

The ALLERGY ARCHIVES

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Pioneers and Milestones

A historical review of bone marrow transplantation for immunodeficiencies

Bone marrow transplantation was first successful in the treatment of patients with lethal primary immunodeficiency diseases just after the major human histocompatibility system (HLA) was discovered in 1968.¹ In that year, immune function was conferred on 2 children with primary immunodeficiency diseases (Wiskott-Aldrich syndrome and X-linked severe combined immunodeficiency [SCID]) by transplanting into them unfractionated HLA-identical sibling bone marrow cells.^{2,3} The 2 teams of physicians performing the transplantations were led by Dr Fritz Bach and Dr Robert Good, respectively. Dr Good (Fig 1), who passed away in 2003 at the age of 81 years, was a pioneer in the study of primary immunodeficiency diseases and in the use of bone marrow transplantation for the treatment of them. The correction of these and later many other types of primary immunodeficiency diseases by means of bone marrow transplantation taught us that the defects in most such conditions are intrinsic to cells of one or more hematopoietic lineages and not caused by failure of the microenvironment to support the growth and development of those cells.

The 2 early successes in immune reconstitution of primary immunodeficiency diseases in 1968 were followed over the next decade and a half by many disappointments because of the rare availability of HLA-matched sibling donors for patients with lethal primary T-cell defects. In the first report of the outcomes of bone marrow transplantation for SCID in 1977, only 14 of 69 patients with SCID given marrow or fetal tissue transplants worldwide were alive with functional grafts.⁴ Until 1980, only HLA-identical unfractionated bone marrow could be used for bone marrow transplantation because of the lethal graft-versus-host disease (GVHD) that ensued if mismatched donors were used (Fig 2).⁴



FIG 1. Robert A. Good, MD, PhD, DSc (May 21, 1922–June 13, 2003), a pioneer in the study of patients with primary immunodeficiency diseases and in the use of bone marrow transplantation for their correction.

In the late 1970s, studies in rats⁵ and mice⁶ showed that removal of all (or nearly all) postthymic T cells from MHC nonidentical donor marrow or spleen cell suspensions enabled successful rescue of lethally irradiated animals without causing fatal GVHD. This was accomplished in rats by treating donor marrow or spleen cells with anti-T-cell antisera⁵ and in mice by agglutinating the unwanted cells with plant lectins.⁶ The remaining immature marrow or splenic non-T cells restored lymphohematopoietic function in the ablated MHC-disparate animals.

Following the leads from their own work in mice,⁶ Reisner et al⁷ demonstrated, in the early 1980s, that removal of most mature T cells from half-matched parental marrow allowed successful immune reconstitution of human infants with SCID by the remaining cells without subsequent GVHD. Since that time, this approach has been successfully applied numerous times to the treatment of SCID.⁸⁻¹⁴ Moreover, the resulting chimeras have proved extremely useful in the study of human T- and B-cell ontogeny,^{8,11,12,15,16} tolerance induction,¹⁷ and mechanisms of MHC restriction for antigen presentation.¹⁸

Over the past 36 years, remarkable progress has been made in the use of bone marrow transplantation for the successful treatment of primary immunodeficiency diseases.

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FIG 2. An infant with SCID who had lethal GVHD from a nonirradiated packed RBC transfusion. Photograph courtesy of Dr Fred Rosen.

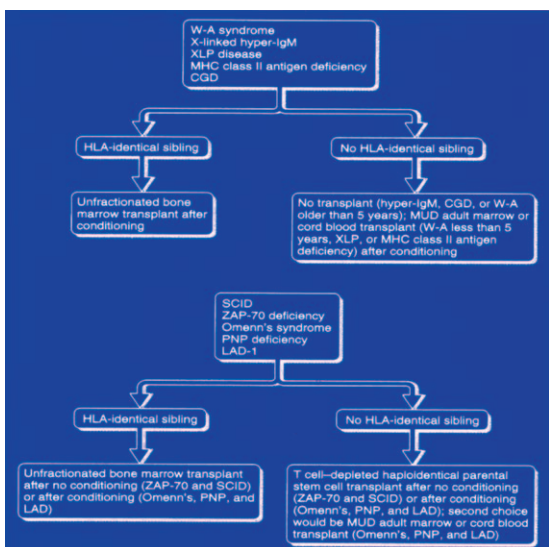


FIG 3. Algorithm showing decision points about transplantation for patients with primary immunodeficiency. W-A, Wiskott-Aldrich syndrome; XLP, X-linked lymphoproliferative disease; LAD, leukocyte adhesion deficiency. Reproduced with permission from Buckley RH. Bone marrow transplantation. In: Leung DYM et al, editors. Pediatric allergy: principles and practice. Philadelphia: Harcourt Health Sciences; 2003. p. 193-203.

CURRENT INDICATIONS FOR BONE MARROW TRANSPLANTATION

Except for infants with complete DiGeorge syndrome, who have no HLA-identical donors and who therefore need a cultured allogeneic thymic transplantation,¹⁹ all infants and children with genetic defects in immune function that lead to death at an early age are potential candidates for allogeneic bone marrow or blood stem cell transplantation (Fig 3). Patients with many different types of immune defects have been given such transplants, with varying degrees of success. These include SCID, Wiskott-

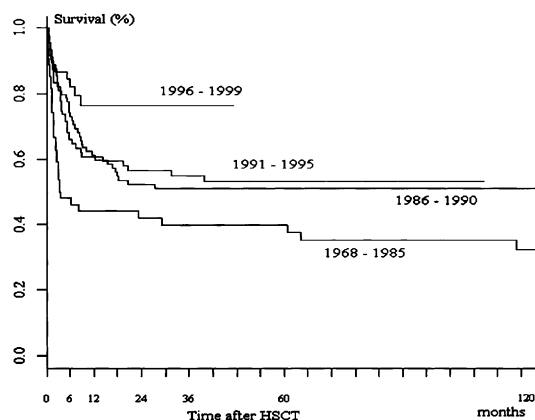


FIG 4. Cumulative probability of survival in patients with SCID given HLA-mismatched transplants according to year of transplantation. Reprinted with permission from Elsevier (*The Lancet*, 2003, 361, 553-60).

Aldrich syndrome, combined immunodeficiency, Omenn syndrome, leukocyte adhesion deficiency, MHC antigen deficiency, Chediak-Higashi syndrome, chronic granulomatous disease (CGD), DiGeorge syndrome, purine nucleoside phosphorylase deficiency, cartilage hair hypoplasia, hyper-IgM syndrome, IL-2 deficiency, and X-linked lymphoproliferative disease.

EFFECTIVENESS OF BONE MARROW TRANSPLANTATION FOR THE TREATMENT OF PRIMARY IMMUNODEFICIENCY DISEASES

Although precise figures are not available, more than 1300 patients worldwide with many different forms of genetically determined immunodeficiency have undergone bone marrow transplantation over the past 36 years in attempts to correct their underlying immune defects. Possibly because of both earlier diagnosis before untreatable opportunistic infections develop and the availability of better antimicrobials to treat infections, the results of bone marrow transplantation have improved considerably over the last 2 decades (Fig 4).^{8,11,13,14,20-23} A worldwide survey conducted by the author from 1994 to 1997 with subsequent additions of published cases from the literature revealed that 239 (79%) of 302 patients with primary immunodeficiency transplanted with HLA-identical marrow over a period of 29 years were alive.

Most encouraging, however, were the results of T cell-depleted haploidentical (half-matched) marrow transplantations in patients with primary immunodeficiency. From the same survey, it was ascertained that 646 such transplantations had been performed, and of these, 363 (56%) patients were alive. The significance is even more impressive when it is realized that most of the 646 recipients would have died had not T cell-depletion techniques been developed.



FIG 5. Infant with X-linked SCID who experienced varicella 3 times before the diagnosis of SCID was made. The child survived because of the availability of acyclovir and the ability to give a haploidentical bone marrow transplant from his mother.

Nine Abnormal Genes in SCID

- Cytokine Receptor Genes
 - *IL2RG*
 - *JAK3*
 - *IL7Ra*
- Antigen Receptor Genes
 - *RAG1*
 - *RAG2*
 - *Artemis*
 - *CD3δ*
- Other Genes
 - *ADA*
 - *CD45*

FIG 6. Classification of the 9 known genes that, when mutated, cause human SCID.

SCID

Bone marrow transplantation has been more widely applied and more successful in infants with SCID than in any other primary immunodeficiency. Without immune reconstitution, these infants die from infection during infancy (Fig 5). Since the first bone marrow transplantation in a patient with SCID in 1968, there has been remarkable progress in the discovery of the fundamental causes of many primary immunodeficiency diseases. This has been particularly true for SCID, for which the initial understanding was limited to the facts that there appeared to be autosomal recessive and X-linked forms of the disease. Just within the past decade, the molecular bases of 8 of the 9 known molecular types of SCID have been elucidated (Fig 6). The frequencies of the various molecular types of SCID evaluated by the author over the past 3 decades are shown in Fig 7. Regardless of the molecular defect, infants with SCID lack T cells; thus there is no need to administer pretransplantation chemotherapy because they cannot reject grafts. In the author's survey and

172 SCIDs: Genetic Types

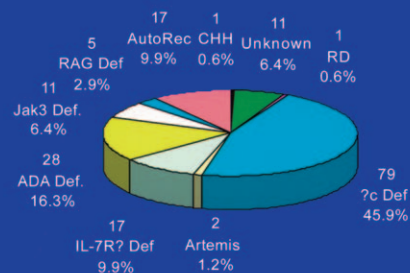


FIG 7. Relative frequencies of the different genetic types of SCID among 172 patients seen consecutively by the author.

literature review, only 126 infants with SCID were reported as having received HLA-identical marrow, and 106 (84%) were alive. By contrast, 477 infants with SCID had received haploidentical marrow, and 301 (63%) survived worldwide; however, the haploidentical transplants were not T cell depleted until after 1980. Nevertheless, this is a major accomplishment because SCID is 100% fatal without marrow transplantation or, in the case of patients with adenosine deaminase-deficient SCID, enzyme replacement therapy. The latter is helpful for only a small percentage of patients with SCID because adenosine deaminase deficiency accounts for only approximately 16% of cases of SCID.^{13,22,24} Only 17 patients with SCID were reported as having received matched unrelated donor (MUD) transplants, and 12 (71%) were alive. Six patients with SCID were reported as having received related or unrelated cord blood transplants, and 5 were alive. Reviews of the European experience with unfractionated HLA-identical and T cell-depleted (or non-T cell-depleted) haploidentical or matched unrelated bone marrow transplants in patients with SCID have reported mean survival rates of 77% for HLA-identical and 54% for mismatched transplants, but they also showed that survival had improved over time.^{23,25-27} A retrospective analysis of the influence of the SCID phenotype on the outcome of haploidentical marrow transplants by the European Group for Bone Marrow Transplantation and the European Society for Immunodeficiency found the disease-free survival to be significantly better for patients with B+ SCID (60%) than for those with B– SCID (35%; $P = .002$).^{23,28} However, 12 (75%) of 16 infants with the B– Athabaskan form of SCID caused by Artemis deficiency were reported as alive after bone marrow transplantation in this country.²⁹

Over the past 22 years, the author and her associates have transplanted 134 infants with SCID, and 103 (77%) of these are currently alive from 1 month to 22 years after transplantation. No pretransplantation conditioning was given except to 3 infants who also

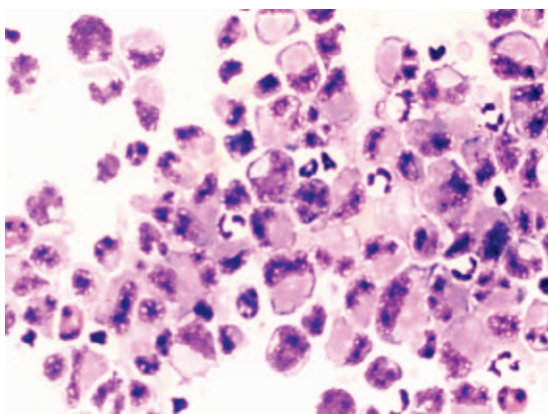


FIG 8. Morphology of donor bone marrow cells remaining in the final fraction after soy lectin and SRBC rosette depletion of T cells. The cells have the appearance of immature myeloid cells and stain negatively for CD3. Dendritic cells are present. Some stain positively for CD34, and others stain positively for CD7.

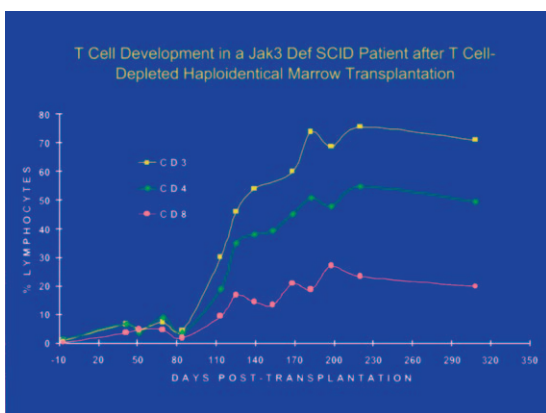


FIG 9. Kinetics of T-cell development after a T cell-depleted HLA-haploidentical maternal bone marrow transplantation was made into an infant with Jak3-deficient SCID.

underwent cord blood transplantation. Only 15 had HLA-identical donors; all 15 survive with functioning grafts. One hundred nineteen patients with SCID received half-matched related donor stem cells prepared by the soy lectin, SRBC resetting, T cell-depletion technique,⁷ and 88 (74%) of these patients survive. After administration of such T cell-depleted marrow cells (Fig 8), we have seen that it takes between 90 and 120 days for the stem cells to mature into phenotypically and functionally normal T cells (Figs 9 and 10). This experience has shown that such transplantation can provide normal numbers of T cells and normalize T-cell function in all molecular types of SCID. Despite the fact that all SCIDs have vestigial thymi (Fig 11), we have demonstrated that the T cells that emerge after transplantation in these chimeras are thymically derived^{14,16} and that the thymus gland can achieve a normal size (Fig 12). The emerging T cells are CD45RA⁺ and contain extrachromosomal DNA circles formed during intrathymic T-cell development

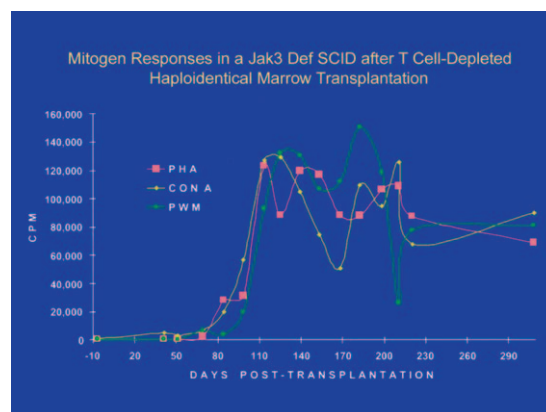


FIG 10. Kinetics of development of T-cell responsiveness to mitogens after a T cell-depleted HLA-haploidentical maternal bone marrow transplantation was made into the same male infant whose T-cell phenotype is depicted in Fig 9. All dividing cells were shown to have an XX karyotype.

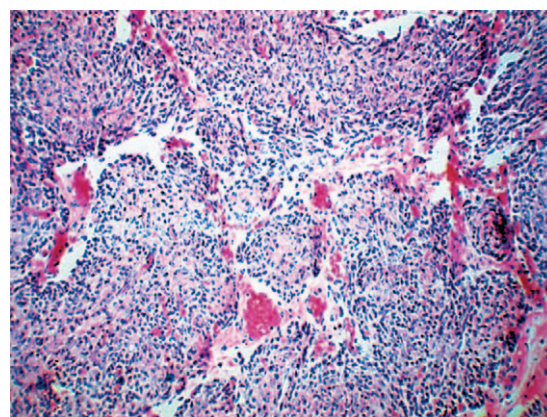


FIG 11. Thymus from an infant with SCID. Epithelium is present, but there are no thymocytes and no Hassall bodies. The organ weighed less than a gram.

(TRECs). Before transplantation, neither the few host T cells that are present nor any transplacentally transferred maternal T cells contain TRECs, and they are CD45RO⁺. However, after transplantation, there is the gradual emergence of both CD45RA⁺ and TREC-containing T cells, coinciding with the development of T-cell function. These observations also taught us that the thymus appears to function normally in all types of SCID once normal stem cells are provided. Most impressive is the fact that 36 (97%) of 37 infants we transplanted in the first 3.5 months of life currently survive (Fig 13).^{14,30} Thus there appears to be no advantage in performing such transplantations in utero as opposed to performing them soon after birth.^{31,32} In utero transplantations also carry the risks associated with injecting the fetus and the inability to detect GVHD during gestation. The importance of early diagnosis cannot be overemphasized. Unfortunately, there is no newborn screening for this syndrome anywhere in the world.

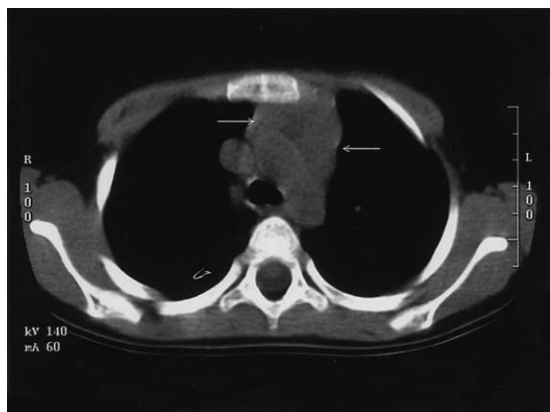


FIG 12. Computed tomographic scan of the anterior mediastinum of a patient with Jak3-deficient SCID 4 years after transplantation. Thymic tissue is in the normal position (arrows), and the greatest transverse dimension measures 3.8 cm, which is normal for age. From: Myers LA. Hematopoietic stem cell transplantation for severe combined immunodeficiency (SCID) in the neonatal period leads to superior thymic output and improved survival. *Blood* 2002;99:872-8. Copyright American Society of Hematology, used with permission.¹⁴

Wiskott-Aldrich syndrome

The second largest group of immunodeficient patients undergoing bone marrow transplantations since 1968 are those with the Wiskott-Aldrich syndrome.^{33,34} In a report from the International Bone Marrow Transplant Registry,³⁵ 170 patients with Wiskott-Aldrich syndrome had undergone transplantation, and the 5-year probability of survival for all subjects was 70% (95% CI, 63% to 77%). Probabilities differed by donor type: 87% (95% CI, 74% to 93%) with HLA-identical sibling donors, 52% (95% CI, 37% to 65%) with other related donors, and 71% (95% CI, 58% to 80%) with unrelated donors ($P = .0006$). Boys who had received an unrelated donor transplant before age 5 years had survivals similar to those receiving HLA-identical sibling transplants. Many of the deaths were from EBV-associated B-lymphocyte lymphoproliferative disorders.²⁰

Combined immunodeficiency

Patients with combined immunodeficiencies characterized by less severe T-cell defects than in SCID constituted the third largest group of patients undergoing bone marrow transplantation since 1968.²¹ Thirty-three (51%) of 65 patients so treated were reported as alive. HLA-identical marrow transplants were clearly more successful (13/17 [76%]) than T cell-depleted haploidentical (15/38 [39%])²⁷ or MUD adult marrow (0/2) transplants, but 5 of 7 recipients of cord blood transplants were alive.³⁶

Omenn syndrome

Forty-five patients with Omenn syndrome were reported in the literature^{20,27,37,38} or to the author as

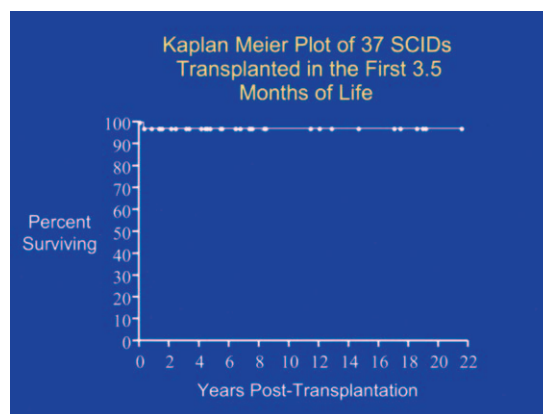


FIG 13. Kaplan-Meier survival curve for 37 consecutive infants with SCID who received bone marrow transplantations at the author's institution from HLA-identical ($n = 5$) or HLA-haploidentical ($n = 32$) donors before they were 3.5 months of age without pretransplantation chemoablation or posttransplantation GVHD prophylaxis. Thirty-six (97%) infants survive for periods of 2 months to 22 years after transplantation. The 1 death occurred from a CMV infection.

having undergone marrow transplantation since 1968, and 23 (51%) were alive at the time. As with the other non-SCID defects, however, the greatest success was with HLA-identical sibling transplants, 9 (75%) of 12 of whom were alive, whereas only 11 (41%) of 27 haploidentical marrow and 3 (50%) of 6 MUD marrow recipients were alive.

Leukocyte adhesion deficiency

Twenty-five (76%) of 33 patients with leukocyte adhesion deficiency were alive after bone marrow transplantation at the time of the survey and review.^{20,27,39,40} All types of marrow transplantation were successful in this condition: 6 (75%) of 8 HLA-identical sibling transplants, 15 (71%) of 21 T cell-depleted haploidentical marrow transplants, 2 (100%) of 2 MUD adult marrow transplants, and 2 of 3 cord blood transplants.

MHC antigen deficiency syndromes

Fourteen (54%) of 26 patients with the bare lymphocyte syndrome were reported alive after having undergone marrow transplantation.^{20,41,42} These included 4 (44%) of 9 who received HLA-identical sibling marrow but only 7 (35%) of 20 who received T cell-depleted haploidentical marrow, 2 (100%) of 2 who received MUD marrow, and 1 (100%) of 1 (100%) who received a related cord blood transplant.^{20,41,43,44}

Chediak-Higashi syndrome

Eighteen (78%) of 23 patients with Chediak-Higashi syndrome who underwent bone marrow transplantation were reported to be alive.^{20,45-47} These included 10 (83%) of 12 who received HLA-

identical sibling marrow, 1 (20%) of 5 who received haploidentical marrow, and 6 (100%) of 6 who received MUD marrow.

CGD

Twenty (71%) of 28 patients with CGD who had undergone bone marrow transplantation were reported as alive, and a majority of these were chimeric.⁴⁸⁻⁵³ The overall survival figures included 18 (72%) of 25 HLA-identical sibling marrow recipients and 2 (67%) of 3 recipients of MUD marrow.⁵⁴ Success has been reported in treating patients with CGD with the "mini-transplant" approach by using HLA-identical sibling donors.^{52,55} Impressively, a recent review of the European experience with HLA-identical sibling bone marrow transplantation for CGD from 1985 to 2000 with myeloablative or myelosuppressive conditioning regimens revealed that 23 of 27 patients were alive, and all but one of the 23 were cured of their disease.⁵⁶

DiGeorge syndrome

Eleven patients with the complete DiGeorge syndrome were initially reported to the author as undergoing marrow transplantation, and 4 more underwent fetal thymus or cultured mature thymic tissue transplantation.^{57,58} The only survivors were 2 of the 3 who received unfractionated HLA-identical sibling marrow, and 2 of the 2 who were recipients of explants of cultured thymic epithelium. Twenty-six more were identified from the literature by Goldsobel et al⁵⁷ in 1987 as having undergone fetal thymus or cultured thymic epithelial transplantation, and at the time of their review, only 8 were alive and well. However, more recently, 12 more infants with complete DiGeorge syndrome underwent transplantation with cultured thymic tissue, and 7 of these are alive.¹⁹

Other primary immunodeficiencies

Other disorders treated successfully by means of bone marrow transplantation include X-linked hyper-IgM (13/21 alive),⁵⁹⁻⁶⁴ reticular dysgenesis (12/21 alive),^{36,65,66} purine nucleoside phosphorylase deficiency (4/9 alive),^{67,68} cartilage hair hypoplasia (4/7 alive), X-linked lymphoproliferative syndrome (6/9 alive),^{64,69-71} pigmentary dilution (Griscelli) syndrome (3/7 alive),⁷² IL-2 deficiency (2/2 alive),²¹ common variable immunodeficiency (0/4 alive), chronic mucocutaneous candidiasis (0/1 alive), ataxia telangiectasia (0/4 alive), and Fas (CD95) deficiency (1/1 alive).⁷³

The author and her associates have performed transplantations in 57 patients with non-SCID immunodeficiency, and the survival rates are shown in Table I.

TABLE I. Survival rates of patients with non-SCID immunodeficiency

Non-SCID defects treated by the author	No. transplanted	No. (%) alive
Combined immunodeficiency	27	11 (41)
Purine nucleoside phosphorylase deficiency	4	2 (50)
ZAP70 deficiency	2	2 (100)
LAD 1	8	5 (67)
Omenn syndrome	5	2 (40)
Chediak-Higashi	2	2 (100)
CGD	2	2 (100)
Wiskott-Aldrich syndrome	2	1 (50)
IFN γ R2 deficiency	2	1 (50)
CD40 ligand deficiency	3	3 (100)
Griscelli syndrome	1	0 (0)

LAD, Leukocyte adhesion deficiency.

CONCLUSIONS AND CHALLENGES FOR THE FUTURE

Clearly allogeneic bone marrow transplantation has been a life-saving and life-extending procedure for many patients with primary immunodeficiency diseases that lead to a very short life expectancy. The most important advance in this field over the past 2 decades was the discovery that haploidentical donors could be used for infants with SCID. Before that, very few such infants could be treated successfully. Bone marrow transplantation will continue to be the treatment of choice for these lethal defects until gene therapy is perfected and the problem of how to prevent insertional oncogenesis is solved. However, bone marrow transplantation is not a perfect treatment; there are risks (death from infection, veno-occlusive disease, and/or GVHD) that preclude its use for patients with defects characterized by only antibody deficiency. Such individuals can survive many years with intravenous immunoglobulin replacement therapy and appropriate antibiotic therapy. The most successful application of bone marrow transplantation has been in the treatment of SCID, in large part because of the fact that these infants do not have T cells and thus do not require pretransplantation chemotherapy or posttransplantation GVHD prophylaxis. If bone marrow transplantation is to be improved for patients with genetic defects in the immune system, early diagnosis will be essential before untreatable infections develop. Screening tests for these defects need to be established, not only at birth but at several time points throughout life. Finally, safer conditioning methods need to be developed for those defects that require chemoablation to prevent rejection, as do improved means of controlling GVHD without delaying the desired immune reconstitution.

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REFERENCES

- Amos DB, Bach FH. Phenotypic expressions of the major histocompatibility locus in man (HL-A): leukocyte antigens and mixed leukocyte culture reactivity. *J Exp Med* 1968;128:623-37.
- Bach FH, Albertini RJ, Joo P, Anderson JL, Bortin MD. Bone marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet* 1968;2:1364-6.
- Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet* 1968;2:1366-9.
- Bortin MM, Rimm AA. Severe combined immunodeficiency disease. Characterization of the disease and results of transplantation. *JAMA* 1977;238:591-600.
- Muller-Ruchholtz W, Wotgte HU, Muller-Hermelink HK. Bone marrow transplantation in rats across strong histocompatibility barriers by selective elimination of lymphoid cells in donor marrow. *Transplant Proc* 1976;8:537-41.
- Reisner Y, Itzicovitch L, Meshorer A, Sharon N. Hematopoietic stem cell transplantation using mouse bone marrow and spleen cells fractionated by lectins. *Proc Natl Acad Sci U S A* 1978;75:2933-6.
- Reisner Y, Kapoor N, Kirkpatrick D, Pollack MS, Cunningham-Rundles S, Dupont B, 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;61:341-8.
- Buckley RH, Schiff SE, Sampson HA, Schiff RI, Markert ML, Knutsen AP, et al. Development of immunity in human severe primary T cell deficiency following haploidentical bone marrow stem cell transplantation. *J Immunol* 1986;136:2398-407.
- O'Reilly RJ, Keever CA, Small TN, Brochstein J. The use of HLA-non-identical T cell depleted marrow transplants for correction of severe combined immunodeficiency disease. *Immunodef Rev* 1989;1:273-309.
- Dror Y, Gallagher R, Wara DW, Colombe BW, Merino A, Benkerrou M, et al. Immune reconstitution in severe combined immunodeficiency disease after lectin-treated, T cell depleted haplocompatible bone marrow transplantation. *Blood* 1993;81:2021-30.
- Giri N, Vowels M, Ziegler JB, Ford D, Lam-Po-Tang R. HLA non-identical T cell depleted bone marrow transplantation for primary immunodeficiency diseases. *Aust N Z J Med* 1994;24:26-30.
- Wijnaendts L, LeDeist F, Griscelli C, Fischer A. Development of immunologic functions after bone marrow transplantation in 33 patients with severe combined immunodeficiency. *Blood* 1989;74:2212-9.
- Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, et al. Hematopoietic stem cell transplantation for the treatment of severe combined immunodeficiency. *N Engl J Med* 1999;340:508-16.
- 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;99:872-8.
- Moen RC, Horowitz SD, Sondel PM, Borchering WR, Trigg ME, Billing R, et al. Immunologic reconstitution after haploidentical bone marrow transplantation for immune deficiency disorders: treatment of bone marrow cells with monoclonal antibody CT-2 and complement. *Blood* 1987;70:664-9.
- 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;342:1325-32.
- Schiff SE, Buckley RH. Modified responses to recipient and donor B cells by genetically donor T cells from human haploidentical bone marrow chimeras. *J Immunol* 1987;138:2088-94.
- Roberts JL, Volkman DJ, Buckley RH. Modified MHC restriction of donor-origin T cells in humans with severe combined immunodeficiency transplanted with haploidentical bone marrow stem cells. *J Immunol* 1989;143:1575-9.
- Markert ML, Sarzotti M, Ozaki DA, Sempowski GD, Rhein ME, Hale LP, et al. Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. *Blood* 2003;102:1121-30.
- Fischer A, Landais P, Friedrich W, Gerritsen B, Fasth A, Porta F, et al. Bone marrow transplantation (BMT) in Europe for primary immunodeficiencies other than severe combined immunodeficiency: a report from the European Group for BMT and the European Group for Immunodeficiency. *Blood* 1994;83:1149-54.
- Berthet F, Le Deist F, Duliege AM, Griscelli C, Fischer A. Clinical consequences and treatment of primary immunodeficiency syndromes characterized by functional T and B lymphocyte anomalies (combined immune deficiency). *Pediatrics* 1994;93:265-70.
- Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, de Saint-Basile G, et al. Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 cases. *J Pediatr* 1993;123:564-72.
- Antoine C, Muller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, et al. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968-99. *Lancet* 2003;361:553-60.
- Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, et al. Human severe combined immunodeficiency (SCID): genetic, phenotypic and functional diversity in 108 infants. *J Pediatr* 1997;130:378-87.
- Haddad E, Landais P, Friedrich W, Gerritsen B, Cavazzana-Calvo M, Morgan G, et al. Long-term immune reconstitution and outcome after HLA-nonidentical T-cell-depleted bone marrow transplantation for severe combined immunodeficiency: a European retrospective study of 116 patients. *Blood* 1998;91:3646-53.
- Fischer A, Landais P, Friedrich W, Morgan G, Gerritsen B, Fasth A, et al. European experience of bone marrow transplantation for severe combined immunodeficiency. *Lancet* 1990;336:850-4.
- Lanfranchi A, Verardi R, Tettoni K, Neva A, Mazzolari E, Pennacchio M, et al. Haploidentical peripheral blood and marrow stem cell transplantation in nine cases of primary immunodeficiency. *Haematologica* 2000;85(suppl 11):41-6.
- Bertrand Y, Landais P, Friedrich W, Gerritsen B, Morgan G, Fasth A, et al. Influence of severe combined immunodeficiency phenotype on the outcome of HLA non-identical T cell-depleted bone marrow transplantation. *J Pediatr* 1999;134:740-8.
- O'Marcaigh AS, DeSantes K, Hu D, Pabst H, Horn B, Li L, et al. Bone marrow transplantation for T-B- severe combined immunodeficiency disease in Athabaskan-speaking native Americans. *Bone Marrow Transplant* 2001;27:703-9.
- Kane L, Gennery AR, Crooks BN, Flood TJ, Abinun M, Cant AJ. Neonatal bone marrow transplantation for severe combined immunodeficiency. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F110-3.
- Wengler GS, Lanfranchi A, Frusca T, Verardi R, Neva A, Brugnani D, et al. In-utero transplantation of parental CD34 haematopoietic progenitor cells in a patient with X-linked severe combined immunodeficiency (SCIDX1). *Lancet* 1996;348:1484-7.
- Flake AW, Roncarolo MG, Puck JM, Almeida-Porada G, Evans MI, Johnson MP, et al. Treatment of X-linked severe combined immunodeficiency by in utero transplantation of paternal bone marrow. *N Engl J Med* 1996;335:1806-10.
- Miano M, Porta F, Locatelli F, Miniero R, La Nasa G, di Bartolomeo P, et al. Unrelated donor marrow transplantation for inborn errors. *Bone Marrow Transplant* 1998;21(suppl 2):S37-41.
- Ozsahin H, Le Deist F, Benkerrou M, Cavazzana-Calvo M, Gomez L, Griscelli C, et al. Bone marrow transplantation in 26 patients with Wiskott-Aldrich syndrome from a single center. *J Pediatr* 1996;129:238-44.
- Filipovich AH, Stone JV, Tomany SC, Ireland M, Kollman C, Pelz CJ, et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. *Blood* 2001;97:1598-603.
- Knutsen AP, Wall DA. Kinetics of T-cell development of umbilical cord blood transplantation in severe T-cell immunodeficiency disorders. *J Allergy Clin Immunol* 1999;103:823-32.
- Gomez L, Le Deist F, Blanche S, Cavazzana-Calvo M, Griscelli C, Fischer A. Treatment of Omenn syndrome by bone marrow transplantation. *J Pediatr* 1995;127:76-81.
- Loechelt BJ, Shapiro RS, Jyonouchi H, Filipovich AH. Mismatched bone marrow transplantation for Omenn syndrome: a variant of

- severe combined immunodeficiency. *Bone Marrow Transplant* 1995;16:381-5.
39. LeDeist F, Blanche S, Keable H. Successful HLA non-identical bone marrow transplantation in three patients with leukocyte adhesion deficiency. *Blood* 1989;74:512.
 40. Thomas C, LeDeist F, Cavazzana-Calvo M, Benkerrou M, Haddad E, Blanche S, et al. Results of allogeneic bone marrow transplantation in patients with leukocyte adhesion deficiency. *Blood* 1995;86:1629-35.
 41. Canioni D, Patey N, Cuenod B, Benkerrou M, Brousse N. Major histocompatibility complex class II deficiency needs an early diagnosis: report of a case. *Pediatr Pathol Lab Med* 1997;17:645-51.
 42. Klein C, Cavazzana-Calvo M, Le Deist F, Jabado N, Benkerrou M, Blanche S, et al. Bone marrow transplantation in major histocompatibility complex class II deficiency: a single center study of 19 patients. *Blood* 1995;85:580-7.
 43. Casper JT, Ash RA, Kirchner P, Hunter JB, Havens PL, Chusid MJ. Successful treatment with an unrelated donor bone marrow transplant in an HLA-deficient patient with severe combined immune deficiency ("bare lymphocyte syndrome"). *J Pediatr* 1990;116:262-5.
 44. Bonduel M, Pozo A, Zelazko M, Raslawski E, Delfino S, Rossi J, et al. Successful related umbilical cord blood transplantation for graft failure following T cell-depleted non-identical bone marrow transplantation in a child with major histocompatibility complex class II deficiency. *Bone Marrow Transplant* 1999;24:437-40.
 45. Fischer A, Durandy A, De Villartay JP, Vilmer E, Le Deist F, Gerota I, et al. HLA-haploidentical bone marrow transplantation for severe combined immunodeficiency using E rosette fractionation and cyclosporine. *Blood* 1986;67:444-9.
 46. Haddad E, Le Deist F, Blanche S, Benkerrou M, Rohrlach P, Vilmer E, et al. Treatment of Chediak-Higashi syndrome by allogeneic bone marrow transplantation: report of 10 cases. *Blood* 1995;85:3328-33.
 47. Liang JS, Lu MY, Tsai MJ, Lin DT, Lin KH. Bone marrow transplantation from an HLA-matched unrelated donor for treatment of Chediak-Higashi syndrome. *J Formos Med Assoc* 2000;99:499-502.
 48. Hobbs JR, Monteil M, McCluskey DR, Jorges E, El Tumi M. Chronic granulomatous disease 100% corrected by displacement bone marrow transplantation from a volunteer unrelated donor. *Eur J Pediatr* 1992;151:806-10.
 49. Kamani N, August CS, Campbell DE, Hassan NF, Douglas SD. Marrow transplantation in chronic granulomatous disease: an update, with 6-year follow up. *J Pediatr* 1988;113:697-700.
 50. di Bartolomeo P, Girolamo G, Angrilli P, Schettini F, De Mattie D, Manzionna MM, et al. Reconstitution of normal neutrophil function in chronic granulomatous disease by bone marrow transplantation. *Bone Marrow Transplant* 1989;4:695-700.
 51. Rapoport JM, Newburger PE, Goldblum RM, Goldman AS, Nathan DG, Parkman R. Allogeneic transplantation for chronic granulomatous disease. *J Pediatr* 1982;101:952-5.
 52. Horwitz ME, Barrett AJ, Brown MR, Carter CS, Childs R, Gallin JJ, et al. Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell-depleted hematopoietic allograft. *N Engl J Med* 2001;344:881-8.
 53. Ozsahin H, von Planta M, Muller I, Steinert HC, Nadal D, Lauener R, et al. Successful treatment of invasive aspergillosis in chronic granulomatous disease by bone marrow transplantation, granulocyte colony-stimulating factor-mobilized granulocytes, and liposomal amphotericin-B. *Blood* 1998;92:2719-24.
 54. Seger RA, Ezekowitz RAB. Treatment of chronic granulomatous disease. *Immunodeficiency* 1994;5:113-30.
 55. Nagler A, Ackerman A, Kapelushnik J, Or R, Naparstek E, Slavin S. Donor lymphocyte infusion post-non-myeloablative allogeneic peripheral blood stem cell transplantation for chronic granulomatous disease. *Bone Marrow Transplant* 1999;24:339-42.
 56. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, di Bartolomeo P, 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;100:4344-50.
 57. Goldsobel AB, Haas A, Stiehm ER. Bone marrow transplantation in DiGeorge syndrome. *J Pediatr* 1987;111:40-4.
 58. Markert ML, Boeck A, Hale LP, Kloster AL, McLaughlin TM, Batchvarova MN, et al. Thymus transplantation in complete DiGeorge syndrome. *N Engl J Med* 1999;341:1180-9.
 59. Thomas C, de Saint Basile G, Le Deist F, Theophile D, Benkerrou M, Haddad E, et al. Brief report: correction of X-linked hyper-IgM syndrome by allogeneic bone marrow transplantation. *N Engl J Med* 1995;333:426-9.
 60. Scholl PR, O'Gorman MR, Pachman LM, Haut P, Kletzel M. Correction of neutropenia and hypogammaglobulinemia in X-linked hyper-IgM syndrome by allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1998;22:1215-8.
 61. Fasth A. Bone marrow transplantation for hyper-IgM syndrome. *Immunodeficiency* 1993;4:323.
 62. Duplantier JE, Seyama K, Day NK, Hitchcock R, Nelson RP Jr, Ochs HD, et al. Immunologic reconstitution following bone marrow transplantation for X-linked hyper IgM syndrome. *Clin Immunol* 2001;98:313-8.
 63. Khawaja K, Gennery AR, Flood TJ, Abinun M, Cant AJ. Bone marrow transplantation for CD40 ligand deficiency: a single centre experience. *Arch Dis Child* 2001;84:508-11.
 64. Ziegner UH, Ochs HD, Schanen C, Feig SA, Seyama K, Futatani T, et al. Unrelated umbilical cord stem cell transplantation for X-linked immunodeficiencies. *J Pediatr* 2001;138:570-3.
 65. De Santes KB, Lai SS, Cowan MJ. Haploidentical bone marrow transplants for two patients with reticular dysgenesis. *Bone Marrow Transplant* 1996;17:1171-3.
 66. Bertrand Y, Muller SM, Casanova JL, Morgan G, Fischer A, Friedrich W. Reticular dysgenesis: HLA non-identical bone marrow transplants in a series of 10 patients. *Bone Marrow Transplant* 2002;29:759-62.
 67. Broome CB, Graham ML, Saulsbury FT, Hershfield MS, Buckley RH. Correction of purine nucleoside phosphorylase deficiency by transplantation of allogeneic bone marrow from a sibling. *J Pediatr* 1996;128:373-6.
 68. Carpenter PA, Ziegler JB, Vowels MR. Late diagnosis and correction of purine nucleoside phosphorylase deficiency with allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1996;17:121-4.
 69. Williams LL, Rooney CM, Conley ME, Brenner MK, Krance RA, Heslop HE. Correction of Duncan's syndrome by allogeneic bone marrow transplantation. *Lancet* 1993;342:587-8.
 70. Gross TG, Filipovich AH, Conley ME, Pracher E, Schmiegelow K, Verdirame JD, et al. Cure of X-linked lymphoproliferative disease (XLP) with allogeneic hematopoietic stem cell transplantation (HSCT): report from the XLP registry. *Bone Marrow Transplant* 1996;17:741-4.
 71. Pracher E, Panzer-Grumayer ER, Zoubek A, Peters C, Gadner H. Successful bone marrow transplantation in a boy with X-linked lymphoproliferative syndrome and acute severe infectious mononucleosis. *Bone Marrow Transplant* 1994;13:655-8.
 72. Schneider LC, Berman RS, Shea CR, Perez-Atayde AR, Weinstein H, Geha RS. Bone marrow transplantation (BMT) for the syndrome of pigmentary dilution and lymphohistiocytosis (Griscelli's syndrome). *J Clin Immunol* 1990;10:146-53.
 73. Benkerrou M, Le Deist F, De Villartay JP, Caillat-Zucman S, Rieux-Laucat F, Jabado N, et al. Correction of Fas (CD95) deficiency by haploidentical bone marrow transplantation. *Eur J Immunol* 1997;27:2043-7.