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Stem cell transplantation for primary immunodeficiency diseases: The North American Experience

Sung-Yun Pai^{a,b,c} and Morton J. Cowan^d

^aDivision of Hematology-Oncology, Boston Children's Hospital, Boston, Massachusetts, USA

^bDepartment of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

^cDepartment of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

^dDivision of Pediatric Allergy, Immunology, and Blood and Marrow Transplant, Benioff Children's Hospital, University of California San Francisco, San Francisco, CA, USA

Abstract

Purpose of the Review—This review describes recent studies on outcomes after allogeneic hematopoietic cell transplantation (HCT) for primary immunodeficiency (PID) in North America including severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD).

Recent Findings—Using uniform diagnostic criteria, the Primary Immune Deficiency Treatment Consortium (PIDTC) described the baseline characteristics of newly diagnosed infants with SCID in North America. Analysis of outcomes of HCT for SCID in North America from 2000–2009 showed that young infants, and older infants without active infection, had excellent survival irrespective of type of donor, or transplant approach with regards to conditioning. While pre-transplant conditioning with chemotherapy had a clear and strong negative impact on survival in infants with active infection at the time of transplant, among survivors, conditioning was associated with improved immune reconstitution. However, the potential late effects of conditioning in these infants remain to be characterized. Advances in transplant outcomes for WAS and CGD support the strategy of early transplantation before the onset of severe complications; additional multicenter studies are needed to fully define optimal approaches.

Summary—The formation of the PIDTC, a multi-institutional North American consortium, has contributed to our understanding of outcomes after transplant for PID.

Keywords

Severe combined immunodeficiency; Wiskott-Aldrich syndrome; chronic granulomatous disease; hematopoietic stem cell transplantation; immune reconstitution

Correspondence to Sung-Yun Pai, Division of Hematology-Oncology, Boston Children's Hospital, One Blackfan Circle, Boston, MA 02115, USA sung-yun.pai@childrens.harvard.edu.

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Introduction

Successful HLA-matched sibling bone marrow transplants for severe combined immunodeficiency (SCID) were first reported from Minnesota for X-linked SCID in 1968¹ and for SCID due to adenosine deaminase deficiency (ADA-SCID) from Boston in 1975,² followed closely by reports of a unrelated donor transplant from New York in 1977³ and haploidentical related donor transplants in New York,⁴ California⁵ and North Carolina⁶ from 1983–1986. Similarly, North American centers made important historical contributions in advancing the treatment of non-SCID PID with HCT. Transient reconstitution after matched sibling bone marrow transplant for Wiskott-Aldrich Syndrome (WAS) was first reported from Wisconsin in 1968,⁷ followed by successful multi-lineage reconstitution from Boston in 1978.⁸ Investigators from New York described the use of busulfan and cyclophosphamide in 3 patients with Wiskott-Aldrich syndrome in 1981,⁹ establishing the backbone for myeloablative transplant for other nonmalignant disorders including other PIDs, hemoglobinopathies and inborn errors of metabolism.

In contrast to Europe where an active multi-institutional registry has reported outcomes after transplant since 1968,¹⁰ results from North America after 1985 have been mostly limited to single institution studies. The largest of these describes results of up to 161 unconditioned matched sibling and T cell depleted haploidentical transplants for SCID from Duke University Medical Center, with 77% survival and high rates of T cell reconstitution, albeit sometimes after multiple infusions.^{11–13} The only combined institution study reported outcome of 94 infants transplanted in Toronto, Canada and Brescia, Italy; survival in the 41 matched unrelated donor recipients was 80% and in the T cell depleted haploidentical recipients only 50%, perhaps related to the receipt of conditioning.¹⁴

The participants at two workshops held at NIH in 2007 and 2008^{15, 16} concluded that such single institution or limited multi-institution studies of rare PIDs were insufficient, as no single center's experience was large enough to appreciate the complexities of these disorders and the variety of therapeutic approaches available. That each center tended to utilize their own preferred protocols made the study of this patient population very difficult. In light of this, in 2009, the Primary Immune Deficiency Treatment Consortium (PIDTC) was formed. The PIDTC is an NIH-funded group of 33 centers whose goals are to analyze the results of HCT, gene therapy and enzyme replacement therapy for PIDs in North America, collaborate with Patient Advocacy Groups, promote involvement of trainees and junior faculty in the study and definitive cure of PID, and foster international collaboration to study PID.¹⁷ The ultimate goal of the consortium is to develop prospective intervention trials. The following review focuses on PIDTC studies of SCID, and key advances in the field of HCT for non-SCID PIDs.

Newborn screening for SCID and its impact on SCID diagnosis and treatment

Previous studies have noted better survival after HCT for SCID in young infants, either <3.5 months or <6 months of age at the time of transplant,^{10, 11, 18} a finding confirmed in the United Kingdom and by the European SCETIDE registry.^{19, 20} These data combined with

the known negative impact of infection on survival^{10, 20} fueled the development of universal newborn screening (NBS) for SCID in the United States. Puck and others²¹ pioneered the detection of T cell receptor excision circles (TREC) in dried blood spots as a means of finding infants lacking substantive numbers of newly generated circulating T cells. Pilot NBS studies using the TREC assay in Wisconsin²² and Massachusetts²³ demonstrated the effectiveness of this approach leading to the addition of TREC measurements to the Recommended Universal Newborn Screening Panel by the United States Secretary of Health and Human Services in 2010. The largest individual state experience has been recently reported by Kwan et al from California,²⁴ demonstrating the high specificity of the TREC assay; of 993,724 infants screened, only 0.08% required a second test, 0.016% required lymphocyte phenotyping by flow cytometry, and 0.005% (50 infants) had significant T-cell lymphopenia requiring evaluation.

The introduction of NBS for SCID in the United States emphasized the need for well-conducted prospective natural history and retrospective studies of outcomes after HCT, laying the groundwork for developing prospective multicenter therapeutic trials focused on the special needs of very young infants. To facilitate determination of eligibility for such studies, the PIDTC established diagnostic criteria for typical SCID and SCID-related disorders including leaky SCID, Omenn's syndrome, and reticular dysgenesis, and further refined these in the course of reviewing newly identified and historical cases of SCID undergoing HCT at PIDTC centers.²⁵ Among 50 newly diagnosed infants with SCID identified at 17 centers from August 2010 to May 2012, 13 of 50 (26%) had SCID-related disorders, a higher frequency than previously anticipated.²⁶ Of the 37 infants with typical SCID, the 12 identified by universal NBS and the 10 by family history had a younger age at diagnosis (14 days vs. 179 days) and at HCT (67 days vs. 214 days) than the 15 identified by symptoms. Currently, 21 states are screening for SCID, accounting for ~62% of births in the United States. As more states establish SCID NBS programs, further information on the phenotypic and genotypic distribution of screened versus non-screened SCID populations and importantly, on the anticipated improvement in outcomes for SCID will be forthcoming.

Update on outcomes after HCT for SCID in North America

Transplant centers in North America have followed disparate approaches to alternative donor transplant for SCID patients who lack a matched sibling donor, namely T cell depleted transplant from a haplocompatible related donor with or without pre-transplant conditioning versus a well-matched unrelated donor or cord blood transplant, most often with busulfan-based, myeloablative or reduced intensity conditioning. While all of these approaches result in T cell reconstitution, many have noted that B cell reconstitution is more variable and likely impacted by conditioning,²⁷ i.e., conditioning with busulfan or similar agents is associated with a higher chance of engraftment with donor-derived B cells and also a higher chance of being independent of intravenous immunoglobulin substitution (IVIG).

The PIDTC conducted an analysis of 5-year survival and immune reconstitution of 240 patients with typical SCID, defined by PIDTC criteria after rigorous central review, transplanted at 25 North American centers from 2000 through 2009.²⁸ In addition to confirming key findings of registry studies in Europe, namely improved survival in young

infants (<3.5 months at time of HCT) and poorer survival in those with active infection, this study dissected the relative importance of age and infection, demonstrating that older infants whose infection had resolved had similar survival to older infants who were never infected or young infants with/without infection (82% versus 90% versus 94% respectively). Within these categories, survival after haploidentical transplant without conditioning, haploidentical transplant with conditioning, matched unrelated donor transplant and umbilical cord transplant were all similar, further supporting the importance of early identification and protection from infection on outcome. Among actively infected infants, survival after unrelated donor, umbilical cord blood or haploidentical transplant with conditioning were inferior (53%, 40%, 39% respectively) to haploidentical transplant without conditioning (65%), and all were far inferior to matched sibling donor transplants (93%). Among survivors, while 92% of patients had recovery of T cell function, only 70% had a CD3+ T cell count >1000/microliter, 49% had a CD4+ T cell count >500/microliter, and 74% were independent from IVIG therapy at 2–5 years post-transplant. The association with IVIG independence and busulfan-based conditioning was confirmed; interestingly, conditioning was associated with higher CD3+ T and higher naïve CD45RA+ CD4+ T cell counts. This study only analyzed 5-year survival; ongoing PIDTC retrospective and cross-sectional studies will describe the adverse late effects of conditioning on babies with SCID.

Key collaborative studies in subpopulations of SCID

Retrospective registry studies of SCID, while informative, do not have the granularity of data required to answer questions for specific SCID genotypes or outcomes after specific transplant approaches. Two collaborative international studies including patients from both North American and Europe have yielded important insights for specific populations.

T⁻B⁻NK⁺ SCID represents about 15% of all SCID patients based on recent NBS data (JS Puck, personal communication). The most common cause of T⁻B⁻NK⁺ SCID is biallelic mutations in one of the recombination activating genes (*RAG1*, *RAG2*) followed by defects in *DCLRE1C* resulting in Artemis deficiency (ART-SCID). There is a high incidence of ART-SCID among Athabascan-speaking Native Americans, in particular the Navajo and Apache Indians.²⁹ These abnormalities result in absent or defective V(D)J recombination and the absence of both T and B lymphocyte development.³⁰ Interestingly, while *RAG1/2* initiates the process of V(D)J recombination, the role of Artemis is to repair and recombine the various DNA segments that ultimately code for T and B cell receptors that result in the diversity of the adaptive immune system. Artemis is a critical component of the non-homologous end joining (NHEJ) pathway of DNA repair and mutations in *DCLRE1C* or other key NHEJ genes including *PRDKC* (DNA-PKcs), *LIG4* (DNA ligase), and *NHEJ1* (Cernunnos or XLF) all typically result not only in T⁻B⁻NK⁺ SCID but also increased sensitivity to alkylating agents and ionizing radiation.^{31, 32}

Previous studies suggested that ART-SCID patients have a poorer outcome when exposed to alkylating agents as part of their pre-transplant conditioning.³³ Recently, investigators in San Francisco, Paris and Ulm collaborated to compare early and late outcomes of 69 patients with ART-SCID to 76 patients with *RAG1/2*-SCID.³⁴ There were no differences in survival regardless of exposure to alkylating agents. Secondary malignancies were not found and

immune reconstitution was comparable. However, in patients surviving beyond 2 years post transplant, the ART-SCID patients had a significantly higher occurrence of infections (34% vs 13%), and were more likely than RAG-SCID patients to have short stature after receiving alkylating agents (49% vs 9%). Also, abnormal dental development (21% vs 0%) and non-autoimmune mediated endocrine late effects (15% vs 0%) were associated with alkylating therapy in ART-SCID patients compared to those with RAG-SCID. Thus, identifying those patients with a defect in the NHEJ pathway prior to instituting transplant therapy, and characterizing the late effects of high dose chemotherapy conditioning in very young babies are critical.

Matched sibling transplant recipients with typical SCID have high rates of T and B cell reconstitution even when no pre-conditioning is used.^{28, 35} To test the hypothesis that matched unrelated donor grafts would behave similarly, Dvorak et al recently published the results of a combined PIDTC and European Blood and Marrow Transplant Inborn Errors Working Party (EBMT-IEWP) study, analyzing 37 unrelated donor and 66 matched sibling donor transplants occurring at 16 centers between July 1993 and November 2012.³⁶ T cell reconstitution was comparable between the recipients of unrelated donor and matched sibling donor grafts (92% vs 97%, respectively). However, in contrast to 72% of the matched sibling donor recipients, only 17% ($P < 0.001$) of the unrelated donor recipients achieved B cell reconstitution. While survival was worse for the unrelated donor compared to the matched sibling donor recipients (71% vs 92%, $P < 0.01$), if serotherapy (anti-thymocyte globulin or alemtuzumab) was used prior to unrelated donor transplant, 5-year overall survival for URD recipients was 100%. Acute and chronic GVHD was also higher in the unrelated donor group, although this might be in part due to the relatively limited GVHD prophylaxis that was used. Thus, the use of unrelated donor grafts without pre-conditioning may be considered for patients with SCID, provided appropriate GVHD prophylaxis including serotherapy is administered prior to the transplant. Further studies are needed to define optimal GVHD regimens.

Key single institution and collaborative studies in WAS and CGD

In 2001, the International Bone Marrow Transplant Registry/National Marrow Donor Program reported outcomes of 170 boys with WAS. The results clearly established age as an important negative factor for survival after unrelated donor transplant, with 0/15 children over the age of 5 years at the time of transplant surviving. Recently, Moratto et. al. reported the results of survival, immune reconstitution and lineage specific chimerism in 194 boys transplanted in Europe, North America and South America, including 91 unrelated adult donor and 24 unrelated umbilical cord blood recipients.³⁷ This study showed vastly improved outcomes after unrelated adult donor transplant compared to historical experience, though the effect of age within this group remains, when comparing recipients > 5 years versus < 2 years (73.3% versus 91.1%). Umbilical cord blood transplant recipients had poorer survival. The improvement in survival after unrelated donor transplant in the era after 2000 was recapitulated in a single institution study of 47 patients.³⁸ In Moratto et. al., an Ochs clinical score³⁹ of 3–4 or 5 at time of transplant was associated with a higher risk of post-transplant complications including graft failure, graft-versus-host disease, autoimmunity, infections requiring hospitalization, or malignancy (53.6, 56.1%) compared

to score of <3 (32.1%).³⁷ Lineage specific chimerism was unstable in the first year post-transplant in ~20% of patients, and more frequent among recipients of unrelated donor transplants. Myeloid chimerism of >50% was generally associated with platelet counts >50,000/microliter. Similar to a previous study from Europe,⁴⁰ the authors also found an association between clinical autoimmunity and having lower donor chimerism in T, B, and myeloid lineages.³⁷

Improvements in HLA typing, expansion of the donor registries and targeted delivery of IV busulfan have led to substantial improvements in outcomes for CGD after unrelated donor transplant, even in patients with severe infections or inflammatory disease.⁴¹ The European experience reported from 1985–2000 of 27 patients showed that all 4 patients with active fungal infections at time of transplant died.⁴² In contrast, 2 single institution reports of 11 children at Baylor Texas Children's Hospital and 12 children at Duke University have demonstrated excellent survival and engraftment.^{43, 44} One reported 100% survival of 4 matched sibling and 7 unrelated donor grafts, with no graft failures, despite a high percentage of high risk patients and myeloablative conditioning.⁴³ The other reported 100% survival of 5 matched sibling bone marrow, 6 unrelated umbilical cord blood and 1 sibling umbilical cord blood recipients despite 2 graft failures and myeloablative conditioning.⁴⁴ While all but 2 patients in these series had >90% donor chimerism, the rate of acute and chronic graft versus host disease after umbilical cord blood transplant remained substantial.

Conclusion

The formation of a multi-institutional consortium dedicated to studying and improving cellular therapy for PID in North America is now bearing fruit with regards to prospective natural history studies and retrospective studies of outcomes, particularly after SCID. The implementation of NBS for SCID in the US presents unique opportunities to examine the impact of early diagnosis and treatment on survival and immune reconstitution, study the psychosocial impact of the diagnosis of SCID in asymptomatic newborns, and devise safe and effective methods that minimize toxicity in very young infants. Plans are underway for a dose escalation PIDTC study of busulfan in infants identified at birth, to determine the minimum exposure that results in T cell and B cell reconstitution.

Prospective natural history, retrospective and cross-sectional studies similar to those conducted in SCID are planned for WAS and CGD by the PIDTC, with anticipated enrollments of 355 and 273 patients respectively. The CGD study will compare a cohort of ~475 untransplanted contemporary patients, matching for NADPH oxidase activity, which has been shown to correlate with survival.⁴⁵ The CGD study includes international collaborators, and studies of quality of life in WAS patients with and without HCT. Nearly 50 years after the first successful transplant for PID, investigators in the field are now poised to make advances in the biology and treatment of PID that can only be afforded by multi-institutional cross-national cooperation.

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References

1. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet*. 1968; 2:1366–1369. [PubMed: 4177932]
2. Parkman R, Gelfand EW, Rosen FS, Sanderson A, Hirschhorn R. Severe combined immunodeficiency and adenosine deaminase deficiency. *N Engl J Med*. 1975; 292:714–719. [PubMed: 1089883]
3. O'Reilly RJ, Dupont B, Pahwa S, et al. Reconstitution in severe combined immunodeficiency by transplantation of marrow from an unrelated donor. *N Engl J Med*. 1977; 297:1311–1318. [PubMed: 21351]
4. Reisner Y, Kapoor N, Kirkpatrick D, et al. Transplantation for severe combined immunodeficiency with HLA-A,B,D,DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. *Blood*. 1983; 61:341–348. [PubMed: 6217853]
5. Cowan MJ, Wara DW, Weintrub PS, Pabst H, Ammann AJ. Haploidentical bone marrow transplantation for severe combined immunodeficiency disease using soybean agglutinin-negative, T-depleted marrow cells. *J Clin Immunol*. 1985; 5:370–376. [PubMed: 3910675]
6. Buckley RH, Schiff SE, Sampson HA, et al. Development of immunity in human severe primary T cell deficiency following haploidentical bone marrow stem cell transplantation. *The Journal of Immunology*. 1986; 136:2398–2407. [PubMed: 2869085]
7. Bach FH, Albertini RJ, Joo P, Anderson JL, Bortin MM. Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet*. 1968; 2:1364–1366. [PubMed: 4177931]
8. Parkman R, Rapoport J, Geha R, et al. Complete correction of the Wiskott-Aldrich syndrome by allogeneic bone-marrow transplantation. *N Engl J Med*. 1978; 298:921–927. [PubMed: 347289]
9. Kapoor N, Kirkpatrick D, Blaese RM, et al. Reconstitution of normal megakaryocytopoiesis and immunologic functions in Wiskott-Aldrich syndrome by marrow transplantation following myeloablation and immunosuppression with busulfan and cyclophosphamide. *Blood*. 1981; 57:692–696. [PubMed: 7008865]
10. Antoine C, Müller S, Cant A, et al. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968–99. *Lancet*. 2003; 361:553–560. [PubMed: 12598139]
11. Buckley RH, Schiff SE, Schiff RI, et al. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *N Engl J Med*. 1999; 340:508–516. [PubMed: 10021471]
12. Patel DD, Gooding ME, Parrott RE, Curtis KM, Haynes BF, Buckley RH. Thymic function after hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *N Engl J Med*. 2000; 342:1325–1332. [PubMed: 10793165]
13. Railey MD, Lokhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. *J Pediatr*. 2009; 155:834–840. e1. [PubMed: 19818451]
14. Grunebaum E, Mazzolari E, Porta F, et al. Bone marrow transplantation for severe combined immune deficiency. *JAMA*. 2006; 295:508–518. [PubMed: 16449616]
15. Griffith LM, Cowan MJ, Kohn DB, et al. Allogeneic hematopoietic cell transplantation for primary immune deficiency diseases: current status and critical needs. *J Allergy Clin Immunol*. 2008; 122:1087–1096. [PubMed: 18992926]
16. Griffith LM, Cowan MJ, Notarangelo LD, et al. Improving cellular therapy for primary immune deficiency diseases: recognition, diagnosis, and management. *J Allergy Clin Immunol*. 2009; 124:1152–1160. e12. [PubMed: 20004776]
17. Griffith LM, Cowan MJ, Notarangelo LD, et al. Primary Immune Deficiency Treatment Consortium (PIDTC) report. *J Allergy Clin Immunol*. 2014; 133:335–347. [PubMed: 24139498]

This workshop summary describes the membership, workings and goals of the PIDTC, a group of North American investigators dedicated to advancing the treatment of PID.

18. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. *Blood*. 2002; 99:872–878. [PubMed: 11806989]
19. Brown L, Xu-Bayford J, Allwood Z, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. *Blood*. 2011; 117:3243–3246. [PubMed: 21273302]
20. Gennery AR, Slatter MA, Grandin L, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better? *J Allergy Clin Immunol*. 2010; 126:602–610. [PubMed: 20673987]
21. Chan K, Puck JM. Development of population-based newborn screening for severe combined immunodeficiency. *J Allergy Clin Immunol*. 2005; 115:391–397. [PubMed: 15696101]
22. Routes JM, Grossman WJ, Verbsky J, et al. Statewide newborn screening for severe T-cell lymphopenia. *JAMA*. 2009; 302:2465–2470. [PubMed: 19996402]
23. Hale JE, Bonilla FA, Pai S-Y, et al. Identification of an infant with severe combined immunodeficiency by newborn screening. *J Allergy Clin Immunol*. 2010; 126:1073–1074. [PubMed: 20933257]
24. Kwan A, Church JA, Cowan MJ, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: Results of the first 2 years. *J Allergy Clin Immunol*. 2013; 132:140–147. By virtue of its high birth rate, and economically and ethnically diverse population, the state of California in the United States provides a wealth of information not only about the feasibility and efficacy of NBS for SCID, but also the unexpected genetic and phenotypic heterogeneity of disorders that result in T cell lymphopenia. Through this study, the incidence of SCID is indeed established to be higher than estimated in the era prior to NBS. Additional primary and secondary conditions detected by SCID NBS are described.
25. Shearer WT, Dunn E, Notarangelo LD, et al. Establishing Diagnostic Criteria for SCID, Leaky SCID, and OMENN Syndrome: the Primary Immune Deficiency Treatment Consortium Experience. *J Allergy Clin Immunol*. 2014; 133:1092–1098. [PubMed: 24290292] While most experienced clinicians agree on the diagnosis of SCID, surprisingly there were few established criteria for diagnosis of classic or typical SCID, atypical or leaky SCID, Omenn's syndrome or other related disorders. This paper establishes a set of criteria which were in turn refined by applying the criteria to 332 children whose data were submitted for study entry.
26. Dvorak CC, Cowan MJ, Logan BR, et al. The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the primary immune deficiency treatment consortium prospective study 6901. *Journal of Clinical Immunology*. 2013; 33:1156–1164. [PubMed: 23818196] By reporting the immunologic and clinical features of newly diagnosed patients with SCID and SCID-related disorders at North American centers, the authors capture a cohort of patients including some identified by NBS, in turn giving insight into the prevalence of atypical forms of SCID and the impact of early identification on time to HCT.
27. Haddad E, Leroy S, Buckley RH. B-cell reconstitution for SCID: Should a conditioning regimen be used in SCID treatment? *J Allergy Clin Immunol*. 2013; 131:994–1000. [PubMed: 23465660]
28. Pai S-Y, Logan BR, Griffith LM, et al. Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009. *N Engl J Med*. 2014; 371(5):434–446. [PubMed: 25075835] This first report of the PIDTC retrospective registry describes baseline features, transplant characteristics and transplant outcomes of 240 well-curated cases of typical SCID. Reflecting the modern era of supportive care and HLA matching, the cohort can serve as a comparison for outcomes in states with active NBS programs. The importance of early detection and protection from infection is highlighted. The multi-institutional nature of the study allows for comparison between different methods of transplantation stratified by infectious status, and revealed that among actively infected infants receiving T cell depleted haploidentical related transplants, conditioning of any type, including immunosuppression alone, was associated with substantially worse survival. To the extent to which immune reconstitution studies had been performed retrospectively, the effect of donor type and chemotherapy conditioning on T and B cell reconstitution was explored to a greater extent than in the literature to date.

29. Li L, Moshous D, Zhou Y, et al. A founder mutation in Artemis, an SNM1-like protein, causes SCID in Athabascan-speaking Native Americans. *J Immunol.* 2002; 168:6323–6329. [PubMed: 12055248]
30. De Villartay J-P. V(D)J recombination deficiencies. *Adv Exp Med Biol.* 2009; 650:46–58. [PubMed: 19731800]
31. van der Burg M, Ijspeert H, Verkaik NS, et al. A DNA-PKcs mutation in a radiosensitive T-B-SCID patient inhibits Artemis activation and nonhomologous end-joining. *J Clin Invest.* 2009; 119:91–98. [PubMed: 19075392]
32. Enders A, Fisch P, Schwarz K, et al. A severe form of human combined immunodeficiency due to mutations in DNA ligase IV. *J Immunol.* 2006; 176:5060–5068. [PubMed: 16585603]
33. O'Marcaigh AS, Desantes K, Hu D, et al. Bone marrow transplantation for T-B- severe combined immunodeficiency disease in Athabascan-speaking native Americans. *Bone Marrow Transplant.* 2001; 27:703–709. [PubMed: 11360109]
34. Schuetz C, Neven B, Dvorak CC, et al. SCID patients with ARTEMIS vs RAG deficiencies following HCT: increased risk of late toxicity in ARTEMIS-deficient SCID. *Blood.* 2014; 123:281–289. [PubMed: 24144642] This multi-institutional international collaborative study examined HCT for two subtypes of SCID, capitalizing on the pooling of data to understand the impact of these specific genotypes on survival and early and late outcomes. The study defined what has been suggested from smaller series, namely that defects in DNA repair in SCID due to Artemis deficiency result in important late toxicities after exposure to alkylating agents administered as conditioning. This study can guide clinicians in selecting the HCT regimen for RAG1/2 versus ART-SCID, and provide anticipatory counseling for families regarding expected outcome.
35. Buckley RH. Transplantation of hematopoietic stem cells in human severe combined immunodeficiency: longterm outcomes. *Immunol Res.* 2011; 49:25–43. [PubMed: 21116871]
36. Dvorak CC, Hassan A, Slatter MA, et al. Comparison of outcomes of hematopoietic stem cell transplantation without chemotherapy conditioning by using matched sibling and unrelated donors for treatment of severe combined immunodeficiency. *Journal of Allergy and Clinical Immunology.* 2014 In Press. Due to improvements in HLA matching techniques, it has been suspected that grafts from fully matched unrelated donor at high resolution, whether derived from volunteer adults or umbilical cord blood, might reconstitute immunity in SCID patients even when administered without conditioning, as is typically done for matched sibling related grafts. This multi-institutional international study gathered such cases of SCID and retrospectively compared survival and immune reconstitution. While outcomes of the unrelated donor transplants were inferior to matched sibling transplants, the demonstration that the approach is feasible and results in high rates of T-cell engraftment provides an option to clinicians facing the dilemma of how to treat a child with SCID who lacks a matched sibling donor and who cannot tolerate chemotherapy conditioning.
37. Moratto D, Giliati S, Bonfim C, et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980–2009: an international collaborative study. *Blood.* 2011; 118:1675–1684. [PubMed: 21659547]
38. Shin CR, Kim M-O, Li D, et al. Outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome. *Bone Marrow Transplant.* 2012; 47:1428–1435. [PubMed: 22426750]
39. Zhu Q, Zhang M, Blaese RM, et al. The Wiskott-Aldrich syndrome and X-linked congenital thrombocytopenia are caused by mutations of the same gene. *Blood.* 1995; 86:3797–3804. [PubMed: 7579347]
40. Ozsahin, Cavazzana-Calvo, Notarangelo, et al. Long-term outcome following hematopoietic stem cell transplantation in Wiskott-Aldrich syndrome: collaborative study of the European Society for Immunodeficiencies and the European Group for Blood and Marrow Transplantation. *Blood.* 2007; 111:439–465. [PubMed: 17901250]
41. Kang EM, Marciano BE, DeRavin S, Zarembek KA, Holland SM, Malech HL. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. *J Allergy Clin Immunol.* 2011; 127:1319–1318. [PubMed: 21497887]

42. Seger RA, Gungor T, Belohradsky BH, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985–2000. *Blood*. 2002; 100:4344–4350. [PubMed: 12393596]
43. Martinez CA, Shah S, Shearer WT, et al. Excellent survival after sibling or unrelated donor stem cell transplantation for chronic granulomatous disease. *J Allergy Clin Immunol*. 2012; 129:176–183. [PubMed: 22078471]
44. Tewari P, Martin PL, Mendizabal A, et al. Myeloablative transplantation using either cord blood or bone marrow leads to immune recovery, high long-term donor chimerism and excellent survival in chronic granulomatous disease. *Biol Blood Marrow Transplant*. 2012; 18:1368–1377. [PubMed: 22326631]
45. Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. *N Engl J Med*. 2010; 363:2600–2610. [PubMed: 21190454]

Key points

- Age and infectious status are key determinants of survival in SCID patients undergoing HCT, with patients <3.5 months and patients of any age who do not have active infection having the best outcome.
- The implementation of newborn screening for SCID in the United States is anticipated to lead to virtually universal survival in these patients.
- Chemotherapy conditioning, if given, is associated with better immune reconstitution in patients with SCID but have high impact on patients with SCID due to Artemis deficiency; long-term effects on other genotypes must be explored.
- Advances in the safety and efficacy of HCT for WAS and CGD have expanded the range of patients for whom this treatment may be offered.