

## ORIGINAL ARTICLE

# Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009

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## ABSTRACT

**BACKGROUND**

The Primary Immune Deficiency Treatment Consortium was formed to analyze the results of hematopoietic-cell transplantation in children with severe combined immunodeficiency (SCID) and other primary immunodeficiencies. Factors associated with a good transplantation outcome need to be identified in order to design safer and more effective curative therapy, particularly for children with SCID diagnosed at birth.

**METHODS**

We collected data retrospectively from 240 infants with SCID who had received transplants at 25 centers during a 10-year period (2000 through 2009).

**RESULTS**

Survival at 5 years, freedom from immunoglobulin substitution, and CD3+ T-cell and IgA recovery were more likely among recipients of grafts from matched sibling donors than among recipients of grafts from alternative donors. However, the survival rate was high regardless of donor type among infants who received transplants at 3.5 months of age or younger (94%) and among older infants without prior infection (90%) or with infection that had resolved (82%). Among actively infected infants without a matched sibling donor, survival was best among recipients of haploidentical T-cell–depleted transplants in the absence of any pretransplantation conditioning. Among survivors, reduced-intensity or myeloablative pretransplantation conditioning was associated with an increased likelihood of a CD3+ T-cell count of more than 1000 per cubic millimeter, freedom from immunoglobulin substitution, and IgA recovery but did not significantly affect CD4+ T-cell recovery or recovery of phytohemagglutinin-induced T-cell proliferation. The genetic subtype of SCID affected the quality of CD3+ T-cell recovery but not survival.

**CONCLUSIONS**

Transplants from donors other than matched siblings were associated with excellent survival among infants with SCID identified before the onset of infection. All available graft sources are expected to lead to excellent survival among asymptomatic infants. (Funded by the National Institute of Allergy and Infectious Diseases and others.)

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**S**EVERE COMBINED IMMUNODEFICIENCY (SCID) is a genetically heterogeneous and lethal disorder of infancy. It is characterized by severe T-cell lymphocytopenia and a lack of antigen-specific T-cell and B-cell immune responses.<sup>1</sup>

Allogeneic hematopoietic-cell transplantation with the use of bone marrow from an HLA-identical sibling<sup>2</sup> or an unrelated donor,<sup>3</sup> T-cell-depleted marrow or peripheral-blood stem cells from a haploidentical, related donor,<sup>4-7</sup> or umbilical-cord blood<sup>8-10</sup> can fully correct the T-cell deficiency and, less consistently, the B-cell deficiency in patients with SCID.<sup>2-12</sup> Expanded donor availability and advances in supportive care and treatment of infections have improved long-term outcomes after hematopoietic-cell transplantation.<sup>10,13-17</sup> However, owing to the rarity and genetic heterogeneity of SCID, questions remain regarding the contributions of patient characteristics, type of donor and transplant, and conditioning regimen, if used, to survival, immune reconstitution, and the long-term outcome. The development of widespread screening of newborns for SCID<sup>18-21</sup> and reports indicating a survival advantage for children with SCID who receive transplants in the first few months of life<sup>15,22-24</sup> have sharpened questions regarding immediate treatment.

The Primary Immune Deficiency Treatment Consortium (PIDTC), a collaborative network of institutions in North America, was formed to conduct rigorous multicenter studies addressing critical questions in the treatment of SCID.<sup>25</sup> Here we report a retrospective analysis of data from 240 infants with classic SCID who received hematopoietic-cell transplants at 25 PIDTC institutions during a 10-year period.

## METHODS

### STUDY PARTICIPANTS

Data on all infants who had received a transplant for SCID at each of 25 centers between January 1, 2000, and December 31, 2009, were reviewed centrally. Of the 285 infants who met the criteria for SCID, the 240 infants with classic SCID (on the basis of an absolute T-cell count of <300 per cubic millimeter and an absence of T-cell responses to mitogens) who had undergone allogeneic hematopoietic-cell transplantation were included in the study (see the Methods section in the Supplementary Appendix, available with the

full text of this article at NEJM.org; and Shearer et al.<sup>26</sup>). Coded data (age at diagnosis, family history, lymphocyte phenotype, T-cell and B-cell function, genetic subtype, and infection history) were entered into an electronic database with institutional-review-board approval at all centers. Lymphocyte phenotypes were categorized as B<sup>+</sup> (B-cell count, >400 per cubic millimeter), B<sup>low</sup> (50 to 400 per cubic millimeter), or B<sup>-</sup> (<50 per cubic millimeter) and NK<sup>+</sup> (natural killer [NK] cell count, >100 per cubic millimeter), NK<sup>low</sup> (40 to 100 per cubic millimeter), or NK<sup>-</sup> (<40 per cubic millimeter).<sup>27,28</sup>

### TRANSPLANTS

We recorded age at transplantation, infection status, conditioning regimen, donor type, degree of HLA match, cell source, method of T-cell depletion, and graft-versus-host disease (GVHD) prophylaxis. Infection status was categorized as no infection before transplantation, infection resolved before transplantation, and active infection at the time of transplantation. The categories of conditioning regimen (Table S1 in the Supplementary Appendix) were none, immunosuppression (regimens containing one or more of the following: fludarabine, cyclophosphamide, anti-thymocyte globulin, or alemtuzumab), reduced-intensity conditioning (regimens containing melphalan, anti-CD45 antibodies, 200 to 400 cGy of total-body irradiation, or busulfan administered at a total dose of <12 mg per kilogram of body weight), and myeloablative conditioning (regimens containing busulfan at a total dose ≥12 mg per kilogram). A boost was defined as an additional transplant from the same donor without conditioning. A second transplant was defined as an additional transplant from a different donor (with or without conditioning) or from the same donor with conditioning.

### IMMUNE RECONSTITUTION

Data collected at 100 days, at 6 months, and at 1, 2 to 5, and 6 to 10 years after transplantation included absolute numbers of CD3<sup>+</sup> T cells, CD19<sup>+</sup> or CD20<sup>+</sup> B cells, and CD3-CD56<sup>+</sup> or CD16<sup>+</sup>CD56<sup>+</sup> NK cells; proliferative response to phytohemagglutinin; serum concentrations of IgG, IgA, and IgM; treatment with intravenous immune globulin (IVIG); and whole-blood and lineage-specific chimerism. T-cell immune reconstitution was defined as a CD3<sup>+</sup> count of more than 1000 per cubic millimeter,<sup>16</sup> a CD4<sup>+</sup> count

of more than 500 per cubic millimeter,<sup>16</sup> a phytohemagglutinin response that was more than 30% of the lower limit of the normal range, or a stimulation index (i.e., a response to phytohemagglutinin in counts per minute of radiolabeled thymidine incorporated minus counts per minute of background incorporation, divided by counts per minute of background incorporation) of more than

than 50. B-cell reconstitution was defined as IgA recovery and independence from IVIG treatment.

#### STATISTICAL ANALYSIS

Demographic, disease-related, and transplant-related variables were described with the use of frequencies for categorical variables and the median and range for quantitative variables. The as-

**Table 1. Characteristics of the Infants.\***

Characteristic	All Infants (N=240)
<b>Demographic characteristics</b>	
Age — no. (%)	
≤3.5 mo	68 (28)
>3.5 mo	172 (72)
Sex — no. (%)	
Male	173 (72)
Female	67 (28)
Race or ethnic group — no. (%)†	
Non-Hispanic white	118 (49)
Black	25 (10)
Hispanic	67 (28)
Asian or Native Pacific Islander	9 (4)
Native American	8 (3)
Other	13 (5)
<b>Immunologic characteristics‡</b>	
CD3+ T-cell count — per mm <sup>3</sup>	
Median	20
Range	0–9708
T-cell proliferation in response to PHA — no. (%)	
<10% of lower limit of normal range	180 (75)
10–30% of lower limit of normal range	0
>30% of lower limit of normal range	1 (<1)
Missing data	59 (25)
CD19+ or CD20+ B-cell count — per mm <sup>3</sup>	
Median	582
Range	0–5453
B-cell phenotype — no. (%)§	
B <sup>-</sup>	64 (27)
B <sup>low</sup>	32 (13)
B <sup>+</sup>	129 (54)
Missing data	15 (6)
CD3–CD56+ or CD16+CD56+ NK-cell count — per mm <sup>3</sup>	
Median	76
Range	0–2890
NK-cell phenotype — no. (%)¶	
NK <sup>-</sup>	84 (35)
NK <sup>low</sup>	38 (16)
NK <sup>+</sup>	92 (38)
Missing data	26 (11)

Table 1. (Continued.)	
Characteristic	All Infants (N=240)
<b>Infection  </b>	
Ever had infection — no. (%); no. with active infection at time of transplantation (%)	
Yes	171 (71); 106 (62)
No	69 (29)
Type of infection — no. (%); no. with active infection at time of transplantation (%)	
Bacterial infection	104 (43); 29 (28)
Mycobacterial infection	2 (1); 2 (100)
<i>Pneumocystis jirovecii</i> infection	61 (25); 13 (21)
Respiratory viral infection	50 (21); 37 (74)
RSV infection	12 (5); 9 (75)
Parainfluenza virus infection	23 (10); 20 (87)
Influenza	8 (3); 4 (50)
Rhinovirus infection	12 (5); 5 (42)
DNA viral infection**	26 (11); 22 (85)
CMV infection	17 (7); 15 (88)
EBV infection	1 (0); 1 (100)
Adenovirus infection	6 (2); 3 (50)
HHV-6 infection	2 (1); 2 (100)
Varicella–zoster virus infection	2 (1); 2 (100)
Systemic fungal infection	20 (8); 9 (45)

\* CMV denotes cytomegalovirus, EBV Epstein–Barr virus, HHV-6 human herpesvirus 6, NK natural killer, PHA phytohemagglutinin, and RSV respiratory syncytial virus.

† Race or ethnic group was determined from the medical record when available.

‡ The CD3+ T-cell count was measured in 240 infants, the CD19+ or CD20+ B-cell count in 225 infants, and the CD3–CD56+ NK-cell count in 214 infants.

§ B<sup>-</sup> was defined as a B-cell count of less than 50 per cubic millimeter, B<sup>low</sup> as a count of 50 to 400 per cubic millimeter, and B<sup>+</sup> as a count of more than 400 per cubic millimeter.

¶ NK<sup>-</sup> was defined as an NK-cell count of less than 40 per cubic millimeter, NK<sup>low</sup> as a count of 40 to 100 per cubic millimeter, and NK<sup>+</sup> as a count of more than 100 per cubic millimeter.

|| For the percentages of infants with active infection at the time of transplantation, the denominator is the number of infants who ever had infection or ever had that type of infection.

\*\* Some infants had more than one DNA viral infection.

sociation between variables was assessed with the use of the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. Probabilities of survival after transplantation were calculated with the use of the Kaplan–Meier estimator; data from children who were alive at the last follow-up were censored on that date. Probabilities of a second transplantation, acute GVHD, and chronic GVHD were summarized with the use of a cumulative incidence method, with death considered to be a competing event. Confidence intervals were calculated with the use of a log transformation. Multivariate Cox regression models examining risk factors for transplantation outcomes were built with the use of stepwise forward selection, with a P value of 0.05 or less considered to indicate statistical significance. Variables considered were age at trans-

plantation, sex, race or ethnic group, maternal engraftment, genotype, B-cell and NK-cell phenotypes, family history, infection status, failure to thrive, donor type, use of conditioning, graft type, type of T-cell depletion, and GVHD prophylaxis. All variables met the proportional-hazards assumption.

The prevalence of immune recovery at 2 to 5 years after transplantation was analyzed in the group of children who were alive at 2 years and had not received a second transplant. Frequencies of recovery of CD3+ T cells, CD4+ T cells, phytohemagglutinin responsiveness, donor B cells, and IgA and of the need for IVIG therapy were described, and associations with demographic, disease-related, or transplant-related factors were assessed in a univariate analysis with the use of the chi-square test or Fisher's exact test. Step-

wise multivariate logistic-regression models were built to examine risk factors for each immune-recovery outcome.

## RESULTS

### CHARACTERISTICS OF THE INFANTS AT DIAGNOSIS

Table 1 summarizes the characteristics of the infants. A genetic cause of SCID was identified in 69% of infants, most frequently X-linked mutations in *IL2RG* (Table S2 in the Supplementary Appendix). Certain genotypes had a wider phenotypic variation than heretofore reported (Fig. S1 in the Supplementary Appendix).<sup>1</sup> Maternal T-cell engraftment<sup>29</sup> was documented in 51% of 88 children evaluated (Fig. S1 and Table S2 in the Supplementary Appendix).

Infections were documented before transplantation in 171 of the 240 infants (71%), of whom 106 (62%) remained infected at the time of transplantation (Table 1). Although bacteria

and *Pneumocystis jirovecii* were the most common causes of infection, infections with DNA viruses or respiratory viruses were more likely to be active rather than resolved at the time of transplantation (Table 1).

The median age at diagnosis and at transplantation was 138.5 days and 180.0 days, respectively; the distribution was bimodal, with inflection at approximately 3.5 months for age at transplantation (Table 1, and Fig. S2 in the Supplementary Appendix). As compared with infants older than 3.5 months of age, younger infants were more likely to have a family history of SCID and were less likely to have prior infection, active infection at the time of transplantation, or failure to thrive (Table S3 in the Supplementary Appendix).

### TRANSPLANTATION

Characteristics of transplants and donors and methods of pretransplantation conditioning and

**Table 2. Donor and Transplant Characteristics.\***

Characteristic	All Donors (N = 240)	Matched Sibling Donors (N = 32)	Mismatched Related Donors (N = 138)	Other Related Donors (N = 8)	Unrelated Donors (N = 62)
<b>Graft type</b>					
Bone marrow	139 (58)	31 (97)	85 (62)	8 (100)	15 (24)
Mobilized peripheral blood	58 (24)	1 (3)	53 (38)	0	4 (6)
Umbilical-cord blood	43 (18)	0	0	0	43 (69)
<b>GVHD prophylaxis</b>					
None	15 (6)	11 (34)	1 (1)	1 (12)	2 (3)
T-cell depletion of graft before transplantation	137 (57)	3 (9)	132 (96)	0	2 (3)
Soybean agglutination and E-rosette depletion	71 (30)	1 (3)	70 (51)	0	0
CD34 selection	50 (21)	0	50 (36)	0	0
Other T-cell depletion	16 (7)	2 (6)	12 (9)	0	2 (3)
Medications given after transplantation	88 (37)	18 (56)	5 (4)	7 (88)	58 (94)
CNI-based medications	86 (36)	18 (56)	5 (4)	6 (75)	57 (92)
Other medications	2 (1)	0	0	1 (12)	1 (2)
<b>Conditioning regimen</b>					
None	120 (50)	21 (66)	87 (63)	6 (75)	6 (10)
Immunosuppression	39 (16)	7 (22)	16 (12)	1 (12)	15 (24)
Reduced intensity	35 (15)	2 (6)	10 (7)	1 (12)	22 (35)
Myeloablative	46 (19)	2 (6)	25 (18)	0	19 (31)

\* CNI denotes calcineurin inhibitor, and GVHD graft-versus-host disease.

GVHD prophylaxis are shown in Table 2. Most grafts from HLA-matched siblings and phenotypically HLA-matched related donors, as well as transplants of marrow or peripheral-blood stem cells from unrelated donors and cord blood from HLA-mismatched unrelated donors, were unmodified and administered with immunosuppressive drugs as prophylaxis against post-transplantation GVHD. The majority of grafts from haploidentical, HLA-mismatched related donors were T-cell depleted, by means of soybean agglutinin and E-rosette depletion,<sup>4-7</sup> CD34 selection,<sup>30</sup> or other methods, and administered without additional prophylaxis against GVHD.

Although most infants receiving grafts from matched sibling donors (66%) or mismatched related donors (63%) did not undergo conditioning, 90% of infants receiving grafts from unrelated donors or cord-blood grafts underwent immunosuppression, reduced-intensity conditioning, or myeloablative conditioning. The median time from diagnosis to transplantation was longer for recipients of bone marrow or peripheral-blood stem-cell transplants from unrelated donors than for recipients of transplants from other donor types (88.0 days vs. 28.5 to 39.0 days,  $P<0.001$ ) (Table S2 in the Supplementary Appendix).

#### T-CELL ENGRAFTMENT AND GRAFT FAILURE

Of the 240 infants, 172 (72%) had engraftment and development of donor T cells with or without donor B cells after receiving a single transplant; the rest received a boost, a second transplant, or both (Table 3). The risk of graft failure was lowest among recipients of grafts from matched sibling donors (Fig. 1A). Donor type (Fig. 1A, and Table S4 in the Supplementary Appendix), genotype (Table S4 in the Supplementary Appendix), and use or type of conditioning regimen were not significantly associated with graft failure requiring a second transplant ( $P=0.15$ ,  $P=0.23$ , and  $P=0.44$ , respectively).

#### GVHD

The cumulative incidence of acute GVHD of grade 2 to 4 at 100 days was 20%, the cumulative incidence of acute GVHD of grade 3 or 4 at 100 days was 8%, and the cumulative incidence of chronic GVHD at 2 years was 15% (Fig. 1B and 1C). The incidence did not differ significantly among recipients of grafts from matched sibling donors, recipients of T-cell-depleted grafts from

**Table 3. Transplantation Complications and Outcomes.\***

Complication or Outcome	No. of Infants Who Could Be Evaluated	Value % (95% CI) <sup>†</sup>
<b>Transplant-related event</b>		
Boost or second transplant at 5 yr <sup>‡</sup>	240	18 (13–23)
Acute GVHD of grade 2–4 at 100 days	236	20 (17–28)
Acute GVHD of grade 3–4 at 100 days	236	8 (5–12)
Chronic GVHD at 2 yr	233	15 (10–20)
Overall survival at 5 yr	240	74 (68–79)
<i>no. of infants (%)</i>		
<b>Immune reconstitution at 2–5 yr</b>		
T-cell immunity		
CD3+ count >1000/mm <sup>3</sup>	125	88 (70)
CD4+ count >500/mm <sup>3</sup>	125	49 (39)
T-cell proliferation in response to PHA >30% of lower limit of normal range	111	102 (92)
B-cell immunity		
CD19+ or CD20+ count >400/mm <sup>3</sup>	126	65 (52)
Normal IgA level	117	66 (56)
Independence from IVIG therapy	136	74 (54)
Response to vaccine among children with independence from IVIG therapy		
Protective response	74	39 (53)
Detectable response	74	8 (11)
No response	74	1 (1)
Unknown response	74	26 (35)

\* CI denotes confidence interval, and IVIG intravenous immune globulin.

<sup>†</sup> Percentages for transplant-related events are cumulative incidences.

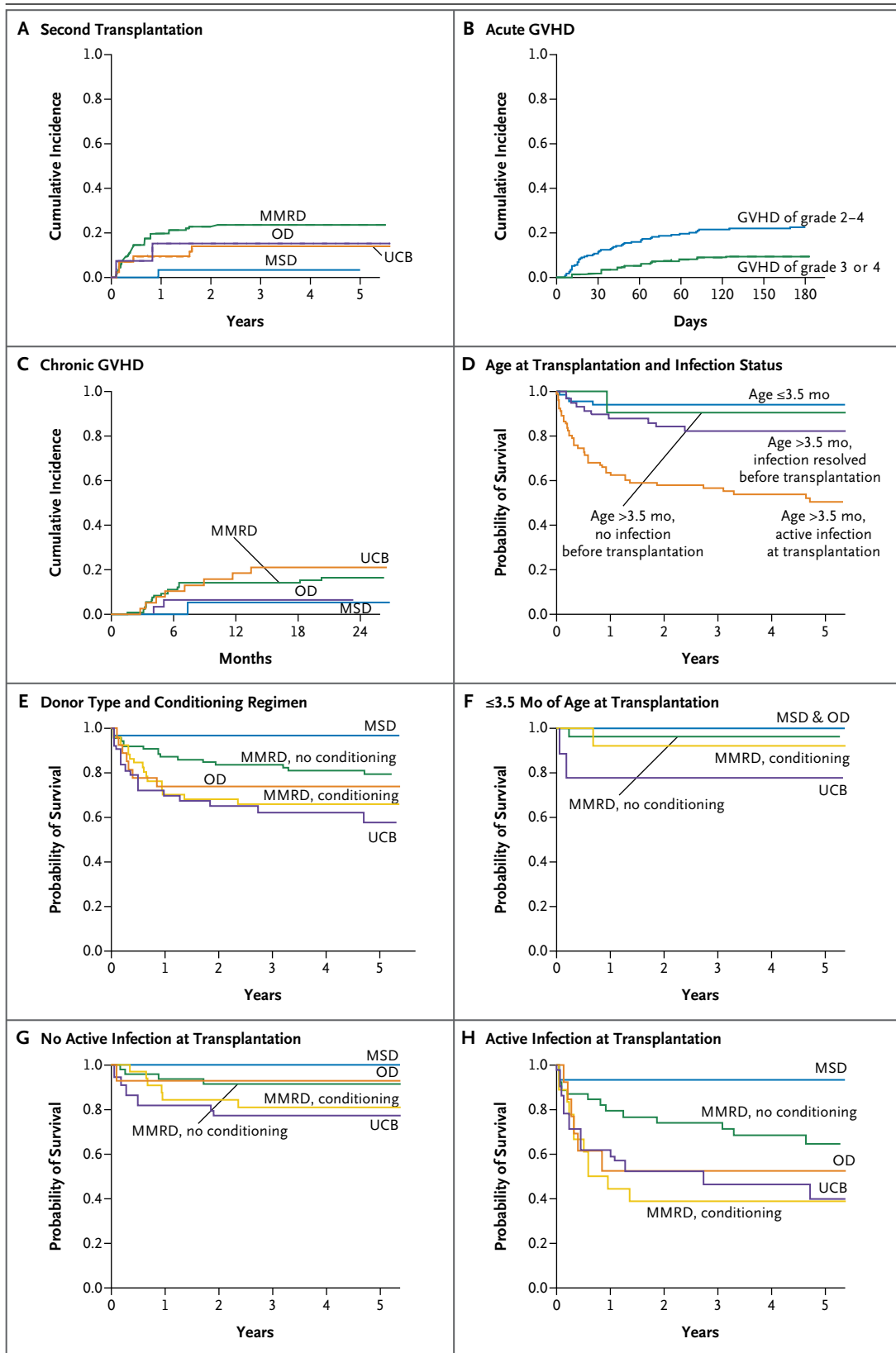
<sup>‡</sup> A total of 23 children received a boost only, 34 received a second transplant only, and 11 received both a boost and a second transplant. A boost was defined as an additional transplant from the same donor without conditioning. A second transplant was defined as an additional transplant from a different donor (with or without conditioning) or from the same donor with conditioning.

mismatched related donors, and recipients of grafts from other donors (unrelated donors and phenotypically matched related donors considered together) (Fig. 1C, and Table S5 in the Supplementary Appendix).

#### SURVIVAL

The overall survival rate at 5 years was 74%, according to the Kaplan–Meier estimate (178 of 240 children) (Table 3). Among children who received a second transplant, the rate was 56% (26 of 45 children). Most deaths occurred in the first





**Figure 1 (facing page). Cumulative Incidence of a Second Transplantation, Cumulative Incidence of Graft-versus-Host Disease (GVHD), and Survival in 240 Infants with Severe Combined Immunodeficiency.**

The cumulative incidence of a second transplantation at 5 years in recipients of grafts from HLA-matched sibling donors (MSD), recipients of umbilical-cord blood (UCB), recipients of bone marrow or peripheral blood from other matched related or unrelated donors (OD), and recipients of grafts from mismatched related donors (MMRD) was 3%, 14%, 15%, and 24%, respectively (Panel A). The cumulative incidence of acute GVHD of grade 2 to 4 at 100 days, acute GVHD of grade 3 or 4 at 100 days, and chronic GVHD at 2 years was 20%, 8%, and 15%, respectively (Panels B and C). For acute GVHD, there were no significant differences according to donor type (Table S5 in the Supplementary Appendix). For chronic GVHD, a four-group comparison of donor types (Panel C) and a comparison including only transplants with rigorous T-cell depletion (Table S5 in the Supplementary Appendix) showed no significant differences. Factors that significantly affected survival in multivariate analyses include age at the time of transplantation and infection status, donor type, and conditioning regimen (Panels D through H). The survival rate at 5 years was higher among infants who received transplants at 3.5 months of age or younger (94%) and among older infants without prior infection (90%) than among older infants with resolved infection (82%) or with active infection (50%) at the time of transplantation (Panel D). Survival among children receiving transplants from alternative donors (MMRD, OD, or UCB) was inferior to that among children receiving MSD transplants; in addition, survival was reduced among recipients of MMRD transplants who underwent a conditioning regimen of immunosuppression, reduced-intensity conditioning, or myeloablative conditioning (Panel E). Infants 3.5 months of age or younger at the time of transplantation had high survival rates regardless of donor type or conditioning (Panel F). The effect of donor type and conditioning on the survival rate was not significant among infants of any age who did not have active infection at the time of transplantation (MSD, 100% among 17 infants; OD, 93% among 14 infants; MMRD with no conditioning, 91% among 48 infants; MMRD with conditioning, 81% among 33 infants; UCB, 77% among 22 infants;  $P=0.16$ ) (Panel G) but was significant among infants with active infection at the time of transplantation (MSD, 93% among 15 infants; MMRD with no conditioning, 65% among 39 infants; OD, 53% among 13 infants; UCB, 40% among 21 infants; MMRD with conditioning, 39% among 18 infants;  $P=0.006$ ) (Panel H).

year after transplantation, and most deaths were due to infections (24 of 62 deaths [39%]) or pulmonary complications (23 of 62 deaths [37%]) (Table S6 in the Supplementary Appendix). Deaths due to pulmonary complications were more common among children who underwent myeloabla-

tive conditioning than among those who underwent reduced-intensity or immunosuppressive conditioning or did not undergo conditioning.

Older age and active infection at the time of transplantation were strongly associated with a lower survival rate. Infants who received transplants at 3.5 months of age or younger had the highest 5-year survival rate (94% [64 of 68 children surviving]). This rate was similar to that among infants older than 3.5 months of age at the time of transplantation and with no history of infection (90% [21 of 23 children surviving]) or whose infection had resolved by the time of transplantation (82% [48 of 58]). The survival rate was lowest for children who were older than 3.5 months of age and had active infection at the time of transplantation (50% [45 of 91 children surviving]) (Table 4 and Fig. 1D).

Donor type was a significant predictor of survival; the survival rate was highest among recipients of grafts from matched sibling donors (97%). Children who received T-cell-depleted grafts from mismatched related donors and did not undergo conditioning had the next highest survival rate (79%,  $P=0.07$ ) (Table 4 and Fig. 1E). The survival rate was similar among children who received grafts from mismatched related donors after undergoing any type of conditioning (66%), cord-blood recipients (58%), and recipients of other grafts (74%).

Survival rates among children 3.5 months of age or younger at the time of transplantation were high for all transplant types (78 to 100%) (Fig. 1F) and ranged from 77 to 100% among children of any age without active infection at the time of transplantation (Fig. 1G). However, among children of any age with active infection at the time of transplantation, survival rates were inferior to that of children who received grafts from matched sibling donors for all alternative donor types except children who received T-cell-depleted grafts from mismatched related donors without any conditioning (Fig. 1H). Among children with active infection who received grafts from mismatched related donors, those who did not undergo conditioning had a higher survival rate than those who did (65% vs. 39%,  $P=0.006$ ). Survival rates among cord-blood recipients (40%) and recipients of grafts from other unrelated donors or matched related non-sibling donors (53%) were similar to the rate among children who received grafts from mis-



**Table 4. Results of Multivariate Analysis of Outcomes and Contributing Factors.**

Outcome and Contributing Factors	Percent with Outcome (95% CI)	Relative Effect (Hazard Ratio for Death)	P Value
<b>Survival at 5 yr</b>			
Age at transplantation and infection status			
0–3.5 mo	94 (85–98)	1.00	
>3.5 mo, active infection	50 (39–61)	10.88	<0.001
>3.5 mo, infection resolved	82 (70–90)	2.88	0.07
>3.5 mo, no infection	90 (67–98)	1.03	0.97
Donor type and conditioning regimen			
Matched sibling donor	97 (79–100)	1.00	
Mismatched related donor, no conditioning	79 (69–87)	6.27	0.07
Mismatched related donor, with conditioning	66 (51–77)	15.70	0.008
Cord-blood donor	58 (40–72)	13.10	0.01
Other unrelated or related donor	74 (53–87)	14.20	0.01
(Odds Ratio)			
<b>CD3+ T-cell count &gt;1000/mm<sup>3</sup> at 2–5 yr</b>			
Donor type			
Matched sibling	76 (55–91)	1.00	
Mismatched related	66 (53–77)	0.18	0.01
Other related or unrelated	76 (58–89)	0.15	0.04
Mismatched related vs. other related or unrelated		1.17	0.82
Conditioning regimen			
None or immunosuppression	62 (51–73)	1.00	
Reduced-intensity or myeloablative conditioning	89 (75–97)	8.84	0.007
Lymphocyte phenotype			
B <sup>+</sup> (vs. B <sup>-</sup> or B <sup>low</sup> )	87 (76–94)	7.82	<0.001
NK <sup>+</sup> (vs. NK <sup>-</sup> or NK <sup>low</sup> )	57 (42–71)	0.23	0.02
<b>Independence from IVIG therapy at 2–5 yr</b>			
Donor type			
Matched sibling	81 (61–93)	1.00	
Mismatched related	37 (26–49)	0.10	<0.001
Other related or unrelated	70 (53–84)	0.21	0.02
Mismatched related vs. other related or unrelated		0.47	0.13
Conditioning regimen			
None or immunosuppression	41 (31–52)	1.00	
Reduced-intensity or myeloablative conditioning	84 (69–93)	8.87	<0.001

matched related donors after undergoing conditioning (Fig. 1H). In contrast to the findings in prior studies, genotype and B<sup>-</sup> phenotype did not significantly affect survival.

#### IMMUNE RECONSTITUTION

Reconstitution of T lymphocytes, B lymphocytes, and immune function at 2 to 5 years after transplantation was analyzed among 149 children who survived to 2 years after receiving a single transplant. Of 111 children tested, 102 (92%) had restoration of T-cell responses to phytohemagglutinin. However, only 88 of 125 children tested (70%) had CD3<sup>+</sup> T-cell counts of more than 1000 per cubic millimeter. In multivariate analyses (Table 4), recipients of grafts from matched sibling donors consistently had CD3<sup>+</sup> T-cell counts that met this threshold, whereas recipients of grafts from mismatched related donors or grafts from other donors were likely to have lower CD3<sup>+</sup> T-cell counts ( $P=0.01$  and  $P=0.04$ , respectively). Conditioning with myeloablative or reduced-intensity regimens, as compared with immunosuppression or no conditioning, enhanced the probability of recovery of CD3<sup>+</sup> T-cells to this level ( $P=0.007$ ). Phenotype influenced T-cell recovery. Children with B<sup>+</sup> SCID were more likely to have recovery of normal levels of CD3<sup>+</sup> T cells than were children with the B<sup>-</sup> or B<sup>low</sup> phenotype ( $P<0.001$ ), and children with NK<sup>+</sup> SCID had poor recovery of T-cell populations as compared with those with the NK<sup>-</sup> or NK<sup>low</sup> phenotype ( $P=0.02$ ). *RAG1*, *RAG2*, and *DCLRE1C* variants were associated with poor CD3<sup>+</sup> T-cell recovery in a univariate analysis (4 of 14 children vs. 49 of 57 children with *IL2RG* variants,  $P<0.001$ ), a finding that is consistent with the phenotype results. Finally, active infection at the time of transplantation was significantly associated with poor CD3<sup>+</sup> T-cell recovery. In univariate analyses, 34 of 39 infants (87%) who had clearance of infection by the time of transplantation and 26 of 37 infants (70%) with no history of infection had a CD3<sup>+</sup> T-cell count of more than 1000 per cubic millimeter, as compared with 28 of 49 infants (57%) with active infection at the time of transplantation ( $P=0.009$ ).

Total CD4<sup>+</sup> T-cell recovery was more likely among recipients of grafts from matched sibling donors and other matched related or unrelated

donors than among recipients of grafts from mismatched related donors (Table S7 in the Supplementary Appendix). Total CD4<sup>+</sup> T-cell recovery was not influenced by conditioning. However, 23 children who underwent reduced-intensity or myeloablative conditioning had evidence of improved thymic output, as indicated by a higher median CD4<sup>+</sup>CD45RA<sup>+</sup> naive T-cell count (1094 per cubic millimeter; range, 98 to 3131) than that in 62 children who underwent immunosuppression or did not undergo conditioning (192 per cubic millimeter; range, 0 to 2870;  $P<0.001$ ) (Fig. S3 in the Supplementary Appendix).

Among children with B<sup>-</sup> SCID, univariate analysis showed that B-cell reconstitution (CD19<sup>+</sup> or CD20<sup>+</sup> B-cell count  $>400$  per cubic millimeter) was associated with reduced-intensity or myeloablative conditioning (9 of 11 children [82%] with reduced-intensity or myeloablative conditioning vs. 9 of 37 children [24%] with immunosuppression or no conditioning,  $P<0.001$ ).

Of 67 children tested, only 13 of 33 recipients of grafts from mismatched related donors (39%) had full or mixed donor B-cell chimerism, as compared with 8 of 10 recipients of grafts from matched sibling donors (80%) and 17 of 24 recipients of grafts from other donors (71%) ( $P<0.001$ ). B-cell chimerism was more common in children who underwent reduced-intensity or myeloablative conditioning (23 of 26 children [88%]) than in those who underwent immunosuppression or did not undergo conditioning (7 of 31 children [23%],  $P<0.001$ ) (Table S8 in the Supplementary Appendix).

Among survivors evaluated at 2 years after transplantation, recipients of grafts from matched sibling donors were significantly more likely to have independence from IVIG therapy and to have normal IgA levels than recipients of grafts from mismatched related donors or other donors (Table 4, and Table S7 in the Supplementary Appendix). Furthermore, among children who received grafts from mismatched related donors or other donors, those who underwent reduced-intensity or myeloablative conditioning were more likely to have normal CD3<sup>+</sup> T-cell counts, B-cell chimerism, normal IgA levels, and independence from IVIG therapy than those who underwent immunosuppression or did not un-

dergo conditioning ( $P=0.005$ ,  $P<0.001$ ,  $P<0.001$ , and  $P<0.001$ , respectively). Moreover, full donor chimerism in whole blood and full or mixed chimerism in B cells or myeloid cells were associated with independence from IVIG therapy ( $P=0.002$  for whole blood,  $P<0.001$  for B cells, and  $P=0.003$  for myeloid cells) (Table S8 in the Supplementary Appendix). Neither phenotype nor genotype was significantly associated with independence from IVIG therapy.

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## DISCUSSION

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Our results confirm previously reported excellent outcomes for children with classic SCID who received transplants from matched sibling donors without undergoing conditioning<sup>2,7,14,15,17</sup> and significantly better outcomes for children who received transplants in early infancy ( $\leq 3.5$  months of age vs.  $>3.5$  months of age) (Fig. 1).<sup>22,24</sup> Even after transplantation of grafts from alternative donor types, these very young infants had excellent outcomes that were similar to those of recipients of grafts from matched sibling donors (Fig. 1F). Because earlier transplantation is more successful, our findings suggest that newborn screening for SCID and early transplantation may improve survival.<sup>31</sup>

Clinicians in regions that have not implemented newborn screening commonly face the dilemma of how to perform a transplantation in an infant with SCID who presents with infection. Controversies include what type of donor should be selected if a matched sibling donor is not available, whether treatment of infection should be attempted before transplantation, and whether to use a conditioning regimen.<sup>13,32-34</sup> In our cohort, survival among infants who had never had infection or had infection that resolved was similar to that among infants 3.5 months of age or younger, irrespective of donor type, a finding that suggests that prevention and successful treatment of infection are predominant determinants of a good transplantation outcome. Furthermore, among children with active infection at the time of transplantation, the use of any conditioning regimen, including immunosuppression, was associated with an adverse effect on survival among recipients of grafts from mismatched related donors (and possibly among cord-blood recipients and recipients of grafts

from unrelated donors, the large majority of whom underwent conditioning). In addition to the acute toxicity of reduced-intensity and myeloablative conditioning regimens (Table S6 in the Supplementary Appendix), these regimens have long-term complications, including infertility, poor growth, and neurocognitive effects.<sup>35-37</sup>

For survivors who received grafts from donors other than matched siblings, however, reduced-intensity or myeloablative conditioning, as compared with immunosuppression or no conditioning, was associated with improved T-cell counts and more consistent B-cell function, findings that are consistent with previous reports.<sup>13,32,34</sup> For selected patients (e.g., uninfected infants with specific genotypes), the high probability of survival and the advantages of complete immune reconstitution may outweigh the risks of conditioning-associated toxicity. However, for patients with active infection, the risks appear to outweigh the benefits. For patients with active infection, transplantation performed without conditioning followed by administration of donor-derived, pathogen-specific T cells, or sequential transplantations (the first performed without conditioning to correct T-cell deficiencies and the second performed with a conditioning regimen that secures B-cell engraftment), might improve overall results while reducing both mortality soon after transplantation and morbidity in the long term.

In summary, our data indicate that children with classic SCID diagnosed at birth or before the onset of infection who receive transplants from mismatched related donors, transplants from unrelated donors, or cord-blood transplants soon after diagnosis have more than a 90% probability of survival with T-cell and variable B-cell immune reconstitution. We found that mortality was increased for patients who had active infection at the time of transplantation. For such patients who did not receive transplants from matched donor siblings, the survival rate was highest among those who received T-cell-depleted grafts from mismatched, related haploidentical donors without undergoing conditioning.

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#### APPENDIX

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