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**Considerations for hematopoietic stem cell transplantation in primary immunodeficiency disorders**

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**Abstract**

Primary immunodeficiency disorders (PID) result from inborn errors in immunity. Susceptibility to infections and oftentimes severe autoimmunity pose life-threatening risks to patients with these disorders. Hematopoietic cell transplant (HCT) remains as the only curative options for many. Furthermore, severe combined immunodeficiency most commonly presents at the time of birth and typically requires emergent HCT in the first few weeks of life. HCT poses an unusual challenge for PID. The selection of donor, whether or not to use a conditioning regimen and, if so, then determining the optimal regimen to use in large part drives the outcome of transplant in patients with PID. The choice of matched and unmatched, related versus unrelated donors has shown variable outcomes for different subsets of PID. Additionally, there is significant variability in the success of engraftment even within the different lymphocyte populations. While certain cell lines do well without a conditioning regimen, others will not reconstitute unless conditioning is used. The decision to proceed with regimen is further complicated by the fact that not only do primary immunodeficiency disorders already predispose the pre-transplant recipient to life-threatening infections, certain alkylating agents cannot be used in radiosensitive PID. This manuscript reviews some of the unique elements of HCT in PID and evidence-based approaches to HCT in patients with these rare and complex disorders.

**Key words:** Primary immunodeficiency disorders; Hematopoietic stem cell transplant; Autoimmunity; Conditioning regimens

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**Core tip:** Primary immunodeficiency disorders (PID) result from inborn errors in immunity and hematopoietic cell transplant (HCT) still remains as the only curative option for many of these disorders. Severe combined immunodeficiency disorders belong to a subtype of PID that constitutes a medical emergency and requires HCT within weeks from the time of birth. Donor selection, conditioning regimen and outcomes of immune reconstitution vary greatly among these disorders. This manuscript reviews some of the unique elements of HCT in PID and evidence-based approaches to transplant in patients with these rare and complex disorders.

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**INTRODUCTION**

Primary immunodeficiency disorders (PID) result from inborn errors in immunity. Many results in severe life-threatening infections and immune dysregulation that can be fatal if not diagnosed and treated early in life. Hematopoietic cell transplant (HCT) is a curative option for certain PIDs. Besides for donor selection, individual conditioning regimens must be taken into account[1]. The unique defects involved in PIDs and clinical manifestations of these disorders pose their own challenges for the approach to HCT.

**SEVERE COMBINED IMMUNODEFICIENCY DISORDER**

Severe combined immunodeficiency disorders (SCID) are a subgroup of genetic disorders characterized by impaired T-cell development, sometimes also accompanied by B and Natural Killer (NK) cell deficiency. The pathophysiology responsible for the subtypes of SCID determines the cellular phenotype of the disorder. Reticular dysgenesis is an autosomal recessive variant of SCID that is a product of adenylate kinase 2 (AK2) deficiency and presents as T-B-NK- SCID. Defects in the ability to clear toxic metabolites, such as due to adenosine deaminase (ADA) or purine nucleoside phosphorylase deficiency, results in a T-B-NK-phenotype. Cytokine signaling abnormalities common to T and NK cell development such as defects in IL-2R common gamma chain, JAK3 and IL-7 receptor result in T-B+NK-SCID. T-cell receptor abnormalities due to CD45, CD3 and CORO1A affect T cell development and therefore will still have B and NK cells present. A similar presentation occurs with abnormalities in thymic development as seen in DiGoerge syndrome (22q.11 deletion) and FOXN1 defect. Receptor chain (VDJ) recombination defects result in T-B-NK+ SCID. All of SCID subtypes are autosomal recessive with the exception of the IL-2R gamma chain which is the only known X-linked SCID and DiGeorge syndrome which can be de novo or autosomal dominant[2]. Since the introduction of T cell receptor excision circle assay to the newborn screening program in many countries, SCID has been diagnosed at a younger age, allowing avoidance of infectious complications[2,3].

While ADA deficiency can be, at least temporarily, treated with enzyme replacement therapy[3] and gene therapy is investigated for x-linked SCID, HCT still remains as the only curative treatment option for other SCIDs and many PIDs.

As with all HCT, donor selection is of critical importance. HLA-matched related donors (MRD) are preferred, but unrelated donor (URD) HCT still have excellent survival rates particularly in the first 3.5 mo of life or in older infants without prior infections. Both of these sources have the benefit of short engraftment time compared to others. A consideration to take into account with matched sibling donors (MSD) is that a family member may be a carrier for the disease. Infants with active infection without a MSD have fared best with haploidentical T-cell-depleted transplants in the absence of any pretransplantation conditioning. Reduced-intensity or myeloablative pretransplantation conditioning was associated with an increased likelihood of a CD3+ T cell recovery more than 1000/mm3[5]. Graft-*vs*-host disease (GVHD) occurs when mature T cells are not removed from the donor source, resulting in inflammation and rejection of the graft. Mature T cell removal from the graft minimizes the risk for GVHD. A MRD HLA-identical sibling is a donor of choice for HCT in cases of SCID. Acceptable alternatives include matched URD, haploidentical parent or a mismatched unrelated donor (MMRD) or umbilical cord donor (UCB). T-cell depleted haploidentical donors and UCB transplants carry a higher risk for viral infections. UCB also involves a longer engraftment time[4].

SCID marked by an absence of host T cells implies little resistance to the graft. Therefore, pre-transplant conditioning recommendations vary. Immunosuppression regimens include: fludarabine, cyclophosphamide, anti-thymocyte globulin, alemtuzumab, rituximab and other monoclonal antibodies. Myeloablative therapy includes cyclophosphamide, fludarabine, antithymocyte globulin (ATG) and alemtuzumab. T-cell negative SCID typically does not require myeloablative therapy. Partly myeloablative agents are busulfan, melphalan, treosulfan. Reduced intensity conditioning (RIC) is a myeloablative approach that is less toxic than the fully myeloablative chemotherapy regimens. Agents include melphalan, anti-CD45 antibodies, total-body irradiation, thiotepa, and/or busulfan at a lower dose than one used for membrane attack complex (MAC). SCID with incomplete penetrance, such as Omenn syndrome, is more prone to graft rejection and requires some degree of myeloablative chemotherapy. B cell negative SCIDs have better rates of T cell engraftment after a myeloablative regimen. There are no uniform guidelines regarding the approach to conditioning when MMRDs are used.

Primary Immune Deficiency Treatment Consortium identified factors that impact outcome of immune reconstitution and survival of 100 SCID patients post-HCT. Active infection at the time of HCT negatively impacted survival with a rate of 80% for those over 3.5 mo of age and with an active infection at the time of HCT. CMV was one of the most common infections in these patients. MSD recipients had the best clinical outcomes for SCID and good survival was identified for all alternative donor recipients. However, in the study 6 of 11 UCB recipients died. There was no significant difference in the short-term survival of patients who received chemotherapy-based conditioning (RIC/MAC) compared with those transplanted without conditioning or with immunosuppression conditioning (IS) that included one of the following: fludarabine, cyclophosphamide, ATG, or alemtuzumab. However, 9 of 11 (82%) patients who died received IS, RIC, or MAC. The use of RIC or MAC was associated with a decreased need for a second HCT and an increased likelihood of independence from immunoglobulin replacement[5,6].

Among recipients of non-MSD HCT, multivariate analysis showed that the SCID genotype strongly influenced survival and immune reconstitution. Overall survival was similar for patients with RAG, IL2RG, or JAK3 defects and was significantly better compared with patients with *ADA* or *DCLRE1C* mutations who had the worst outcomes, with poor T cell reconstitution. Patients with *RAG* or *DCLRE1C* mutations had poorer immune reconstitution than other genotypes. Patients with RAG defects, however, had better survival than did those with *DCLRE1C* mutations despite both conferring a T-B-NK+ phenotype. Among the *DCLRE1C*-deficient patients, 64% of deaths were due to noninfectious causes compared with 9% in *RAG*-deficient patients, suggesting that the difference in survival may be related to increased sensitivity to alkylating chemotherapy in patients with *DCLRE1C* genotype, which is associated with a DNA-repair defect[6].

Younger age and freedom from infection at time of HCT had a positive impact on survival. Infection status significantly affected survival of patients who underwent HCT at ≥ 3.5 mo of age but not those who underwent HCT at < 3.5 mo of age. Genotype was not associated with treatment failure overall. Although survival did not correlate with the type of conditioning regimen, recipients of reduced-intensity or myeloablative conditioning had a lower incidence of treatment failure and better T- and B-cell reconstitution, but a higher risk for GVHD, compared with those receiving no conditioning or immunosuppression only. Conditioning regimen and genotype had a strong impact on T- and B-cell reconstitution after non-MSD HCT. Genotypes associated with lack of B cells (*RAG*, *DCLRE1C*) or nonfunctional B cells (IL2RG/JAK3) were associated with a poorer B-cell reconstitution than genotypes associated with functional B cells (IL7R/CD3/CD45). The use of RIC/MAC was associated with improved T-cell reconstitution. CD4+ and CD4+CD45RA+ cell counts at 6 and 12 mo post-HCT as biomarkers predictive of overall survival and long-term T-cell reconstitution[6].

**ADULT PATIENTS**

Although early HCT for PIDs is preferred, atypical presentation and late diagnosis results in the need to address HCT in an adult subgroup of patients, especially in non-SCID scenarios[7]. Fox *et al*[8] reported the outcome of HCT in 29 young adult patients with PIDs. PIDs included common variable immunodeficiency, GATA2 deficiency, X-linked lymphoproliferative disease and SCID among others. Reduced-intensity, T-cell–depleted HCT had an overall survival rate of 85.2% at 3 years. There was no significant difference in outcome between those undergoing MRD transplants and matched or 1 antigen MMUD transplants. Acute GVHD (aGVHD) incidence had a rate of 6.5% and 31% had chronic GVHD (cGVHD) only 31% of patients developed cGVHD. With the exception of one patient, all with cGVHD were able to discontinue systemic immune suppression 3 mo after HCT[8].

**DNA REPAIR PID**

A subgroup of primary immunodeficiencies have unique defects in the DNA-double strand breakage repair system. Such disorders include DNA ligase 4 deficiency, Cernunnos-XLF deficiency (XLF or NHEJ1), Nijmegen Breakage Syndrome and Ataxia-Telangiectasia (AT). Patients with such disorders are at a higher risk of mortality from chemotherapy or ionizing radiation administered prior to HCT. Slack *et al*[9] report survival was significantly superior when RIC was used in these patients suggesting that an RIC regimen should be used in patients with radiation sensitivity. In patients with AT, overall survival was 25%. 67% of the 6 patients who died experienced GVHD grade 2-3. Death was due to multi-organ failure, viral activation or post-transplant lymphoproliferative disorder[9].

**DONOR SOURCE**

Compared to patients with MSD or familial-mismatched donor transplant, recipients of URD HCT showed an inferior survival rate (100% *vs* 58.8%, *P* = 0.042). The survival of patients who received a combination of CSA and methotrexate treatment for GVHD prophylaxis was significantly lower (47.5%) than that of patients administered other treatment (CSA only prophylaxis, CSA plus mycophenolate mofetil combination prophylaxis, or no prophylaxis)[10].

Dvorak *et al*[11] reported outcomes of HCT without chemotherapy conditioning using matched sibling and URDs for treatment of SCID. Authors admitted a selection bias of patients who were deemed unlikely to be able to tolerate chemotherapy. The majority of patients had one or more opportunistic infections. Majority of patients engrafted donor T cells (94%) and subsequently survived (5-year OS 71%). 92% of patients undergoing URD HCT achieved donor T-cell engraftment, compared to 97% for MSDs. However, estimated 5-year overall and event-free survival were worse for URD recipients (71% and 60%, respectively), compared to MSD recipients (92% and 89%, respectively). The use of ATG was associated with an improved overall survival in the URD recipients. Interestingly, the development of GVHD in URD was associated with donor myeloid or B cell chimerism. cGVHD was 5% in MSD patients compared to the 33% in URD recipients. Among the URD recipients, the use of serotherapy resulted in an estimated 5-year event-free survival (EFS) of 71% compared to 38% in the non-serotherapy group, although this did not reach statistical significance. However, as all re-transplanted patients survived, the use of serotherapy was associated with a higher estimated 5-year OS of 100% compared to the 51% of those patients that did not receive serotherapy. 63% of MSD recipients reached freedom from gammaglobulin replacement compared to 8% of URD recipients. MSD recipients with NK− forms of SCID were more likely to recover B cell function (85%; 35/41) compared to those with NK+ forms of SCID (56%; 9/16). An effectively normal immune system was seen in significantly more MSD recipients (72%; 41/57) compared to URD recipients (26%; 6/23) who survived without a conditioned second HCT. Conditioned second HCTs were more common in NK-positive forms of SCID undergoing URD HCT (38%) *vs* NK negative (4%)[11].

**IMMUNE RECONSTITUTION**

Conditioning generally improves the likelihood of T cell reconstitution and is usually needed for B cell reconstitution. However, certain SCID subtypes are more permissive to T cell reconstitution even when conditioning is not used. SCID that does not involve B cell impairment usually results in T cell reconstitution from any type of donor. However, when using donors other than matched siblings, B cell function is not regained unless conditioning is used. SCID with strictly a T cell deficiency does not require conditioning if a MSD is available and immune reconstitution is expected in such cases but less data is available for matched URDs. SCID of T-B-NK+ phenotype rarely sees B cell recovery unless conditioning is used. In cases of T-B-NK- SCID B cell function is best recovered after MSD even without a conditioning regimen. B cell reconstitution is less predictable in unconditioned mismatched related donors and URDs[11,12].

T-cell reconstitution is necessary for an appropriate B-cell function. B cell recovery therefore tends to lag behind T cell reconstitution. Although studying a small cohort, Scarselli *et al*[12] reported that good humoral function was usually associated with the presence of donor B-cell chimerism and promoted by myeloablative conditioning regimen. The majority of patients were able to discontinue supplemental immune globulin. CD19+ CD27+ memory B cells were significantly below normal at 1 and 2 years and increased starting 3-5 years of follow up. Interestingly, switched memory B-cells (CD19+CD27+IgD-IgM-) were restored earlier and better than IgM-memory B-cells (CD19+CD27+IgD+IgM+), which remained significantly reduced in the long-term cohort. B-cell absolute counts and percentage did not differ between MSD and MMRD transplant in long-term surviving patients, but the latter group displayed a reduced frequency of memory B-cells[12].

**IMMUNE POLYENDOCRINOPATHY, ENTEROPATHY X-LINKED**

Immune polyendocrinopathy, enteropathy X-linked (IPEX) is a rare x-linked immune dysregulatory disorder. The classic presentation is a triad of enteropathy resulting in failure to thrive, autoimmune endocrinopathy and dermatitis early in male infants. Management revolves around immunosuppressive treatment, but HCT remains the only curative option.

The underlying mechanism for the disorder is a mutation in the transcription factor FOXP3 which is a transcription factor responsible for regulatory T (Treg) cell development. Treg are critical in maintaining immune homeostasis[13].

Barzaghi *et al*[14] reported findings of long-term follow-up of patients with IPEX, comparing outcomes between patients who received immunosuppression versus HCT. IPEX patients had similar overall survival, regardless of the treatment option received. Disease-free survival, however, of HCT patients showed resolution of autoimmunity as compared to the disease progression seen in the non-transplanted patients. IPEX patients with severe organ impairment at HCT had the lowest chance of survival even after receiving a RIC regimen pre-HCT. Variable such as stem cell source, type of donor and chimerism were not correlated with outcome[14].

Kucuk *et al*[15] reported a single-center experience of HCT for 7 patients with IPEX. Median age at diagnosis was 4.5 years, and 6.7 years at HCT. Full donor engraftment, but 6/7 had mixed chimerism. 5/8 received RIC while the remainder received a myeloablative regimen. All recipients initially demonstrated full donor engraftment but all except for one patient had mixed chimerism. One patient with mixed chimerism experienced cGVHD while the remainder developed autoimmune cytopenias. Older age at transplantation was associated with an increased risk of decreasing donor chimerism. Two of the 3 patients who did not survive received myeloablative conditioning. Nonmyeloablative conditioning regimens led to complete or mixed chimerism with reconstitution of donor FOXP3 cells[15].

**CHRONIC GRANULOMATOUS DISEASE**

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder of the NADPH oxidase complex that results in a phagocytic functional defect secondary to the impairment of reactive oxygen species (ROS) production. The impairment of neutrophils and monocytes results in recurrent severe life-threatening infections. CGD is also marked by significant immune dysregulation and autoimmunity carries its own significant risk of morbidity[16]. The overall incidence of CGD in the US is approximately 1/200000 live births[17].

The NADPH oxidase complex is composed of the cell membrane-bound glycoprotein gp91phox (*CYBB* gene) and non-glycosylated protein p22phox (*CYBA*), as well as p47phox (*NCF1*), p67phox (*NCF2*) and p40phox (*NCF4*) which are cytosolic proteins. Mutations in any of these components result in defective ROS production and clinical CGD manifestations. A mutation in the x-linked *CYBB* is responsible for approximately 65% of the cases CGD. *CYBA* and *NCF1* mutations account for 20% of cases, *NCF2* and *CYBA* mutations result in 5% of cases and *NCF4* being rarest with only one reported case[16,18].

X-linked CGD patients generally have more severe disease due to the lower superoxide productionthan the autosomal recessive phenotypes. Most cases of CGD present in early childhood and typically as severe invasive infections. Catalase positive bacteria and fungi are the pathognomonic agents of these infections. Aspergillus is the most commonly isolated pathogen, while *Burkholderia* infection is associated with the greatest severity. S. aureus, Nocardia and Serratia are also among the common pathogens associated with CGD[19]. Bacille Calmette-Guerin (BCG) and Mycobacterium tuberculosis are pathogens identified in developing countries[16].

Allogeneic hematopoietic stem cell transplantation (HSCT) still remains the only curative treatment for CGD. Guidelines do not exist for the timing and conditioning regimen of HCT in CGD. Unlike with SCID which typically presents early in life, CGD may not be diagnosed until relatively later in life and the question then arises about the success of HCT in this adult group of patients. In a subgroup analysis of a Korean cohort, 11 CGD patients received HCT. Three of 11 CGD patients in the study received HCT when they were 19 or older. Two identical twins were diagnosed at 1 mo of age, while another received his diagnosis at 5 years old. All three patients had successful engraftment[10].

As with all cases of HCT prior infections can increase post-transplant complications and therefore adversely affect outcomes. Historically, the use of myeloablative therapy was not standard due to the concern for infections in these already immunocompromised patients[20]. However, reports of RIC for CGD patients reported a high rate of graft failure. Seger *et al*[20] reported a 27 CGD patient cohort and 23 of those patients received a myeloablative busulfan-based regimen with donors being HLA-identical siblings. The successful outcomes of this patient cohort suggested that myeloablative conditioning followed by transplant is a feasible option for these patients. Martinez and colleagues[21] reported the outcomes of eleven children after matched sibling (4/11) and URD (MUD, 7/11) transplantation with the mean age of 3.8 years. 70% of these patients had intractable infections or steroid-dependent CGD at the time of transplantation. Martinez[21] reported 100% survival of all patients and stable engraftment with full donor chimerism in 9 of 11 patients with a follow up range of 1-9 years. The MUD conditioning regimen used was busulfan, cyclophosphamide, fludarabine and alemtuzumab. Hoenig *et al*[22] report a case of a hemizygous CYBB male patient who underwent a haploidentical HSCT after myeloablative conditioning with successful engraftment. Parta and colleagues[23] reported the first case of a successful haploidentical transplantation and stable neutrophil engraftment using post-transplant high dose cyclophosphamide in a male patient with a CYBB mutation who also had refractory infectious pericarditis.

Patients with CGD and intractable infections or severe autoimmunity, are a unique group in which myeloablative therapy carries the risk of increased mortality. Güngör *et al*[24] reported 56 patients with CGD and these high risk features who received RIC. The conditioning regimen consisted of six doses of intravenous fludarabine, anti-thymocyte globulin. In HLA-matched unrelated-donor transplants, low-dose (defined as < 1 mg/kg) alemtuzumab was recommended. Busulfan was administered at days 5 to 3 and sometimes on day 2. OS was 93% at a median follow up time of 21 mo and EFS was 89%. Graft failure occurred in 5% of patients. aGVHD of grade III–IV was 4% and cGVHD was 7%. 93% achieved ≥ 90% donor chimerism[24].

Yanir *et al*[25] reported a higher incidence of autoimmune disease after HCT for CGD. This was attributed to the preparative regimen of 4 doses of alemtuzumab on days 5 to 2 compared to a previously reported cohort of patients that received alemtuzumab in 3 doses on days 8 to 6 or ATG instead. This regimen was suggested to cause a greater depletion and subsequent slower reconstitution of regulator T cells[25].

**WISKOTT-ALDRICH SYNDROME**

Wiskott-Aldrich syndrome (WAS) is an x-linked immunodeficiency disorder caused by defect in a gene that encodes the Wiskott-Aldrich syndrome protein (WASp). WASp is a regulator of the actin cytoskeleton in hematopoietic cells. When mutated it not only predisposes to PID but also malignancy[26]. WAS manifests as microthrombocytopenia, eczema and susceptibility to infections. HCT is curative for WAS. Ngwube *et al*[27] reported findings of a retrospective review of 12 patients who received HCT for WAS with a pre-transplant myeloablative regimen, most receiving anti-thymocyte globulin. Four patients received MRD, 5 received URD and 3 obtained a mismatched unrelated graft. 1 patient received UCB cells while bone marrow was the source for the remainder donor cells. OS was 92% at 5-year post-HCT follow up. Mixed donor chimerism was observed in 45% of patients. Immune reconstitution was not affected by chimerism status. Two patients received a second transplant with RIC[27].

The use of UCB for WAS HCT has been reported as well[28,29]. In a study of 90 recipients of UCB, most received myeloablative conditioning with anti-thymocyte globulin. OS at 5 years was 75%. Age less than 2 years was associated with improved event-free survival[29].

The use of pre-transplant RIC has been reported in HCT for patients with WAS[30,31]. Thakkar and colleagues[30] reported three patients with WAS who underwent RIC prior to receiving HCT. MUD, T-cell replete haploidentical and T-cell receptor αβ and CD19-depleted haploidentical HCT were performed. All patients reached donor chimerism. GVHD was limited to one patient who demonstrated grade 1 aGVHD and all patients became transfusion independent[30].

Identifying a suitable matched donor often poses a challenge. When matched donors are not available, alternate donor sources are considered[32]. A prospective study of 5 patients who received haploidentical stem cell transplant and post-transplantation cyclophosphamide showed an overall 100% survival and an average of 27.5 d to platelet counts over 50000/mm3. With an average follow-up time of 2 years all recipients showed 100% donor chimerism[33].

Similar considerations are taken into account for the treatment of dedicator of cytokinesis 8 (DOCK8) deficiency. DOCK8 deficiency is an autosomal recessive combined immunodeficiency that presents with a recurrent severe cutaneous and systemic infections and atopic disease. These patients are also at a higher risk for malignancy[34]. Haploidentical transplants have also been used for treatment of this disorder[35]. HCT is the only curative treatment for this disorder. A retrospective study of 81 patients showed that RIC resulted improved survival in these patients compared to a myeloablative regimen[36].

**CONCLUSION**

PID comprises a unique set of disorders with its own specific transplant challenges and needs. Individual considerations need to be taken into account considering the genetic defect involved. Future studies will improve our understanding of the immune reconstitution needs of patients with these disorders.

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