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Review Article

A National Consensus on Hematopoietic Stem Cell Transplantation for Patients with Inborn Errors of Immunity

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Abstract

At present, a national consensus on hematopoietic stem cell transplantation (HSCT) for patients with inborn errors of immunity (IEI) is lacking. This consensus is written based on a combination of scientific literature and comments from the expert panel of Iranian immunologists. We formed a panel of clinical immunologists at a meeting titled "Second Meeting on the Diagnosis of IEI by IEI Experts" to receive their comments in this field. All authors reviewed and agreed on the current consensus. This consensus guideline provides recommendations on donor selection, stem cell source, conditioning regimen, mobilization and collection, stem cell infusion, engraftment and chimerism assessment, and post-transplant care for patients with IEI. The current recommendations reflect Iranian practice and do not necessarily represent global preferences.

Keywords: Consensus; Hematopoietic Stem Cell Transplantation(HSCT); Inborn Errors of Immunity; IEI

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Introduction

Inborn errors of immunity (IEI), also known as primary immunodeficiency diseases, are a group of rare heterogeneous diseases that result from defects in any of the components of the immune system. Over 500 monogenic IEIs have been recognized thus far, with most affected patients being children (1). Patients with IEI manifest severe life-threatening infections and immune dysregulation, which predisposes them to early mortality if not diagnosed and treated promptly (2).

Hematopoietic stem cell transplantation (HSCT), sometimes referred to as bone marrow transplant, is considered a curative treatment for some entities of IEI patients (3). Previous reports demonstrated that early transplantation can remarkably reduce severe and significant post-transplant complications if performed prior to the occurrence of severe infectious and inflammatory complications, resulting in better outcomes for IEI patients (4, 5). Most reports have focused on severe combined immunodeficiency (SCID) patients, and the best survival outcomes have been observed in this group (6). Although the survival rate is high following HSCT, morbidity remains significant due to post-transplant complications (7). Despite numerous studies on HSCT outcomes in IEI, the long term consequences of post-transplant complications are still being observed. Hence, we need further long term cohorts to understand the long term outcome of HSCT in IEI patients.

In this national consensus, we recommend a guideline for HSCT on patients with IEI based on a combination of published data and the comments of the expert panel of Iranian clinical immunologists.

Consensus Recommendations and Discussion on HSCT in IEIs

Since 1968, HSCT has been established as a curative treatment for many patients with IEI. The decision to perform HSCT in patients with IEI depends on multiple factors, such as clinical features, past and current infections, current and anticipated future organ failure, genetic diagnosis, psychological and social considerations such as quality of life and fertility, and the process of obtaining informed consent. Given that patients with SCID represent the most severe form of IEI and typically die within the first year without transplantation, HSCT should be performed immediately for these patients. Additionally, HSCT can be performed for other non-SCID IEIs (3, 8-10).

In **Figure 1**, we provided a flowchart of the HSCT process from donor selection to long-term support in six steps. We present the recommendations for each step in the following sections.

1. HSCT Indications in IEI

HSCT has demonstrated progressively improving success rates in recent years for patients with IEI. The survival of patients with IEI who have undergone HSCT is now reaching 90% or more, however, complications of HSCT remain a significant challenge, with significant morbidity and mortality, especially in recipients of HLA-non-

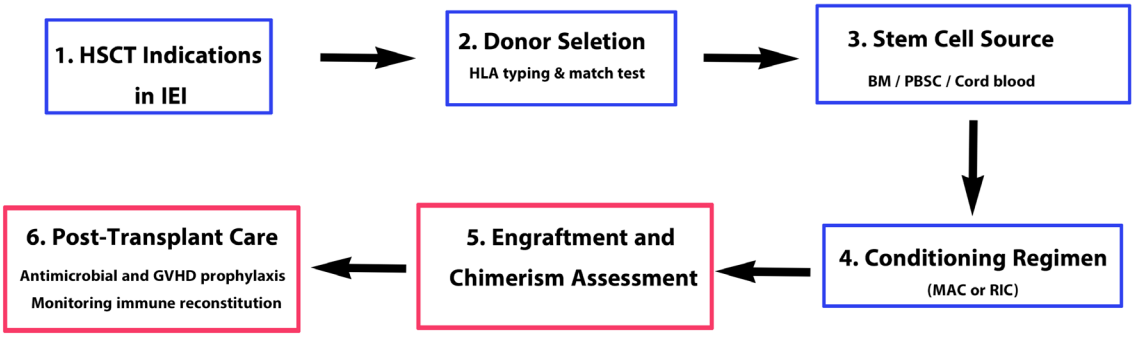

Figure 1. A flowchart of the HSCT process from donor selection to long-term support in six steps. Blue boxes represent pre-HSCT stages, and red boxes represent post-HSCT stages.

identical grafts (11). Decisions about whether and when to undergo HSCT must carefully weigh the risks of transplantation against the risks of disease progression and should be tailored not only to the specific IEI but also to the individual patient's clinical profile. We propose the following recommendations regarding HSCT indications for various forms of IEI:

Recommendation 1: HSCT is recommended as life-saving treatment in all forms of SCID, including X-linked SCID, JAK3 deficiency, IL7R deficiency, RAG-deficient SCID, Omenn syndrome, and reticular dysgenesis (12).

Recommendation 2: It is recommended that patients with IEI, especially those with SCID, have genetic testing performed as early as possible, as it affects treatment options (HSCT, enzyme replacement therapy, or gene therapy) (13).). However, for some IEIs such as CGD and LAD, the decision to proceed with HSCT can be made based on established clinical and laboratory criteria even before genetic confirmation is available.

Recommendation 3: HSCT is curative and improves long-term survival of patients with CGD who manifest severe infections or refractory inflammation, as well as in those with leukocyte adhesion deficiency (LAD-I and clinically significant LAD-III). Of note, the best outcomes are achieved when transplantation is performed before irreversible organ damage has occurred (12, 14).

Recommendation 4: For SCID, HSCT should be performed as early as possible, ideally before 3 months of age, assuming donor availability and clinical stabilization. For CID and CGD, early childhood remains the preferred timing for HSCT, with transplantation individualized based on disease severity and clinical course.

Recommendation 5: Patients with combined immunodeficiencies (CID) that present early, progress over time, or cause severe infections, autoimmunity, or granulomatous disease, including ZAP70 deficiency, RAG deficiency, MHC-II deficiency, CD40L/CD40 deficiency, CD3 signaling defects, and other functional T-cell disorders is indicated for HSCT (12, 14). Regarding MHC-II deficiency, the decision to proceed with HSCT depends on the patient's clinical condition and the availability of a suitable donor, although survival outcomes are poorer compared with other IEIs (12).

Recommendation 6: HSCT should be considered for IEIs associated with substantial risk of immune dysregulation, severe infections, or malignancy, including DOCK8 deficiency, Wiskott–Aldrich syndrome, ARPC1B deficiency, and WIP deficiency, particularly in patients with severe clinical phenotypes (12, 15).

Recommendation 7: HSCT is recommended for metabolic IEIs in which the immune defect arises from hematopoietic-derived cells and can be corrected by donor-derived hematopoiesis, including ADA deficiency and reticular dysgenesis (12).

Recommendation 8: HSCT should be considered for immune dysregulation syndromes such as IPEX, LRBA deficiency, CTLA-4 haploinsufficiency, and STAT3 gain-of-function disease, particularly in patients with severe or progressive disease, refractory organ-damaging autoimmunity, or impaired quality of life, with targeted medical therapies (e.g., abatacept, PI3K inhibitors, or JAK inhibitors) often serving as bridging or stabilizing treatments prior to transplantation (12, 14).

Recommendation 9: HSCT for conditions such as CVID, agammaglobulinemia, DiGeorge syndrome, and NEMO deficiency is still controversial (12).

Recommendation 10: HSCT should be performed in patients with primary/familial HLH, ideally once inflammatory activity is at least partially controlled, to reduce the risk of relapse (12, 14).

Recommendation 11: HSCT may be considered for selected patients with DNA double-strand break repair disorders, taking into account neurological involvement, disease severity, and associated comorbidities; however, evidence on outcomes remains limited.

Recommendation 12: For patients with severe congenital neutropenia, HSCT can be considered if treatment with granulocyte colony-stimulating factor is ineffective, or when the disease progresses to myelodysplastic syndrome or acute myeloid leukemia (14).

2. Donor Selection

Access to an appropriate donor of hematopoietic progenitor cells is essential for allogeneic HSCT. To achieve this, HLA typing must be performed. In our setting, HLA typing is typical-

ly performed at either low resolution (for initial screening) or high resolution (allele-level typing), which is preferred for final donor selection. Detecting HLA matched donor remarkably reduces the risks of graft failure and GVHD. There are several potential donor sources for HSCT, including an HLA-identical sibling, a matched related donor (MRD), a matched unrelated donor (MUD), a mismatched related donor (MisRD), a haploidentical related donor (HRD), and cord blood (CB). Overall, HLA-identical sibling and MRD are the best candidates, followed by MUD, CB, and mismatched family donor/mismatched related donor (MMFD/MMRD) (16). We propose the following recommendations for each of these donor sources:

Recommendation 13: HLA typing for allele-level HLA-A, -B, -C, and -DRB1, -DQB1 is compulsory for all donors, except CB. Given the low alloreactivity of neonatal immune cells, intermediate resolution is acceptable for the CB unit (8).

Recommendation 14: For HLA-identical sibling, the recipient and selected sibling donor should be matched at least at 6/6 for HLA-A and HLA-B (at intermediate or higher resolution), and -DRB1 (typed at high resolution); however, additional HLA loci, such as HLA-C and -DQB1, may also be considered (8, 17).

Recommendation 15: For unrelated donors, it is recommended to consider full allele-level matching at HLA-A, -B, -C, and -DRB1, -DQB1 loci (12/12 match) (8), as higher-resolution matching is associated with improved survival and reduced transplant-related mortality (18-20).

Recommendation 16: For a one-locus mismatched related donor, the recipient and selected related donor should have either a 9/10 or an 11/12 allele-level HLA match, depending on the loci used for matching. Extended HLA testing can also support the selection of suitable donors for HLA-sensitized patients to prevent the potential risk of graft failure (21, 22).

Recommendation 17: For HRD donors, the recipient and donor should be matched for HLA-A, -B, and -C typed at intermediate or higher resolution, and for HLADRB1 typed at high resolution. Ideally, familial haplotypes should be assigned to confirm haploidentity between the donor and recipient (17).

Recommendation 18: When a matched donor is unavailable for IEI patients with an urgent need for HSCT, transplantation from an HRD or a mismatched unrelated CB is the preferred choice (8).

Recommendation 19: For CB donors, HLA-A and -B should be typed at intermediate resolution (or higher) and HLA-DRB1 at high resolution for both the recipient and the cord blood unit, with a minimum requirement of a 4/6 HLA match across these loci (17).

Recommendation 20: In all inherited IEIs, related donors must be evaluated to exclude clinical or subclinical disease. Genetic testing is not mandatory for all related donors. However, in X-linked IEIs (such as X-linked CGD and Wiskott–Aldrich syndrome), genetic testing is required for potential male related donors to confirm they are not affected (23).

3. Stem Cell Source

The sources of stem cells for HSCT include bone marrow, peripheral blood stem cells (PBSC), and CB, and each has its own advantages and disadvantages.

Recommendation 21: The choice of stem-cell source (bone marrow vs peripheral blood) in IEI patients should be individualized. Bone marrow is traditionally associated with a lower risk of chronic GVHD, whereas peripheral blood typically yields higher $CD34^+$ cell counts and results in faster engraftment, as also demonstrated in previous studies from Iran (24). In addition, conditioning regimen and the underlying disease influence the optimal stem-cell source; therefore, no single source can be universally recommended.

Recommendation 22: If we aim to reach a quick neutrophil or immune reconstitution, PBSC are recommended for transplantation. However, given PBSC contain higher numbers of T cells and carry an increased risk of GVHD, the use of T-cell depletion strategies should be considered when appropriate.

Recommendation 23: When matched related or unrelated donor is unavailable, CB is recommended for transplantation due to less stringent HLA matching (25).

Recommendation 24: Recommended stem-cell doses should be specified according to the graft

source:

1. Bone Marrow—Unmanipulated grafts (MRD/MUD)

• A $CD34^+$ cell dose of approximately 3–5 × 10^6 $CD34^+$ cells/kg is recommended, as TNC-based thresholds apply primarily to cord blood and not to bone marrow grafts(8).

2. PBSC—T-replete matched donors

• An optimal target of 5–8 × 10^6 $CD34^+$ cells/kg is advised.

• If higher $CD34^+$ doses are used, the infused $CD3^+$ T-cell dose should not exceed 300–500 × 106 $CD3^+$ cells/kg to limit GVHD risk (26).

3. CB

• CB units should be ≥7/8 HLA matched, with:
  o TNC ≥ 3.0 × 10^7/kg for 8/8 units,
  o TNC ≥ 5.0 × 10^7/kg for 7/8 units,
  o $CD34^+$ ideally >1.7 × 10^5/kg after thawing (8).

4. Conditioning Regimen

The goal of conditioning is to achieve sufficient immunosuppression and create marrow niche space for donor stem cells, while minimizing short- and long-term side effects. Suitable conditioning reduces the risk of graft rejection and indirectly inhibits GVHD, ultimately supporting stable engraftment and long-term cure of the underlying condition. There is a growing number of conditioning regimens, but major categories remain myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC). MAC, which eradicates the bone marrow of the recipient, is used when high levels of donor engraftment or "chimerism" are required or when maximal immunosuppression is necessary to ensure successful engraftment. RIC, which involves lower doses or nonmyeloablative combinations, is used to decrease regimen-related toxicity but is associated with a higher incidence of mixed chimerism following HSCT (27).

Recommendation 25: Given children with IEI exhibit notable comorbidities when undergoing HSCT, and that MAC is associated with substantial toxicity, a relatively high risk of transplant-related mortality, and long-term complications, RIC regimens are now generally recommended for patients with IEI (28).

Recommendation 26: Children with SCID have limited or absent ability to reject donor grafts; therefore, HSCT without conditioning may be considered only in specific situations. According to the EBMT/ESID IEWP 2021 guidelines conditioning can be omitted when (8):

• The donor is an HLA-identical sibling for a patient with typical SCID, particularly in the setting of life-threatening infection or poor tolerance for toxicity;

• The SCID phenotype is T–B+NK–, where the absence of NK cells reduces the risk of rejection;

• The patient has ADA-SCID and an HLA-identical family donor.

In contrast, conditioning remains necessary for SCID subtypes with NK-cell activity (e.g., T–B–NK+), Omenn syndrome, radiosensitive disorders (e.g., DCLRE1C/Artemis), and in AK2 deficiency where the risk of graft failure is high without conditioning.

Recommendation 27: For the selection of a conditioning regimen, factors such as the genetic cause of IEI, the level of chimerism required for disease correction, comorbidities, previous radiation exposure, patient age, institutional experience, toxicity risk, radiosensitivity, and the source of the harvested hematopoietic stem cells and donor type should be considered. The disease-specific considerations and examples of commonly used MAC and RIC regimens are summarized in the accompanying **Table 1**.

5. Engraftment and Chimerism Assessment

The migration and homing of hematopoietic stem cells to bone marrow niches is essential for achieving sufficient engraftment following transplantation. Whether hematopoietic recovery after transplantation of hematopoietic stem cells and the final clinical outcome are successful or not depends on the number and quality of donor cells colonized in bone marrow. These cells are typically assessed by measuring cells expressing CD34. Recovery of peripheral blood cell lineages following HSCT is different. Absolute neutrophil count recovers within 8-40 days after HSCT, while this reconstitution takes months or years for B and T cells (29).

Chimerism assessment is performed by identifying and measuring polymorphic genetic markers that uniquely distinguish donor cells from those of the recipient (30). PCR-based Short

Table 1. Conditioning Regimen Strategies for HSCT in Inborn Errors of Immunity

No	IEI Category	Commonly Used MAC Regimens	Commonly Used RIC Regimens	Key Considerations for Choosing Intensity
1	**SCID (non-radiosensitive) e.g. IL2RG, JAK3, ADA, most classical T^-B^+/T^-B^-**	• Busulfan–fludarabine at myeloablative AUC (EBMT protocol A). • Treosulfan–fludarabine ± thiotepa at "MAC-equivalent" doses (EBMT protocol B, treosulfan 3×10–14 g/m² + Flu + Thio).	• Treosulfan + fludarabine (without thiotepa) at reduced intensity. • Lower-dose busulfan + fludarabine ("reduced-toxicity MAC" but often grouped functionally as RIC in IEI series).	• Many SCID can engraft with little or no conditioning, but this is associated with higher risk of mixed/poor myeloid and B-cell chimerism and late graft failure. • Current trend: avoid "no conditioning", use at least RIC/"reduced-toxicity" regimens to secure stable engraftment while minimizing toxicity.
2	**Non-SCID CID (incl. WAS, DOCK8, CD40L, CD40, other CID)**	• Busulfan + fludarabine at myeloablative dosing, often with thiotepa in high-risk patients. • Treosulfan + fludarabine ± thiotepa when a toxicity-reduced MAC is preferred (e.g. WAS, DOCK8).	• Treosulfan + fludarabine at lower systemic exposure. • Reduced-dose busulfan + fludarabine or fludarabine + melphalan in older/comorbid CID patients.	• For WAS and some severe CID, high donor chimerism is desirable; many centers favour MAC or "near-MAC" treosulfan-based regimens. • In milder CID or high-risk patients, RIC/"reduced-toxicity" regimens are used to limit early and late toxicity, accepting the possibility of mixed chimerism.
3	**Phagocytic disorders CGD, LAD and other neutrophil defects**	• Myeloablative busulfan + fludarabine (often now preferred over busulfan + cyclophosphamide). • Treosulfan + fludarabine ± thiotepa at doses aiming for full myeloid correction.	• Treosulfan + fludarabine at reduced intensity ("reduced-toxicity" RIC). • Lower-dose busulfan + fludarabine in high-risk or comorbid patients.	• CGD and LAD usually require robust myeloid chimerism for cure; too-weak RIC increases risk of graft failure or inflammatory relapse. • Prospective CGD data show excellent survival with RIC Bu-Flu and Treo-Flu, but careful dosing and monitoring are crucial.
4	**Immune dysregulation / HLH-related IEI HLH, XIAP, XLP, etc.**	• Historically: myeloablative busulfan- or cyclophosphamide-based regimens for HLH and some severe PIRD, but now used more selectively because of toxicity	• Fludarabine + melphalan, or treosulfan + fludarabine ± thiotepa, are widely used RIC/"reduced-toxicity" regimens in HLH and other immune dysregulation disorders.	• Modern data in HLH and PIRD show better survival and less toxicity with RIC/"reduced-toxicity" regimens, and stable mixed chimerism is often clinically sufficient. • Pre-HSCT control of inflammation (HLH activity, colitis, autoimmunity) is critical for outcome regardless of MAC vs RIC.
5	**DNA-repair / radiosensitive IEI**	• Conventional high-dose busulfan- or TBI-based MAC is contraindicated because of severe acute and late toxicity.	• Modified "Fanconi-type" fludarabine-based RIC with reduced doses of alkylating agents (e.g. cyclophosphamide or low-dose busulfan/treosulfan), avoiding radiotherapy.	• EBMT/ESID and multiple cohort studies emphasise using gentle, RIC-type regimens with minimized alkylator dose and no TBI in double-strand DNA repair defects. • These patients clearly illustrate where RIC is mandatory, and long-term toxicity is a major endpoint.

All information summarized in this table is derived from three core references (8, 28, 40).

Tandem Repeat (STR) analysis is one of the most commonly methods which provides quantitative donor–recipient percentages in whole blood or specific cell subsets. For identifying low-level microchimerism early after transplantation or in cases with dynamic mixed chimerism, real-time quantitative PCR offer higher sensitivity compared with STR. When highly precise detection is required, Next-generation sequencing (NGS)-based chimerism analysis is recommended.

Recommendation 28: Immune reconstitution should be monitored according to expected recovery kinetics: neutrophils recover at ~14 days after PBSC, ~21 days after BM, and ~30 days after

UCB HSCT; NK cells by ~30–100 days; T cells at ~100 days with full $CD4^+$ recovery over 1–2 years; and B cells normalize after ≥1–2 years (31). Monitoring should be scheduled to detect deviations from these expected patterns and to guide clinical management.

Recommendation 29: The desired level of donor chimerism should be defined based on the underlying IEI and lineage requirements. Full donor chimerism is preferred in conditions where mixed chimerism is associated with inferior outcomes (e.g., WAS and many CIDs), whereas stable mixed chimerism can be acceptable in disorders where tolerance or lineage-restricted correction is adequate (e.g., immune dysregulation disorders and phagocytic disorders) (5, 32, 33).

Recommendation 30: In IEIs where disease correction can be achieved through lineage-restricted donor cell function (e.g., >20% donor myeloid cells in CGD; sufficient donor T-regulatory chimerism in immune dysregulation disorders), stable mixed chimerism may be considered a successful engraftment goal, provided donor contribution remains durable and clinically protective (8). In cases of mixed chimerism, lineage-specific chimerism (e.g., myeloid, T-cell, or T-reg subsets) should be evaluated to determine the functional effectiveness of the graft and the adequacy of disease correction.

6. Post-Transplant Care

Infections following HSCT are a significant concern and are associated with high morbidity and mortality. This highlights the use of antimicrobial prophylaxis for preventing infection after HSCT. In addition, other major post-transplant complications, including GVHD, graft failure or rejection, and hepatic veno-occlusive disease (VOD), require prompt and appropriate management. Patients after HSCT should be monitored for immune reconstitution to ensure disease correction (34).

Recommendation 31: It is recommended that patients with IEI who undergo HSCT should be monitored long time for evaluating immune recovery. Immunologic evaluations should be performed at defined intervals, typically at 1, 3, 6, and 12 months' post-transplant, and annually thereafter. They should be evaluated for T, B, and NK cell subsets, naïve and memory T cells, T cell function (eg, proliferation assays), B cell function (immunoglobulin levels and specific antibodies), and lineage-specific chimerism to track graft stability and immune reconstitution (35-37).

Recommendation 32: Given the high risk of infection after HSCT), antimicrobial prophylaxis, particularly against Pneumocystis jirovecii, should be maintained until the cessation of immunosuppressive treatment and adequate recovery of T cell function is achieved (38). In addition, monthly IVIG replacement is recommended until B-cell reconstitution and adequate endogenous immunoglobulin production and vaccine-specific antibody responses are documented.

Recommendation 33: It is recommended to start antibacterial prophylaxis on the first day post-transplant. It should be continued until neutropenia has ceased (38). Antifungal prophylaxis is also essential and should be maintained throughout the period of neutropenia and impaired immune recovery.

Recommendation 34: Post-HSCT patients should be re-vaccinated with inactivated vaccines after adequate immune recovery and discontinuation of immunoglobulin therapy, whereas live vaccines should only be given to patients with confirmed T-cell recovery, no chronic GVHD, no immunosuppression, and no ongoing need for immunoglobulin, with monitoring of vaccine antibodies (37).

Recommendation 35: It is recommended to use GVHD prophylaxis through either rabbit anti thymocyte globulin (rATG) or post-transplant cyclophosphamide (PTCy) for all IEI patients undergoing HSCT from MUD or mismatched unrelated donors (39).

Recommendation 36: Allergist/immunologists should be aware of GVHD for two main reasons: (1) to discuss the risks and benefits of long-term medical management versus HSCT and support shared decision-making with patients, and (2) to effectively monitor and manage long-term post-transplant immune function by understanding how GVHD treatment impacts immune recovery.

Conclusions

We provide the first national consensus guideline on HSCT for patients with IEI in IRAN in light of scientific literature and comments from

the expert panel of Iranian clinical immunologists. We hope this national consensus guideline will raise awareness among clinicians and improve the management of IEI patients who receive HSCT.

Conflict of Interest

The authors have no conflicts of interest.

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