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Considerations for hematopoietic stem cell transplantation in primary immunodeficiency disorders

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Abstract

Primary immunodeficiency disorders (PIDs) 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 the only curative option for many. Severe combined immunodeficiency disorders (SCID) most commonly present at the time of birth and typically require emergent HCT in the first few weeks of life. HCT poses an unusual challenge for PIDs. Donor source and conditioning regimen often impact the outcome of immune reconstitution after HCT in PIDs. The use of matched or unmatched, as well as related versus unrelated donor has resulted in variable outcomes for different subsets of PIDs. Additionally, there is significant variability in the success of engraftment even for a single patient's lymphocyte subpopulations. While certain cell lines do well without a conditioning regimen, others will not reconstitute unless conditioning is used. The decision to proceed with a conditioning regimen in an already immunocompromised host is further complicated by the fact that alkylating agents should be avoided in radiosensitive PIDs. This manuscript reviews some of the unique elements of HCT in PIDs and evidence-based approaches to transplant in patients with these rare and challenging disorders.

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

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Core tip: Primary immunodeficiency disorders (PIDs) result from inborn errors in immunity and hematopoietic cell transplant (HCT) still remains the only curative option for many of these disorders. Severe combined immunodeficiency disorders are a medical emergency and require HCT within the first few weeks of life. Optimal 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 PIDs and



evidence-based approaches to transplant in patients with these rare and complex disorders.

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INTRODUCTION

Primary immunodeficiency disorders (PIDs) result from inborn errors in immunity. Many PIDs present with 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 many PIDs. Besides for donor selection, individual conditioning regimens must be taken into account when considering a successful outcome of HCT^[1]. The unique immunologic defects involved in PIDs and clinical manifestations of these disorders pose unique challenges to the immunologist and transplant specialist.

SEVERE COMBINED IMMUNODEFICIENCY DISORDER

Severe combined immunodeficiency disorders (SCID) belong to a subgroup of genetic disorders characterized by impaired T-cell development, sometimes also accompanied by B cell and Natural Killer (NK) cell deficiency. The genetic pathophysiology responsible for a subtype of SCID determines the cellular phenotype of the specific disorder.

Reticular dysgenesis is an autosomal recessive variant of SCID that is a product of adenylylase kinase 2 (AK2) deficiency and presents as T-B-NK- SCID. A defect in the ability to clear toxic products of purine metabolism due to adenosine deaminase (ADA) deficiency also results in a T-B-NK-phenotype whereas the presentation of the rarer purine nucleoside phosphorylase (PNP) deficiency is more variable with T cell function being most severely affected.

Cytokine signaling abnormalities common to T and NK cell pathways such as IL-2R common gamma chain and JAK3 result in T-B+NK- SCID, whereas a defect in the IL-7R alpha chain results in T-B+NK+ SCID. T-cell receptor abnormalities due to an absence of CD45, CD3 and CORO1A affect T cell development and therefore will still allow for B cell and NK cell production. Thymic hypoplasia, as seen in DiGeorge syndrome due to 22q11.2 deletion as well as FOXP1 deficiency, also results in T cell deficiency. Lymphocyte receptor chain (VDJ) recombination defects due to the absence of RAG1, RAG2 and ARTEMIS proteins result in T-B-NK+ SCID.

All SCID subtypes follow an autosomal recessive inheritance pattern with the exceptions of the IL-2R gamma chain, which is the only known X-linked SCID, as well as DiGeorge syndrome which can result from a de novo or autosomal dominant mutation^[2]. Since the introduction of T cell receptor excision circle (TREC) assay to the newborn screening program in the United States and other countries, SCID has been diagnosed at a younger age thereby preventing many serious 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 the only curative 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 has excellent survival rates particularly in the first 3.5 mo of life or in older infants without prior infections. Both of these donor sources have the benefit of short engraftment time compared to others. 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). A consideration to take into account with matched sibling donors (MSD) is that a family member may be a carrier for the disease. There are no uniform guidelines regarding the approach to conditioning when MMRDs are used. Infants with active infections and who do not have a MSD have fared best with haploidentical T-cell-depleted transplants in the

absence of any pretransplant conditioning. Generally, however, reduced-intensity or myeloablative pretransplant conditioning was associated with an increased likelihood of a CD3+ T cell recovery to 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. T-cell depleted haploidentical and UCB transplants, however, carry a higher risk for viral infections. UCB also results in a longer engraftment time[4].

SCID marked by an absence of host T cells implies potentially less 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 and agents include melphalan, anti-CD45 antibodies, total body irradiation, thiopeta, and/or busulfan. Partial defects in known SCID-causing genes, as is the case with Omenn syndrome, allow for limited T cell production. Such disorders are more prone to graft rejection and require some degree of myeloablative chemotherapy. B cell negative SCIDs have better rates of T cell engraftment after a myeloablative regimen.

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, the study reported that 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 than for patients with *ADA* or *DCLRE1C* mutations who had the worst outcomes. 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 the time of HCT had a positive impact on survival. Infection status significantly affected survival of patients who underwent HCT at older than 3.5 mo of age but not those who underwent HCT at younger than 3.5 mo of age. Genotype was not associated with overall treatment failure. Although survival did not correlate with the type of conditioning regimen that was used, recipients of reduced-intensity or myeloablative conditioning had a lower incidence of treatment failure, better T- and B-cell reconstitution but a higher risk for GVHD compared with those who did not receive conditioning or who received only immunosuppression. Genotype and conditioning regimen had a strong impact on B- and T-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 served 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 that 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). With the exception of one patient, all with cGVHD were able to discontinue systemic immune suppression 3 mo after HCT^[8].

DNA REPAIR-ASSOCIATED PID

Although data supports the use of conditioning with alkylating agents in order to increase the likelihood of full T and particularly B cell reconstitution, caution must be used in the use of alkylating agents and ionizing radiation in PIDs with defects in the DNA-repair pathway. While scattered reports exist, there is still limited data on survival, engraftment and long-term effects of using such agents in these patients. Slack *et al* collected HCT outcome data for DNA ligase 4 deficiency, Cernunnos-XLF deficiency, Nijmegen Breakage Syndrome and Ataxia-Telangiectasia (AT). MAC and RIC regimens were used. The authors reported that overall survival was significantly superior when RIC was used 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 in SCID without chemotherapy conditioning in MSD and URD recipients. For those subjects who had a genetic diagnosis, defects include IL2RG, JAK3, ADA (NK-SCID) and RAG, DCLRE1C, LIG4 mutations (NK+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 was 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 gamma globulin replacement compared to 8% of URD recipients. MSD recipients with NK- SCID were more likely to recover B cell function (85%; 35/41) compared to those with NK+ 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+ SCID undergoing URD HCT (38%) *vs* NK- (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 an isolated T cell deficiency generally does not require conditioning if a MSD is available and immune reconstitution is expected in such cases. However, 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 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. 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 percentages did not differ between MSD and MMRD in long-term surviving patients, but the latter group had lower counts 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 early onset of enteropathy resulting in failure to thrive, autoimmune endocrinopathy and dermatitis 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 responsible for regulatory T (Treg) cell development. Tregs are critical for 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 systemic 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. Variables such as stem cell source, type of donor and chimerism did not correlate 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. Recipients showed 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 the autoimmunity that accompanies this disorder carries its own significant risk of morbidity^[16]. The overall incidence of CGD in the US is approximately 1/200,000 live births^[17].

The NADPH oxidase complex is composed of the cell membrane-bound glycoprotein gp91^{phox} (CYBB gene) and non-glycosylated protein p22^{phox} (CYBA), as

well as p47^{phox} (NCF1), p67^{phox} (NCF2) and p40^{phox} (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 CGD cases. *NCF1* mutations account for 20% of cases, *NCF2* and *CYBA* mutations are less common with a rate of 5% each, while *NCF4* is the rarest with only one reported case^[16,18].

X-linked CGD patients generally have more severe disease due to the lower superoxide production than the autosomal recessive phenotypes. Most cases of CGD present in early childhood with severe invasive infections, however late diagnosis has also been reported. 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 option 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 years old or older. Two identical twins were diagnosed at 1 mo of age, while another received his diagnosis at 5 years of age. 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. The authors 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] reported 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. 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 prior to transplant. 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 regulatory T cells^[25].

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency disorder caused by a defect in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp). WASp is a regulator of the actin cytoskeleton in hematopoietic cells. A pathogenic mutation in this gene 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. There was no statistically significant difference in outcome between MRD, MUD, and MMURD^[27].

The use of UCB for WAS HCT has been reported in a larger cohort 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 as well as T-cell receptor $\alpha\beta$ 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 suitably 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 50,000/mm³. All recipients showed 100% donor chimerism, with an average follow-up time of 2 years^[33].

DOCK-8 DEFICIENCY

Dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive combined immunodeficiency that presents with recurrent severe and primarily viral, cutaneous and systemic infections as well as atopic disorders such as anaphylaxis, atopic dermatitis and asthma. Patients with DOCK8 deficiency are also at a higher risk for malignancy^[34]. HCT is the only cure for this PID and successful haploidentical transplants have been reported. Shah *et al* reported outcomes in 7 patients (age range 7 to 25 years) with DOCK8 deficiency who underwent haploidentical related donor HCT. Conditioning included low-dose cyclophosphamide, fludarabine, busulfan and 200 cGy total body irradiation. Patients also received cyclophosphamide as post-transplantation GVHD prophylaxis. All patients attained over 90% donor engraftment by day 30 post-HCT. While 4/7 developed aGVHD, none developed cGVHD (follow up range of 9.5 to 31.7 mo). One patient died at day 165 post-HCT from possible pneumonia as well as worsening pulmonary fibrosis which was suggested to have been a complication of his frequent pulmonary infections^[35].

A retrospective study of 81 patients with DOCK8 deficiency showed that RIC resulted in 97% survival compared to 78% with a fully myeloablative regimen. Matched related HCT showed better survival (89%) than unrelated HCT (81%). The study also reported that whereas 78% of patients older than 8yo survived, those younger than 8yo fared better at 96% survival. Overall, 89% of HCT recipients achieved over 90% donor T-cell chimerism^[36].

CONCLUSION

PIDs pose unique diagnostic and treatment challenges. In addition to predisposing to life-threatening infections and serious complications arising from immune dysregulation, these disorders also require individualized approaches to HCT that are often dictated by the genetic defects involved. Combining currently available data with future larger studies that assess factors that impact survival and long-term outcomes of HCT in PIDs will lead the way in improving standardization of HCT in these patients.

REFERENCES

1. Worth AJ, Booth C, Veys P. Stem cell transplantation for primary immune deficiency. *Curr Opin Hematol* 2013; 20: 501-508 [PMID: 24104410 DOI: 10.1097/MOH.0b013e328365a13b]

- 2 **Cirillo E**, Giardino G, Gallo V, D'Assante R, Grasso F, Romano R, Di Lillo C, Galasso G, Pignata C. Severe combined immunodeficiency--an update. *Ann N Y Acad Sci* 2015; **1356**: 90-106 [PMID: [26235889](#) DOI: [10.1111/nyas.12849](#)]
- 3 **Kohn DB**, Hershfield MS, Puck JM, Aiuti A, Blincoe A, Gaspar HB, Notarangelo LD, Grunebaum E. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol* 2019; **143**: 852-863 [PMID: [30194989](#) DOI: [10.1016/j.jaci.2018.08.024](#)]
- 4 **Mitchell R**. Hematopoietic Stem Cell Transplantation Beyond Severe Combined Immunodeficiency: Seeking a Cure for Primary Immunodeficiency. *J Allergy Clin Immunol Pract* 2019; **7**: 776-785 [PMID: [30832892](#) DOI: [10.1016/j.jaip.2018.12.011](#)]
- 5 **Pai SY**, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, Kapoor N, Hanson IC, Filipovich AH, Jyonouchi S, Sullivan KE, Small TN, Burroughs L, Skoda-Smith S, Haight AE, Grizzle A, Pulsipher MA, Chan KW, Fuleihan RL, Haddad E, Loechecht B, Aquino VM, Gillio A, Davis J, Knutsen A, Smith AR, Moore TB, Schroeder ML, Goldman FD, Connelly JA, Porteus MH, Xiang Q, Shearer WT, Fleisher TA, Kohn DB, Puck JM, Notarangelo LD, Cowan MJ, O'Reilly RJ. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med* 2014; **371**: 434-446 [PMID: [25075835](#) DOI: [10.1056/NEJMoa1401177](#)]
- 6 **Haddad E**, Logan BR, Griffith LM, Buckley RH, Parrott RE, Prockop SE, Small TN, Chaisson J, Dvorak CC, Murnane M, Kapoor N, Abdel-Azim H, Hanson IC, Martinez C, Bleesing JJH, Chandra S, Smith AR, Cavanaugh ME, Jyonouchi S, Sullivan KE, Burroughs L, Skoda-Smith S, Haight AE, Tumlin AG, Quigg TC, Taylor C, Dávila Saldaña BJ, Keller MD, Seroogy CM, Desantes KB, Petrovic A, Leidig JW, Shyr DC, Decaluwe H, Teira P, Gillio AP, Knutsen AP, Moore TB, Kletzel M, Craddock JA, Aquino V, Davis JH, Yu LC, Cuvelier GDE, Bednarski JJ, Goldman FD, Kang EM, Shereck E, Porteus MH, Connelly JA, Fleisher TA, Malech HL, Shearer WT, Szabolcs P, Thakar MS, Vander Lugt MT, Heimall J, Yin Z, Pulsipher MA, Pai SY, Kohn DB, Puck JM, Cowan MJ, O'Reilly RJ, Notarangelo LD. SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery. *Blood* 2018; **132**: 1737-1749 [PMID: [30154114](#) DOI: [10.1182/blood-2018-03-840702](#)]
- 7 **Freeman AF**. Hematopoietic Stem Cell Transplantation in Primary Immunodeficiencies Beyond Severe Combined Immunodeficiency. *J Pediatric Infect Dis Soc* 2018; **7**: S79-S82 [PMID: [30590619](#) DOI: [10.1093/jpids/piy114](#)]
- 8 **Fox TA**, Chakraverty R, Burns S, Carpenter B, Thomson K, Lowe D, Fielding A, Peggs K, Kottaridis P, Uttenthal B, Bigley V, Buckland M, Grandage V, Denovan S, Grace S, Dahlstrom J, Workman S, Symes A, Mackinnon S, Hough R, Morris E. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. *Blood* 2018; **131**: 917-931 [PMID: [29279357](#) DOI: [10.1182/blood-2017-09-807487](#)]
- 9 **Slack J**, Albert MH, Balashov D, Belohradsky BH, Bertaina A, Bleesing J, Booth C, Buechner J, Buckley RH, Ouachée-Chardin M, Deripapa E, Drabko K, Eapen M, Feuchtinger T, Finocchi A, Gaspar HB, Ghosh S, Gillio A, Gonzalez-Granado LI, Grunebaum E, Güngör T, Heilmann C, Helminen M, Higuchi K, Imai K, Kalwak K, Kanazawa N, Karasu G, Kucuk ZY, Laberko A, Lange A, Mahlaoui N, Meisel R, Moshous D, Muramatsu H, Parikh S, Pasie S, Schmid I, Schuetz C, Schulz A, Schultz KR, Shaw PJ, Slatter MA, Sykora KW, Tamura S, Taskinen M, Wawer A, Wolska-Kuśnierz B, Cowan MJ, Fischer A, Gennery AR. Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and the European Society for Immunodeficiencies; Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE); Center for International Blood and Marrow Transplant Research; Primary Immunodeficiency Treatment Consortium. Outcome of hematopoietic cell transplantation for DNA double-strand break repair disorders. *J Allergy Clin Immunol* 2018; **141**: 322-328.e10 [PMID: [28392333](#) DOI: [10.1016/j.jaci.2017.02.036](#)]
- 10 **Yi ES**, Choi YB, Lee NH, Lee JW, Sung KW, Koo HH, Kang ES, Kim YJ, Yoo KH. Allogeneic Hematopoietic Cell Transplantation in Patients with Primary Immunodeficiencies in Korea: Eleven-Year Experience in a Single Center. *J Clin Immunol* 2018; **38**: 757-766 [PMID: [30151618](#) DOI: [10.1007/s10875-018-0542-7](#)]
- 11 **Dvorak CC**, Hassan A, Slatter MA, Hönig M, Lankester AC, Buckley RH, Pulsipher MA, Davis JH, Güngör T, Gabriel M, Bleesing JH, Bunin N, Sedlacek P, Connelly JA, Crawford DF, Notarangelo LD, Pai SY, Hassid J, Veys P, Gennery AR, Cowan MJ. 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**: 935-943.e15 [PMID: [25109802](#) DOI: [10.1016/j.jaci.2014.06.021](#)]
- 12 **Scarselli A**, Di Cesare S, Capponi C, Cascioli S, Romiti ML, Di Matteo G, Simonetti A, Palma P, Finocchi A, Lucarelli B, Pinto RM, Rana I, Palumbo G, Caniglia M, Rossi P, Carsetti R, Cancrini C, Aiuti A. Longitudinal Evaluation of Immune Reconstitution and B-cell Function After Hematopoietic Cell Transplantation for Primary Immunodeficiency. *J Clin Immunol* 2015; **35**: 373-383 [PMID: [25875698](#) DOI: [10.1007/s10875-015-0154-4](#)]
- 13 **Attias M**, Al-Aubodah T, Piccirillo CA. Mechanisms of human FoxP3⁺ T_{reg} cell development and function in health and disease. *Clin Exp Immunol* 2019; **197**: 36-51 [PMID: [30864147](#) DOI: [10.1111/cei.13290](#)]
- 14 **Barzaghi F**, Amaya Hernandez LC, Neven B, Ricci S. Primary Immune Deficiency Treatment Consortium (PIDTC) and the Inborn Errors Working Party (IEWP) of the European Society for Blood and Marrow Transplantation (EBMT). Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. *J Allergy Clin Immunol* 2018; **141**: 1036-1049.e5 [PMID: [29241729](#) DOI: [10.1016/j.jaci.2017.10.041](#)]
- 15 **Kucuk ZY**, Bleesing JJ, Marsh R, Zhang K, Davies S, Filipovich AH. A challenging undertaking: Stem cell transplantation for immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. *J Allergy Clin Immunol* 2016; **137**: 953-5.e4 [PMID: [26559324](#) DOI: [10.1016/j.jaci.2015.09.030](#)]
- 16 **Arnold DE**, Heimall JR. A Review of Chronic Granulomatous Disease. *Adv Ther* 2017; **34**: 2543-2557 [PMID: [29168144](#) DOI: [10.1007/s12325-017-0636-2](#)]
- 17 **Winkelstein JA**, Marino MC, Johnston RB, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)* 2000; **79**: 155-169 [PMID: [10844935](#) DOI: [10.1097/00005792-200005000-00003](#)]
- 18 **Matute JD**, Arias AA, Wright NA, Wrobel I, Waterhouse CC, Li XJ, Marchal CC, Stull ND, Lewis DB, Steele M, Kellner JD, Yu W, Meroueh SO, Nauseef WM, Dinanuer MC. A new genetic subgroup of

- chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. *Blood* 2009; **114**: 3309-3315 [PMID: [19692703](#) DOI: [10.1182/blood-2009-07-231498](#)]
- 19 **Marciano BE**, Spalding C, Fitzgerald A, Mann D, Brown T, Osgood S, Yockey L, Darnell DN, Barnhart L, Daub J, Boris L, Rump AP, Anderson VL, Haney C, Kuhns DB, Rosenzweig SD, Kelly C, Zelazny A, Mason T, DeRavin SS, Kang E, Gallin JI, Malech HL, Olivier KN, Uzel G, Freeman AF, Heller T, Zerbe CS, Holland SM. Common severe infections in chronic granulomatous disease. *Clin Infect Dis* 2015; **60**: 1176-1183 [PMID: [25537876](#) DOI: [10.1093/cid/ciu1154](#)]
 - 20 **Seger RA**, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, Flood T, Landais P, Müller S, Ozsahin H, Passwell JH, Porta F, Slavin S, Wulffraat N, Zintl F, Nagler A, Cant A, Fischer A. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985-2000. *Blood* 2002; **100**: 4344-4350 [PMID: [12393596](#) DOI: [10.1182/blood-2002-02-0583](#)]
 - 21 **Martinez CA**, Shah S, Shearer WT, Rosenblatt HM, Paul ME, Chinen J, Leung KS, Kennedy-Nasser A, Brenner MK, Heslop HE, Liu H, Wu MF, Hanson IC, Krance RA. Excellent survival after sibling or unrelated donor stem cell transplantation for chronic granulomatous disease. *J Allergy Clin Immunol* 2012; **129**: 176-183 [PMID: [22078471](#) DOI: [10.1016/j.jaci.2011.10.005](#)]
 - 22 **Hoenig M**, Niehues T, Siepermann K, Jacobsen EM, Schütz C, Furlan I, Dückers G, Lahr G, Wiesneth M, Debatin KM, Friedrich W, Schulz A. Successful HLA haploidentical hematopoietic SCT in chronic granulomatous disease. *Bone Marrow Transplant* 2014; **49**: 1337-1338 [PMID: [24955782](#) DOI: [10.1038/bmt.2014.125](#)]
 - 23 **Parta M**, Hilligoss D, Kelly C, Kwatema N, Theobald N, Malech H, Kang EM. Haploidentical Hematopoietic Cell Transplantation with Post-Transplant Cyclophosphamide in a Patient with Chronic Granulomatous Disease and Active Infection: A First Report. *J Clin Immunol* 2015; **35**: 675-680 [PMID: [26453586](#) DOI: [10.1007/s10875-015-0204-y](#)]
 - 24 **Güngör T**, Teira P, Slatter M, Stussi G, Stephens P, Moshous D, Vermont C, Ahmad I, Shaw PJ, Telles da Cunha JM, Schlegel PG, Hough R, Fasth A, Kentouche K, Gruhn B, Fernandes JF, Lachance S, Bredius R, Resnick IB, Belohradsky BH, Gennery A, Fischer A, Gaspar HB, Schanz U, Seger R, Rentsch K, Veys P, Haddad E, Albert MH, Hassan M; Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. *Lancet* 2014; **383**: 436-448 [PMID: [24161820](#) DOI: [10.1016/S0140-6736\(13\)62069-3](#)]
 - 25 **Yanir AD**, Hanson IC, Shearer WT, Noroski LM, Forbes LR, Seeborg FO, Nicholas S, Chinn I, Orange JS, Rider NL, Leung KS, Naik S, Carrum G, Sasa G, Hegde M, Omer BA, Ahmed N, Allen CE, Khaled Y, Wu MF, Liu H, Gottschalk SM, Heslop HE, Brenner MK, Krance RA, Martinez CA. High Incidence of Autoimmune Disease after Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease. *Biol Blood Marrow Transplant* 2018; **24**: 1643-1650 [PMID: [29630926](#) DOI: [10.1016/j.bbmt.2018.03.029](#)]
 - 26 **Keszei M**, Kritikou JS, Sandfort D, He M, Oliveira MMS, Wurzer H, Kuiper RV, Westerberg LS. Wiskott-Aldrich syndrome gene mutations modulate cancer susceptibility in the p53[±] murine model. *Oncotarget* 2018; **7**: e1468954 [PMID: [30393584](#) DOI: [10.1080/2162402X.2018.1468954](#)]
 - 27 **Ngwube A**, Hanson IC, Orange J, Rider NL, Seeborg F, Shearer W, Noroski L, Nicholas S, Forbes L, Leung K, Sasa G, Naik S, Hegde M, Omer B, Ahmed N, Allen C, Gottschalk S, Wu MF, Liu H, Brenner M, Heslop H, Krance R, Martinez C. Outcomes after Allogeneic Transplant in Patients with Wiskott-Aldrich Syndrome. *Biol Blood Marrow Transplant* 2018; **24**: 537-541 [PMID: [29196075](#) DOI: [10.1016/j.bbmt.2017.11.019](#)]
 - 28 **Chen CY**, Chiou YH, Su HW, Chang YH. Unrelated umbilical cord stem cell transplantation in an eleven-month-old male infant with Wiskott-Aldrich syndrome. *Kaohsiung J Med Sci* 2018; **34**: 122-123 [PMID: [29413229](#) DOI: [10.1016/j.kjms.2017.09.001](#)]
 - 29 **Shekhovtsova Z**, Bonfim C, Ruggeri A, Nichele S, Page K, AlSerafiy A, Barriga F, de Toledo Codina JS, Veys P, Boelens JJ, Mellgren K, Bittencourt H, O'Brien T, Shaw PJ, Chybicka A, Volt F, Giannotti F, Gluckman E, Kurtzberg J, Gennery AR, Rocha V; Eurocord, Cord Blood Committee of Cellular Therapy and Immunobiology Working Party of the EBMT, Federal University of Parana, Duke University Medical Center and Inborn Errors Working Party of the EBMT. A risk factor analysis of outcomes after unrelated cord blood transplantation for children with Wiskott-Aldrich syndrome. *Haematologica* 2017; **102**: 1112-1119 [PMID: [28255019](#) DOI: [10.3324/haematol.2016.158808](#)]
 - 30 **Thakkar D**, Katewa S, Rastogi N, Kohli S, Nivargi S, Yadav SP. Successful Reduced Intensity Conditioning Alternate Donor Stem Cell Transplant for Wiskott-Aldrich Syndrome. *J Pediatr Hematol Oncol* 2017; **39**: e493-e496 [PMID: [28859032](#) DOI: [10.1097/MPH.0000000000000959](#)]
 - 31 **Ali S**, Gacsadi A, McDougall E, Armstrong C, Krueger J, Schechter T, Ali M. Successful Reduced Intensity Allogeneic Transplant With Full Donor Chimerism and Good Quality of Life in Adolescent Patient With Wiskott-Aldrich Syndrome. *J Pediatr Hematol Oncol* 2017; **39**: e267-e269 [PMID: [28538502](#) DOI: [10.1097/MPH.0000000000000851](#)]
 - 32 **Kreetapirom P**, Hongeng S, Manuyakorn W, Anurathapan U, Pakakasama S, Sirachainan N, Andersson BS. Successful HLA haploidentical HSCT with post-transplant cyclophosphamide in Wiskott-Aldrich syndrome. *Bone Marrow Transplant* 2017; **52**: 913-914 [PMID: [28287640](#) DOI: [10.1038/bmt.2017.25](#)]
 - 33 **Yue Y**, Shi X, Song Z, Qin J, Li J, Feng S, Liu R. Posttransplant cyclophosphamide for haploidentical stem cell transplantation in children with Wiskott-Aldrich syndrome. *Pediatr Blood Cancer* 2018; **65**: e27092 [PMID: [29745014](#) DOI: [10.1002/pbc.27092](#)]
 - 34 **Aydin SE**, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, Kostyuchenko L, Genel F, Kütükçüler N, Karaca N, Gonzalez-Granado L, Abbott J, Al-Zahrani D, Rezaei N, Baz Z, Thiel J, Ehl S, Marodi L, Orange JS, Sawalle-Belohradsky J, Keles S, Holland SM, Sanal Ö, Ayvaz DC, Tezcan I, Al-Mousa H, Alsum Z, Hawwari A, Metin A, Matthes-Martin S, Hönig M, Schulz A, Picard C, Barlogis V, Gennery A, Ifversen M, van Montfrans J, Kuijpers T, Bredius R, Dückers G, Al-Herz W, Pai SY, Geha R, Notheis G, Schwarze CP, Tavit B, Aziz F, Bienemann K, Grimbacher B, Heinz V, Gaspar HB, Aydin R, Hagl B, Gathmann B, Belohradsky BH, Ochs HD, Chatila T, Renner ED, Su H, Freeman AF, Engelhardt K, Albert MH. Inborn errors working party of EBMT. DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. *J Clin Immunol* 2015; **35**: 189-198 [PMID: [25627830](#) DOI: [10.1007/s10875-014-0126-0](#)]
 - 35 **Freeman AF**, Shah NN, Parta M, Su HC, Brofferio A, Gradus-Pizlo I, Butty S, Hughes TE, Kleiner DE, Avila D, Heller T, Kong HH, Holland SM, Hickstein DD. Haploidentical related donor hematopoietic stem

- cell transplantation with post-transplantation cyclophosphamide for DOCK8 deficiency. *J Allergy Clin Immunol Pract* 2016; 4: 1239-1242.e1 [PMID: 27641484 DOI: 10.1016/j.jaip.2016.06.028]
- 36 **Aydin SE**, Freeman AF, Al-Herz W, Al-Mousa HA, Arnaout RK, Aydin RC, Barlogis V, Belohradsky BH, Bonfim C, Bredius RG, Chu JI, Ciocarlie OC, Doğu F, Gaspar HB, Geha RS, Gennery AR, Hauck F, Hawwari A, Hickstein DD, Hoenig M, Ikinciogullari A, Klein C, Kumar A, Ifversen MRS, Matthes S, Metin A, Neven B, Pai SY, Parikh SH, Picard C, Renner ED, Sanal Ö, Schulz AS, Schuster F, Shah NN, Shereck EB, Slatter MA, Su HC, van Montfrans J, Woessmann W, Ziegler JB, Albert MH. Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation and the European Society for Primary Immunodeficiencies. Hematopoietic Stem Cell Transplantation as Treatment for Patients with DOCK8 Deficiency. *J Allergy Clin Immunol Pract* 2019; 7: 848-855 [PMID: 30391550 DOI: 10.1016/j.jaip.2018.10.035]



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