The First Fifty Years of Stem Cell Transplantation in Severe Combined Immunodeficiency (SCID)

Amene Saghazadeh[1,2], Andrew J. Cant[3], Nima Rezaei[1,4,5]

[1] *Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Systematic Review and Meta-Analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

[3] *Department of Pediatric Immunology, Great North Children's Hospital, Newcastle Upon Tyne, United Kingdom*

[4] *Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Network of Immunity in Infection Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

Received: 11 Feb. 2024; Accepted: 18 Oct. 2024

Abstract- Since the first successful hematopoietic stem cell transplantation (HSCT) in 1968 for severe combined immunodeficiency (SCID), clinical studies have commenced. However, there is a high heterogeneity across studies. This is a review of studies evaluating the efficacy of SCT in SCID. There were 25 multi-center studies (MCSs) and 60 single-center studies (SCSs). Overall, MCSs provided a full range of survival rates (30-88.5%), though 80% of MCSs reported a survival rate of ≥60%. All MCSs, except one, that reported an overall survival of <60% were performed before the year 2000. Also, all MCSs that reported an overall survival rate of ≥80% were conducted in American/European centers. Totally, 85%, 60%, 31.67%, and 8.33% of SCSs reported a survival rate of ≥60%, 70%, 80%, and 90%, respectively. Asian studies reported the broadest range (16.6-86.67%) of survival rate compared to American (58.3-88%) and European studies (48.39-100%). Consistent with MCSs, SCSs with survival rates of <40% were conducted across Asian countries. The outcomes of SCT in SCID patients varies widely according to the center where the study is conducted, the sample size, the study period, age at SCT, race, lung or viral infection before SCT, active infection at the time of SCT, the protected environment used at SCT, early development of T-cell reconstitution after SCT, prophylaxis against GvHD, SCID phenotype and molecular diagnosis, conditioning regimen, and donor type. Therefore, future investigations are needed to discover the chief determinants of such a different survival rate in SCID patients who underwent SCT.

Acta Med Iran 2024;62(November-December):297-332.

Keywords: Cell therapy; Gene therapy; Donor; Stem cell transplantation; Severe combined immunodeficiency; Survival

Introduction

SCID, also known as “bubble boy disease”, describes a heterogeneous group of inherited diseases associated with different disease genotypes with distinctive lymphocyte profiles (Table 1) (1). SCID is usually diagnosed by six months of age and is chiefly characterized by failure to thrive and life-threatening infections with both opportunistic and common pathogens. The disease is fatal in infancy or early childhood in children unless effective treatment is given promptly. Thus, although rare, SCID should be considered as a pediatric emergency, and early diagnosis and management are essential if these patients are to survive.

The newborn screening programs (NSP) for SCID have confirmed that the spectrum of SCID disorders, including typical SCID, leaky SCID, and Omenn syndrome, have an incidence of 1 per 58,000 infants in the United States (2). The evidence is accumulating that

Corresponding Author: N. Rezaei
Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166929234, E-mail address: rezaei_nima@tums.ac.ir

such screening programs contribute effectively to early diagnosis and treatment of SCID (3), resulting in high survival rates (~90%) of SCID infants (2). Nevertheless, there is no clear international consensus for universal NSP (4).

Hematopoietic stem cells are multipotent cells derived from the bone marrow, which are capable of differentiating into myelomonocytic cells, B cells, or T cells through the reconstitution of the various blood cell types (5). It has been estimated that allogeneic HSCT is now carried out twice as often as autologous HSCT. In parallel with this, the incidence of diseases treated by allogeneic HSCT has increased (6). Cancers (particularly leukemia, lymphoma, neuroblastoma, ovarian cancer, germ-cell tumors, and myeloma), autoimmune diseases, and amyloidosis have been the three commonly treated diseases with autologous HSCT. Allogeneic HSCT is commonly used for treatments of certain types of cancer (particularly leukemia, lymphoma, and myeloma) and anemia (including aplastic anemia, paroxysmal nocturnal hemoglobinuria, Fanconi's anemia, Blackfan–Diamond anemia, and sickle cell anemia), and other diseases, including Thalassemia major, SCID, Wiskott–Aldrich syndrome, and inborn errors of metabolism. Of note, one of the first two successful HSCT was done in a child with X-linked form of SCID in the United States in 1968 (7). Since then, HSCT has been considered as the treatment of choice for various types of SCID and proved to make normal the mortality rates of these patients over six years after treatment (8). Here we will present evidence of clinical studies evaluating the efficacy of SCT for patients with SCID.

1. Multi-center Studies

All the multi-center studies (MCSs) included in the present review (9-32) were retrospective except one (33), which was a prospective study (Table 2). The studies included 3173 SCID patients, and the mean number of patients per study was 126.92 (range, 6-699). Most of the MCSs (20/25) reported a survival rate of greater than 60% (Figure 1). However, overall, the studies provided a full range of survival rates (range: ~30-88.5%).

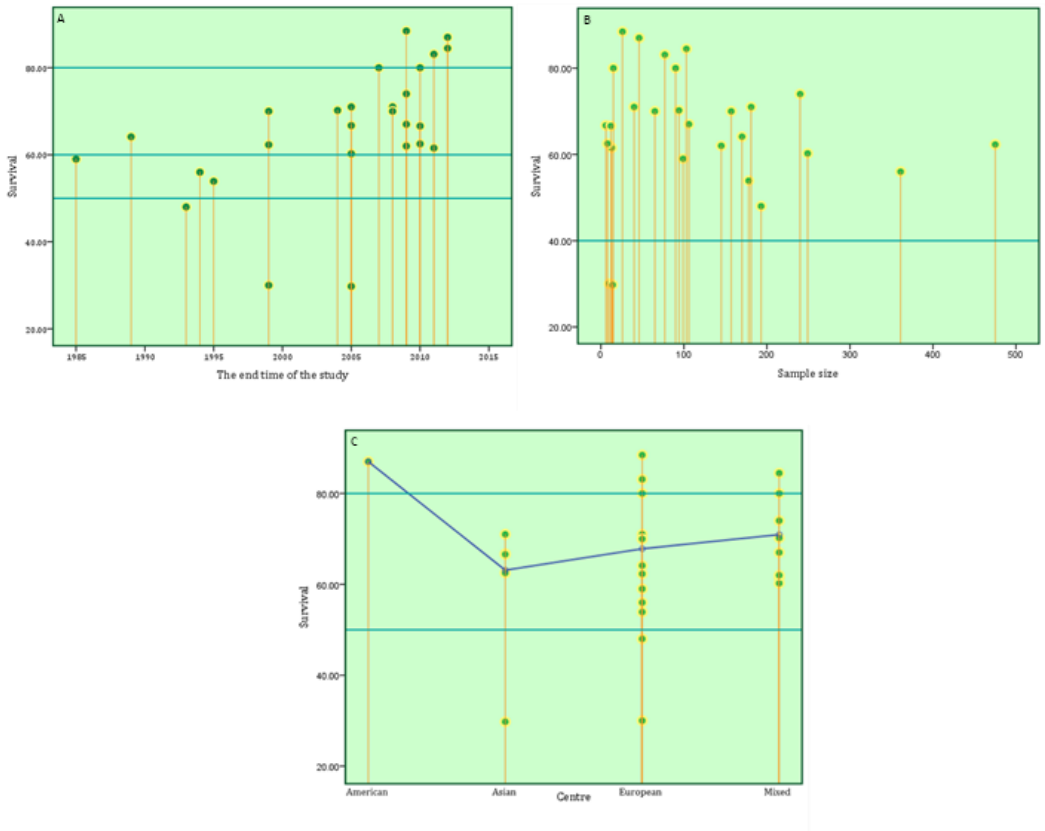

Figure 1. The outcome of SCID patients according to the evidence from multi-center studies by: A) the end time of the study B) the sample size, and C) the center at which the study has been conducted; there seems to be a noticeable reduction in the mean survival rate provided by Asian SCSs compared to that reported by American and European SCSs

The MCSs were classified according to the study center(s) and study period. Potential factors that might influence the outcome of SCID patients after transplantation are then discussed in an attempt to refine the ranges of survival rates.

American studies

Dvorak *et al.*, (33) conducted a prospective study in 33 centers across North America from 2010 to 2012. The study population consisted of 37 typical ($T^-B^+NK^-$: 22, $T^-B^-NK^+$: 5, $T^-B^+NK^+$: 6, ADA-SCID: 1, SCID with intestinal atresia: 1) and 13 atypical (Omenn: 6, leaky SCID: 6, reticular dysgenesis: 1) SCID patients. Over 90% of patients received HSCT in the first 1-2 months of life. In both typical and atypical SCID patients, the infection was identified as the trigger for diagnosis in most patients, and other triggers for diagnosis were family history, newborn screening, and other symptoms. Of 37 typical SCID patients, 33 received HCT; 16 with transplants from related donor (MRD-BM/PBSC: 4, MMRD-TCD-BM/PBSC: 12) and 17 from an unrelated donor (UD-BM/PBSC: 6, UD-UCB: 11). No conditioning regimen (CR) was used for most patients receiving transplants from a related donor, whereas myeloablative conditioning (MAC) was used for most patients receiving transplants from an unrelated donor. In the atypical SCID group, three patients were transplanted with HSCs from MRD-BM/PBSC, seven from UD-BM/PBSC, and three from UD-UCB. MAC regimen was used for almost half of atypical SCID patients and reduced-intensity conditioning (RIC) regimen for the remaining patients. A survival rate of ~87% within a short-term follow-up (median: 9.2 mon, range: 3.3-17.5 mon) was reported. The authors did not provide information about the main causes of death and the difference in death rates among different transplant groups.

Asian studies

Lee *et al*., (16) performed a cohort study in 5 tertiary medical centers across Taiwan from 1985 to 2006 to assess the distribution and outcome of different primary immunodeficiencies. SCT was done for 6 SCID patient (T^-B^+: 4, and T^-B^- : 2) with a median age at transplantation (AAT) of 6mon (range: 2-8 mon). Two patients were transplanted with BM from their HLA-identical sibling (no CR), one with haploidentical BM from her father (TCD and Cyc, and Bus), one with haploidentical BM from his mother (Cyc and Bus), one with fetal thymus from his sibling (no CR), and one with UCB from an unrelated donor (ATG). The authors reported that two patients died (survival rate= ~66.7%) due to sepsis; however, the duration of the follow-up has not been mentioned.

Arpacı *et al*., (18) evaluated the efficacy and outcomes of HSCT from an HLA-haploidentical donor in SCID patients transplanted at six medical centers in Turkey between 2000 and 2005. The study population included 4 T^-B^+- and 10 T^-B^--SCID patients and, with the median follow-up of 8.8 years, the 3-year overall survival was estimated ~81%.

Lee *et al*., (20) carried out a cohort study in 12 Chinese and Southeast Asian SCID infants (median AAT: 8mon, range: 2-11mon) from 1999-2010. The SCID types included $T^-B^-NK^+$: 6, $T^-B^+NK^-$: 4, $T^-B^+NK^+$: 1, and $T^+B^-NK^+$: 1. The stem cell source and donor type were BM-haploidentical father (n=2), BM-identical sibling (n=2), BM-MUD (n=2), PBSC-haploidentical mother (n=1), PBSC-MMRD mother (n=1), and UCB-UD (n=4). TCD was done for only one patient who received BMT from her father. MAC, containing Cyc and Bus, with or without ATG, was used for three and RIC, containing Fludarabin and melphalan, was used for four patients. No CR was used for the remaining patients (n=4). With the mean follow-up duration of 6.3 ys (range: 0.25-18 ys), the authors reported the survival rate of ~67%. 3 out of 4 deaths occurred in the first two months after SCT and that the main causes of death were a multi-organ failure (2/3) and idiopathic pneumonia (1/3). The fourth death occurred 11mon after SCT due to chronic GvHD.

Lee *et al.*, (22) conducted a nationwide population-based study using a "computer database at Chang Gung Memorial Hospital, a nationwide PIDs resource center covering 23 million people" from 1985 to 2010. The authors assessed the outcome of 8 Taiwanese children with SCID who underwent SCT from; fetal thymus-sibling (n=1), BM-haploidentical father (n=1), BM-MUD (n=1), UCB-UD (n=2), BM-haploidentical mother (n=1), and BM-identical sibling (n=2). No CR was used for three patients who received transplants from their HLA-identical siblings. ATG was used for three patients who received transplants from a UD. The combination of Cyc and Bus was used for two patients who received transplants from their parents. TCD was done for only one patient who was transplanted with BM from her father. The authors reported that two patients died due to sepsis and one due to respiratory failure (survival rate=~62.5%) however, the duration of the follow-up has not been mentioned.

Morio *et al*., (23) examined the Japan Cord Blood

Bank Network (JCBBN) from 1998 to 2008 and assessed the outcome of UCBT from a UD in 40 Japanese patients with SCID. The median AAT was 6.5 mon (range: 0-27 mon). RIC and MAC regimens were respectively used for 45% and 25% of patients, while no CR was used for the remaining patients (30%). The overall survival at 5-year was estimated at 71%, and the leading causes of death included viral, bacterial and fungal infections, veno-occlusive disease, GvHD, and adrenal insufficiency.

European studies

Most of the MCSs included in the present review (11/25) were carried out across European centers. Below we discuss these studies according to the study time.

Fischer *et al*., (10) studied the outcome of BMT for SCID patients at 14 European centers from 1969 to 1985 including 99 SCID patients. The transplant subgroups included 46 patients who received TCD-BMT from an HLA-MMD, 41 patients who received BMT from an HLA-MD, and 11 patients who received BMT from an HLA-MMD without TCD. The follow-up was≥ 5 mon. The disease-free survival (DFS) rates were 57%, 68%, and 18.2%, respectively, for each of the subgroups. Genotypically identical BM and the AAT below 6mon, but not the type of SCID, were shown to influence the DFS of SCID patients transplanted with HLA-identical BM. In contrast, the type of SCID, but not the degree of HLA-mismatching and the method of TCD, significantly affected the DFS of patients transplanted with TCD-BM from MMD. ADA-SCID patients had the worst prognosis compared to patients suffering from other types of SCID.

Fischer *et al*., (9) analyzed the survival rate of 183 SCID patients who underwent SCT at 15 European centers from 1968 to 1989. The mean±SD AAT was 7.5±7.9 mon and the transplant subgroups included 70 patients who received BMT from an HLA-identical donor and 100 patients who received TCD-BMT from an HLA-nonidentical donor, and that with the median follow-up of 73 and 46 mon, the survival rates were 70% and 56%, respectively. Only two of 13 patients who received BMT from an HLA-nonidentical donor without TCD survived within the study period. In contrast to the earlier European study described above, this study did not confirm the influence of the type of SCID on the outcome. More precisely, the number of ADA-SCID patients (53%) surviving after HLA-nonidentical BMT was similar to that of patients with other forms of SCID (33-67%). Patients with reticular dysgenesis had the worst prognosis (survival rate of 33%). The presence of lung infection before BMT significantly reduced the chance of survival while using a protected environment significantly increased the chance of survival for patients receiving HLA-nonidentical BMT. Probably, the most important finding of this study was that the survival of recipients of HLA-nonidentical TCD-BMT treated with CR was considerably improved compared to those who were not treated with CR (71% vs. 40%).

Haddad *et al*., (11) designed a retrospective study of 193 SCID patients at 18 European centers from 1982 to 1993 to investigate when the T- and B- cell functions are developed after HLA-nonidentical TCD-BMT. The authors reported the survival rate of 60% at six months and 48% at a median of 6 years. The median time to develop the T-and B-cell functions was 8.7 and 14.9 months, respectively. Less than half of patients who could not develop the normal T-cell function within six months post-BMT had the normal T-cell function at the last follow-up (median of 6 years). Also, there appeared to be a close correspondence between the developments of T- and B-cell functions. According to the findings of multivariate analysis, anti-LFA1 MoAb was the only factor that could exert a significant negative effect on the B-cell function development at six months post-BMT. More interestingly, unlike the B-cell function status, there was an association between good T-cell function status and better survival of patients. Finally, the presence of chronic GvHD and the absence of normal T-cell function at six months post-BMT were the only factors significantly associated with the survival of SCID patients. Note, CR showed no significant effect on the outcome of patients.

Bertrand *et al*., (12) evaluated the outcome of 178 SCID patients who underwent HLA-nonidentical TCD-BMT at 18 European centers from 1982 to 1993. The DFS of 53.5% was estimated. However, with the median follow-up of 57 and 52 months, B^+ and B^- SCID patients showed the DFS of 60% nad 35%, respectively. In addition to the SCID diagnosis, the presence of lung infection begores BMT, AAT, the method of TCD, and the period during which BMT was performed, were associated with the DFS of SCID patients. Some factors, including CR, HLA compatibility, donor/recipient sex, acute GvHD, chronic GvHD, had no statistically significant influence on the outcome of SCID patients receiving HLA-nonidentical TCD-BMT.

Bertrand *et al*., (13) shared their experience of HLA-haploidentical TCD-BMT in 10 patients with reticular dysgenesis (RD) at three European centers from 1979-1999. The median AAT was 2.5 months, and in general, most patients received CR. Interestingly, all who were not treated with CR before the first BMT (n=4) died during the study period, whereas half of the patients (3/6) who

received CR before the first BMT were alive. The study estimated a survival rate of 30% for patients with RD who received BMT from an HLA-haploidentical donor. The most important conclusion we can draw from this study is that the only RD-SCID given CR before HLA-haploidentical TCD-BMT survived.

Antoine *et al*., (14) reported the long-term outcome of 475 SCID patients who received SCT at 37 European centers from 1968-1999. The study population included the following transplant subgroups; HSCT from an HLA-genotypically identical donor (n=104), HSCT from an HLA-phenotypically identical related donor (n=49), HSCT from a mismatched related donor (n=294), and HSCT from an HLA-phenotypically identical unrelated donor (n=28); at 3-year post-HSCT, the survival rates were 81%, 72%, 54%, and 63%. Of note, there was a significant increase in the survival of ADA- and RD-SCID patients who received HSCT from an HLA-matched donor (ADA: 81% and RD: 75%) compared to those who received HSCT from an HLA-mismatched donor (ADA: 29% and RD: 29%). The important findings of this study were; 1) there was an effect of time on the outcome of SCID patients receiving HSCT from both the HLA-identical and nonidentical donors, 2) the SCID phenotype, using a protected environment, and the presence of pulmonary infection before HSCT showed a significant influence on the outcome of SCID patients underwent HSCT from a related HLA-mismatched donor, and 3) the AAT and using prophylaxis against GvHD showed a significant influence on the outcome of SCID patients underwent HSCT from an HLA-identical donor.

Gennery *et al.,* (19) performed an analysis of the outcome of 699 SCID patients who underwent HSCT at European centers from 1965 to 2005 using the electronic SCETIDE database established for EBMT/ESID to register HSCT for PID. The authors of this study, which is the largest MCS included in the present review reported the 5-year survival of patients according to the years of graft as follows; 1) before 1995: 56%, 2) 1995-1999: 70%, and 3) 2000-2005: 71%, indicating the improvement in the outcome of SCID patients who received HSCT over time. The study found that several factors, including years of graft, AAT, SCID phenotype, recipient/donor compatibility, respiratory impairment, septicemia, viral infection, TCD, protected environment, and prophylaxis, could significantly influence the outcome of SCID patients receiving HSCT.

Brown *et al*., (24) compared the outcome of SCT for SCID patients who were the first presenting person in the family (group A) with those who were diagnosed antenatally or at birth because of a diagnosis of SCID in a previous sibling or family member (group B). The study was conducted at two centers in the UK and included 90 SCID patients (group A, n=31, and group B, n=59). The authors showed that patients in group A were more likely to profit from after SCT compared to those in group B (10-year survival: 54% vs. 93%). This study indicates the importance of newborn screening programs for SCID.

Slatter *et al*., (25) performed a study of 26 SCID patients who received SCT at two centers in the UK between 2006 and 2009 to compare the effects and outcomes of conditioning with Treosulfan/fludarabine (n=15) and cyclophosphamide (n=11). With the median follow-up of 25.5 and 17 months, the authors estimated the survival of SCID patients who received Treosulfan/fludarabine, and Treosulfan/ cyclophosphamide was 93.3% and 81.8%, respectively. This study highlighted the benefit of the modified conditioning regimen and the outcome from transplant since 2005.

Mitchell *et al.,* (28) assessed the efficacy of HSCT in 65 SCID patients treated at six Australian and New Zealand Children's Haematology Oncology Group pediatric transplantation centers from 1992 to 2008. The 5-year overall survival was estimated to be about 70%, with the median follow-up of 6.03 years.

Hassan *et al.,* (32) aimed at addressing the question of whether the efficacy and outcomes of SCT in SCID patients were affected by host NK cells. To this end, they carried out a study of 77 SCID patients who received HSCT at two pediatric centers in the UK from 1990-2011. The study population included 24 〖NK〗^+ and 53 〖NK〗^-patients and with the median follow-up of 3070 and 3001 days, the survival rates were around 90% and 60%.

Mixed studies

Grunebaum *et al*., (15) compared the outcome of receiving BMT from a related, unrelated, or mismatched donor at treating SCID patients. The study was conducted in one Canadian and one Italian center from 1990-2004. The study population was composed of 94 SCID patients and three different BMT subgroups; 1) BMT from a related HLA-identical donor (n=13), 2) BMT from an unrelated HLA-matched donor (n=41), and 3) BMT from a related HLA-mismatched donor (n=40). Most patients receiving BM from MUD and MMRD were treated with MAC regimen prior to BMT. Totally, with the median follow-up of 96, 40, and 24 months, the authors reported the survival of ~92.3, 80.5, and 52.5% for the subgroups 1, 2, and 3, correspondingly. This study did not confirm the finding of other studies that the B^--SCID phenotype

is associated with poor outcome post-SCT since the survival rates for the B^--SCID and B^+-SCID patients were respectively estimated at about 84.6 and 78.6% within the MUD transplant subgroup and about 52.9 and 52.1% within the MMRD transplant subgroup. The study also demonstrated that patients who received BMT from MUD were more likely to develop the T-cell function than those who received BMT from MMRD .

Honig *et al*., (17) examined the long-term outcome of 15 ADA-SCID patients who received HSCT at two medical centers (Duke University Medical Center (Durham, NC) and the Children's Hospital, Zurich, Switzerland) since 1982. The mean AAT was 6.4 months (range: 2-30 months) and the transplant subgroups included 1) patients who received HSCT from an MFD without using CR (n=7), 2) patients who received TCD-HSCT from an MMFD using CR (n=6), and 3) patients who received HSCT from a MUD using CR (n=2). All patients treated with HSCT from MFD were alive during the study period (mean: 9.5 years, range: 3.9-13.5 years). However, with the mean follow-up time of 14.6 years (range: 4.6-22.2 years), two and one of the patients in transplant subgroups 2 and 3 respectively, died. The most important finding of this study was that half of the patients who survived during the study period presented severe neurological problems (e.g., mental retardation, motor dysfunction, and hearing deficit) suggest that SCT, in its current form, may not fully overcome these problems.

Marcus *et al*., (21) reported a retrospective study of 13 CD3δ-SCID treated with SCT at seven medical centers, including America, Japan, Spain, and Germany. The transplant subgroups included 1) patients who received HSCT from a MRD (n=1), 2) patients who received TCD-HSCT from a MMRD (n=7), 3) patients who received UCB from an UD (n=2), and 4) patients who received HSCT from a MUD (n=3). Although all the patients in the transplant subgroups 1, 3, and 4 survived during the study period (mean: 6.75 years, range: 1-20 years), only one patient who received TCD-HSCT from an MMRD was still alive, and five patients died due to CMV or GvHD.

Hassan *et al*., (26) analyzed the outcome of 106 ADA-SCID patients treated with HSCT at 16 international transplantation centers from 1981 to 2009. With the median follow-up of 6.5 years, almost 67% of patients survived. However, there were significant differences in the survival rates among transplant subgroups. The study included five transplant subgroups; 1) patients who received HSCT from an HLA-matched sibling donor (n=42), 2) patients who received HSCT from an HLA-matched family donor (n=12), 3) patients who received HSCT from an unrelated HLA-matched donor (n=15), 4) patients who received HSCT from an unrelated HLA-mismatched donor (n=7), and 5) patients who received HSCT from an HLA-haploidentical donor (n=30) and the survival rates within the study period were respectively as follow; 86%, 83%, 67%, 29%, and 43%. Another important finding in this study was that using the MAC regimen was shown to reduce the survival of ADA-SCID patients when compared to patients who were not treated with any CR (54% vs. 81%).

Fernandes *et al*., (27) aimed at comparing the efficacy and outcomes of UCBT from a UD (n=74) with that of HSCT from an MMRD (n=175) in SCID patients treated at 30 European and non-European centers between 1995 and 2005. For SCID patients who received UCBT-UD and HSCT-MMRD, the 5-year overall survival rates were estimated at about 57%±6% and 62%±4% with the median follow-up of 83 and 58 months, respectively. Patients who received UCBT-UD were more likely to develop both acute and chronic GvHD more and also to achieve lymphocyte count recovery earlier than recipients of HSCT-MMRD.

Schuetz *et al*., (29) analyzed the outcomes of HSCT in SCID patients with Artemis (n=69) or RAG1/2 deficiency (n=76). The transplantation was done between 1985 and 2009 at one of the following centers: the University of California, San Francisco Benioff Children's Hospital, Hôpital Necker-Enfants Malades, France (Paris), and at the Department of Pediatric and Adolescent Medicine, University Medical Center Ulm, Germany (Ulm). The median AAT was seven months, and the overall survival was 62% with the median follow-up of 51 and 32 months for Artemis- and RAG1/2-SCID patients, respectively. The transplant subgroups included 1) patients who received HSCT from an HLA-identical donor without CR (n=42), 2) patients who received TCD-HSCT from an HLA-haploidentical donor (n=82), 3) patients who received HSCT from an unrelated HLA-matched donor (n=8), and 4) patients who received HSCT from an HLA-mismatched family donor (n=13) and the survival rates were respectively estimated about 88%, 52.5%, 62.5%, and 46.15% within the study period. This study demonstrated that deaths are likely to occur within two years after HSCT. However, the most important finding of this study was that the HSCT could not avoid long-term complications, e.g., growth retardation, endocrinologic deficiencies, and dental abnormalities in patients with Artemis deficiency .

Pai *et al*., (30) performed a retrospective analysis on 240 SCID infants transplanted at 25 centers between 2000

and 2009. The median AAT was 180 days (range: 8-1162 days), and the overall 5-year survival rate was estimated at 74%. The transplant subgroups included 1) patients who received transplants from a matched sibling donor (n=32), 2) patients who received transplants from a mismatched related donor (n=138), 3) patients who received transplants from other related donors (n=8), and 4) patients who received transplants from an unrelated donor (n=62). The 5-year survival rates among recipients of transplants from MSD, MMRD without CR, MMRD with CR, UCBT from UD, and other unrelated or related donors were as follows; 97%, 79%, 66%, 58%, and 74%, correspondingly. This relatively large study did not confirm the finding of other studies that the B^--SCID phenotype is associated with poor outcome post-SCT.

Dvorak *et al*., (31) conducted an MCS across North America, Europe, and Australia between 1993 and 2012 and compared the efficacy and outcomes of receiving HSCT from an MSD (n=66) with that from a MUD without CR (n=37) in SCID patients. The median AAT among recipients of HSCT from MSD and MUD was 132 and 182 days, and with the median follow-up of 6.9 and 3.9 years, the authors reported the 5-year overall survival of 92% and 71%, respectively. Interestingly, this study implied that children who had received HSCT from MSD did not achieve markedly better long-term results when compared to children who had received HSCT from MUD without using CR prior to transplantation; as the immunological outcomes, including the rate of T-cell engraftment and immune reconstitution, in recipients of HSCT from MUD without CR was good as much as in recipients of HSCT from MSD.

The time effect

All the MCSs, except one (18), that reported an overall survival of less than 60% were performed before the year 2000 (Figure 1.A) (10-13). It highlights that the outcome of stem cell transplantation has dramatically improved over time, which may be, at least in part, due to the development of more advanced techniques.

The center effect

30% (25/6) of the MCSs reported an overall survival rate of ≥80%. All these studies were conducted in American and/or European centers (Figure 1.C) (17,24,25,31-33). In other words, all the MCSs regarding the topic across Asian countries have shown survival rates not higher than 71% (range: 29.76-71%).

The sample size effect

In general, the sample size of both MCSs with a survival rate of less than 40% was really small (10 and 14 patients) (Figure 1.B). Although we excluded studies, including less than 5 SCID patients, transplant subgroups might have included less than 5 SCID patients. The survival rate of such subgroups was very different from others. In the subgroup of SCID patients who received transplants from a matched unrelated donor, exclusion of studies with less than 5 SCID patients narrowed the range for the survival of patients to 62.5-80.5% from a previous 50-100%. Also, in the subgroup of SCID patients who received transplants from an HLA-haploidentical donor, there was found a relatively narrow range of 29.76-52.5% compared to when studies with less than five patients were considered (range: 29.76-100%).

Single-center studies

Sixty SCSs included in the present review were categorized into retrospective (n=40), prospective (n=8), uncontrolled longitudinal study (n=10), case-control study (n=1), and non-randomized controlled trial (n=1). Among 60 single-center studies (34-93), 35 studies were carried out across European countries (16 in the UK, 6 in Italy, 4 in France, 2 in Australia, 2 in the Netherlands, 1 in Denmark, 1 in Germany, 1 in Russia, 1 in Serbia, and 1 in Spain), 15 studies in the United States and Canada, and 10 in Asian countries (3 in Japan, 2 in China, 2 in Jordan, 1 in Israel, 1 in Saudi Arabia, and 1 in Turkey) (Table 3). The studies included 1958 SCID patients, and the mean number of patients per study was 36.64 (range, 5-166).

Table 4 and 5 summarize the efficacy and outcomes of SCT for SCID according to the evidence from MCSs and SCSs. Below is an overview of the main findings of these studies according to the center at which the study was conducted.

Response to treatment

Survival

American studies

SCSs conducted in the United States, and Canada included 450 patients, and the mean No of patients per study was 28.12. Overall, survival rates ranged from 58.3 to 88%. Patients who had received stem cells from a MRD (No of studies: 3 and No of patients: 26) and also recipients of an HLA-identical transplant (No of studies: 1 and No of patients: 5) have the highest survival rate of 100%.Then, patients who had received stem cells from a MMRD (No of studies: 1 and No of patients: 16) demonstrated a survival rate of 93.75% , E) Patients who had received stem cells from an UD (No of studies: 1 and No of patients: 8) and a MMD (No of studies: 1 and No

of patients: 8) displayed the survival rate of 75%. The survival rates of patients who underwent an HLA-haploidentical transplant (No of studies: 4 and No of patients: 90), SCT from a MUD (No of studies: 1 and No of patients: 4), and an unrelated HLA-identical transplant (No of studies: 1 and No of patients: 9) were within the range of 46-67% across studies. When the authors had not provided the donor type and HLA histocompatibility, there was, in general, a range of 63-87% for SCID patients (No of studies: 7 and No of patients: 284).

Asian studies

SCSs conducted in the Asian countries included 191 patients and the mean No of patients per study was 19.1. The studies reveal the relatively broad range of survival rates from 16.6% to 86.67% The range could be narrowed to 77.78-100% among patients who had received stem cells from an MRD (No of studies: 2 and No of patients: 12), an HLA-identical transplant (No of studies: 1 and No of patients: 99), and from a MUD (No of studies: 1 and No of patients: 1). In contrast, a very broad range of survival of 0-83.3% was reported by recipients of an HLA-haploidentical transplant (No of studies: 4 and No of patients: 34) and by patients who had received stem cells from a UD (No of studies: 4 and No of patients: 24). Patients who had received stem cells from an MMRD (No of studies: 1 and No of patients: 6) had a survival rate of 66.7%. When the authors had not provided the donor type and HLA histocompatibility, there was, in general, a range 16.6-50% for SCID patients (No of studies: 3 and No of patients: 15).

European studies

SCSs conducted in the European countries included 1317 patients, and the mean No of patients per study was 37.63. Overall, the survival rates ranged from 48.39 to 100% .

The best survival rate of 100% was observed with SCT from a MMRD (No of studies: 1 and No of patients: 5), MSD (No of studies: 2 and No of patients: 2), and an MMUD (No of studies: 1 and No of patients: 2). The survival rates for recipients of an HLA-identical transplant (No of studies: 10 and No of patients: 107), SCT from an UD (No of studies: 4 and No of patients: 29), and of SCT from a MMD (No of studies: 1 and No of patients: 8) occurred within the range of 60-100%. There was a narrow, but not ideal, survival range of 56-63% among recipients of an HLA-nonidentical transplant (No of studies: 2 and No of patients: 80). The range of survival was broadened to 47.37-100% among recipients of an HLA-identical transplant (No of studies: 16 and No of patients: 440) and to 0-100% among patients who had received stem cells from a MUD (No of studies: 5 and No of patients: 35). When the authors had not provided the donor type and HLA histocompatibility, there was, in general, a range 60-100% for SCID patients (No of studies: 12 and No of patients: 616) .

The time effect

Totally, 85%, 60%, ~31.67%, and ~8.33% of SCSs reported a survival rate of greater than or equal to 60%, 70%, 80%, and 90%, respectively. However, overall, the studies provided a full range of survival rates (range: ~16.6-100%). Overall, the studies provided a full range of survival rates (range: ~16.6-100%) with no significant time effect (Figure 2.A).

The center effect

Figure 2.C illuminates the impact of the center at which the study has been conducted; because of a noticeable reduction in the mean survival rate provided by Asian SCSs compared to that reported by American and European SCSs. Also, all the SCSs with survival rates less than 40% were conducted across the Asian countries.

The sample size effect

As demonstrated in Figure 2.B, there seems to be an effect of sample size on the outcome; the sample size of three studies with a survival rate of less than 40% was extremely small (range: 5-6 patients) .

Factors that affected or did not affect the survival of SCID patients who underwent SCT

TCD has been indicated to help enormously to improve the survival of patients who received HLA-mismatched marrow (10). Factors that could prolong the EFS included genotypically identical marrow and age below six months in recipients of HLA-matched marrow (10). During the absence of T-cell reconstitution six months after BMT, presence of chronic GvHD 6 months after BMT, T^- B^--SCID, and BMT before 1991 appeared to worsen the prognosis and also to threaten the survival of SCID patients transplanted with TCD, HLA-nonidentical marrow (11,12). Interestingly, the presence of pulmonary infection before BMT and the method of TCD have been associated with more reduced survival for T^- B^--, but not T^- B^+-SCID patients (12). Though no association between types of SCID and DFS was found in recipients of HLA-matched marrow (10), patients carrying ADA deficiency displayed significantly poorer prognosis and also lower DFS than patients with other types of SCID transplanted with TCD HLA-mismatched

marrow (10). Other factors that have been recognized to affect the survival of the whole population of SCID patients underwent BMT were race and sex, in the manner that white and female SCID patients were more likely to survive than Hispanic/black and male patients (48). Factors that did not exert any significant impact on survival were included the degree of HLA-mismatching and the method of TCD among patients who received TCD HLA-mismatched marrow (10), type of SCID in recipients of HLA-matched BM (10), and B-cell reconstitution 6months after BMT, HLA compatibility, sex, and GvHD (either acute or chronic) in recipients of TCD, HLA-nonidentical BMT (11). Unlike non-SCID patients, reducing the intensity of conditioning (RIC) regimen before BMT from URD could not significantly improve the survival of SCID patients in comparison with BMT using myeloablative conditioning (MAT) (62). However, the severe limitation of this research was the small sample size of SCID patients (RIC: 6 and MAT: 7) (62). Table 6 summarizes the main findings of some studies that investigated the possible influence of different factors on the survival of SCID patients after transplantation. As well, one study reported the 5-year survival rate of 33% for SCID patients (n=6) who received bone marrow from URD that could be explained by the relatively long interval time between SCID diagnosis and BMT and the catastrophic consequences of myeloablative conditioning (used for four patients) such as veno-occlusive disease and interstitial pneumonitis (63).

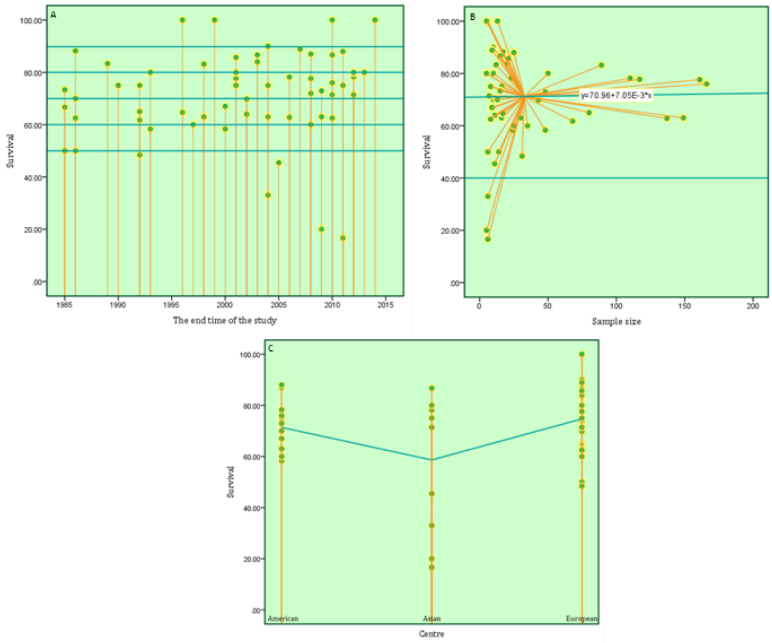

Figure 2. The outcome of SCID patients according to the evidence from single-centre studies. A) The graph demonstrates that 85%, 60%, ~31.67%, and ~8.33% of SCSs reported a survival rate of greater than or equal to 60%, 70%, 80%, and 90%, respectively. Overall, the studies provided a full range of survival rates (range: ~16.6-100%) with no significant time effect. B) The graph shows that the sample size of three studies with a survival rate less than 40% was extremely small (range: 5-6 patients). C) The interpolation line illuminates the impact of centre at which the study has been conducted; there seems to be a noticeable reduction in the mean survival rate provided by Asian SCSs compared to that reported by American and European SCSs. In addition, all the SCSs with survival rate less than 40% were conducted across the Asian countries

Engraftment

Either myeloablative or non-myeloablative CR comprising different degrees of immunosuppressive agents, including Cyclophosphamide (Cyc), anti-thymocyte globulin (ATG), and Busulfan (Bus), were commonly administrated to suppress the host immune system and thereby to minimize the risk of graft failure with HLA-nonidentical, HLA-mismatched or HLA-matched transplants from an unrelated donor. T-cell depletion (TCD), which can be accomplished in different ways, e.g., erythrocyte rosettes, Lectin+rosettes, and monoclonal antibodies (MoAbs), is widely advocated as primary prophylaxis of graft failure and also GvHD after HLA-nonidentical or haploidentical BMT. Other drugs prescribed for the prevention and treatment of post-transplant GvHD included Cyclosporin A, methylprednisolone, methotrexate, and MoAbs such as anti-CD3 and anti-CD6 antibodies. MoAbs used for TCD

included anti-LFA1, anti-CD2, and anti-CD6 antibodies .

Engraftment rate (ER) was slightly, but not significantly, reduced among T^- B^- than T^- B^+-SCID patients who received TCD HLA-nonidentical marrow (~70% vs. 60%) (12). As well, X-linked SCID (n=7) patients underwent an especial transplant protocol comprising megadose of CD34+ HSCs with a fixed number of CD3+ cells without previous myeloablative conditioning demonstrated the T-cell ER of 100%, whereas only half of NK^+-SCID (4/8) achieved that (71). Overall, T-cell ER was enormously increased compared to B-cell ER (~73% vs. 25%) (71). Although, preconditioning with CY and Busulfan proved beneficial for T^- B^--SCID patients transplanted with TCD HLA-nonidentical marrow to have successful engraftment, ER was not under the influence of CR among T^- B^+- SCID patients (12). Similarly, the only patients who profited by anti-LFA1 MoAbs were T^- B^--not T^- B^+-SCID patients SCID transplanted with TCD HLA-nonidentical marrow (12). Meanwhile, the factor that significantly affected ER was maternal engraftment at the time of diagnosis (71).

Immunological function

For the majority of patients, the maximum time for reconstitution of T- and B-cell was six months post-HLA-identical BMT, however, it usually happened between 2 to 4 months (10). SCID people who received TCD, HLA-nonidentical BMT required the median time of 8.7 and 14.9 months for the reconstitution of T-cell and B-cell function, respectively (11). 6 months after TCD, HLA-nonidentical BMT, the absence of T-cell reconstitution has been proved to be a predictor of poor outcome (11). This relationship was not found in the case of B-cell reconstitution (11). In SCID people who received TCD, HLA-nonidentical BMT, T^- B^+-SCID was shown to correlate with earlier and more reconstitution of T- and B-cell function, whereas acute GVHD and chronic GVHD were, respectively, associated with slower and lower development of T-cell function at and later than 6months after transplantation (11). However, the reconstitution of the B-cell function was independent of the presence of GVHD in these patients (11). As expected, donor B-cell engraftment enormously enhanced the reconstitution of B-cell function post-HLA-mismatched BMT (67% vs. 10%) (10). Overall, T-cell reconstitution occurred more, earlier, and stronger than B-cell reconstitution following BMT (11,48), although there was a considerable correlation between them (11). It should be noted that B-cell reconstitution was shown to happen rarely in X-linked SCID patients after HSCT (71).

Complications after stem cell transplantation

Graft failure

Failure to engraft is reported not at all (10,15) or rarely in recipients of HLA-matched or identical marrow, while it has been believed to be the major complication with HLA-mismatched transplantation. In these patients, conditioning before the first graft could enhance the engraftment rate (92% vs. 64%) (10). It is of importance that all the SCID patients except ADA deficiency did not benefit considerably from the conditioning before the first graft and, more interestingly, that there was a decreased survival in conditioned patients that non-conditioned counterparts (69% vs. 47%) (10). It is a salutary lesson to be learned from these lines of evidence that conditioning seems may be able to prevent one complication, i.e., the graft failure, but it develops other dangerous and life-threatening complications, i.e., increasing the rate of infections and death hence (10).

Graft-versus-host disease (GvHD)

As summarized in table 4, overall, the incidence rates of both acute and chronic GvHD varied from 0 to 100%. The incidence of acute GvHD grade II to IV was within the range of 0-66.6% when grades 0 and 1 are considered as acute GvHD absent. Chronic GvHD has demonstrated to develop in 0-46% of SCID patients who underwent SCT. The prevalence of chronic GvHD declined over time post-TCD HLA-nonidentical BMT (11). Overall, there was a slight, but not significant decreased development of GvHD among T^- B^+- than T^- B^--SCID patients after TCD HLA-nonidentical BMT (11,12), elucidating that GvHD development post-BMT is under the influence of the type of SCID. Moreover, chronic GvHD development and post-BMT death were intertwined more closely in T^- B^- than T^- B^+-SCID patients, owing to the survival of 0% and 44% in T^- B^- and T^- B^+-SCID patients who developed chronic GvHD after TCD HLA-nonidentical BMT (12). There was a strong association between the presence of maternal T cells and the development of GvHD in a SCID population being transplanted with TCD, HLA-haploidentical parental BM, or HLA-identical BM from a related donor (48). Neither the pre-HSCT maternal engraftment nor the CD3+ cell dose was shown to have any significant impact on the risk of post-HSCT acute GvHD development (71).

Viral infections: the leading cause of death

Analysis of early and late deaths on SCID patients after BMT indicated that early deaths after HLA-nonidentical BMT have mostly been associated with

infections, whereas late deaths are caused mainly by GvHD and, to a lesser extent, by infections. Overall, infections and GvHD are correspondingly considered as the first and second leading causes of post-BMT-death. However, a relatively small study on nine patients whom all had T^- B^+-SCID and received HLA-matched BM from URD reported GvHD as the leading cause of death (50). Interestingly, both early and late deaths post-BMT happened more in T^- B^--SCID than T^- B^+-SCID patients (12). Infections related to post-BMT death have been elucidated to be caused mainly by viruses, such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), adenovirus, enteroviruses, parainfluenza virus, herpes simplex virus (HSV), and to a lesser extent by other pathogens, for example, candida and Aspergillus. A majority of them were determined to be developed before rather than after transplantation (10,12). Non-infectious causes of death were comprised of GvHD, unrelated mitochondrial defect, immune dysfunction with severe autoimmunity, B-cell lymphoproliferative syndrome, bone marrow aplasia, myocarditis, pulmonary alveolar Proteinosis, multiorgan failure, autoimmune cytopenia, cerebral edema and hemorrhage, and encephalitis .

Long-term complications

The research highlights the excellent survival (~80%) and also the complete immunological reconstitution in patients with ADA deficiency who received HLA-matched HSCT from unrelated donors with conditioning (17). Despite the absence of clinical complications, the treatment was not capable of preventing ADA-associated neurological problems and corroborated to carry a high risk of neurological complications. Totally, over half of survived patients transplanted developed such complications and cognitive impairment. The most common ones contained learning disability and motor dysfunction happened in almost 60% (7/12) of patients, verbal expression in 50% (6/12), hearing deficit in 41.5% (5/12), hyperactivity in 33.5% (4/12), and seizures in 8.5% (1/12) (17). Further, SCID patients who transplanted with TCD, HLA-haploidentical BM from MMRD without CR exhibited more long-term complications compared with recipients of HLA-matched BM from MRD without CR (72). Complications exhibited by patients in the MMRD group were gastrointestinal disorders, growth, and respiratory abnormalities, dermatologic manifestations, and hearing loss, and in the MRD group were dermatologic manifestations, endocrine, respiratory, and neurodevelopmental abnormalities (72).

Future prospects

The evidence is mounting that SCT-base gene therapy is a safe procedure for the management of certain forms of SCID. In Table 7, we summarized 14 studies that have assessed SCT-based gene therapy in SCID patients. The studies have been reported on 78 patients with X-linked- or ADA-SCID. All but four X-linked-SCID patients, who underwent autologous stem cell transplant with gene therapy, were alive at the latest follow-up (range: 1.5 mon-15 years). T-cell reconstitution varies depending on cell dose, clinical condition, and age at the time of treatment among X-linked SCID patients (94).

Regarding ADA-SCID patients, the treatment was rarely unsuccessful due to disease-specific and technical reasons but made real success in recovering the function of the immune system in other patients (95). Although HSCT is usually utilized to rescue patients with SCID, those who received a combination of MSC and allogeneic HSCT have exhibited enhanced engraftment (96), making MSCs favorable for the expeditious treatment of immune-mediated diseases, especially when HSCT alone is failed or rejected. These results are promising enough to realize that research in the fields of HSCT-based gene therapy and the combination of HSCT and MSC-which are regarded as relatively new applications of SCT for treatment of SCID-will be of utmost importance during the current decade.

Our review of studies evaluating the clinical efficacy of SCT for SCID indicates the broad ranges of survival rates and post-transplant complications (e.g., GvHD development) between and in different transplant subgroups. Unlike inter-group differences, which can be attributed mainly to donor type, no certain reasons can explain intra-group differences. Many factors, such as type of SCID, age at transplantation, race, sex, the presence of T-cell reconstitution six months after SCT, the presence of active infections at the time transplantation, and the method of T-cell depletion, have shown influence on the survival of SCID patients. Also, there seems to be an effect of the center (s) at which the study was performed and the sample size. However, future investigations with clearer methodologies and immunological endpoints are required to discover the chief determinants of such a different survival rate in patients enrolled in specific transplant subgroups. Recent reports suggest success for HSCT for PID is rising, with units reporting survival rates of around 90%. As data on HSCT for SCID are published over the next few years, it will be fascinating to see if similar results are obtained for SCID, particularly in countries implementing newborn screening.

Table 1. Severe combined immunodeficiency: genotypes and phenotypes

Severe combined immunodeficiency: genotypes and phenotypes (98)					
T^-B^+-SCID			T^-B^--SCID		
Inheritance	**Defective gene**	**Phenotype**	**Inheritance**	**Defective gene**	**Phenotype**
X-linked recessive	Interleukin-2 receptor gamma-chain (***IL-2RG***)	$T^-B^+NK^-$	Autosomal recessive	Adenosine deaminase deficiency (***ADA***)	$T^-B^-NK^-$
Autosomal recessive	Interleukin-7 receptor subunit alpha (***IL-7RA***)	$T^-B^+NK^+$	Autosomal recessive	Recombination-activating gene (***RAG*)*1***, ***RAG2***	$T^-B^+NK^+$
Autosomal recessive	Janus kinase 3 (***JAK-3***)	$T^-B^+NK^-$	Autosomal recessive	***Artemis***	$T^-B^+NK^+$
Autosomal recessive	***CD45***	$T^-B^+NK^+$	Autosomal recessive	DNA-dependent protein kinase, catalytic subunit (***DNA–PKcs***)	$T^-B^+NK^+$
Autosomal recessive	***CD3*** genes (CD3 delta (CD3D), CD3 epsilon (CD3E), and CD3 zeta (CD3Z).)	$T^-B^+NK^+$	Autosomal recessive	DNA Ligase IV (***LIG4***)	$T^-B^+NK^+$
Autosomal recessive	Actin-regulating protein, coronin 1A (***CORO1A***)	$T^-B^+NK^+$	Autosomal recessive	Cernunnos (***XLF***)	$T^-B^+NK^+$

Table 2. Multi-center studies assessing stem cell transplantation in severe combined immunodeficiency disorders

Study (YOP) Period Design	**Center**	**N**	**Phenotype/genotype of patients**	**Transplant subgroups**		**Age at first transplantation**	**Ref.**
				Type of transplant	**N**		
A Fischer (1986) 1968-1985 Retrospective	M, 14 European centers	99	RD: 2 , ADA: 16, Low T, Low B: 32, Low T: 40, Non-functional T and B: 9	BMT, TCD, MMD BMT, MD BMT, non-TCD, MMD	46 41 11	NA	(10)
A Fischer (1990) 1968-1989 Retrospective	M, 15 European centers	183	RD: 6, ADA: 30, Low T, Low B: 50, low T: 81, nonfunctional T and B cells: 16	BMT, genotypically identical BMT, phenotypically identical, RD BMT, phenotypically identical, UD BMT, TCD, NI BMT, NI without TCD	53 16 1 100 13	Mean±SD: 7.5±7.9mon	(9)
E Haddad (1998) 1982-1993 Retrospective	M, 18 European centers	193	T^-B^+: 107, T^-B^-: 50, ADA: 20, RD: 6, Other types: 10	BMT, TCD, NI	193	NA	(11)
A. Fischer (1999) 1981-1995 Retrospective	M, 18 European centers	178	T^-B^+: 122, T^-B^-: 56	BMT, TCD, NI	178	<6mon (n=62), 6-12mon (n=77), >12mon (n=39)	(12)
Y Bertrand (2002) 1979-1999 Retrospective	M, three European centers (Ulm, Paris, London)	10	RD: 10	HSCT, TCD, HI	10	Med: 2.5mon (R: 0.5-4mon)	(13)
A Fischer (2003) 1968-1999 Retrospective	M, 37 European centers	475	RD: 12, ADA: 51, low T and low B: 137, low T: 217, other: 58	HSCT, genotypically identical HSCT, phenotypically identical, RD HSCT, MMRD HSCT, UD	104 49 294 28	Med: 5.6mon Med: 6.2mon Med: 7.2mon Med: 9.1mon	(14)

Cont. table 2

CM Roifman (2006) 1990-2004 Retrospective	M, two, the Hospital for Sick Children in Toronto, Ontario, and the Department of Pediatrics at the University of Brescia, Italy.	94	ADA: 4, γ_c-Chain: 3, $T^-B^+NK^+$: 1, IL-7Rα: 1, FOXP3: 1, ZAP70: 1, RAG1: 1, Omenn: 1 ADA: 2, γ_c-Chain: 9, JAK3: 3, $T^-B^+NK^+$: 4, $T^-B^+NK^-$: 4, CD3δ: 1, IL-7Rα: 4, RMRP: 1, RAG1: 2, RAG2: 3, ARTEMIS: 2, Omenn: 5, $T^-B^-NK^+$: 1 γ_c-Chain: 7, JAK3: 9, $T^-B^+NK^+$: 7, $T^-B^-NK^+$: 2, RAG1: 7, RAG2: 1, ARTEMIS: 5, Omenn: 2	BMT, FRD, identical BMT, MUD BMT, MMRD	13 41 40	Med AOD: 5mon, Med DTIT: 1mon (R: 0-4mon) Med AOD: 4mon, Med DTIT: 4mon (R: 1-9mon) Med AOD: 4mon, Med DTIT: 2mon (R: 0-11mon)	(15)
W. I. Lee (2006) 1985-2005 Retrospective	M, five tertiary medical centers in Taiwan	6	T^-B^+: 4, T^-B^-: 2	BMT, MSD BMT, father BMT, mother CBT, UD Fetal thymus, MSD	2 1 1 1 1	Both underwent SCT at 8mon 5mon 6mon 6mon 2mon	(16)
W Friedrich (2007) Since 1982 Retrospective	M, two, Duke University Medical Center (Durham, NC) and the Children's Hospital (Zurich, Switzerland).	15	ADA: 15	HSCT, MFD without CR HSCT, TCD, MMFD with CR HSCT, MUD with CR	7 6 2	Mean: 6.4mon (R: 2-30mon)	(17)
F Arpacı (2008) 2000-2005 Retrospective	M, six, Gulhane Military Medical Academy, Ankara, Turkey	14	T^-B^+: 4, T^-B^-: 10	HSCT, HI	14	NA	(18)
A. R. Gennery (2010) 1968-1994 Retrospective	M, the electronic SCETIDE database established for EBMT/ESID to register HSCT for PID.	361	T^-B^+: 181, T^-B^-: 105, ADA: 42, RD: 11, other: 22	HSCT, GI, RD HSCT, PI, RD HSCT, MMRD HSCT, UD	84 33 229 15	Med: 5.8mon Med: 6.2mon Med: 7.2mon Med: 13.1mon	(19)
A. R. Gennery (2010) 1995-1999 Retrospective		157	T^-B^+: 80, T^-B^-: 46, ADA: 15, RD: 3, other: 13	HSCT, GI, RD HSCT, PI, RD HSCT, MMRD HSCT, UD	26 21 90 20	Med: 6.6mon Med: 4.5mon Med: 6.9mon Med: 10.1mon	
A. R. Gennery (2010) 2000-2005 Retrospective		181	T^-B^+: 84, T^-B^-: 55, ADA: 18, RD: 5, other: 19	HSCT, GI, RD HSCT, PI, RD HSCT, MMRD HSCT, UD	25 14 96 46	Med: 4.9mon Med: 4.2mon Med: 7.5mon Med: 9.5mon	
P. P. W. Lee (2011) 1992-2010 Retrospective	M, Chinese and Southeast Asian population.	12	RAG1: 1, IL-2RG: 3, IL-7RA: 1, DCLRE1C: 1, UC: 6	HSCT, GIFD HSCT, PIFD HSCT, MMRD HSCT, MUD UCBT, UD	2 1 3 2 4	Med: 8mon (R: 2-11mon)	(20)
CM Roifman (2011) NA Retrospective	M, seven, North America, Japan, Spain, and Germany.	13	CD3d deficiency: 13	BMT or PBSCT, MRD BMT or PBSCT, TCD, MMRD UCBT, UD BMT, MUD	2 6 2 3	Mean: 7.38mon (R: 25d-23mon)	(21)
W. I .Lee (2011) 1985-2010 Retrospective	M, a computer database at Chang Gung Memorial Hospital, a nationwide PIDs resource center covering 23 million people.	8	NA	Fetal thymus, Sibling BMT, Father/mother BMT, Sibling BMT, UD UCBT, UD	1 2 2 1 2	Med: 5.5mon (R: 2-11mon)	(22)

Cont. table 2

T. Morio (2011) 1998-2008 Retrospective	M, the Japan Cord Blood Bank Network (JCBBN)	40	NA	UCBT	40	Med: 6.5mon (R: 0-27mon)	(23)
H. B Gaspar (2011) 1982-2010 Retrospective	M, two, designated SCID transplantation centers in the United Kingdom	31	Proband cohort of SCID patients who were the first presenting person in the family.	HSCT, MSD HSCT, MFD HSCT, MUD HSCT, MMUD HSCT, HI	6 6 2 1 16	NA	(24)
		59	Sibling cohort of SCID patients who were diagnosed antenatally or at birth because of a diagnosis of SCID in a previous sibling or family member.	HSCT, MSD HSCT, MFD HSCT, MUD HSCT, MMUD UCBT HSCT, HI	11 8 5 3 6 24	NA	
M. A. Slatter (2011) 2006-2009 Retrospective	M, two, United Kingdom supraregional referral centers for PID, Newcastle on Tyne General Hospital and Great Ormond Street Hospital	15	SCID patients who received fludarabine	UCBT, UD BMT, UD BMT, MFD	7 3 5	Med: 7mon (R: 1.4-12mon)	(25)
		11	SCID patients who received cyclophosphamide	UCBT, MSD BMT, MFD BMT+PBT, HI+MSD PBT, HI BMT, UD UCBT, UD	1 3 1 2 1 3	Med: 6mon (R: 1.2-48mon)	
A Hassan (2012) 1981-2009 Retrospective	M, 16 international transplantation centers	106	ADA: 106	HSCT, MSD HSCT, MFD HSCT, MUD HSCT, MMUD HSCT, HI	42 12 15 7 30	Med: 4mon (R: 2w-7y)	(26)
M Cavazzana-Calvo (2012) 1995-2005 Retrospective	M, 30 European and non-European centers	74	RAG1/2: 2, ADA: 7, RD: 3, γ_c-Chain: 15, JAK3: 1, Omenn: 15, UC: 31.	UCBT, UD	74	Med: 6.4mon (R: 1-41mon)	(27)
		175	RAG1/2: 23, ADA: 3, RD: 7, γ_c-Chain: 39, JAK3: 13, Omenn: 23, UC: 67.	HSCT, MMRD	175	Med: 6.5mon (R: 1-35mon)	
C. Dvorak (2013) 2010-2012 Prospective	M, 17 centers including north America	33	Typical SCID	BM/PBSC, MRD BM/PBSC, TCD, MMRD BM/PBSC, UD UCB, UD	4 12 6 11	Med DTIT: 24d (R: 4–33d) Med DTIT: 29d (R: 16–110d) Med DTIT: 65d (R: 55–96d) Med DTIT: 58d (R: 24–147d)	(33)
		13	Atypical SCID	BM/PBSC, MRD BM/PBSC, UD UCB, UD	3 7 3	Med DTIT: 96d (R: 11–151d) Med DTIT: 45d (R: 30–221d) Med DTIT: 62d (R: 38–123d)	
T. A. O'Brien (2013) 1992-2008 Retrospective	M, six Australian and New Zealand Children's Haematology Oncology Group transplantation centers	65	NA	HSCT	65	Med DTIT: 2mon (R: 0-163mon)	(28)
C Schuetz (2014) 1985-2009 Retrospective	M, University of California, San Francisco, Paris Necker, Ulm University	145	ARTEMIS: 69, RAG1/2: 76	HSCT, MSD, identical HSCT, MFD, identical HSCT, MMFD HSCT, TCD, HI HSCT, MUD	24 18 13 82 8	ARTEMIS: Med: 7mon (R: 0.5-56mon) RAG1/2: Med: 7mon (R: 0.6-27mon)	(29)

Cont. table 2

RJ O'Reilly (2014) 2000-2009 Retrospective	M, 25 centers	240	IL-2RG: 86, IL-7R: 22, JAK3: 11, ADA: 14, PNP: 1, RAG1/RAG2: 17, DCLRE1C: 11, CD3D: 2, CD3Z: 1, CD45: 1, UC: 74.	MSD MMRD Other related donors URD	32 138 8 62	Med: 180d (R: 8-1162d)	(30)
CC Dvorak (2014) 1993-2012 Retrospective	M, North America, Europe, and Australia	103	IL2RG: 20, JAK3: 3, ADA: 23, other: 20. IL2RG: 21, JAK3: 0, ADA: 7, other: 9.	HSCT, MSD HSCT, MUD without CR	66 37	Med: 132d (R: 1-2240d) Med: 182d (R: 40-996d)	(31)
W Qasim (2014) 1990-2011 Retrospective	M, two, United Kingdom pediatric centers	77	NK^+: 24 and NK^-: 53	HSCT, MSD HSCT, MFD HSCT, MUD	49 11 17	Med: 3mon (R: 1w-17mon)	(32)

Table 3. Single-Center Studies Assessing Stem Cell Transplantation in Severe Combined Immunodeficiency Disorders

Study (YOP) Period Design	Center	N	Phenotype/genotype of patients	Transplant subgroups		Age at first transplantation	Ref.
				Type of transplant	N		
M. J. Cowan (1985) 1982-1985 Uncontrolled longitudinal study	S, Department of Pediatrics, University of California, San Francisco, California 94143.	9	ADA deficiency: 2, ADA-positive: 7	BMT, TCD, HI	9	Med: 9mon (R: 3-24mon)	(34)
W. Friedrich (1985) 1982-1985 Uncontrolled longitudinal study	S, Department of Pediatrics and Department of Transfusion Medicine, University of Ulm, Germany	15	RD: 1, ADA: 2, Low T, Low B: 2, low T and normal B cell numbers: 8, Omenn: 2	BMT, TCD, HI	15	Med: 4mon (R: 1-10.5mon)	(35)
R. Parkman (1986) 1982-1986 Retrospective	S, Children's Hospital of Los Angeles	10	NA	Antibody-treated BMT	10	NA	(36)
A Fischer (1986) NA Uncontrolled longitudinal study	S, Hôpital des Enfants-Malades, Paris	8	ADA: 2, present but nonfunctional T cells: 2, absence of T cells: 3, Omenn: 1	BMT, TCD, HI	8	Med: 5.5mon (R: 3-42mon)	(37)
R.J. Levinsky (1986) NA Uncontrolled longitudinal study	S, Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London, W.C.1.	6	NA	BMT, TCD, HI	6	NA	(38)
RH Buckley (1986) NA Uncontrolled longitudinal study	S, Department of Pediatrics, Duke University Medical Center, Durham, NC 27710.	17	NA	BMT, TCD, HI	17	Infancy	(39)
R. Hong (1987) 1983-1985 Uncontrolled longitudinal study	S, Department of Pediatrics, University of Wisconsin Clinical Science Center, Madison.	14	ADA deficiency: 3, ADA-positive: 11	BMT, TCD, HI	14	Med: 39.5mon (R: 4-83mon)	(40)
F.E. Halberg (1990) 1981-1988 Retrospective	S, the University of California, San Francisco	8	NA	BMT, TBI, MMD	8	Med: 4.5mon (R: 2-56mon)	(41)

Cont. table 3

A. H. Filipovich (1992) **1987-1990** **Prospective**	S, Bone Marrow Transplant Program University of Minnesota Hospital and Clinic, Minneapolis 55455.	8	Low T, Low B: 2, low T, hypogammaglobulinaemia: 1, absent CD8+ T cells, nonfunctional CD4+ cells: 3, ADA: 1, Omenn: 1	BMT, UD	8	Med: 8.5mon (R: 3-27mon)	(42)
A Fischer (1993) **1970-1992** **Retrospective**	S, Hôpital des Enfants-Malades, Paris	80	NA	BMT, identical BMT, TCD, NI	30 50	NA	(43)
M. J. Cowan (1993) **1982-1991** **Uncontrolled longitudinal study**	S, Division of Pediatric Bone Marrow Transplant and Pediatric Immunology, San Francisco 94143.	24	AR: 10, X-SCID: 3, UC: 11	BMT, TCD, HI	24	Med: 6mon (R: 0.5-117mon)	(44)
R. H. Buckley (1993) **1992-1993** **Retrospective**	S, Department of Pediatrics, Duke University Medical Center, Durham, NC 27710.	50	NA	BMT, TCD, HI, parent BMT, identical	41 9	NA	(45)
J.M. Vossen (1994) **1968-1992** **Retrospective**	S, Department of Pediatrics, Leiden University Hospital, The Netherlands.	31	T^-B^+: 17, T^-B^-: 5, ADA: 2, Omenn: 4, MHC II: 3	BMT, identical, RD BMT, HI, RD BMT, MUD	10 19 2	Med: 8mon (R: 1-94mon)	(46)
AM Dickinson (1997) **1986-1996** **Retrospective**	S, Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne, UK.	17	T^-B^+:11, ADA: 1, Omenn: 1, T^-B^-: 1, T^+: 1, MFE: 2	BMT, TCD, HI, parent	17	Med: 0.7mon (R: 0.2-1mon)	(47)
H Buckley (1999) **1982-1998** **Prospective**	S, Duke University Medical Center	89	γ_c-Chain: 43, JAK3: 6, IL-7Rα: 2, ADA: 13, AR-UC: 20 , CHH: 1, Male-UC: 4	BMT, TCD, HIP BMT, RD, identical PBT, URD + BMT, TCD, HIP	77 12 3	≥3.5mon (n=67) <3.5mon (n=22)	(48)
P. Airo` (1999) **NA** **Case-control**	S, Immunologia Clinica, Spedali Civili Brescia, Piazza Spedali Civili, 1, Italy	12	AR-T^-B^+: 5, XL-T^-B^+: 5, T^-B^+: 1, T^-B^-: 1	BMT, identical, UD BMT, HI, family donor BMT, identical, sibling	4 7 1	Med: 7mon (R: 1-12mon) Med: 7mon (R: 3-15mon) 3mon	(49)
CM Roifman (2000) **1989-1997** **Prospective**	S, the Hospital for Sick Children (Toronto)	9	T^-B^+: 9	BMT, identical, UD	9	Mean: 6.25mon (R: 4.5-6.5mon)	(50)
E.M. Smogorzewska (2000) **1984-1997** **Non-randomized controlled trial**	S, the Division of Research Immunology and Bone Marrow Transplantation at Childrens Hospital Los Angeles.	48	T^-B^+: 27, T^-B^-: 12, T^+B^+: 8, T^+B^-: 1	BMT, TCD, HI BMT, histocompatible RD	37 11	Mean: 9.6mon (R: 1-40mon) Mean: 15.4mon (R: 1-180mon)	(51)

Cont. table 3

M. J. Cowan (2001) **1984-1999** **Retrospective**	S, Pediatric Bone Marrow Transplantation Division, San Francisco, USA	16	SCIDA (a distinct form of autosomal recessive T-B-SCID disease that occurs with a high frequency among Athabascan-speaking Native Americans)	BMT, sibling BMT, parental	9 7	Mean: 2.3mon (R: 1-63mon)	(98)
J. B. Ziegler (2001) **1992-1996** **Retrospective**	S, the Sydney Children's Hospital, Australia	6	X-SCID: 6	BMT, TCD, HI, parent	6	Mean: 5mon (R: 1-8mon)	(52)
A. R. Gennery (2001) **1987-1999** **Retrospective**	S, Department of Paediatric Immunology, Newcastle General Hospital, UK	13	T^-B^+: 7, T^-B^-: 3, ADA: 3	BMT, TCD, HI BMT, phenotypically identical, RD BMT, UD BMT, identical, sibling CBT, sibling	7 1 2 2 1	Med: 45d (R: 7-93d)	(53)
A. R. Gennery (2001) **1987-1998** **Retrospective**	S, Children's Bone Marrow Transplantation Unit, Newcastle upon Tyne Hospitals NHS Trust, UK	30	NA	BMT, TCD, non-identical	30	NA	(54)
L. A. Myers (2002) **1982-2001** **Retrospective/prospective**	S, Duke University Medical Center	21 96	γ_c-Chain: 15, ADA: 2, JAK3: 1, AR-UC: 3 NA	Allogeneic BMT in the first 28 days of life Allogeneic BMT after the first 28 days of life	21 96	Med: 10d (R: 7-24d) NA	(55)
M. Sarzotti (2003) **NA** **Uncontrolled longitudinal study**	S, Department of Immunology, Duke University Medical Center, Box 3010, Durham	15	X-SCID: 7, JAK3: 3, IL-7: 4, AR: 1	BMT, HI BMT, identical	13 2	Mean: 248.5d	(56)
F. Le Deist (2004) **1971-1992** **Retrospective**	S, the Paediatric Immunology and Haematology Unit of Necker-Enfants Malades Hospital, Paris, France	68	NA	Allogeneic HSCT	68	NA	(57)
L. Imberti (2004) **1995-2001** **Retrospective**	S, Spedali Civili Hospital, Brescia (Italy)	5	γ-Chain: 2, IL-7Rα: 1, RAG2: 1, T^-B^--UC: 1	IUT, BMT, father, HI IUT, PBT, mother, HI	4 1	Between the 21st and the 24th week of gestation	(58)
J. L. Roberts (2004) **NA** **Uncontrolled longitudinal study**	S, Duke University Medical Center	10	JAK3: 10	BMT, identical or HI	10	Med: 0.7mon (R: 0.7-14mon)	(59)
AR Gennery (2005) **2000-2004** **Retrospective**	S, Paediatric Immunology Department, Newcastle General Hospital, Newcastle upon Tyne, UK	8	ADA: 4, RD: 1, $T^-B^+NK^+$: 2, UC: 1	CBT, MUD CBT, MSD	7 1	Med: 2.5mon (R: 1.5-5mon) 0.25mon	(60)
P Veys (2005) **1998-2003** **Retrospective**	S, Great Ormond Street Hospital (GOSH) for Children NHS Trust, London, UK	20	NA	BMT, or PBT, or CBT	20	NA	(61)

Cont. table 3

K Rao (2005) **1994-2002** **Retrospective**	S, the Great Ormond Street Hospital for Children, London, UK	6 7	ADA: 1, γ-Chain: 1, RAG: 1, IL15 Ra: 1, UC: 2 ADA: 1, γ-Chain: 5, CD45: 1	BMT, RIC, URD BMT, MACR, URD	6 7	Med: 5.9y (R: 0.19-18y) Med: 1.9y (R: 0.39-13.08y)	(62)
N Sakata (2004) **1992-2004** **Retrospective**	S, Osaka Medical Center and Research Institute for Maternal and Child Health	6	NA	BM, URD	6	NA	(63)
Y Tsuji (2006) **1984-2005** **Retrospective**	S, Department of Pediatrics, National Defense Medical College, Tokorozawa, Japan	11	X-linked: 9, T^-B^-: 1, Omenn syndrome: 1	BMT, TCD, father, HI BMT, UD CBT, UD	5 1 5	Med: 9mon (R: 5-11mon) 15mon Med: 10mon (R: 8-10mon)	(64)
M. J. van Tol (2006) **1968-1997** **Retrospective**	S, the Pediatric Transplant Unit of Leiden University Medical Center	35	NA	HSCT	35	NA	(65)
L. D Notarangelo (2007) **1991-2002** **Retrospective**	S, the Department of Pediatrics, University of Brescia, Italy	43	T^-B^+: 30, T^-B^-: 13 JAK3: 11, γ-Chain: 12, IL-7R: 2, RAG: 4, Artemis: 4, ADA: 1, UC: 9	HSCT	43	NA	(66)
R. H. Buckley (2007) **1982-2006** **Retrospective**	S, Duke University Medical Center, Durham, North Carolina	137	γ-Chain: 64, IL-7R: 15, ADA: 17, JAK3: 12, RAG: 7, CD3: 4, ARTEMIS: 2, AR-UC: 13, male-UC: 3	BMT, identical BMT, TCD, HI	13 124	Med: 165d (R: 7–597d)	(67)
F Porta (2008) **Since 1990** **Retrospective**	S, Oncology-Haematology and BMT Unit, Ospedale dei Bambini, Spedali Civili, Brescia	82	NA	BMT, MFD, identical BMT, PIFD BMT, PMFD, HI BMT, MUD	15 2 47 18	NA	(68)
CD De Heredia (2008) **1996-2002** **Retrospective**	S, the Spanish Paediatric Bone Marrow Transplant Group	11	T^-B^+: 3, T^-B^-: 7, Abnormal T, B^-: 1	CBT-UD	11	Mean: 10.45mon (R: 3-25mon)	(69)
A Al-Ghonaium (2008) **1993-2006** **Retrospective**	S, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia	110	NA	HSCT, identical CBT, UD HSCT, TCD	99 7 4	NA	(70)
CC Dvorak (2008) **2000-2007** **Prospective**	S, the University of California San Francisco (UCSF) Children's Hospital	15	γ_c-Chain: 7, RAG: 4, Artemis: 1, UC: 3	Megadose of CD34+ HSCs with a fixed number of CD3+ cells without previous MACR	15	Med: 5.7mon (R: 0.5-16.5mon)	(71)
NC Patel (2008) **1981-1995** **Retrospective**	S, Texas Children's Hospital in Houston	20 5	IL-2RG: 6, RAG1: 1, UC: 13 IL-2RG: 1, RAG1: 4, UC: 0	BMT, TCD, MMRD, HI BMT, MRD	20 5	Med: 6.5mon (R: 0.5-145mon) Med: 1.8mon (R: 0.5-5mon)	(72)
J B. Ziegler (2008) **1995-2001** **Prospective**	S, the Australian Paediatric Surveillance Unit (APSU)	21	Classical SCID: 21	HSCT	21	Med: 9.8mon (R: 1-36mon)	(73)

Cont. table 3

NC Patel (2009) **1998-2007** **Retrospective**	S, Department of Pediatrics, Section of Allergy and Immunology, Texas Children's Hospital, USA	21 17 10	B^-: 4, B^+: 17 B^-:6, B^+: 11 B^-: 5, B^+: 5	HSCT, MMRD (without CR) HSCT, MMRD or MUD, with CR HSCT, MRD	21 17 10	NA NA NA	(74)
A. Petrovic (2009) **1986-2009** **Retrospective**	S, All Children's Hospital, University of South Florida	16	X-linked: 63%, ADA: 25%, RAG: 6%, functional combined immunodeficiency: 6%	SCT, TCD, HI BMT, MRD (without CR)	15 1	Med: 6mon (R: 1-14mon)	(75)
P. J. Amrolia (2009) **2003-2007** **Phase I/II**	S, Department of Bone Marrow Transplantation, London WC1N 3JH, UK	9	RAG: 1, γ_c-Chain: 2, RD: 1, MHC class 2 deficiency: 1, UC: 3, dyskeratosis congenita: 1	HSCT, MMUD, MIC HSCT, MUD, MIC HSCT, MSD, MIC	2 6 1	5 and 7mon Med: 9.5mon (R: 5-15mon) 10mon	(76)
R. H. Buckley (2009) **1982-2008** **Retrospective**	S, Duke University Medical Center, Department of Pediatrics, Division of Allergy and Immunology	161	NA	BMT, TCD, HI BMT, RD, identical	145 16	≤3.5mon: 48 >3.5mon: 113	(77)
A Fischer (2009) **1972-2004** **Retrospective**	S, the Department of Immuno-Hematology at the Necker Children's Hospital (Paris, France)	149	NA	HSCT	149	NA	(78)
R. H. Buckley (2010) **Over the past 28.3y** **Retrospective**	S, Departments of Pediatrics and Immunology, Duke University Medical Center, USA	166	X-linked: 75, ADA: 24, IL-7RA: 24, JAK3: 9, RAG: 7, CD3 chain: 4, AR-UC: 15, UC: 4, ARTEMIS: 2, CD45: 1, CHH: 1	HSCT, TCD, HI HSCT, TCD, identical HSCT, identical	149 9 8	<3NA.5mon: 48 >3.5mon: 118	(79)
F. Serana (2010) **2002-2010** **Retrospective**	S, the Pediatric Clinic of the Spedali Civili of Brescia (Brescia, Italy)	5	ADA: 5	HSCT, identical HSCT, MUD	3 2	Mean: 4mon (R: 1-7mon) Mean: 13.5mon (R: 7-20mon)	(80)
K. E. Sullivan (2011) **1986-2010** **Retrospective**	S, Division of Oncology, Children's Hospital of Philadelphia	25	ADA: 3, IL-7R: 4, IL2RG: 7, JAK3: 1, RD: 1, MHC-II: 1, RAG: 2, UC: 6	BMT, identical, sibling BMT, MMRD BMT, MUD	5 16 4	Med AOD: 2.15 (R: 0-6.6mon)	(81)
T.-X. Chen (2011) **2004-2009** **Retrospective**	S, Department of Pediatrics, Xinhua Hospital, Research, China	5	NA	HSCT	5	NA	(82)
B. M Triplett (2012) **1991-2010** **Retrospective**	S, St. Jude Children's Research Hospital, Memphis, TN	23	RAG: 3, AR: 3, X-linked: 5, ADA: 4, CHHS: 1, γ_c-Chain: 2, CD3: 1, IL-7R: 2, UC: 2.	HSCT, Parent HSCT, Sibling	19 4	Med: 0.5y (R: 0.0-0.9y)	(83)
R. Somech (2012) **NA** **Prospective**	S, the Sheba Medical Center (Tel Hashomer, Israel)	10	RAG2	PBT, MMRD BMT, MRD UCBT, MUD	6 3 1	Med: 4.5mon (R: 1-7.5mon)	(84)

Cont. table 3

A Ikinciogullari (2012) **2000-2010** **Retrospective**	S, Department of Pediatric Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey.	15	$T^-B^+NK^+$: 4, $T^-B^-NK^-$: 2, $T^-B^-NK^+$: 8, $T^-B^+NK^-$: 1.	HSCT, HI, mother HSCT, HI, father	12 3	Med: 5mon (R: 2-9mon) 5, 5, and 8mon	(85)
A. A. Hussein (2013) **2003-2011** **Retrospective**	S, King Hussein Cancer Center, Jordan	16	$T^-B^+NK^+$: 2, $T^-B^-NK^-$: 6, $T^-B^-NK^+$: 6, $T^-B^+NK^-$: 2.	PBSC, MRD BM, MRD PBSC, HI	6 3 7	Med: 19.5mon (R: 5-57mon) 7, 21, and 60mon Med: 13mon (R: 4-19mon)	(86)
S Kumaki (2013) **NA** **Uncontrolled longitudinal study**	S, Department of Pediatrics, Tohoku University Graduate School of Medicine, Japan	5	Typical X-SCID (mutations in the γ_c-Chain gene were detected in all patients)	UCB, UD	5	Med: 3mon (R: 3-10mon)	(87)
T. X. Chen (2013) **2004-2011** **Retrospective**	S, Shanghai, China	6	NA	HSCT	6	Mean: 11.8mon (R: 3.5-28mon)	(88)
AM Wahadneh (2013) **2008-2010** **Retrospective**	S, Queen Rania Children Hospital, Jordan	7	T^-B^-: 2, T^+B^-: 1, T^-B^+: 4	PBSC, Mother	7	Med: 6mon (R: 3-8mon)	(89)
L Imberti (2014) **1999-2014** **Retrospective**	S, the Department of Pediatrics, Spedali Civili of Brescia, Italy	54	IL2RG: 12, JAK3: 11, RAG1/2: 7, ARTEMIS: 5, IL-7R: 3, ADA: 6, RD: 3, UC: 7.	HSCT, MSD HSCT, MMRD HSCT, MUD	12 22 20	Mean: 10mon	(90)
S. Pasic (2014) **1990-2010** **Retrospective**	S, Mother and Child Health Institute, Medical Faculty, University of Belgrade, Serbia	8	NA	HSCT	8	NA	(91)
D Balashov (2015) **2012-2014** **Prospective**	S, Department of Hematopoietic Stem Cell Transplantation, Russia	5	NA	HSCT, TCRαβ/CD19-depleted, MMRD	5	Mean: 0.82y (R: 0.2-2y)	(92)
A Aiuti (2015) **1997-2012** **Retrospective**	S, Bambino Gesù Children's Hospital (OPBG) in Rome	7	γ-Chain: 3, JAK3: 2, ADA: 1, T^-B^+: 1	BMT, MMRD BMT, MSD	4 3	Mean: 9.71mon (R: 5-13mon)	(93)

Table 4. Outcomes of Stem Cell Transplantation for Severe Combines Immunodeficiency Disorders: Multi-Center Studies

Type of transplant	Follow-up time of the surviving patients	Survival rate	Causes of death	GVHD prevalence			Ref.
				Acute	Chronic	Total	
BMT, TCD, MMD without CR		DFS: 57%	Mainly caused by infections, which in most cases (78%) were present before BMT.	~25%	19%	NA	(10)
BMT, MD without CR		DFS: 68%		5.3%*	0	5.3%	
BMT, non-TCD, MMD		DFS: 18.2%		NA	NA	NA	

Cont. table 4

BMT, identical	Med: 73mon	DFS: 70%	77%: infections	NA	NA	NA	(9)
BMT, NI	Med: 46mon	DFS: 56%	74%: infections, 21%: GvHD	27% (grade II or higher)	25%	NA	
	6mon	~60%	NA	~57.5%	40%	NA	
BMT, TCD, NI	Med: 6y	~48%	19/24: cGVHD and/or viral infection, 2/24: unrecorded, 2/24: immune dysfunction with severe auto-immunity involving the liver, 1/24: cerebral hemorrhage.	NA	16%	NA	(11)
BMT, TCD, NI	T^-B^+: med: 57mon (R:6 to 162mon) T^-B^-: med: 52mon (R:6 to 161mon)	60% 35%	31/46: Infections, 10/46: GVHD, 3/46: BLPS, 2/46: other. 25/36: Infections, 8/36: GVHD, 3/36: other.	12% 18%	32% 46%	44% 64%	(12)
HSCT, TCD, HI	NA	30%	5/7: infections, 2/7: GvHD	30% (grade II-IV)	20%	30%	(13)
HSCT, genotypically identical **HSCT, phenotypically identical, RD** **HSCT, MMRD** **HSCT, UD**	Med: 11y (R: 1-29y) Med: 11y (R: 2.5-28y) Med: 10y (R: 1.1-30y) Med: 6y (R: 2.2-22.5y)	At 3y: 81% At 3y: 72% At 3y: 54% At 3y: 63%	56%: infections, 25%: GvHD, and 5%: B-cell lymphoproliferative syndrome	NA	NA	NA	(14)
BMT, FRD, identical	Med: 96mon (R: 15-168mon)	~92.3%	1/1: Liver failure	30.7%	0%	30.7%	
BMT, MUD	Med: 40mon (R: 1-168mon)	~80.5%	1/8: Myocarditis, 2/8: Gastrointestinal acute GvHD, 1/8: Liver chronic GvHD, 1/8: Sepsis, 1/8: Liver and gastrointestinal acute GvHD, 1/8: Pulmonary alveolar proteinosis, 1/8: CMV interstitial pneumonitis	73.1%	22.85%	75.6%	(15)
BMT, MMRD	Med: 24mon (R: 1-156mon)	~52.5%	2/19: CMV, 1/19: MOF, 2/19: P jiroveci interstitial pneumonitis, 2/19: autoimmune cytopenia, 8/19: Interstitial pneumonitis, 1/19: Encephalitis, 1/19: Cerebral edema, 1/19: Lung chronic GvHD, 1/19: CMV Interstitial pneumonitis	45%	6.45%	45%	
BMT, MSD **BMT, father** **BMT, mother** **CBT, UD** **Fetal thymus, MSD**	NA	100% 0% 100% 100% 0%	0 Graft failure, sepsis: 1/1 0 0 Graft failure, sepsis, DIC: 1/1	NA	NA	NA	(16)
HSCT, MFD without CR	Mean: 9.5y (R: 3.9-13.5y)	100%	0	~14%	0%	14%	
HSCT, TCD, MMFD with CR	Mean: 14.6 y (R: 4.6-22.2 y)	~66.5%	2/2: aspergillosis	~33%	16.5%	~33%	(17)
HSCT, MUD with CR	Mean: 14.6 y (R: 4.6-22.2 y)	50%	1/1: CMV and adenovirus	0%	0%	0%	
HSCT, HI	Med: 167d (R: 14-2204d)	6-y projected: 29.76%	NA	NA	NA	NA	(18)

Cont. table 4

HSCT, GI, RD **HSCT, PI, RD** **HSCT, MMRD** **HSCT, UD**	Med: 8.8y (R: 0.5-27.8y) Med: 9.6y (R: 0.5-32.6y) Med: 9.3y (R: 0.5-22.3y) Med: 8.9y (R: 5.3-12.8y)	3y OS: 81% (73-90) 3y OS: 57% (41-78) 3y OS: 49% (43-56) 3y OS: 53% (33-86)	NA	NA	NA	NA	
HSCT, GI, RD **HSCT, PI, RD** **HSCT, MMRD** **HSCT, UD**	Med: 2.0y (R: 0.4-9.6y) Med: 2.5y (R: 0.4-6.2y) Med: 4.5y (R: 0.2-10.8y) Med: 7.1y (R: 0.9-10.4y)	3y OS: 84% (69-100) 3y OS: 80% (62-100) 3y OS: 69% (60-79) 3y OS: 68% (48-97)	NA	NA	NA	NA	(19)
HSCT, GI, RD **HSCT, PI, RD** **HSCT, MMRD** **HSCT, UD**	Med: 1.0y (R: 0.5-2.1y) Med: 1.2y (R: 0.4-4.9y) Med: 1.4y (R: 0.2-5.0y) Med: 1.8y (R: 0.2-5.4y)	3y OS: 90% (77-100) 3y OS: 83% (58-100) 3y OS: 66% (55-78) 3y OS: 69% (54-89)	NA	NA	NA	NA	
HSCT	Mean: 6.3y (R: 0.25-18y)	~66.6%	2/4: sepsis and multi-organ failure, 1/4: GvHD, 1/4: idiopathic pneumonia syndrome.	50%	~16.6%	50%	(20)
BMT or PBSCT, MRD **BMT or PBSCT, TCD, MMRD** **UCBT, UD** **BMT, MUD**	Mean: 6.75 y (R: 1-20y)	100% 16.7% 100% 100%	0 3/5: CMV, 1/5: GvHD, 1/5: GvHD, DIC, HHV6 0 0	100% NA NA NA	100% 0% 0% 33.3%	100% NA NA NA	(21)
Fetal thymus, Sibling **BMT, Father/mother** **BMT, Sibling** **BMT, UD** **UCBT, UD**	NA	0% (0/1) 50% (1/2) 100% (2/2) 0% (0/1) 100% (2/2)	1/1: failure, sepsis, DIC, pseudomonas sepsis 1/1: failure, sepsis 0 1/1: respiratory failure due to pleural-bronchial fistula 0	NA	NA	NA	(22)
UCBT	NA	5y OS: 71%	2/11: bacterial/fungal infection, 6/11: viral infection, 1/11: VOD, 1/11: GvHD, 1/11: adrenal insufficiency	NA	NA	NA	(23)
HSCT, MSD or MFD or MUD or MMUD or HI **HSCT, MSD or MFD or MUD or MMUD or HI or UCBT**	After transplantation Within 10y After transplantation Within 10y	61% 54% 91.5% 93%	NA	NA	NA	NA	(24)
UCBT, UD (Flu) **BMT, UD (Flu)** **BMT, MFD (Flu)**	Med: 25.5mon (R: 5-47mon)	85.7% 100% 100%	1/1: Pseudomonal sepsis 0 0	20%	~13.3%	20%	(25)

Cont. table 4

UCBT, MSD (CYC) **BMT, MFD (CYC)** **BMT+PBT, HI+MSD (CYC)** **PBT, HI (CYC)** **BMT, UD (CYC)** **UCBT, UD (CYC)**	Med: 17mon (R: 9-25mon)	0% ~66.7% 100% 100% 100% 100%	1/1: severe pneumonitis, pulmonary hypertension 1/1: VOD and sudden liver failure 0 0 0 0	~18.2%	~6.7%	~27.3%	
HSCT, MSD **HSCT, MFD** **HSCT, MUD** **HSCT, MMUD** **HSCT, HI**	Med: 6.5y (R: 1.6-27.6y)	86% 83% 67% 29% 43%	Overall, in the first 100 days after HCT, >50% of deaths: pneumonitis/respiratory failure and sepsis, 15% of deaths: GvHD, 11% of deaths: fungal infection; deaths after 100 days after HCT, 15% of deaths: chronic GvHD, 85% of deaths: nontransplant-related complications.	NA	NA	NA	(26)
UCBT	Med: 83mon (R: 5-162mon)	5y OS: 57%±6%	9/30: infection, 6/30: GvHD, 6/30: ARDS, 2/30: rejection, 2/30: cardiac toxicity, 2/30: MOF, 1/30: secondary malignancy, 2/30: other.	34%±6% (grade II-IV)	22%±5%	NA	(27)
MMRD	Med: 58mon (R: 1-157mon)	5y OS: 62%±4%	31/67: infection, 6/67: GvHD, 15/67: ARDS, 5/67: rejection, 2/67: SOS, 1/67: MOF, 2/67: secondary malignancy, 5/67: other.	22%±3% (grade II-IV)	10%±2%	NA	
SCT, MRD or MMRD or UD	Med: 9.2mon (R: 3.3–17.5mon)	~87%	NA	NA	NA	NA	(33)
HSCT	Med: 6.03y (R: 0.39-17.31y)	5y OS: 70%	NA	At d+100: 25% (grade II-IV)	At y+1: 11%	NA	(28)
HSCT, MSD or MFD, identical **HSCT, TCD, HI** **HSCT, MUD** **HSCT, MMFD**	ARTEMIS: Med: 51mon (R: 0.5-333) RAG1/2: Med: 32mon (R: 1-333)	88%* ~52.5%* 62.5%* 46.15%*	1/51: toxicity, 28/51: infection, 11/51: GvHD/autoimmunity, 9/51: other, 2: UC.	NA	After y+2: ~7.6%	After y+2: ~7.6%	(29)
MSD **MMRD without CR** **MMRD with CR** **UCBT** **Other unrelated or related donor**	At 100 d, 6mon, and 1, 2 to 5, and 6 to 10y PoT	At 5-y: 97% At 5-y: 79% At 5-y: 66% At 5-y: 58% At 5-y: 74%	24/62: infections, 23/62: pulmonary, 3/62: acute GvHD, 1/62: chronic GvHD, 1/62: graft rejections or failure, 8/62: other organ toxicity, 2/62: unknown.	At d+100: 20% (grade II-IV)	At y+2: 15%	NA	(30)
HSCT, MUD without CR	Med: 3.9y (R: 1-19 y)	5y EFS: 60% 5y OS: 71%	2/10: acute GvHD, 1/10: chronic GvHD, 2/10: ongoing Neuro, 1/10: ongoing Paraflu, 1/10: chronic GvHD, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and 1/10: intraoperative complication, 1/10: chronic GvHD, RSV, 1/10: ongoing respiratory failure.	65%	39%	NA	(31)
HSCT, MSD	Med: 6.9y (R: 1-18.9 y)	5y EFS: 89% 5y OS: 92%	1/6: chronic GvHD, RSV, 1/6: probable sepsis, 1/6: metabolic, 1/6: CMV, 2/6: unknown.	33%	5%	NA	
HSCT, MSD or MFD **HSCT, MUD**	NK^+: med: 3070d (R: 760-7300d) NK^-: med: 3001d (R: 760-7300d)	90% 60%	NA	NA	NA	NA	(32)

Table 5. Outcomes of Stem Cell Transplantation for Severe Combines Immunodeficiency Disorders: Single-Center Studies

Type of transplant	Follow-up time of the surviving patients	Survival rate	Causes of death	GVHD prevalence			Ref.
				Acute	Chronic	Total	
BMT, TCD, HI	Med: 20.5mon (R: 12-35mon)	~66.67%	1/3: staphylococcal pneumonia, 1/3: disseminated atypical mycobacterial infection, 1/3: unknown etiology.	~33.33%	~22.22%	~44.44%	(34)
BMT, TCD, HI	Med: 18mon (R: 4-31mon)	~73.33%	2/4: sepsis, 1/4: lymphoma, 1/4: pneumonia	~6.67%	0	~6.67%	(35)
Antibody-treated BMT	NA	70%	NA	37.5%	0	37.5%	(36)
BMT, TCD, HI	≥ 6mon	62.5%	2/3: prior infections, 1/3: B cell lymphoproliferative syndrome	37.5%	0	37.5%	(37)
BMT, TCD, HI	> 5mon	DFS: 50%	NA	NA	0	NA	(38)
BMT, TCD, HI	R: 6-41mon	~88.23%	2/2: viral infections	~17.65%	0	~17.65%	(39)
BMT, TCD, HI	Med: 15mon (R: 5-39mon)	50%	The major cause of death was infection.	~35.71% (grade II or higher)	0	~35.71%	(40)
BMT, TBI, MMD	Med: 13.5mon (R: 7-72mon)	75%	1/2: pneumonia, 1/2: aspergillous	0	0	0	(41)
BMT, UD	Med: 28.5mon (18-47mon)	75%	1/2: aspergillosis, 1/2: CNS hemorrhage	~14.28%	0	0	(42)
BMT, identical **BMT, TCD, NI**	Med: 129mon Med: 34mon	80% 56%	NA	NA NA	NA 7.14%	NA NA	(43)
BMT, TCD, HI	Med: 55.5mon (R: 7-118mon)	~58.3%	4/10: sepsis, 1/10: SIDS, 1/10: atypical mycobacterium, 1/10: pneumonia/chronic lung disease, 1/10: aspergillus pneumonia, NA: 2	NA	NA	12.5%	(44)
BMT, TCD, HI, parent **BMT, identical**	Up to almost 11 years	~75.61% 100%	NA	NA	NA	NA	(45)
BMT, identical, RD **BMT, HI, RD** **BMT, MUD**	Med: 6y (R: 1-24y)	60% ~47.37% 0%	3/16: graft failure, 6/16: respiratory failure, 1/16: accidental cardiac tamponade, 1/16: intracranial lymphoproliferative syndrome, 2/16: GvHD, 1/16: cardiac arrest, 1/16: intracranial bleeding, 1/16: intracranial lymphoproliferative syndrome	36%	~23.8%	36%	(46)
BMT, TCD, HI, parent	Med: 3.5y (R: 3mon-8y)	~64.7%	2/6: parainfluenza III pneumonitis, 1/6: parainfluenza I pneumonitis, 1/6: RSV pneumonitis, 1/6: maternal/fetal GvHD/pulmonary complications, 1/6: generalized aspergillus infections.	~41.18%	NA	NA	(47)
BMT, TCD, HIP **BMT, RD, identical** **PBT, URD +** **BMT, TCD, HIP**	Med: 5.6y (R: 3mon-16.5y)	78% 100% 66.5%	15/17: viral infections (6: CMV, 3: EBV, 2: adenovirus, 2: enteroviruses, 1: PIV 3, 1: HSV), 1/17: sepsis due to candida infection, 1/17: unrelated mitochondrial defect	NA NA NA	NA NA NA	36% 50% 66.5%	(48)

Cont. table 5

BMT, identical, UD **BMT, HI, family donor** **BMT, identical, sibling**	Med: 45.5mon (R: 29-60mon) Med: 35mon (R: 10-75mon) 26mon	100% ~71.43% 100%	0 NA 0	100% ~28.57% 0	0 ~28.57% 0	100% ~42.86% 0	(49)
BMT, identical, UD	Med: 54.5mon (R 18–72mon)	67%	2/3: GvHD, 1/3: BM aplasia	~22.22% (grade II-IV)	~22.22%	~44.44%	(50)
BMT, TCD, HI		46%	9/20: opportunistic infections, 8/20: EBV-LPD, 3/20: GvHD			47%	
BMT, histocompatible RD	R: 3-13y	100%	0	NA	NA	27%	(51)
BMT, sibling	Med: 49mon (R: 2-150mon)	100%	0				
BMT, parental	Med: 89mon (R: 5-141mon)	~42.86%	1/4: severe HUS, 1/4: sepsis, 1/4: severe AIHA, 1/4: parainfluenza virus	0 (more than grade II)	NA	NA	(98)
BMT, TCD, HI, parent	R: 4-7.5y	100%	0	NA	NA	NA	(52)
BMT, TCD, HI **BMT, phenotypically identical, RD** **BMT, UD** **BMT, identical, sibling** **CBT, sibling**	Med: 3y (R: 0.5-11.5y)	100%	0	~46.15%	~15.38%	~46.15%	(53)
BMT. TCD, non-identical	Med: 5.3y (R: 1.33-12y)	63%	Mainly caused by pre-existing infections	NA	NA	NA	(54)
Allogeneic BMT in the first 28 days of life	Up to more than 19 years after BMT	95%	1/1: CMV encephalitis	~38%	NA	NA	(55)
Allogeneic BMT after the first 28 days of life		74%	NA	NA	NA	NA	
BMT, HI **BMT, identical**	Med: 6.4y (R: 2.4-18.1y) 10.8y and 12.9y	~8507% 100%	1/1: varicella infection	NA	NA	NA	(56)
Allogeneic HSCT	Minimum of 10y for 41 of 42 surviving patients	~61.76%	NA	NA	NA	NA	(57)
IUT, BMT, father, HI **IUT, PBT, mother, HI**	NA	75% 100%	EBV-LPD: 1/1 0	0%	0%	0%	(58)
BMT, identical or HI	Med: 9y (R: 3-18y)	90%	Persistent vaccine-derived varicella infection and a drug-resistant Candida albicans infection: 1/1	10%	0%	10%	(59)
CBT, MUD **CBT, MSD**	Med: 2y (R: 0.5-6y)	~71.43% 100%	MOF due to pre-existing infection/inflammation: 2/2 0	~14.3% 0	0 0	~14.3% 0	(60)
BMT, or PBT, or CBT	≤64mon	~84%	NA	NA	NA	NA	(61)
BMT, RIC, URD	Med: 40mon	83%	NA	NA	NA	NA	(62)
BMT, MACR, URD	Med: 104mon	70%	NA	NA	NA	NA	(62)
BMT, URD	Med: 20mon (R: 3-96mon)	~33%	2/4: VOD, 2/4: IP	NA	NA	NA	(63)
BMT, TCD, father, HI **BMT, UD** **CBT, UD**	Med: 85.6mon (R: 3.3-168mon)	0% 100% 80%	GvHD: 1/5, CMV: 1/5, EBV-LPD: 1/5, sepsis: 2/5 0 VOD: 1/1	60% 100% 40%	20% 0 20%	60% 100% 60%	(64)
HSCT	5y	At 5y: 60%	NA	NA	NA	NA	(65)

Cont. table 5

HSCT	Med: 132mon (R: 68-196mon)	69.8%	Interstitial pneumonia, encephalitis, autoimmune hemolytic anemia, disseminated CMV infection, tumors, systemic vasculitis, severe acute GvHD, LPD	NA	0	NA	(66)
BMT, identical or HI	5y	At 5y: ~62.8%	Viral infections: 8/51, other causes have not been reported by the authors.	~35.77%	NA	NA	(67)
BMT, MFD **BMT, PIFD** **BMT, PMFD** **BMT, MUD**	R: 0-180mon	DFS: 100% DFS: 100% DFS: 55.6% DFS: 88.5%	NA	NA	NA	NA	(68)
CBT-UD with CR	Med: 64 mon (R: 54–132mon)	~64%	3/4: GVHD, 1/4: progressive interstitial lung disease	82%	NA	NA	(69)
HSCT, identical **CBT, UD** **HSCT, TCD**	NA	80% 71% 50%	NA	NA	NA	NA	(70)
Megadose of CD34+ HSCs with a fixed number of CD3+ cells without previous MACR	Med: 39mon (R: 10-95mon)	87%	1/2: pseudomonas sepsis, 1/2 : unknown	58%	17%	58%	(71)
BMT, TCD, MMRD, HI	BMT was done during 1981-1995 and the last follow-up was done during 2007-2008.	50%	2/10: EBV, 2/10: PMS, 1/10: PMS and grade IV GVHD, 1/10: chronic GvHD, 1/10: PCP with concurrent GvHD, 1/10: aspergillosis infection	100%	20%	100%	(72)
BMT, MRD		100%	0	100%	20%	100%	
HSCT	NA	~85.7%	3/3: NA (they died soon after transplantation)	NA	NA	NA	(73)
HSCT, MMRD (without CR)	HSCT was done during 1981-2007	At 1y, B^-: 25%, B^+: 71%	NA	52% (grade II-IV)	NA	NA	(74)
HSCT, MMRD or MUD, with CR		At 1y, B^-: 67%, B^+: 73%	1/5: PCP, enterococcus faecalis, sepsis, 1/5: adenovirus, enterocolitis and sepsis, 1/5: RSV, pneumonia and sepsis, 1/5:culture-negative sepsis, 1/5: HHV6 pneumonitis, aGvHD, sepsis	12% (grade II-IV)	NA	NA	
HSCT, MRD		At 1y, B^-: 100%, B^+: 100%	NA	10% (grade II-IV)	NA	NA	
SCT	R: 4mon-20y	63%	VOD: 1/6, LPD: 1/6, EBV post-transplant LPD: 1/6, Rhizopus: 1/6, disseminated BK and Adenovirus, MOF: 1/6, 1/6: graft failure.	31.25%	6.25%	31.25%	(75)
HSCT, MMUD, MIC **HSCT, MUD, MIC** **HSCT, MSD, MIC**	34 and 62mon Med: 38mon (R: 19-48mon) 25mon	100% ~83.3% 100%	0 Late sepsis: 1/1 0	50% 50% 0	50% ~33.3% 0	50% 50% 0	(76)
BMT, TCD, HI **BMT, RD, identical**	Med: 8.7y (R: 6mon-26y)	75% 100%	Viral infections present at diagnosis: 28/37, pulmonary disease: 4/37, Candida bloodstream infection: 2/37, an unrelated mitochondrial defect: 1/37, nephrotic syndrome following chemotherapy given prior to referral: 1/37, VOD: 1/37.	NA	NA	NA	(77)

Cont. table 5

HSCT	Med: 14y (R: 2-34y)	At 2y: 63%	NA	NA	NA	NA	(78)
HSCT, HI or identical	Med: 10y (R: 2mon-28.3y)	76%	CMV: 9, Adenovirus: 9, EBV/lymphoma: 6, Enterovirus, Rotovirus: 4, Parainfluenza 3: 4, Varicella: 2, Herpes simplex: 1, RSV: 1, Pulmonary disease: 4, Candida sepsis: 2, Mitochondrial defect: 1, CNS infection: 1, Nephrotic syndrome/chemo: 1,VOD: 1.	~34.33%	NA	NA	(79)
HSCT, identical **HSCT, MUD**	Med: 67mon (R: 20-142mon)	100%	0	20%	0	20%	(80)
BMT, identical, sibling **BMT, MMRD** **BMT, MUD**	Med: 34.5mon (R: 3-145mon)	100% 93.75% 50%	0 1/1: respiratory failure 1/2: encephalitis, 1/2: intra-cranial hemorrhage	60% 37.5% 50%	8%	NA	(81)
HSCT	NA	20%	NA	NA	NA	NA	(82)
HSCT, TCD, Parent **HSCT, Sibling**	Med: 7.45y	~73.7% 100%	4/5: invasive infection, 1/5: rapid pulmonary failure	NA NA	~5.5% NA	NA NA	(83)
PBT, MMRD **BMT, MRD** **UCBT, MUD**	Med: 64mon (R: 4-150mon)	~66.7% 100% 100%	2/2: severe infections 0 0	~66.7% ~33.3% 100%	50% ~33.3% 0%	~83.3% ~66.7% 100%	(84)
HSCT, HI, mother **HSCT, HI, father**	Med: 33mon (R: 4-74mon)	~83.3% 0%	2/2: graft failure 1/3: encephalitis, 2/3: graft failure	70% 100%	0% 100%	70% 100%	(85)
PBSC, MRD **BM, MRD** **PBSC, HI**	Med: 27mon (R: 1-67mon)	~83.3% ~66.7% ~71.4%	1/1: sepsis and respiratory distress 1/1: sepsis and respiratory distress 2/2: sepsis and liver derangement	50% ~66.7% ~57.1%	50% ~33.3% ~42.8%	50% ~66.7% ~57.1%	(86)
UCB, UD	Med: 68mon (R: 48–73mon)	80%	1/1: sepsis due to a catheter infection.	60%	40%	60%	(87)
HSCT	49mon (for only one patient remained alive after transplantation)	~16.6%	5/5: severe transplant-related complications (e.g. lung infection)	50%	NA	NA	(88)
PBSC, Mother	Med: 15mon (R: 3w-36mon)	B^+: 50% B^-: 100%	1/5: VOD and Acinetobacter sepsis, 1/5: severe GvHD and disseminated CMV infection, 2/5: severe pneumonitis, 1/5: alveolar hemorrhage and bronchiolitis obliterans.	~71.4%	NA	~71.4%	(89)
HSCT, MSD or MMRD or MUD	Mean: 95mon	NA	NA	~54%	~7.4%	NA	(90)
HSCT	NA	62.5%	3/3: complications of previously acquired viral infection or graft failure.	NA	NA	NA	(91)
HSCT, TCRαβ/CD19-depleted, MMRD	Mean: 524.4d (R: 187-840d)	100%	0	40%	0%	40%	(92)
BMT, MMRD **BMT, MSD**	Mean: 6.64y (R: 1.2-10y)	~71.4%	1/2: CMV encephalitis, 1/2: fungal sepsis.	14%	0%	14%	(93)

Table 6. Factors That Affected or Didn't Affect the Survival of SCID Patients Who Underwent SCT

Type of transplant	Factors that affected survival and prognosis	Factors that didn't affect survival and prognosis	Ref.
TCD, HLA-mismatched BM	Type of SCID	The degree of HLA-mismatching, the method of TCD	(10)
HLA-identical BM	Genotypically identical marrow and age at BMT (<6 months vs. >6 months)	Type of SCID	
HLA-nonidentical BMT	Lung infection before BMT and protected environment used at BMT	Protracted diarrhea before BMT, malnutrition before BMT, viral infection before BMT, disseminated BCG infection before BMT, maternofetal GvHD before BMT, donor, HLA incompatibility, GvHD prophylaxis, acute GvHD, sex of donor and recipient	(9)
TCD, HLA-nonidentical BMT	T-cell reconstitution 6 months after BMT, chronic GVHD 6 months after BMT , type of SCID (T^-B^+ vs. T^-B^-), the period during which BMT was performed (before 1991 vs. after 1991), age at BMT(<6 months vs. >6 months) among T^-B^+-SCID patients, pulmonary infection among T^-B^--SCID patients, the method of TCD among T^-B^--SCID patients	B-cell reconstitution 6months after BMT, HLA compatibility, sex , acute GVHD, chronic GVHD, age at BMT(<6 months vs. >6 months) among T^-B^--SCID patients, pulmonary infection among T^-B^+-SCID patients, the method of TCD among T^-B^+-SCID patients	(11,12)
TCD, HLA-haploidentical parental BM **HLA-identical BM from a related donor** **PBT from unrelated donors in addition to TCD, HLA-haploidentical parental BM**	Race, sex	Genetic type of SCID	(48)
HLA-identical HSCT	Age at transplantation Prophylaxis	--	(14)
HLA-mismatched HSCT	SCID phenotype Protected environment Pulmonary infection before HSCT	--	
HLA-nonidentical HSCT	MAC regimen in T^-B^--SCID patients	--	
HLA-identical BM from family-related donor	--	Sex, specific molecular defects causing SCID, the period during which BMT was performed	(15)
BM from MUDs	--	SCID phenotype (T^-B^+ vs. T^-B^-), sex, specific molecular defects causing SCID, transplant center, the period during which BMT was performed	
BM from MMRDs	--	SCID phenotype (T^-B^+ vs. T^-B^-), sex, specific molecular defects causing SCID, the period during which BMT was performed	
MSDs + MMRDs + Other related donors + URDs	Age, active infection at the time of transplantation, donor type	Specific molecular defects causing SCID SCID phenotype (T^-B^+ vs. T^-B^-)	(30)
HSC from MURDs without CR	--	Serotherapy, age, presence of infections before transplantation, the period during which BMT was performed	(31)
HSCT, HI or identical	Age, race	Genetic type of SCID, except for ARTEMIS and male UC	(79)
HSCT	Donor type (HLA-identical vs. HLA-haploidentical), presence of viral infection prior to HCT, age at diagnosis (< 3 months vs. > 3 months), presence of cGVHD, and need for retransplantation	Molecular diagnosis of SCID, use of myeloablative conditioning regimen	(29)

Table 7. Summary of Studies Assessing Stem Cell Transplantation-based Gene Therapy in Severe Combined Immunodeficiency Disorders

Study (YOP) Period Center	Procedure	Follow-up time of the surviving patients	No. and trait of patients (AAGT)	Survival	Main causes of death	Authors' conclusion	Ref.
R. M. Blaese (1993) 1990-1993 Cellular Immunology Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.	Periodic infusions of autologous culture-expanded T cells genetically corrected by insertion of a normal ADA gene using retroviral-mediated gene transfer with the LASN vector	NA	2, ADA-SCID 4y and NA	100%	No deaths occurred during the study period.	*Both patients have tolerated the treatments without complication and are able to participate fully in school and social activities.	(99)
P. M. Hoogerbrugge (1996) Department of Medical Biochemistry, University of Leiden, Rijswijk, Netherlands	Retrovirus-mediated gene transfer into CD34+ bone marrow cells	NA	3, ADA-SCID NA	100%	No deaths occurred during the study period.	*The gene was present in the marrow of one of the patients at 6 months after gene transfer. * Expression of the gene was not detected. *There was no selective advantage of the genetically corrected progenitor cells.	(100)
D. B. Kohn 1993-1995 Division of Research Immunology/Bone Marrow Transplantation, USA.	A single infusion for each of retroviral vector-transduced autologous umbilical cord blood CD34+ cells	18mon	3, ADA-SCID Neonatal	100%	No deaths occurred during the study period.	*The continued presence and expression of the introduced gene in leukocytes from bone marrow and peripheral blood for 18 months demonstrates that umbilical cord blood cells may be genetically modified with retroviral vectors and engrafted in neonates for gene therapy.	(101)
D. B. Kohn 1993-1997 Division of Research Immunology/Bone Marrow Transplantation, USA	A single infusion for each of retroviral vector-transduced autologous umbilical cord blood CD34+ cells	4 years	3, ADA-SCID Neonatal	100%	No deaths occurred during the study period.	*The frequency of gene-containing T lymphocytes has risen to 1–10%, whereas the frequencies of other hematopoietic and lymphoid cells containing the gene remain at 0.01–0.1%. *Enzyme replacement therapy in one subject led to a decline in immune function, despite the persistence of gene-containing T lymphocytes. *Despite the long-term engraftment of transduced stem cells and selective accumulation of gene-containing T lymphocytes, improved gene transfer and expression will be needed to attain a therapeutic effect.	(102)

Cont. table 7

M Cavazzana-Calvo (2005) Brief report Department of Biotherapy, Hoˆpital Necker, 74743 Paris	Gene transfer to bone marrow CD34+ cells	At least 180d	2, SCID-X1 20y and 15y	50%	Respiratory failure: 1/1	*Gene therapy for SCID-X1 patients should be performed as soon as possible.	(103)
A Aiuti (2007) Clinical trial The San Raffaele Scientific Institute and Hadassah University Ethical Committees and National Regulatory authorities	BM CD34+ cells/kg transduced with an ADA-expressing MLV vector after low-dose conditioning with busulphan	Med: 3.1y (R: 1.5-47mon)	5, ADA-SCID NM	100%	No deaths occurred during the study period.	*Clonal analysis of long-term repopulating cell progeny in vivo revealed highly polyclonal T cell populations and shared retroviral integrations sites among multiple lineages, demonstrating the engraftment of multipotent HSCs. *GT seems to be safe and effective in the treatment of ADA-SCID.	(104)
S Hacein-Bey –Abina (2010) Clinical trial 1999-2002 The Necker−Enfants Malades Hospital	Ex vivo retrovirus-mediated transfer of γ chain to autologous CD34+ bone marrow cells	Med: 9y (R: 8-11y)	9, SCID-X1 Med: 7mon (R: 1-11mon)	~88.9%	1/1: T-cell acute lymphoblastic leukemia	*Although GT may be an option for patients who do not have an HLA-identical donor for HSCT, this treatment is associated with a risk of acute leukemia. *All patients showed sig TCR.	(105)
A. J Thrasher (2011) Phase I/II clinical trial The Centre for Immunodeficiency, London, UK	Autologous CD34+ HSCs and PCs transduced with a conventional gRV without myelosuppressive conditioning	Med: 80mon (R: 54-107mon)	10, X-linked SCID Med: 10mon (R: 4-46mon)	100%	No deaths occurred during the study period.	*TCR varied depending on cell dose, clinical condition and age at the time of treatment. *Th HIRs were partially restored. *Adverse outcomes: T-ALL as a result of vector-mediated insertional mutagenesis	(94)
H. B Gaspar (2011) Long term clinical trial The Centre for Immunodeficiency, London, UK	Autologous CD34+ HSCs and PCs transduced with a conventional gRV encoding the human ADA gene with pre-treatment mild chemotherapy	Med: 43mon (R: 24-84mon)	6, ADA-SCID Med: 36mon (R: 6-39mon)	100%	No deaths occurred during the study period.	*4 of 6 patients had recovered immune function. *Treatment failed in 2 of 6 patients due to disease-specific and technical reasons.	(95)
M. Cavazzana-Calvo (2002) Clinical trial 1999-2000 The Laboratoire de Thérapie Cellulaire et Génique, Hôpital Necker Enfants Malades, 149 rue de Sèvres, France	Autologous CD34+ HSCs transduced with the *γc* gene	Mean: 1.78y (R: 0.7-2.5y)	5, X-linked SCID Mean: 6.6mon (R: 1-11mon)	100%	No deaths occurred during the study period.	*80% (4/5) of the patients developed TCR and NKR within 4mon PoT. *The therapeutic procedure was safe. *There were no serious adverse events PoT.	(106)
H. L. Malech (2007) Clinical trial NIH, Department of Health and Human Services, Bethesda	Autologous CD34+ HSCs transduced with the *γc* gene	Mean: 21.66mon (R: 12-30mon)	3, X-linked SCID Mean: 11.66y (R: 10-14y)	100%	No deaths occurred during the study period.	*All patients showed retroviral marking in multiple leukocyte lineages. *The therapeutic procedure was safe. *There were no serious adverse events PoT.	(107)

Cont. table 7

D. B. Kohn (2012) Phase I/II clinical trial	Autologous CD34+ HSCs transduced with a conventional gRV encoding the human ADA gene without pre-HSCT cytoreduction (n = 4) or with low-dose Busulfan (n = 6)	Mean: 6.1y (R: 2.5-10y)	10, ADA-SCID Mean: 11.6y (R: 15mon-20y)	100%	No deaths occurred during the study period.	*Non-myeloablative pre-transplantation conditioning was indicated to improve the therapeutic effects of gene therapy.	(108)
C. C. Dvorak (2013) 2010-2012 Prospective	Autologous gene transfer	Med: 15.7mon (R: 10.6-28.5mon)	3, X-linked or ADA-SCID Med: 114d (R: 90-172d)	100%	No deaths occurred during the study period.		(33)
Touzot F (2015) 2000-2013 Retrospective The Necker Children's Hospital (Paris, France)	HSCT, HI (n=13)	Med of 6y (R: 1-12y)	13, SCID-X1 Med: 7mon (R: 1-15mon)	~84.6%	1/2: respiratory viral infection, 1/2: severe dysimmune enteropathy.	*Authors concluded that there is a clear advantage in terms of T-cell development of gene therapy over HSCT with a mismatched donor.	(109)
	Gene therapy (n=14)	Med of 12y (R: 1-15y)	14, SCID-X1 Med: 8mon (R: 1-11mon)	~85.7%	1/2: adenoviral infection, 1/2: chemoresistant T-cell acute lymphoblastic leukemia.		

References

1. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, et al. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 1997;130:378-87.
2. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA 2014;312:729-38.
3. Chan K, Puck JM. Development of population-based newborn screening for severe combined immunodeficiency. J Allergy Clin Immunol 2005;115:391-8.
4. Gaspar HB, Hammarström L, Mahlaoui N, Borte M, Borte S. The case for mandatory newborn screening for severe combined immunodeficiency (SCID). J Clin Immunol 2014;34:393-7.
5. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. Science 1988;241:58-62.
6. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813-26.
7. Gatti R, Meuwissen H, Allen H, Hong R, Good R. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 1968;292:1366-9.
8. Eapen M, Ahn KW, Orchard PJ, Cowan MJ, Davies SM, Fasth A, et al. Long-term survival and late deaths after hematopoietic cell transplantation for primary immunodeficiency diseases and inborn errors of metabolism. Biol Blood Marrow Transplant 2012;18:1438-45.
9. 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.
10. Fischer A, Griscelli C, Friedrich W, Kubanek B, Levinsky R, Morgan G, et al. Bone-marrow transplantation for immunodeficiencies and osteopetrosis: European survey, 1968-1985. Lancet 1986;2:1080-4.
11. 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.
12. 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 transplantationA retrospective European survey from the

European Group for Bone Marrow Transplantation and the European Society for Immunodeficiency. J Pediatr 1999;134:740-8.

13. 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.
14. 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.
15. Grunebaum E, Mazzolari E, Porta F, Dallera D, Atkinson A, Reid B, et al. Bone marrow transplantation for severe combined immune deficiency. JAMA 2006;295:508-18.
16. Lee WI, Jaing TH, Hsieh MY, Kuo ML, Lin SJ, Huang JL. Distribution, infections, treatments and molecular analysis in a large cohort of patients with primary immunodeficiency diseases (PIDs) in Taiwan. J Clin Immunol 2006;26:274-83.
17. Honig M, Albert MH, Schulz A, Sparber-Sauer M, Schutz C, Belohradsky B, et al. Patients with adenosine deaminase deficiency surviving after hematopoietic stem cell transplantation are at high risk of CNS complications. Blood 2007;109:3595-602.
18. Arpaci F, Tezcan I, Kuzhan O, Yalman N, Uckan D, Kurekci AE, et al. G-CSF-mobilized haploidentical peripheral blood stem cell transplantation in children with poor prognostic nonmalignant disorders. Am J Hematol 2008;83:133-6.
19. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, 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;126:602-10.e1-11.
20. Lee PP, Chan KW, Chen TX, Jiang LP, Wang XC, Zeng HS, et al. Molecular diagnosis of severe combined immunodeficiency--identification of IL2RG, JAK3, IL7R, DCLRE1C, RAG1, and RAG2 mutations in a cohort of Chinese and Southeast Asian children. J Clin Immunol 2011;31:281-96.
21. Marcus N, Takada H, Law J, Cowan MJ, Gil J, Regueiro JR, et al. Hematopoietic stem cell transplantation for CD3delta deficiency. J Allergy Clin Immunol 2011;128:1050-7.
22. Lee WI, Huang JL, Jaing TH, Shyur SD, Yang KD, Chien YH, et al. Distribution, clinical features and treatment in Taiwanese patients with symptomatic primary immunodeficiency diseases (PIDs) in a nationwide population-based study during 1985-2010. Immunobiology 2011;216:1286-94.
23. Morio T, Atsuta Y, Tomizawa D, Nagamura-Inoue T, Kato K, Ariga T, et al. Outcome of unrelated umbilical cord blood transplantation in 88 patients with primary immunodeficiency in Japan. Br J Haematol 2011;154:363-72.
24. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood 2011;117:3243-6.
25. Slatter MA, Rao K, Amrolia P, Flood T, Abinun M, Hambleton S, et al. Treosulfan-based conditioning regimens for hematopoietic stem cell transplantation in children with primary immunodeficiency: United Kingdom experience. Blood 2011;117:4367-75.
26. Hassan A, Booth C, Brightwell A, Allwood Z, Veys P, Rao K, et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. Blood 2012;120:3615-24.
27. Fernandes JF, Rocha V, Labopin M, Neven B, Moshous D, Gennery AR, et al. Transplantation in patients with SCID: mismatched related stem cells or unrelated cord blood? Blood 2012;119:2949-55.
28. Mitchell R, Nivison-Smith I, Anazodo A, Tiedemann K, Shaw P, Teague L, et al. Outcomes of hematopoietic stem cell transplantation in primary immunodeficiency: a report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. Biol Blood Marrow Transplant 2013;19:338-43.
29. Schuetz C, Neven B, Dvorak CC, Leroy S, Ege MJ, Pannicke U, et al. SCID patients with ARTEMIS vs RAG deficiencies following HCT: increased risk of late toxicity in ARTEMIS-deficient SCID. Blood 2014;123:281-9.
30. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. N Engl J Med 2014;371:434-46.
31. Dvorak CC, Hassan A, Slatter MA, Hönig M, Lankester AC, Buckley RH, 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. J Allergy Clin Immunol 2014;134:935-43.
32. Hassan A, Lee P, Maggina P, Xu JH, Moreira D, Slatter M, et al. Host natural killer immunity is a key indicator of permissiveness for donor cell engraftment in patients with severe combined immunodeficiency. J Allergy Clin Immunol 2014;133:1660-6.
33. Dvorak CC, Cowan MJ, Logan BR, Notarangelo LD,

Griffith LM, Puck JM, 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. J Clin Immunol 2013;33:1156-64.

34. 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;5:370-6.
35. Friedrich W, Goldmann SF, Ebell W, Blutters-Sawatzki R, Gaedicke G, Raghavachar A, et al. Severe combined immunodeficiency: treatment by bone marrow transplantation in 15 infants using HLA-haploidentical donors. Europ J Pediatr 1985;144:125-30.
36. Parkman R. Antibody-treated bone marrow transplantation for patients with severe combined immune deficiency. Clin Immunol Immunopathol 1986;40:142-6.
37. 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.
38. Morgan G, Linch DC, Knott LT, Davies EG, Sieff C, Chessells JM, et al. Successful haploidentical mismatched bone marrow transplantation in severe combined immunodeficiency: T cell removal using CAMPATH-I monoclonal antibody and E-rosetting. Br J Haematol 1986;62:421-30.
39. 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.
40. Moen RC, Horowitz SD, Sondel PM, Borcherding 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.
41. Halberg FE, Wara WM, Weaver KE, Wara DW, Ablin AR, Matthay KK, et al. Total body irradiation and bone marrow transplantation for immunodeficiency disorders in young children. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiother Oncol 1990;18:114-7.
42. Filipovich AH, Shapiro RS, Ramsay NK, Kim T, Blazar B, Kersey J, et al. Unrelated donor bone marrow transplantation for correction of lethal congenital immunodeficiencies. Blood 1992;80:270-6.
43. 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 patients. J Pediatr 1993;123:564-72.
44. 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.
45. Buckley RH, Schiff SE, Schiff RI, Roberts JL, Markert ML, Peters W, et al. Haploidentical bone marrow stem cell transplantation in human severe combined immunodeficiency. Seminars in hematology. 1993;30:92-101.
46. van Leeuwen JE, van Tol MJ, Joosten AM, Schellekens PT, van den Bergh RL, Waaijer JL, et al. Relationship between patterns of engraftment in peripheral blood and immune reconstitution after allogeneic bone marrow transplantation for (severe) combined immunodeficiency. Blood 1994;84:3936-47.
47. Dickinson AM, Reid MM, Abinun M, Peak J, Brigham K, Dunn J, et al. In vitro T cell depletion using Campath 1M for mismatched BMT for severe combined immunodeficiency (SCID). Bone marrow transplant 1997;19:323-9.
48. 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.
49. Brugnoni D, Airo P, Pennacchio M, Carella G, Malagoli A, Ugazio AG, et al. Immune reconstitution after bone marrow transplantation for combined immunodeficiencies: down-modulation of Bcl-2 and high expression of CD95/Fas account for increased susceptibility to spontaneous and activation-induced lymphocyte cell death. Bone marrow Transplant 1999;23:451-7.
50. Dalal I, Reid B, Doyle J, Freedman M, Calderwood S, Saunders F, et al. Matched unrelated bone marrow transplantation for combined immunodeficiency. Bone marrow Transplant 2000;25:613-21.
51. Smogorzewska EM, Brooks J, Annett G, Kapoor N, Crooks GM, Kohn DB, et al. T cell depleted haploidentical bone marrow transplantation for the treatment of children with severe combined immunodeficiency. Arch Immunol Ther Exp (Warsz) 2000;48:111-8.
52. Ting SS, Tangye SG, Wood J, Ffrench RA, Ziegler JB. Reduced memory B-cell populations in boys with B-cell dysfunction after bone marrow transplantation for X-linked severe combined immunodeficiency. Br J Haematol 2001;112:1004-11.
53. Kane L, Gennery AR, Crooks BN, Flood TJ, Abinun M,

Cant AJ. Neonatal bone marrow transplantation for severe combined immunodeficiency. Archives of disease in childhood Fetal and neonatal edition. 2001;85:F110-3.

54. Gennery AR, Dickinson AM, Brigham K, Barge D, Spickett GP, Curtis A, et al. CAMPATH-1M T-cell depleted BMT for SCID: long-term follow-up of 19 children treated 1987-98 in a single center. Cytotherapy 2001;3:221-32.
55. 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.
56. Sarzotti M, Patel DD, Li X, Ozaki DA, Cao S, Langdon S, et al. T cell repertoire development in humans with SCID after nonablative allogeneic marrow transplantation. J Immunol 2003;170:2711-8.
57. Laffort C, Le Deist F, Favre M, Caillat-Zucman S, Radford-Weiss I, Debre M, et al. Severe cutaneous papillomavirus disease after haemopoietic stem-cell transplantation in patients with severe combined immune deficiency caused by common gammac cytokine receptor subunit or JAK-3 deficiency. Lancet 2004;363:2051-4.
58. Pirovano S, Notarangelo LD, Malacarne F, Mazzolari E, Porta F, Lanfranchi A, et al. Reconstitution of T-cell compartment after in utero stem cell transplantation: analysis of T-cell repertoire and thymic output. Haematologica 2004;89:450-61.
59. Roberts JL, Lengi A, Brown SM, Chen M, Zhou YJ, O'Shea JJ, et al. Janus kinase 3 (JAK3) deficiency: clinical, immunologic, and molecular analyses of 10 patients and outcomes of stem cell transplantation. Blood 2004;103:2009-18.
60. Bhattacharya A, Slatter MA, Chapman CE, Barge D, Jackson A, Flood TJ, et al. Single centre experience of umbilical cord stem cell transplantation for primary immunodeficiency. Bone Marrow Transplant 2005;36:295-9.
61. Veys P, Rao K, Amrolia P. Stem cell transplantation for congenital immunodeficiencies using reduced-intensity conditioning. Bone marrow transplantation. 2005;35:S45-7.
62. Rao K, Amrolia PJ, Jones A, Cale CM, Naik P, King D, et al. Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen. Blood 2005;105:879-85.
63. Sakata N, Kawa K, Kato K, Yabe H, Yabe M, Nagasawa M, et al. Unrelated donor marrow transplantation for congenital immunodeficiency and metabolic disease: an update of the experience of the Japan Marrow Donor Program. Int J Hematol 2004;80:174-82.
64. Tsuji Y, Imai K, Kajiwara M, Aoki Y, Isoda T, Tomizawa D, et al. Hematopoietic stem cell transplantation for 30 patients with primary immunodeficiency diseases: 20 years experience of a single team. Bone Marrow Transplant 2006;37:469-77.
65. Borghans JA, Bredius RG, Hazenberg MD, Roelofs H, Jol-van der Zijde EC, Heidt J, et al. Early determinants of long-term T-cell reconstitution after hematopoietic stem cell transplantation for severe combined immunodeficiency. Blood 2006;108:763-9.
66. Mazzolari E, Forino C, Guerci S, Imberti L, Lanfranchi A, Porta F, et al. Long-term immune reconstitution and clinical outcome after stem cell transplantation for severe T-cell immunodeficiency. J Allergy Clin Immunol 2007;120:892-9.
67. Keller MD, Chen DF, Condron SA, Liu N, Reinsmoen NL, Buckley RH. The effect of natural killer cell killer Ig-like receptor alloreactivity on the outcome of bone marrow stem cell transplantation for severe combined immunodeficiency (SCID). J Clin Immunol 2007;27:109-16.
68. Porta F, Forino C, De Martiis D, Soncini E, Notarangelo L, Tettoni K, et al. Stem cell transplantation for primary immunodeficiencies. Bone Marrow Transplant 2008;41:S83-6.
69. De Heredia CD, Ortega JJ, Diaz MA, Olive T, Badell I, Gonzalez-Vicent M, et al. Unrelated cord blood transplantation for severe combined immunodeficiency and other primary immunodeficiencies. Bone Marrow Transplant 2008;41:627-33.
70. Al-Ghonaium A. Stem cell transplantation for primary immunodeficiencies: King Faisal Specialist Hospital experience from 1993 to 2006. Bone Marrow Transplant 2008;42:S53-s6.
71. Dvorak CC, Hung GY, Horn B, Dunn E, Oon CY, Cowan MJ. Megadose CD34+ cell grafts improve recovery of T cell engraftment but not B cell immunity in patients with severe combined immunodeficiency disease undergoing haplocompatible nonmyeloablative transplantation. Biol Blood Marrow Transplant 2008;14:1125-33.
72. Patel NC, Chinen J, Rosenblatt HM, Hanson IC, Brown BS, Paul ME, et al. Long-term outcomes of nonconditioned patients with severe combined immunodeficiency transplanted with HLA-identical or haploidentical bone marrow depleted of T cells with anti-CD6 mAb. J Allergy Clin Immunol 2008;122:1185-93.
73. Yee A, De Ravin SS, Elliott E, Ziegler JB. Severe combined immunodeficiency: a national surveillance study. Pediatr Allergy Immunol 2008;19:298-302.
74. Patel NC, Chinen J, Rosenblatt HM, Hanson IC, Krance

RA, Paul ME, et al. Outcomes of patients with severe combined immunodeficiency treated with hematopoietic stem cell transplantation with and without preconditioning. J Allergy Clin Immunol 2009;124:1062-9.e1-4.

75. 76. Petrovic A, Dorsey M, Miotke J, Shepherd C, Day N. Hematopoietic stem cell transplantation for pediatric patients with primary immunodeficiency diseases at All Children's Hospital/University of South Florida. Immunologic research. 2009;44(1-3):169-78.
76. Straathof KC, Rao K, Eyrich M, Hale G, Bird P, Berrie E, et al. Haemopoietic stem-cell transplantation with antibody-based minimal-intensity conditioning: a phase 1/2 study. Lancet 2009;374:912-20.
77. 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;155:834-40.e1.
78. Neven B, Leroy S, Decaluwe H, Le Deist F, Picard C, Moshous D, et al. Long-term outcome after hematopoietic stem cell transplantation of a single-center cohort of 90 patients with severe combined immunodeficiency. Blood 2009;113:4114-24.
79. Buckley RH. Transplantation of hematopoietic stem cells in human severe combined immunodeficiency: longterm outcomes. Immunol Res 2011;49:25-43.
80. Serana F, Sottini A, Chiarini M, Zanotti C, Ghidini C, Lanfranchi A, et al. The different extent of B and T cell immune reconstitution after hematopoietic stem cell transplantation and enzyme replacement therapies in SCID patients with adenosine deaminase deficiency. J Immunol 2010;185:7713-22.
81. Dinardo L, Brown V, Perez E, Bunin N, Sullivan KE. A single-center study of hematopoietic stem cell transplantation for primary immune deficiencies (PIDD). Pediatr Transplant 2012;16:63-72.
82. Wang LL, Jin YY, Hao YQ, Wang JJ, Yao CM, Wang X, et al. Distribution and clinical features of primary immunodeficiency diseases in Chinese children (2004-2009). J Clin Immunol 2011;31:297-308.
83. Triplett BM, Wang C, Yang J, Dallas M, Hartford C, Howard V, et al. Effects of conditioning regimens and T cell depletion in hematopoietic cell transplantation for primary immune deficiency. Biol Blood Marrow Transplant 2012;18:1911-20.
84. Lev A, Simon AJ, Bareket M, Bielorai B, Hutt D, Amariglio N, et al. The kinetics of early T and B cell immune recovery after bone marrow transplantation in RAG-2-deficient SCID patients. PLoS One 2012;7:e30494.
85. Cipe FE, Dogu F, Aytekin C, Yuksek M, Kendirli T, Yildiran A, et al. HLA-haploidentical transplantations for primary immunodeficiencies: a single-center experience. Pediatr Transplant 2012;16:451-7.
86. Amayiri N, Al-Zaben A, Ghatasheh L, Frangoul H, Hussein AA. Hematopoietic stem cell transplantation for children with primary immunodeficiency diseases: single center experience in Jordan. Pediatr Transplant 2013;17:394-402.
87. Kumaki S, Sasahara Y, Kamachi Y, Muramatsu H, Morio T, Goi K, et al. B-cell function after unrelated umbilical cord blood transplantation using a minimal-intensity conditioning regimen in patients with X-SCID. Int J Hematol 2013;98:355-60.
88. Yao CM, Han XH, Zhang YD, Zhang H, Jin YY, Cao RM, et al. Clinical characteristics and genetic profiles of 44 patients with severe combined immunodeficiency (SCID): report from Shanghai, China (2004-2011). J Clin Immunol 2013;33:526-39.
89. Wahadneh AM, Bin Dahman HA, Abu Shukear ME, Habahbeh ZM, Ajarmeh MA, Zyood RM, et al. Mismatched related hematopoietic stem cell transplantation in primary immunodeficiency. Saudi J Kidney Dis Transpl 2013;24:1137-43.
90. Valotti M, Sottini A, Lanfranchi A, Bolda F, Serana F. Long-lasting production of new T and B cells and T-cell repertoire diversity in patients with primary immunodeficiency who had undergone stem cell transplantation: a single-centre experience. J Immunol Res 2014;2014:240453.
91. Pasic S, Vujic D, Veljkovic D, Slavkovic B. Severe combined immunodeficiency in Serbia and Montenegro between years 1986 and 2010: a single-center experience. J Clin Immunol 2014;34:304-8.
92. Balashov D, Shcherbina A, Maschan M, Trakhtman P, Skvortsova Y, Shelikhova L, et al. Single-Center Experience of Unrelated and Haploidentical Stem Cell Transplantation with TCRalphabeta and CD19 Depletion in Children with Primary Immunodeficiency Syndromes. Biol Blood Marrow Transplant 2015;21:1955-62.
93. Scarselli A, Di Cesare S, Capponi C, Cascioli S, Romiti M, Di Matteo G, et al. Longitudinal Evaluation of Immune Reconstitution and B-cell Function After Hematopoietic Cell Transplantation for Primary Immunodeficiency. J Clin Immunol 2015;35:373-83.
94. Gaspar HB, Cooray S, Gilmour KC, Parsley KL, Adams S, Howe SJ, et al. Long-term persistence of a polyclonal T cell repertoire after gene therapy for X-linked severe combined immunodeficiency. Sci Transl Med 2011;3:97ra79.
95. Gaspar HB, Cooray S, Gilmour KC, Parsley KL, Zhang F,

Adams S, et al. Hematopoietic stem cell gene therapy for adenosine deaminase-deficient severe combined immunodeficiency leads to long-term immunological recovery and metabolic correction. Sci Transl Med 2011;3:97ra80.

96. Le Blanc K, Samuelsson H, Gustafsson B, Remberger M, Sundberg B, Arvidson J, et al. Transplantation of mesenchymal stem cells to enhance engraftment of hematopoietic stem cells. Leukemia 2007;21:1733-8.
97. Tasher D, Dalal I. The genetic basis of severe combined immunodeficiency and its variants. Appl Clin Genet 2012:5:67-80.
98. 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 Athabascan-speaking native Americans. Bone Marrow Transplant 2001;27:703-9.
99. Blaese RM. Development of gene therapy for immunodeficiency: adenosine deaminase deficiency. Pediatr Res 1993;33:S49-53.
100. Hoogerbrugge PM, van Beusechem VW, Fischer A, Debree M, le Deist F, Perignon JL, et al. Bone marrow gene transfer in three patients with adenosine deaminase deficiency. Gene Ther 1996;3:179-83.
101. Kohn DB, Weinberg KI, Nolta JA, Heiss LN, Lenarsky C, Crooks GM, et al. Engraftment of gene-modified umbilical cord blood cells in neonates with adenosine deaminase deficiency. Nat Med 1995;1:1017-23.
102. Kohn DB, Hershfield MS, Carbonaro D, Shigeoka A, Brooks J, Smogorzewska EM, et al. T lymphocytes with a normal ADA gene accumulate after transplantation of transduced autologous umbilical cord blood CD34+ cells in ADA-deficient SCID neonates. Nat Med 1998;4:775-80.
103. Thrasher AJ, Hacein-Bey-Abina S, Gaspar HB, Blanche S, Davies EG, Parsley K, et al. Failure of SCID-X1 gene therapy in older patients. Blood 2005;105:4255-7.
104. Aiuti A, Cassani B, Andolfi G, Mirolo M, Biasco L, Recchia A, et al. Multilineage hematopoietic reconstitution without clonal selection in ADA-SCID patients treated with stem cell gene therapy. J Clin Invest 2007;117:2233-40.
105. Hacein-Bey-Abina S, Hauer J, Lim A, Picard C, Wang GP, Berry CC, et al. Efficacy of gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 2010;363:355-64.
106. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, et al. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 2002;346:1185-93.
107. Chinen J, Davis J, De Ravin SS, Hay BN, Hsu AP, Linton GF, et al. Gene therapy improves immune function in preadolescents with X-linked severe combined immunodeficiency. Blood 2007;110:67-73.
108. Candotti F, Shaw KL, Muul L, Carbonaro D, Sokolic R, Choi C, et al. Gene therapy for adenosine deaminase–deficient severe combined immune deficiency: clinical comparison of retroviral vectors and treatment plans. Blood 2012;120:3635-46.
109. Touzot F, Moshous D, Creidy R, Neven B, Frange P, Cros G, et al. Faster T-cell development following gene therapy compared with haploidentical HSCT in the treatment of SCID-X1. Blood 2015;125:3563-9.