow-up for definitive treatment. In this conference report of immune deficiency experts and HCT physicians who care for patients with PIDs, we present expert guidance for (1) PID diagnoses that are indications for HCT, including severe combined immunodeficiency disease (SCID), combined immunodeficiency disease, and other non-SCID diseases; (2) the critical importance of a high degree of suspicion of the primary care physician and timeliness of diagnosis for PIDs; (3) the need for rapid referral to an immune deficiency expert, center with experience in HCT, or both for patients with PIDs; (4) medical management of a child with suspicion of SCID/combined immunodeficiency disease while confirming the diagnosis, including infectious disease management and workup; (5) the posttransplantation follow-up visit schedule; (6) antimicrobial prophylaxis after transplantation, including gamma globulin administration; and (7) important indications for return to the transplantation center after discharge. Finally, we discuss the role of high-quality databases in treatment of PIDs and HCTas an element of the infrastructure that will be needed for productive multicenter clinical trials in these rare diseases.

Keywords

Allogeneic hematopoietic stem cell transplantation; gene therapy; primary immunodeficiency; clinical trial

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A collaborative network of North American investigators who care for patients with primary immunodeficiency diseases (PIDs), the Primary Immune Deficiency Treatment Consortium (PIDTC), will be launched in the near future. Representatives of this group met previously to identify critical needs and propose and prior-itize future clinical studies in hematopoietic stem cell transplantation (HCT) for PIDs.[1] At that time, to assess the feasibility of such studies, we surveyed a large number of centers as to previous experience with allogeneic HCT for PIDs. We discovered, in contrast to our expectation of referral to specialty centers, that many patients had in fact received HCT for PIDs in programs with experience of only a few cases of this type. The objectives of the present 1.5-day workshop were to summarize current expert opinion for the early detection and diagnosis and clinical management in anticipation of, during, and after definitive treatment for PIDs. Therapeutic options for these patients include allogeneic HCT, enzyme replacement, and gene therapy (GT). Our goal is to provide guidance for health care staff, including those having limited opportunity to care for patients with PIDs.

We have previously reviewed the many distinct variants of severe combined immunodeficiency (SCID; see Table I of our previous publication).[1] In addition, there are a number of combined immunodeficiency diseases (CIDs; eg, NEMO, ZAP-70 deficiency, and IL-12R/IFN-γR

deficiency) and non-SCID PID diseases (eg, Wiskott-Aldrich syndrome [WAS], chronic granulomatous disease [CGD], and cartilage hair hypoplasia) that are of sufficient immunologic severity that consideration of HCT also is appropriate. CIDs might be partially permissive for T-cell development because they affect later stages in T-cell development or are due to hypomorphic mutations. Because even experts in PIDs have difficulty in defining the spectrum of CIDs, we present in Table I the group expert opinion of diagnostic criteria and findings supportive of CID. In preparation for the workshop and development of this article, 5 working groups were established to focus on diagnosis of SCID, pre-HCT management, management of non-SCID PIDs, post-HCT management, and the role of databases in future clinical trials. To identify factors affecting the diagnosis and treatment of children with SCID and to determine current practices for managing children with SCID/CID before and after transplantation, 3 separate surveys were done of immunologists and transplantation physicians from the United States and Canada. The discussions of the working groups, as well as results from the surveys, helped to form the basis of this report.

EARLY SUSPICION FOR A DIAGNOSIS OF PID

Recognition of the features of congenital immunodeficiency

Early diagnosis (Fig 1) makes possible early definitive therapy and avoids the complications of pretreatment infections that damage the lungs, liver, kidneys, and other vital organs.[2-4] Timely diagnosis critically depends on the ascertainment of family history, if positive, and the awareness of primary caregivers of the early signs, symptoms, and laboratory features that indicate a potentially serious underlying problem of cellular immunodeficiency.[5] Once a diagnosis is made, powerful reconstitution measures must be put into place without delay to provide an immune system sufficiently robust to enable survival and good health.

Role of the primary care physician in diagnosis of SCID

The key to a timely diagnosis of PID is suspicion by the primary care provider (Fig 2). At the same time, a timely diagnosis has the potential to be life-saving for the patient, with enormous benefit for the child involved, the family, and society in general. Infants undergoing transplantation in the first 3.5 months of life have a much higher rate of survival than those undergoing transplantation later.[6] If not the primary care pediatrician, it is usually the allergist, pulmonologist, and/or intensive care physician or gastroenterologist who first comes in contact with a child with SCID/CID.

It is possible to identify children with a cellular immune defect with a few relatively simple tests and procedures. Many cases of T-cell immunodeficiency can be predicted on the basis of obtaining an absolute lymphocyte count (ALC) either at birth or in the first 3 months of life.[6] T cells normally comprise 70% of circulating lymphocytes. Because most infants with SCID lack T cells, they are often (but not always) lymphopenic. Correct interpretation of the ALC requires evaluation in the context of age-specific reference intervals.7 The ALC reference interval is 3,400 to 7,600 cells/mm^3 for healthy newborns. A low lymphocyte count for age and low/absent quantitative IgA and IgM levels, although not always present in patients with SCID/CID, should raise the possibility of a severe immunodeficiency. IgG is not useful in young infants because it is largely maternal. In addition, a chest radiograph is indicated to look for a thymic shadow, which is often absent in patients with SCID. Not to be forgotten is the value of performing a physical examination of the patient, noting growth and development, abnormal physical findings (eg, DiGeorge facies), and the presence or absence of tonsils or lymph nodes. With the X-linked form representing nearly 45% of cases of SCID, occurrence in maternal male relatives is particularly important.[8] A history of recurrent or persistent infections is important. Patients with opportunistic infections, such as *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia (PCP), or viral pneumonias with, for example,

cytomegalovirus (CMV), respiratory syncytial virus, or parainfluenzae that do not resolve must raise the possible diagnosis of SCID/CID. These patients often present with failure to thrive associated with chronic diarrhea and persistent skin rashes.

If there appears a red flag of suspicion of immunodeficiency, the crucial next step by the primary care provider is referral of the patient to an immune deficiency specialist who is expert in the diagnosis, treatment, and management of cellular immunodeficiencies. This individual will have the knowledge to quickly perform definitive sophisticated tests to rule in or out the presence of SCID and to arrange for HCT if the diagnosis is confirmed.

Role of the immune deficiency expert in diagnosis of SCID

With referral to the immune deficiency specialist (Fig 3), the patient will have a more extensive evaluation of his or her lymphocytes by means of flow cytometry using antibodies to CD3, CD4, CD8, CD19, and CD16/CD56 to determine whether the infant has normal percentages of T cells and subsets, B cells, and natural killer (NK) cells and to determine whether there are naive ($CD45RA^+$) T cells present.[9] The function of T cells will be determined by means of lymphoproliferation *in vitro* in response to stimulation with mitogens, such as PHA, concanavalin A, and pokeweed mitogen, and to antigens, such as *Candida* species and tetanus (the latter only if the infant has been immunized). Infants with severe T-cell defects will have low numbers of all T-cell subsets; either high, normal, or low numbers of B cells; absent, normal, or high numbers of NK cells; and very low (usually <10% of normal) or no *in vitro* lymphocyte proliferation. Although transplacentally transferred maternal T cells can rarely result in a normal ALC, the transferred cells do not afford immune reconstitution for the infant. 10 General classes of potential gene defects can be predicted based on the immunophenotypic pattern observed in the patients with SCID,5 although exceptions are well described. Although not required for HCT, genomic DNA sequencing of specific SCID genes can enable the immunologist to better inform parents of the potential future outcomes of their child once treated with HCT and to provide genetic counseling.[11] A subgroup of patients with SCID (Artemis and ligase IV deficiency) who lack both T and B cells ($T^-B^-NK^+$ SCID) will have a defect that makes them more susceptible to alkylating agents and ionizing radiation, which are often used as conditioning agents for HCT.

Newborn screening for PIDs

Universal newborn screening for SCID is not yet available, although pilot trials are in progress. It has been suggested that every newborn should have a complete blood count with differential performed to detect those who might have a serious cellular immunodeficiency. If lymphopenia is found, then flow cytometry should be performed to determine whether T cells are missing. Another method of gaining similar information by using heel-stick blood already obtained in the newborn nursery on every child would be to assay for T-cell receptor excision circles, which are byproducts of thymocyte antigen receptor gene rearrangement.[12,13] Low or absent T-cell receptor excision circles indicate impaired production of new naive T cells. There are currently 3 newborn screening pilot studies ongoing in Wisconsin,[14] Massachusetts, and the Navajo Indian Reservation using the latter technology.

Referral to a center with experience in PIDs

Because children with a high suspicion of having SCID/CID need to be managed carefully and quickly, referral to an immune deficiency specialist and transplant center with experience in diagnosing and treating PIDs should be made as soon as possible. When a diagnosis of SCID is made, the immune deficiency specialist, transplantation physician, or both proceeds rapidly to prepare the patient for HCT or, in certain settings, enzyme replacement or GT (see Fig E1 in this article's Online Repository at www.jacionline.org). It is recognized that transplantation options for patients with SCID vary considerably, ranging from infusion of HLA-matched

sibling bone marrow or T cell–depleted, HLA-mismatched, related stem cells without prior conditioning[15] or post-HCT immunosuppression, to infusion of T cell–replete unrelated cord blood or adult stem cells after immunosuppressive or myeloablative conditioning. Pretransplantation conditioning regimens, method and use of T-cell depletion, and/or graft-versus-host disease (GVHD) prophylaxis vary widely among transplantation centers. Transplantation regimens are often influenced by the genetic cause of the immunodeficiency, the degree of HLA matching between donor and host, the clinical status of the patient, and the technology and experience available for hematopoietic stem cell processing. Tissue typing of the patient and close relatives or the search for matched related donors, as well as using national resources to search for a matched unrelated donor or cord blood, will enable determination of the best donor of hematopoietic stem cells. In addition, haploidentical donors (typically a parent) are an important source for HCT after removal of mature T cells by means of negative selection with soy lectin and sheep erthrocytes[16] or anti–T-cell mAbs17 or by means of positive selection with anti-CD34 mAbs.17,18 Different centers have individual approaches to the type of donor cells to use and whether to use no conditioning or to provide myeloablative or nonmyeloablative conditioning, prophylactic GVHD treatments, or both to the patient.[6,17-20]

Similarly, if a therapeutic alternative to HCT is considered preferable after evaluation of the patient with a PID, then referral to the appropriate treatment specialists should be made. For example, options available for treatment of SCID caused by adenosine deaminase (ADA) deficiency include enzyme replacement therapy with pegylated, bovine polyethylene glycol adenosine deaminase or autologous hematopoietic stem cell GT.[21] GT for ADA SCID has been shown to be effective for a cohort of 10 children22 without the complications of insertional mutagenesis that were seen after GT in patients with X-linked SCID.23 GT for ADAwas effective for ADA SCID, even after treatment failure with pegylated ADA.24

MANAGEMENT OF SCID/CID BEFORE HCT

Management of the child with suspected SCID/CID while confirming diagnosis

Supportive care of a patient with SCID/CID should begin at the time of initial contact, when the suspicion of severe immunodeficiency first arises (Table II). Meanwhile, certain prophylactic measures both in terms of isolation and pharmacologic therapy should be instituted. The child should be placed in protective isolation with good handwashing procedures to minimize exposure to hospital-acquired infections. Prophylaxis for PCP and bacterial infections should be started as soon as possible, and other fungal and viral prophylaxis should also be considered. Avoidance of breast-feeding is probably one of the more difficult measures to institute, given the importance of this to both the infant and mother. The likelihood of transmission of CMV to babies with SCID from breast milk is sufficiently significant that many immunologists/transplantation centers recommend stopping breast-feeding pending determination of the mother's CMV serologic status. Live attenuated viral vaccines, such as rotavirus[25] and varicella, should be avoided, including vaccination of siblings with varicella. Every effort should be made to identify infections that might be relatively asymptomatic in patients with PIDs because of a lack of immune response in this highly susceptible patient population. Treatment should be instituted when infectious organisms are identified while efforts are underway to select a donor for corrective cellular therapy. Previous therapies, such as blood transfusions, are also important factors in patient morbidity. All blood products (platelets and erythrocytes) should be CMV seronegative, leukodepleted, or both to prevent transmission of CMV and irradiated to eliminate the risk of fatal transfusion-associated GVHD.[26,27]

Management of infectious diseases in the child with possible SCID/CID

All children, even if asymptomatic, should have screening studies for a variety of viral agents (Table III). Depending on laboratory studies and/or clinical indicators, such as increased transaminase values or respiratory symptoms, various progressively invasive procedures are recommended. Importantly, because of their T- and B-cell defects and absent immune responses, these patients are often relatively less symptomatic for any given degree of infection. Chest radiographic results might be normal, whereas high-resolution chest computed tomographic scans will show significant parenchymal disease. Bronchoalveolar lavage (and sometimes lung biopsy) might be the only way to diagnose PCP and viral pneumonias because sputum is not very sensitive or practical for detecting these organisms in infants and young children. Identification and treatment for respiratory syncytial virus, adenovirus, CMV, and EBV infections is critical.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH NON-SCID PIDs

Non-SCID PIDs that are correctable by means of HCT, including WAS, CGD, familial hemophagocytic lymphohistiocytosis (HLH), and other diseases, are presented in Table E1 in this article's Online Repository at www.jacionline.org. The risks of HCT must be compared with the expected long-term clinical outcome without HCT. For example, in patients with familial HLH, the prognosis without HCT is extremely poor. Unfortunately, the risk/benefit ratio over the short-term for WAS and CGD can be difficult to predict in the less severe phenotypes because of insufficient natural history information and known variability in clinical course for these disorders. In general, for these HCT procedures, an HLA-matched family donor or matched unrelated donor and myeloablative conditioning have been used. Clinical investigation of the efficacy and safety of reduced-intensity regimens compared with standard myeloablative regimens is needed. GT clinical trials have been and/or are being performed for CGD, leukocyte adhesion deficiency type 1, and WAS and have generated results that encourage further development of gene transfer as an alternative therapeutic option for non-SCID PID (see Table E1).

MANAGEMENT OF CHILDREN WITH PIDs AFTER HCT OR OTHER DEFINITIVE TREATMENT

Posttreatment antimicrobial prophylaxis, reimmunization, and long-term follow-up of children with SCID and other PIDs after HCT or GT

It is expected that patients undergoing transplantation for severe immunodeficiencies will be closely monitored by the transplantation center for at least the first year after HCT or GT (see Table E2 in this article's Online Repository at www.jacionline.org). After this time, much of the patient's care might shift to the referring immune deficiency specialist or primary care physician because of proximity to the patient's home or insurance constraints. The posttransplantation guidelines suggested for years 1 to 5 and beyond are intended to provide information about potential problems that might arise during those time periods that are unique to patients with PIDs.[28] If possible, during years 1 to 5, the patient should return to the transplantation center at least once a year for an evaluation of the immune system. Patients can experience autoimmune disease[29,30] or atypical GVHD. The presentation of atypical GVHD includes cytopenias, steroid-responsive pneumonitis, and kidney disease, as well as the more typical skin, liver, and gastrointestinal disease.[31-33] If the patient has recurrent or unusual infections or any manifestation of GVHD, including diarrhea, they should be referred back to the transplantation center. After 5 years, the patient should return to the transplantation center at least once every 2 years. The transplantation center will continue to monitor immune reconstitution and chimerism and medical problems particular to this later time period after HCT.

The duration and intensity of antimicrobial prophylaxis for patients with PIDs after HCT depends on the expected time course of immunologic reconstitution and the patient's pre- and post-HCT infectious disease history. Table E3 (available in this article's Online Repository at www.jacionline.org) provides expert opinion regarding antimicrobial prophylaxis of PCP, HSV, and EBV; yeast and mold[34]; and CMV after HCT for PIDs. As described in Table E4 (available in this article's Online Repository at www.jacionline.org), gamma globulin supplementation is provided for antibacterial prophylaxis in the early posttransplantation period. To determine when to discontinue gamma globulin, a variety of criteria are considered, including duration of therapy; trough levels of serum IgM, IgG, or both; and/or the ability to make antigen-specific antibody after immunization. More stringent criteria for discontinuation are used for patients having pre-existing or ongoing infection. Also, for patients receiving immunosuppressive therapy for GVHD or autoimmune conditions, gamma globulin replacement should be continued. The majority of patients lacking donor B cells will require immunoglobulin replacement for life. For patients with PIDs receiving T-replete HCT and preparative conditioning, many of the guidelines developed for allogeneic HCT for malignant indications apply. Much of this guidance, including medications and dosages, has been recently updated.[35] However, many patients with SCID who receive HLA-matched sibling grafts will not have B-cell reconstitution because they are not conditioned. Also, for children with SCID who receive T cell–depleted, HLA-mismatched, related family donor transplants with or without prior cytoreduction, a significantly different strategy of management is needed due in part to the lesser extent of B-cell chimerism achieved.

General principles of management after HCT for PIDs

Critical issues in post-HCT management for PIDs include the antimicrobial regimens used and duration of prophylaxis, which might vary depending on the type of HCT regimen received and the standard practices of the center. In general, CD4 cell counts of greater than 200/μL and PHA proliferative responses of greater than 50% of normal control values are used as cellular immunity parameters to discontinue prophylaxis (see Fig E2 in this article's Online Repository at www.jacionline.org). For patients with acute or chronic GVHD, antimicrobial prophylaxis is continued until these milestones have been met and immunosuppressive therapy has been discontinued. Patients having pre-existing infections will require specific treatment until clinical, imaging, and laboratory assessments of disease are negative. Growth and development should be monitored carefully. If the patient received a preparative regimen, endocrine problems, neurocognitive delays, osteopenia, and dental problems can arise.

When to return to the transplantation center after discharge

Importantly, we list problems that should elicit immediate return to the transplantation center after HCT for evaluation and recommendations as to appropriate care (see Fig E3 in this article's Online Repository at www.jacionline.org). These include any need for hospitalization, management of GVHD or critical infection, and indicators of reduced numbers or function of cellular immunity, humoral immunity, or both after HCT.

Long-term outcomes after HCT for SCID

Multiple advances in the diagnosis and treatment of SCID and other PIDs have occurred in the last decade, resulting in growing numbers of affected children surviving long-term.[28,36] Observation of the long-term outcomes of HCT-treated patients with SCID is now receiving special emphasis.[28,37-39] Complications of HCT or pre-existing infections, such as chronic GVHD, incomplete immune reconstitution, or neurodevelopmental delay, require careful assessment by the immunologist and related subspecialists. There are recently recognized concerns for the mental health, quality of life, and well-being of patients rescued by heroic measures and their families. In the long-term follow-up reports now appearing in the literature,

the encouraging news is that immunodeficient children treated with HCT have achieved educational goals, and some have produced normal off-spring.[4,28,37] Genetic counseling of the parents before and after transplantation is important for family expectations of their child's overall health and what clinical problems to expect, including neurodevelopmental problems, and long-term immune function.[37,39,40]

ROLE OF DATABASES

It is anticipated that a close interaction between 2 databases that collect information about patients with immune deficiency, the Center for Blood and Marrow Transplant Research (CIBMTR) and the United States Immunodeficiency Network (USIDNET), will facilitate operations of the PIDTC in the study of outcomes for patients with PIDs who receive HCT as primary therapy. Although the CIBMTR operates under a Department of Health and Human Services mandate to collect outcomes for all patients who receive either related or unrelated allogeneic HCT therapy in the United States, the USIDNET is a voluntary registry of patients given diagnoses of PIDs. The 2 databases collaborated in 2008 to harmonize data collection forms for pretransplantation and posttransplantation evaluation of patients with immune deficiency, including SCID, CGD, and WAS. As of the time of publication of this report, these revised forms are available online at the CIBMTR Web site and for electronic submission through CIBMTR's FormsNet application. In addition, USIDNET and CIBMTR have agreed to generate new and/or harmonized data forms for 4 additional types of PID, in particular familial HLH, X-linked lymphoproliferative syndrome, DiGeorge syndrome, and pigmentary dilution disorders. A strategy similar to that used for the SCID, WAS, and CGD forms will be followed to develop harmonized forms for these disorders. A team of content experts and data collection specialists representing USIDNET and CIBMTR will work together to revise current data collection forms or develop new forms using standard formats and incorporate data elements essential for understanding outcomes of treatment for these rare diseases. The purpose of this new series of disease-specific forms will be to collect data to perform cross-sectional and longitudinal studies and to compare outcomes in patients who receive HCT or thymic transplantation (for DiGeorge syndrome) versus alternative treatments. The patients' data will be collected by USIDNET and CIBMTR, and they will be shared in an agreed standard format to create final unified datasets for analytic purposes. Data will be shared for single studies that might include both patients undergoing transplantation and those not undergoing transplantation.

Longer term, it is anticipated that USIDNET and CIBMTR will endeavor to develop a uniform strategy for data sharing. In addition, in discussion at the current workshop, it became apparent that enhancement of USIDNET as a resource would also benefit collaborative studies of patients with PIDs who receive other primary therapy. These cases are sufficiently rare that multicenter and international collaborations are essential to develop a foundation of knowledge about current practice that can be used to develop the prospective clinical research protocols of the future. Availability of efficient resource databases will be critical to the success of such collaborative projects.

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

The expert opinion provided here for diagnosis and management of PIDs before, during, and after HCT represents the career experience of more than 30 immunologists and transplantation physician investigators. Although it would be desirable to provide more formal guidelines, PIDs are rare, and this level of evidence-based recommendation is not yet available. We are hopeful that the collaborative studies of the PIDTC will contribute to the development of a database sufficiently robust that evidence-based guidelines can be provided in the future.

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APPENDIX E1

EXPERT OPINION AND WORKSHOP PARTICIPANTS

Expert opinion

Early suspicion for a diagnosis of PID. Rebecca H. Buckley, Thomas A. Fleischer, Jennifer M. Puck (Co-Chairs), Jacob J. H. Bleesing, Marcia Boyle, Kimberly Risma, John M. Routes, William T. Shearer, Troy R. Torgerson

Management of SCID/CID before HCT. Morton J. Cowan, Chaim M. Roifman (Co-Chairs), Lauri Burroughs, Charlotte Cunningham-Rundles, Suk See DeRavin, Christopher C. Dvorak, H. Bobby Gaspar, Naynesh Kamani, Neena Kapoor, Donald B. Kohn, Joshua D. Milner, Luigi D. Notarangelo, Richard J. O'Reilly, Jennifer M. Puck, Paul Szabolcs

Diagnosis and management of patients with non-SCID PIDs. Fabio Candotti, Elizabeth M. Kang, Kimberly E. Nichols (Co-Chairs), Michael H. Albert, Elie Haddad, Hans D. Ochs, Jordan Orange, David J. Rawlings

Management of children with PIDs after HCT or other definitive treatment. Mary Ellen Conley, Trudy N. Small (Co-Chairs), Javier Chinen, Louise M. Markert, Sung-Yun Pai, Kirk R. Schultz, Paul Szabolcs

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TABLE E1

Non–SCID PIDs: Management

	HCT			
Disease and confirmatory diagnostic criteria	**Indication to HCT**	**Recommended conditioning**	**Chimerism**	**Non-HCT and/or pre-HCT management**
Cartilage hair hypoplasia				
Mutation analysis of the *RMRP* gene	HCT is recommended in patients with severe T-cell deficiency, especially if MFD or MUD is available. Haploidentical transplants might also have a role in	Limited published experience for HCT is based on conditioning with Bu +Cy.[E1,E2] Studies are needed to evaluate the efficacy of the RIC regimen that would be preferred in cases with significant pretreatment risk factors.	Mixed donor chimerism is not expected to have negative consequences in this disease.	Supportive and/or pretreatment management (eg, TMP/SMX or IVIG/SCIG) for numeric or functional T-cell deficiency and antibody defects. GT is not available.

Disease and confirmatory diagnostic criteria	HCT			
	Indication to HCT	Recommended conditioning	Chimerism	Non-HCT and/or pre-HCT management
	the management of this disease, when clinically appropriate. Importantly, HCT will not improve skeletal abnormalities.			
CD40 ligand deficiency				
Mutation analysis of the *CD40LG* gene Clinical and laboratory diagnostic criteria have been published[E4] and are available on the Web site of the European Society for Immunodeficiency (http://www.esid.org/workingparty.php?party=3&sub=2&id=73).	HCT is recommended if MFD is available. Transplants from other donor sources (MUD or haploidentical donors) should be strongly considered in the presence of severe disease complications.	Published experience for HCT is based on conditioning with Bu+Cy.[E3] Studies are needed to evaluate the efficacy of the RIC regimen that would be preferred in cases with significant pretreatment risk factors.	Mixed donor chimerism is likely to be beneficial.	General: TMP/SMX, Supportive and/or pretreatment management (eg, TMP/SMX or IVIG/SCIG) should be implemented together with careful avoidance of and surveillance for *Cryptosporidium* species infection. If present, *Cryptosporidium* species infection should be aggressively treated to eradicate this pathogen. GT is not available.
Chediak-Higashi syndrome				
Mutation analysis of the *LYST* gene Clinical and laboratory diagnostic criteria are available on the Web site of Genereviews (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=chediak-higashi).	HCT is recommended if MFD or MUD is available. Haploidentical transplants might also have a role in the management of this disease when clinically appropriate.	Published experience for HCT is mostly based on conditioning with Bu+Cy or TBI+Cy. Late neurologic complications are not prevented despite successful HCT. Studies are needed to evaluate the efficacy of the RIC regimen that would be preferred in cases with significant pretreatment risk factors.	Mixed donor chimerism is likely to be beneficial.	Induction of remission of accelerated phase before HCT seems to improve disease-free survival.[E5,E6] GT is not available.
CGD				
Diagnosis can be confirmed with mutation analysis of the *gp91, p22, p47,* or *p67 phox* genes. Clinical and laboratory diagnostic criteria have been published[E4] and are available on the Web site of the European Society for Immunodeficiency (http://www.esid.org/workingparty.php?party=3&sub=2&id=73).	HCT is recommended for gp91phox-deficient patients (X-CGD) if MFD is available. Transplants of X-CGD from MUD or of other genetic variants from MFD or MUD are considered in the presence of severe disease complications or poor compliance to medical management. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.	Published experience for HCT is mostly based on conditioning with Bu+Cy,[E7,E8] although the use of nonmyeloablative conditioning has also been reported[E9] as an essential option in cases with significant pre-HCT risk factors.	Mixed donor chimerism is likely to be beneficial.	Supportive and/or pretreatment management with antibiotic and antifungal prophylaxis should be implemented together with regular imaging and medical follow-up. Aggressive treatment of infections with antibiotics, antimycotics, leukocyte transfusions, and G-CSF is warranted. Steroid treatment is useful for cases of severe inflammation (ie, pulmonary disease and colitis). Administration of IFN-γ can be recommended, although there is no consensus on its long-term efficacy in diminishing the risk of severe infections. GT is available and has been used both as a curative attempt and as a bridge to HCT in patients with severe infections.[E10,E11]
Griscelli syndrome type 2				

	HCT			
Disease and confirmatory diagnostic criteria	**Indication to HCT**	**Recommended conditioning**	**Chimerism**	**Non-HCT and/or pre-HCT management**
Diagnosis can be confirmed with mutation analysis of the *RAB27A* gene.	HCT from any available donor source is recommended for all patients who have not experienced severe neurologic involvement. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.	Published experience for HCT is mostly based on conditioning with Bu + Cy,[E12,E13] although the use of nonmyeloablative conditioning can be considered.	Mixed chimerism is sufficient to stabilize disease.	Dexamethasone, VP16 and cyclosporine. Remission of hemophagocytic syndrome/ accelerated phase should be attempted before performing HCT. Transplantation should not be postponed because of only partial remission. GT is not available.
HLH				
Diagnosis can be confirmed with mutation analysis of the *PRF1*, *UNC13D*, or *STX11* genes, although mutations of these are not found in all patients with HLH. Clinical and laboratory diagnostic criteria are available on the Web site of Genereviews (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hlh).	HCT from any available donor source is recommended as soon as the hemophagocytic syndrome is controlled. Neurologic disease is associated with a poor outcome.	Published experience for HCT is mostly based on conditioning with Bu+Cy,[E13,E14] although the use of nonmyeloablative conditioning can be considered.	Mixed chimerism with ≥20% of donor leukocytes is associated with sustained remission of the disease.	Dexamethasone, VP16 and cyclosporine. Complete remission of hemophagocytic syndrome/ accelerated phase should be attempted before performing HCT, but transplantation should not be postponed because of only partial remission. GT is not available.
IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome				
Diagnosis can be confirmed with mutation analysis of the *FOXP3* gene. Clinical and laboratory diagnostic criteria are available on the Web site of Genereviews (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=ipex).	HCT from MFD or MUD is recommended and should preferably be performed early before onset of diabetes.	Published experience for HCT is limited and is based on RIC.	Partial donor chimerism can result in sustained remission of the disease.[E15-E21]	Pre-HCT management with T-cell inhibitors, such as tacrolimus, rapamycin, and cyclosporine A, possibly combined with other immunosuppressive drugs (eg, azathioprine, methotrexate, or steroids) can be useful. Rituximab can be beneficial for autoantibody-mediated autoimmunity. GT is not available.
Leukocyte adhesion deficiency type 1				
Flow cytometric analysis of CD18 expression on leukocytes and confirmation with mutation analysis of the CD18 gene (*ITGB2*) Clinical and laboratory diagnostic criteria have been published[E4] and are available on the Web site of the European Society for Immunodeficiency (http://www.esid.org/workingparty.php?party=3&sub=2&id=73).	HCT from MSD or MUD is recommended because of long-term disease risks. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.	The majority of published HCT experience is based on myeloablative regimens, although recent use of RIC has suggested an improved safety profile.	Mixed donor chimerism at even relatively low levels is likely beneficial for infection control and can result in lack of significant symptoms.[E22]	Initial GT attempts have been unsuccessful.[E23] However, with optimization of vector choice and transduction conditions, gene transfer is likely to be beneficial in the future.
WAS				

	HCT			
Disease and confirmatory diagnostic criteria	**Indication to HCT**	**Recommended conditioning**	**Chimerism**	**Non-HCT and/or pre-HCT management**
Diagnosis is aided by flow cytometric analysis of WAS protein expression in leukocytes and can be confirmed with mutation analysis of the *WAS* gene. Clinical and laboratory diagnostic criteria have been published[E4] and are available on the Web site of the European Society for Immunodeficiency (http://www.esid.org/workingparty.php?party=3&sub=2&id=73).	HCT from MFD or MUD is recommended. The preferred donors are MFD/MUD (70% to 80% survival) versus haploidentical donors (40% survival).	Because long-term mixed chimerism is associated with autoimmune complications,[E24] it is generally accepted that myeloablative conditioning should be used.	Long-term mixed chimerism is undesirable because it is associated with autoimmune complications.	Supportive and/or pretreatment management with antibiotic prophylaxis (eg, TMP/SMX) and IVIG/SCIG should be implemented in severe cases. Topical emollients and steroids are useful for treatment of eczema. Exacerbations of thrombocytopenia can be managed with systemic steroids and high-dose IVIG. Acute bleeding with platelet numbers <10,000/μL requires platelet transfusions. For autoimmune processes, danazol and rituximab are available options. GT trials are at the early stages.[E25]
WAS–X-linked thrombocytopenia				
See above.	The decision to perform HCT might be made based on biomarkers (WAS protein expression levels, response to vaccination, and immune laboratory values) or case-specific clinical reasons.	Likely myeloablative regimens.		There is lack of consensus on how to manage patients with WAS who present with thrombocytopenia with or without eczema in the absence of recurrent infections, autoimmunity, and malignancy. In addition to measures described above for the thrombocytopenia seen in severe WAS cases, splenectomy might be considered for intractable bleeding complications but can result in higher rate of infectious complications. Antibiotic prophylaxis after splenectomy is mandatory. Thrombopoietic agents (eg, eltrombopag) are under study. Current and planned GT trials exclude patients with mild WAS from enrollment.
X-linked lymphoproliferative syndrome				
Diagnosis can be confirmed with mutation analysis of the *SH2D1A* or *XIAP* genes. Clinical and laboratory diagnostic criteria have been published[E4] and are available on the Web site of the European Society for Immunodeficiency (http://www.esid.org/workingparty.php?party=3&sub=2&id=73).	HCT from MSD or MUD is recommended, preferably before development of lymphoma, hemophagocytic syndrome, or other disease complications. Haploidentical transplants might also have a role in the management of this disease, when clinically appropriate.	Studies are needed to evaluate the efficacy of the RIC regimen that would be preferred in cases with significant pretreatment risk factors.	Mixed donor chimerism is likely to be beneficial and is not expected to have negative consequences in this disease.	GT is not available.
Severe congenital neutropenia				

	HCT			
Disease and confirmatory diagnostic criteria	**Indication to HCT**	**Recommended conditioning**	**Chimerism**	**Non-HCT and/or pre-HCT management**
Acquired truncation mutations of the G-CSFR gene and neutrophil elastase accumulation in cytoplasm are believed to be the basis of this disorder.	G-CSF resistance leaves no alternative therapy. MFD or MUD has proved successful in the European experience.	High-grade myeloablative pretransplantation conditioning is essential because of normal T-cell responses.	Mixed chimerism might be beneficial.	Supportive care with prophylactic antimicrobial agents and white blood cell transfusions might offer some temporary relief. GT is not available.
MHC class II deficiency				
Defects in promoters occupying DNA-binding protein, such as CIITA transactivators, are responsible for the “bare lymphocyte” syndrome.	Early demise without HCT prompts treatment but poor survival (54% with MFD and 32% with haploidentical donors) at 1 y after HCT.	Nonmyeloablative conditioning is frequently unsuccessful. Lack of expression of HLA class II antigens on thymic epithelium prevents normal $CD4^+$ T-cell production.	Mixed chimerism is beneficial.	General supportive care with TMP/SMX, IVIG, or SCIG before HCT is helpful. Chronic diarrhea is a serious problem that requires eradication of intestinal pathogens.

Bu, Busulfan; *CIITA*, MHC (major histocompatibility complex) Class II Trans-Activator; *Cy*, cyclophosphamide; *G-CSF*, granulocyte colony-stimulating factor; *G-CSFR*, granulocyte colony stimulating factor receptor; *IVIG*, intravenous immunoglobulin; *LYST*, lysosomal trafficking regulator; *MFD*, matched family donor; *MUD*, matched unrelated donor; *phox*, phagocyte oxidase protein; *RIC*, reduced-intensity conditioning; *RMRP*, mitochondrial RNA processing endoribonuclease; *SCIG*, subcutaneous immunoglobulin; *TBI*, total body irradiation; *TMP/SMX*, trimethoprim-sulfamethoxazole; *VP16*, VePesid (etoposide).

TABLE E2

Follow-up schedule after transplantation

Years 1-5	
If possible, the patient should return to the HCT treatment center at least once a year for an evaluation of the patient's immune system. Patients can have autoimmune disease or atypical GVHD during this period. This includes cytopenias, steroid-responsive pneumonitis, and kidney disease, as well as the more typical skin, liver, and gastrointestinal disease. If the patient has recurrent or unusual infections or any manifestation of GVHD, including diarrhea, he or she should be referred back to the treatment center.	
Growth and development should be monitored carefully. If the patients received a preparative regimen, endocrine problems, neurocognitive delays, osteopenia, and dental problems can arise.	
In general, lineage-specific chimerism should be evaluated approximately every 6 to 12 mo after HCT.	
First year	Monthly PE, including blood pressure, and assessment of growth (height, weight, and head circumference) with a growth chart Every 3 mo: complete blood count with differential, lymphocyte phenotype (minimum: T, B, NK, $CD4^+CD45RA^+$, CD8) and function (minimum PHA), and serum immunoglobulin measurement
	Six and 12 mo: LFTs, chemistry 7 metabolic test panel, clinical pulmonary assessment, urinalysis, and PFTs (if too young, pulse oximetry with 6-minute walk). If any chronic pulmonary symptoms, abnormal PFTs, or abnormal chest computed tomographic scan, refer to pediatric pulmonologist, if possible.
	12 mo: Dental, ophthalmologic, chest radiograph (if abnormal, computed tomographic scan), thyroid function, and echocardiogram
Second year	Every 3 mo: PE, assessment of growth, and lymphocyte phenotype and function
	24 mo: dental, ophthalmology, chest radiograph (if abnormal, computed tomographic scan of the chest and sinuses), thyroid function, and neurocognitive testing

Years 1-5	
Years >2	If off immunoglobulin replacement and normal T-cell function, yearly PE, assessment of growth, lymphocyte phenotype and function, and immunoglobulin measurement If on IVIG, PHA <50% of normal value, or both, same as above, but every 6 mo; yearly chest radiograph if with respiratory tract infections (if abnormal, computed tomographic scan of the chest and sinus) All patients: yearly dental, ophthalmology, endocrine, PFTs (if too young, pulse oximetry with 6-minute walk)
Follow-up after 5 y	
If possible, the patient should return to the treatment center at least once every 2 years. The treatment center will continue to monitor immune reconstitution and chimerism. The medical problems that are described above, growth failure, endocrine dysfunction, neurocognitive problems, and dental problems, can persist or develop. In addition, some patients have intractable warts. Secondary malignancies should be considered. When the patient reaches adolescence, genetic counseling should be offered.	

IVIG, Intravenous immunoglobulin; *LFT*, liver function test; *PE*, physical examination; *PFT*, pulmonary function test.

TABLE E3

Antimicrobial prophylaxis after transplantation

PCP	Although all patients with SCID should receive PCP prophylaxis, the duration of this prophylaxis varies from center to center. In patients undergoing continued immunosuppression, PCP prophylaxis is continued after HCT until patients are no longer undergoing GVHD prophylaxis or treatment and demonstrate return of immunologic function. PCP prophylaxis is continued in some centers until the CD4 T-cell count exceeds a threshold (≥200/μL or ≥500/μL) and/or in combination with T-cell proliferative responses to PHA of at least 50% of the lower limit of normal.
HSV and EBV	Acyclovir prophylaxis is generally given to all patients with an HSV-seropositive donor, particularly those who have recurrent cold sores. Some centers also use acyclovir for EBV prophylaxis. For patients receiving conditioning followed by a T-replete transplant, most centers recommend acyclovir at the start of conditioning and continued until at least 30 d after HCT. Practices vary for recipients for an HLA-matched sibling HCT or T cell–depleted, mismatched related HCT in the absence of conditioning, from no prophylaxis to prophylaxis continued until the CD4 cell count is ≥200 cells/μL, or ≥500 cells/μL, ± PHA response of at least 50% of the lower limit of normal. In HLA-mismatched, T-replete cord blood transplantation, it is common practice to continue prophylaxis until all immunosuppressive agents are discontinued, typically not before a year after UCBT In many centers, particularly those in which T cell–replete alternative donor HCT for PID is performed, PCR for EBV viral DNA is monitored at least weekly for the first 3 mo after HCT.
Yeast and mold	Risk factors for invasive fungal infections include neutropenia, mucositis, an indwelling catheter, and prolonged antibiotic and corticosteroid use. Therefore the risk for a patient with a PID will depend on how many of these factors exist in an individual patient. For patients who do not receive conditioning and have no evidence of GVHD, some centers do not provide systemic prophylaxis unless the patient has evidence of thrush. Other centers start patients on fluconazole after diagnosis, continuing until milestones of immune reconstitution are met. For patients with PIDs at risk for invasive *Aspergillus* species infection (ie, those with GVHD), prophylaxis against *Aspergillus* species is warranted, similar to patients undergoing transplantations for malignant disorders.
CMV	CMV infection is a major risk factor of mortality in patients with SCID after HCT, particularly in recipients of unmodified alternative donor HCTs. All patients should receive CMV-seronegative and/or filtered blood products. Patients, particularly those with CMV-seropositive donors, should be monitored closely for CMV reactivation, similar to patients undergoing transplantation for malignant disorders. Patients with evidence of CMV viremia should receive pre-emptive therapy with ganciclovir or foscarnet. Patients undergoing immunosuppressive therapy and/or those with acute or chronic GVHD should be monitored closely until CD4 cell counts are >200/μL, PHA responses are >50% of the lower limit of normal, and immunosuppressive therapy is discontinued.

HSV, Herpes simplex virus; *UCBT*, umbilical cord blood transplantation.

TABLE E4

Intravenous gamma globulin after transplantation

IVIG administration	
All centers administer gamma globulin supplementation in the early posttransplantation period to achieve a trough IgG level of approximately 500 to 700 mg/dL, the higher level for patients with pre-existing or ongoing pulmonary complications, such as bronchiectasis.	
A variety of criteria are used to discontinue gamma globulin. Some centers taper or discontinue the gamma globulin after 6-12 mo. Some wait until the serum IgM level has reached a near-normal concentration. Others immunize the patient to an antigen for which there is no antibody in the therapeutic gamma globulin preparations. There is general agreement that it is important to immunize the patient after the gamma globulin therapy has been discontinued and verify antigen-specific antibody levels. If the patient is unable to make antigen-specific antibody after immunization, gamma globulin therapy should be restarted.	
Patients lacking donor B cells continue to receive gamma globulin unless there is evidence of host antibody responses, such as increasing trough serum IgG levels while on stable gamma globulin doses and antigen-specific antibody titers to immunizations.	
Gamma globulin replacement should be continued in patients undergoing immunosuppressive therapy for GVHD or autoimmune conditions.	
The following should be noted:	
1	The majority of patients lacking donor B cells will require IVIG for life.
2	The presence of normal serum IgM or IgA levels, the presence of isohemagglutinins, or both DO NOT always indicate an ability to make antigen-specific IgG.
When to stop IVIG	
For patients off immunosuppressive therapy, without GVHD, immunoglobulin replacement can be stopped when the trough serum IgG level is >600 mg/dL on stable immunoglobulin replacement doses. Some centers prefer to continue IVIG until there is evidence of donor B cells, preferably immunoglobulin-switched B cells. Consider increasing the interval between IVIG doses by 2 weeks. If the serum IgG level remains >600 mg/dL, the replacement can be discontinued. Monitoring IgG levels and specific antibody responses after stopping IVIG is essential because reinstitution of IVIG might be needed for adequate protection.	
Vaccine administration	
After discontinuation of the immunoglobulin therapy, administration of vaccines can begin on a schedule similar to that given to normal infants, with the exception of live vaccines. Prevaccine and postvaccine titers must be measured to determine responses. Vaccinations with toxoid, such as DTaP, or protein-conjugated polysaccharide vaccines (HIB and 7-valent pneumococcal conjugate vaccine) can be initiated immediately after criteria for discontinuation of IVIG have been met. In contrast, immunization with live vaccines (chicken pox, MMR, and rotavirus) should not be considered until at least 2 y after HCT AND should not be initiated until at least 12-15 mo after cessation of IVIG. In addition, for live vaccines, the patient should be off of all immunosuppressive therapy without evidence of GVHD. Some groups also recommend evidence of response to at least 2 posttransplantation killed vaccines before administering any live vaccines.	
Example of potential revaccination schedule	DTaP ×3, IPV ×3, HIB ×3, Prevnar ×3, hepatitis B ×3 Killed influenza vaccine, yearly starting 6 mo after HCT Booster: DTaP, HIB, Prevnar, IPV 12 mo after primary series completed

DTaP, Diphtheria, tetanus, and pertussis vaccine; *HIB*, *Haemophilus influenzae* type b vaccine; *IPV*, inactivated (Salk) polio vaccine; *IVIG*, intravenous immunoglobulin; *MMR*, measles-mumps-rubella.

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Abbreviations used

ADA	Adenosine deaminase
ALC	Absolute lymphocyte count
CGD	Chronic granulomatous disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CID	Combined immunodeficiency disease
CMV	Cytomegalovirus
CT	Computed tomography
Cy	Cyclophosphamide
GT	Gene therapy
GVHD	Graft-versus-host disease
HCT	Hematopoietic stem cell transplantation
HLH	Hemophagocytic lymphohistiocytosis
NK	Natural killer
PCP	*Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia
PE	Physical examination
PID	Primary immunodeficiency disease
PIDTC	Primary Immune Deficiency Treatment Consortium
SCID	Severe combined immune deficiency
TMP/SMX	Trimethoprim-sulfamethoxazole
USIDNET	United States Immunodeficiency Network
WAS	Wiskott-Aldrich syndrome

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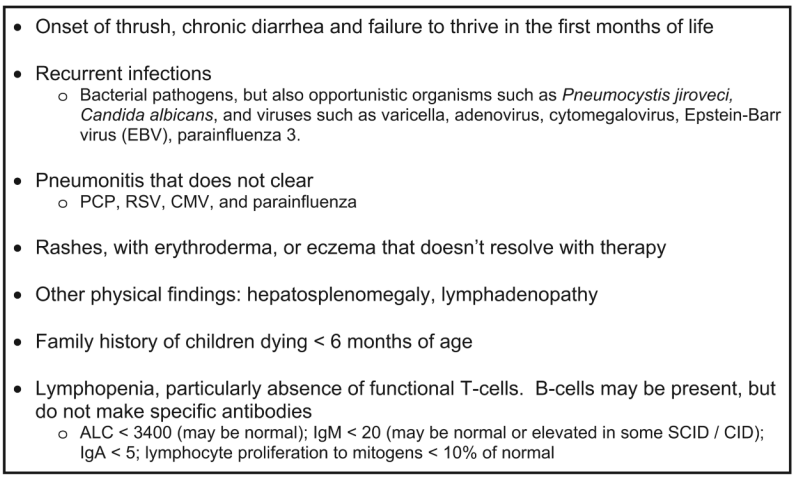

FIG 1.
Features of congenital cellular immunodeficiency.

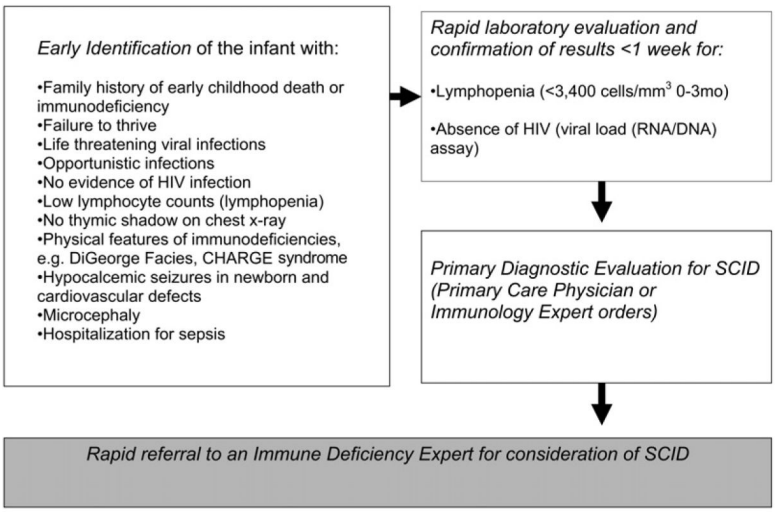

FIG 2.
The primary care physician's role in the diagnosis of SCID.

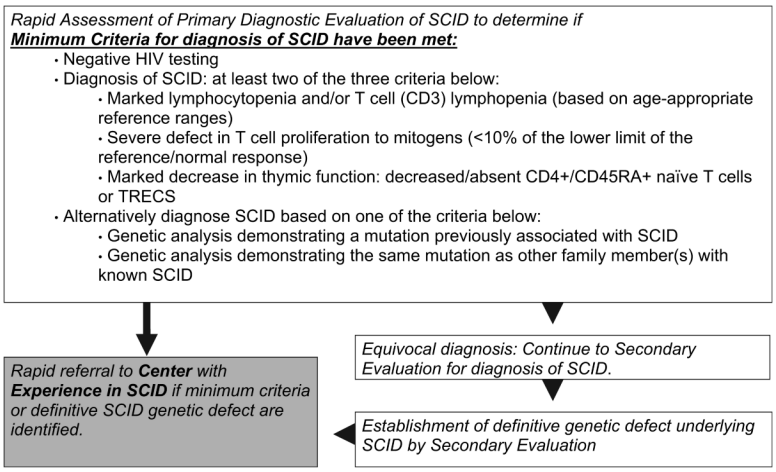

FIG 3.

The immune deficiency expert's role in the diagnosis of SCID. TREC, T-cell receptor excision circle.

- Transfer of patient to a facility with experience in HCT treatment of SCID
- Assessment for maternally transferred or transfusion acquired T cells
- Selection of donor
  - HLA matched sibling; haplotype disparate
  - Related or unrelated adult
  - Unrelated cord blood
- Type of transplant and residual T cell contamination
  - T-cell depleted using lectin or T-cell antibodies
  - CD34+ hematopoietic stem cell enriched
  - Unmodified
- Pretransplantation conditioning
  - None
  - Myeloablative
  - Reduced intensity
  - Immunosuppressive
- Post-transplantation prophylaxis against GVHD (Yes or No)
- Prophylaxis and treatments of infection
  - Gammaglobulin, IV or SC
  - Antibiotics, antivirals
  - Isolation at home or in hospital

FIG E1.
Preparation of patients with SCID for HCT. *IV*, Intravenous; *SC*, subcutaneous.

- For SCID patients receiving T-cell depleted HCT without conditioning
    - Antimicrobial regimens and duration of prophylaxis vary widely between centers, from IVIG and only PCP prophylaxis, to IVIG plus prophylaxis against PCP, HSV, and fungus
    - CD4 counts > 200 / ul and PHA proliferative responses > 50% of normal control are used as cellular immunity parameters to discontinue prophylaxis.
- For patients receiving T replete (unmodified) HCT from alternative donors
    - There is more consensus among centers as to prophylaxis guidelines for infants and children receiving unmodified HCT for PID
    - Guidelines for PID are similar to those of HCT for other diseases, with some important exceptions (ie, duration of IVIG and revaccination schedules).
- Patients with pre-existing infections will be monitored and treated differently
    - Patients with pre-existing viral (HSV, CMV, adenovirus, RSV), PCP, toxoplasmosis, other fungal, or other infections, need targeted antimicrobial treatment until clinical symptoms resolve, microbial tests and scans are negative and immune phenotype and function are restored.

FIG E2.
Management after HCT for PIDs. *HSV*, Herpes simplex virus; *IVIG*, Intravenous immunoglobulin.

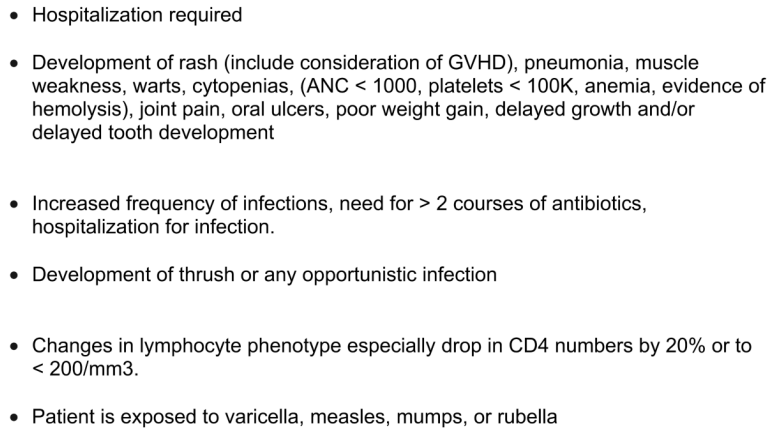

FIG E3.
When to call the transplantation center after discharge. *ANC*, absolute neutrophil count.

TABLE I

Combined immunodeficiency: Working definition

Definitions	
CID	A group of inherited immune disorders that share profound T-cell dysfunction, which is defined as an irreversible, inherited, life-threatening condition that can be dramatically reversed with HCT
"Leaky" SCID	CID includes "leaky" SCID, which is often caused by a known genetic abnormality, such as hypomorphic mutations in common γ-chain, Janus kinase 3, recombinase activating gene, Artemis, and others. The altered gene product possesses a reduced level of activity, or the wild-type gene product is expressed at a reduced level.
Profound immunodeficiency associated with various multisystem syndromes	Profound immunodeficiency can also be associated with various multisystem syndromes, such as cartilage hair hypoplasia or DNA ligase 4 defects. Less severe T-cell deficiencies can be observed in cartilage hair hypoplasia or in other more common conditions, such as common variable immunodeficiency. However, in most of these latter cases, it is believed that the condition might not severely affect life expectancy, or hematopoietic stem cell therapy is not justified because of the risk associated with the procedure, or both.
CID: Criteria and supportive findings	
Criteria	After excluding other secondary causes of immunodeficiency, such as HIV and drugs, CID might be suspected by fulfilling at least 2 of the following criteria: **1** presentation with typical infections (eg, PCP, CMV-induced pneumonitis, oral thrush, and recurrent invasive infections) and/or lymphoid malignancy and/or <2 y of age with granuloma/autoimmunity; **2** confirmed reduced numbers, decreased function, or both of circulating T cells; **3** low T-cell receptor excision circle numbers, restricted diversity of the T-cell repertoire, or both; **4** significant mutation in a gene involved in T-cell function, evidence of defective expression/function of the encoded protein, or both.
Supportive findings	1. Family history of profound T-cell deficiency 2. Signs and symptoms relevant to syndromes that might be associated with profound T-cell deficiency, such as: short stature (eg, cartilage hair hypoplasia), microcephaly (eg, DNA ligase 4), mental retardation (eg, ADA deficiency), and progressive neurodegeneration (eg, purine nucleoside phosphorylase) deficiency 3. Abnormal thymus morphology (dysplastic changes, such as lack of Hassal corpuscles and abnormal architecture)

Note: It was recognized by the group that this "definition" of CID has been developed based on experience with immunodeficient patients and that it is a useful working diagnosis that will require validation in future studies.

TABLE II

Management of a child with suspicion for SCID/CID while confirming diagnosis

Management	Details
Refer to transplantation center as soon as possible.	1. Protect against ill contacts.
	2. Place in protective isolation with mandatory good hand washing to minimize exposure to hospital-acquired infections.
	3. Manage as outpatient if clinically indicated.
	4. A high degree of suspicion for infection is important, because infections can be clinically relatively asymptomatic due to immunity which is defective, in this highly susceptible patient population.
	Notes: The additional use of gowns, gloves and masks varies from center to center, with more than half using all of these isolation approaches with admittedly little to no documented proof of their efficacy.
Start PCP prophylaxis.	1. Can start trimethoprim-sulfamethoxazole at 1 to 4 wk of age if total bilirubin level is not increased and monitor LFT results.
	2. At 4-6 wk old, start trimethoprim-sulfamethoxazole or can use atovaquone, dapsone, or intravenous pentamidine (the latter is given every 2 wk).
	3. At >6 wk old, trimethoprim-sulfamethoxazole is given orally 2-3 d/wk.
	Notes: Although trimethoprim-sulfamethoxazole is not recommended for children <6 wk of age because of possible hepatic toxicity, some experienced centers start it as early as 1 wk of age if the total bilirubin level is not increased and with careful monitoring of liver transaminase levels. The standard PCP prophylactic agent is trimethoprim-sulfamethoxazole administered orally 2-3 d/wk. Alternative therapies are available if trimethoprine-sulfamethoxazole cannot be given.
Consider fungal prophylaxis, especially for *Candida* species.	1. Diflucan (fluconazole)
	2. Monitor LFTs.
	3. If liver inflammation is present, caspofungin is an alternative.
	Notes: Fluconazole should be considered to prevent primarily *Candida* species infection, again with careful monitoring of LFT results.
Start bacterial prophylaxis.	1. IVIG: monitor IgG trough level and maintain >500-800; or fixed dose of 400-500 mg/kg per dose every 3 to 4 wks.
	2. Subcutaneous gamma globulin is an option.
Consider viral prophylaxis.	1. Acyclovir
	2. Maintain adequate hydration.
	Notes: In terms of viral prophylaxis, there appears to be no consensus among immunologists/ transplantation centers, with about half starting acyclovir at the time of diagnosis.
Breast-feeding	1. Not an issue in terms of GVHD risk
	2. Stop nursing until CMV status of mother is known; if seronegative, then it is okay to breast-feed.

Management	Details
	Notes: The likelihood of transmission of CMV to babies with SCID from breast milk is sufficiently significant that many immunologists/ transplantation centers recommend stopping breast-feeding until the mother's CMV serologic status can be determined; if negative, then breast-feeding can be resumed. Development of GVHD from maternal lymphocytes known to be present in breast milk does not appear to be the case in human subjects. There are no documented cases of maternal-infant GVHD in babies with SCID as a result of breast milk, although it is obviously difficult, if not impossible, to differentiate from maternal-fetal GVHD, a known presenting feature of SCID.
Immunizations	1. Avoid live vaccines, including rotavirus, MMR, Flu-mist, and BCG.
	2. Siblings should NOT get varicella vaccine.
	Notes: Unfortunately, the early application of the live attenuated rotavirus vaccine has resulted in symptomatic infections in patients given subsequent diagnoses of SCID (personal communication, M. Cowan). Vaccination of healthy siblings with the varicella vaccine should be avoided.
Blood products	1. Red blood cells and platelets should be CMV negative, if possible; leukodepleted; and irradiated. If CMV-negative blood is not available, then leukodepletion is essential.
	2. Fresh frozen plasma does not require irradiation.
	Notes: A previous blood transfusion with nonirradiated blood has potential to transfer T lymphocytes capable of producing fatal transfusion-associated GVHD.

IVIG, intravenous immunoglobulin; *LFT*, liver function test; *MMR*, measles-mumps-rubella vaccine.

TABLE III

Infectious disease management and workup

Symptoms/organisms	Comments
Screening studies are mandatory, regardless of symptoms.	1. Quantitative PCR on blood for HIV, CMV, EBV, adenovirus, and human herpes virus-6
	2. Nasal wash for respiratory viruses
	Notes: Because of their T- and B-cell defects and absent immune responses, these patients often are relatively less symptomatic for any given degree of infection.
Increased transaminase levels	1. Hepatitis B surface antigen and quantitative PCR for hepatitis C virus
Any respiratory symptoms	1. Arrange to transfer to transplantation center.
	2. Nasal wash for respiratory viruses
	3. Note polymicrobial infection is common.
	4. Chest radiography, O_2 saturation
Cough and/or O_2 requirement and/or tachypnea and/or retractions	1. Consider chest computed tomography because chest radiography might not reveal infiltrates.
	2. If clinically stable, consider bronchoalveolar lavage, even if radiologic results are negative.
	3. If no improvement on empiric therapy, consider lung biopsy, depending on clinical condition.
	4. Start treatment for bacterial, fungal (*Candida* species), PCP, and CMV infections while waiting for results of cultures.
	Notes: Chest radiographic results might be normal while high-resolution chest computed tomographic scans will show significant parenchymal disease. Bronchoalveolar lavage (and sometimes lung biopsy) might be the only way to diagnose PCP and viral pneumonias because sputum is not very sensitive for detecting these organisms in infants and young children.
RSV	1. Aerosolized ribavirin should be given until symptoms improve.
	2. Preferred administration is for 2 h (every 8 h).
	3. Consider giving intravenous Synagis (palivizumab).
	Notes: RSV infection should be treated in children with possible SCID/CID, even if it appears to be in the upper airway only. The efficacy of these approaches has not been documented in this patient population, and it is clear that the most important therapy is cellular correction of the underlying immune deficiency. However, the life-threatening nature of RSV and its potential for long-term effects on lung function result in many centers using these drugs sometimes until immunity can be restored and the RSV infection is cleared.
Adenovirus	1. Cidofovir is the treatment of choice.
	Notes: Use cidofovir until the adenovirus has cleared.
CMV	1. Ganciclovir is first-line therapy.
	2. Foscarnet/cidofovir is second-line therapy.
	3. If the patient is neutropenic/thrombocytopenic, foscarnet can be given.
	4. Foscarnet can be added to ganciclovir/cidofovir if poor response to single agent.
	Notes: The combination of foscarnet and ganciclovir should be considered if there appears to be a poor response to the single agent.
EBV (infection of B cells)	1. Rituximab is first-line therapy but is contraindicated with HBV infection and possibly with PCP infection.

Symptoms/organisms	Comments
	2. Ganciclovir is second-line therapy with questionable efficacy; avoid, if possible, because of marrow suppression and renal toxicity.
	Notes: Rituximab should be avoided in patients with HBV infections and possibly those with PCP. The use of ganciclovir is controversial in that although it is effective *in vitro*, there is little if any documented evidence that it is useful *in vivo*. Given the marrow suppression and possible renal toxicity of ganciclovir, it should be used with caution.

RSV, Respiratory syncytial virus