

# The challenges associated with HSCT for adult patients with primary immune deficiency

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**The most common types of Primary Immunodeficiencies (PIDs) observed in adult patients include:**

**Common Variable Immunodeficiency (CVID):** CVID is one of the most prevalent PIDs in adults. It is characterized by impaired antibody production, leading to recurrent infections and complications.

**Chronic Granulomatous Disease (CGD):** While often diagnosed in childhood, CGD can persist into adulthood. It involves impaired phagocytic function, resulting in recurrent bacterial and fungal infections.

**Selective IgA Deficiency:** Adult patients with selective IgA deficiency lack or have low levels of immunoglobulin A (IgA), making them more susceptible to respiratory and gastrointestinal infections.

**IgG Subclass Deficiencies:** Certain adults may experience deficiencies in specific IgG subclasses, impacting the immune response against bacterial infections.

**Specific Antibody Deficiency (SAD):** SAD is marked by inadequate production of antibodies in response to infections, particularly polysaccharide antigens, increasing the vulnerability to bacterial infections.

## Treatment options for primary immune deficiency in adults?

- ❖ *Immunoglobulin replacement therapy*
- ❖ *Gene therapy*
- ❖ *Hematopoietic stem cell transplantation (HSCT)*

## Treatment options for primary immune deficiency in adults?

**Immunoglobulin replacement** therapy is the main therapeutic tool in some PID and is used to control the disease and prevent infections.

**Gene therapy** is an innovative approach that uses autologous hematopoietic stem cell transplantation to deliver stem cells with added or edited versions of the missing or malfunctioning gene.

**Allogeneic HSCT** is a curative option that has been used over decades as a mainstay of specific treatment modality for PID.

The survival following allogeneic HSCT for PID is now **generally >80%** and toxicity is acceptable.

However, there are **several challenges** associated with stem cell transplantation for adult patients with primary immune deficiency.

The main challenges associated with HSCT for adult patients with primary immune deficiency including:

1. **Finding a suitable donor:** The chances of finding a matched sibling donor decrease with age, and the likelihood of finding an unrelated matched donor is also lower compared to pediatric patients.
2. **Optimal timing** of allo-HSCT in adults with PID
3. **Conditioning regimen:** For the successful transplant outcome, the choice of optimal pretransplant conditioning regimen is important especially in adults with underlying health conditions or organ dysfunction.
4. **Graft-versus-host disease (GVHD) prevention:** Adult patients may have a higher risk of developing GVHD due to longer exposure to potential triggers.
5. **Post-HSCT Immune reconstitution** and Infection risk: Adult patients may be more susceptible to post-HSCT infections due to their longer exposure to environmental pathogens and higher likelihood of previous infections.



CLINICAL TRIALS AND OBSERVATIONS

# Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity

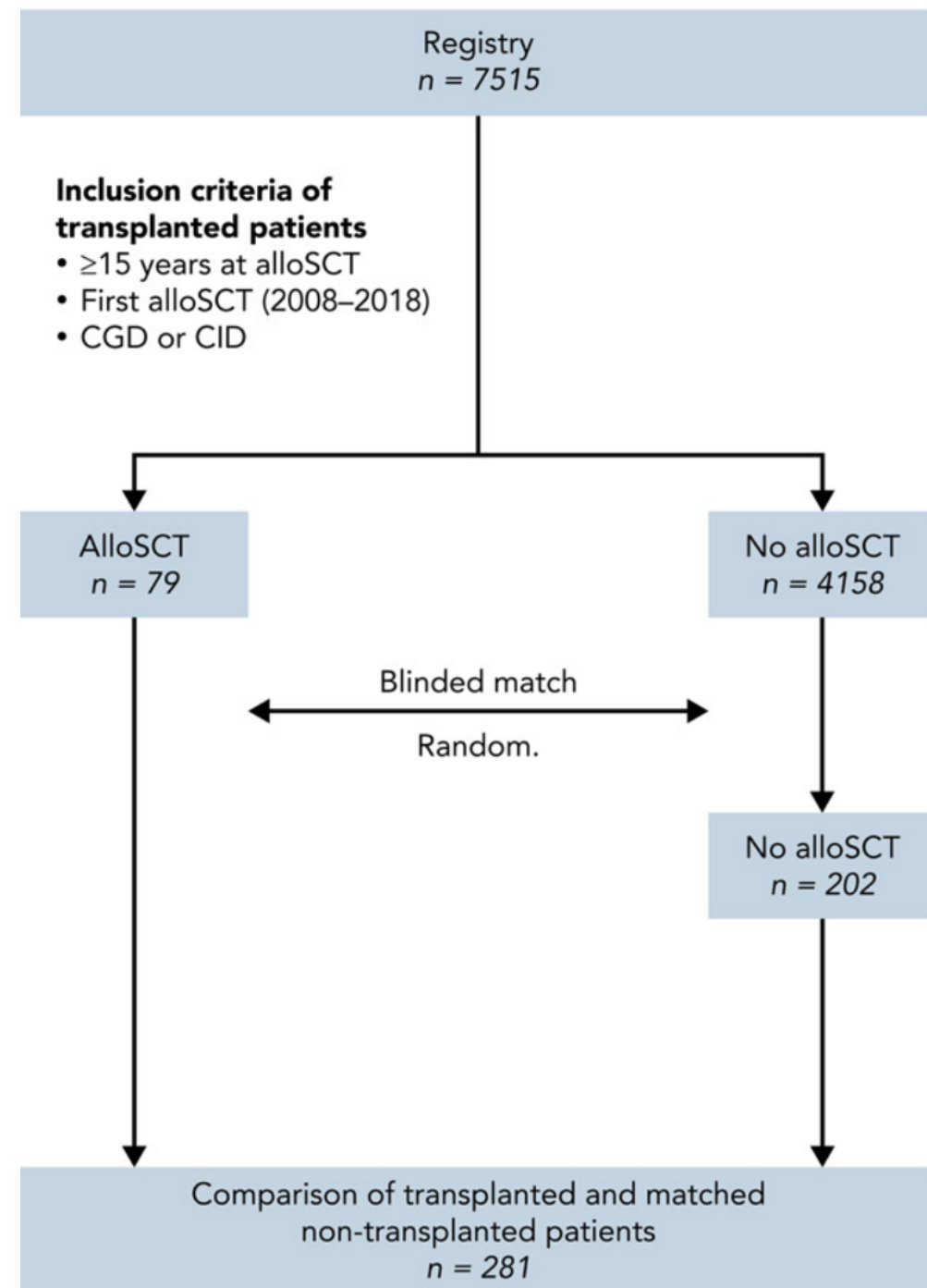
Morgane Cheminant<sup>1 2 3</sup>, Thomas A. Fox<sup>4 5 6</sup>,

We retrospectively compared outcomes of transplanted with matched non-transplanted adults with severe IEI.

Seventy-nine patients (aged  $\geq 15$  years) underwent alloSCT between 2008 and 2018 for IEI, including chronic granulomatous disease (CGD, n=20) and various combined immune deficiencies (CID, n=59).

281 patients were included (79 transplanted, 202 non-transplanted). Median age at transplant was 21 years.

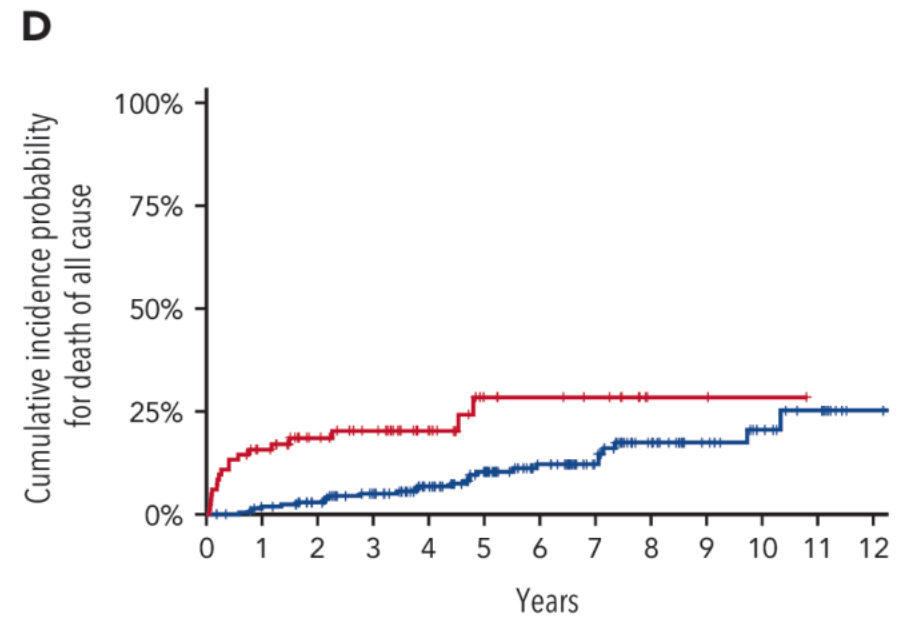
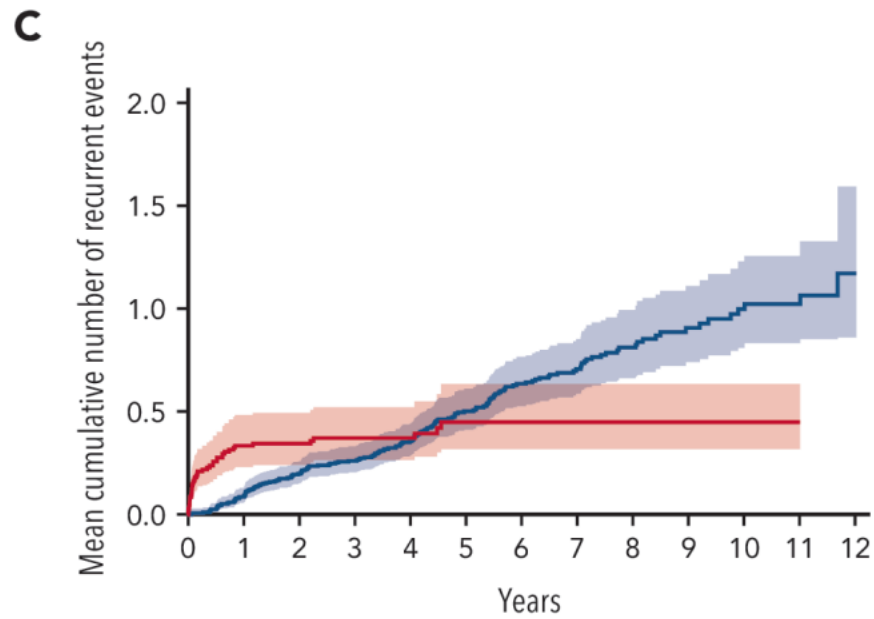
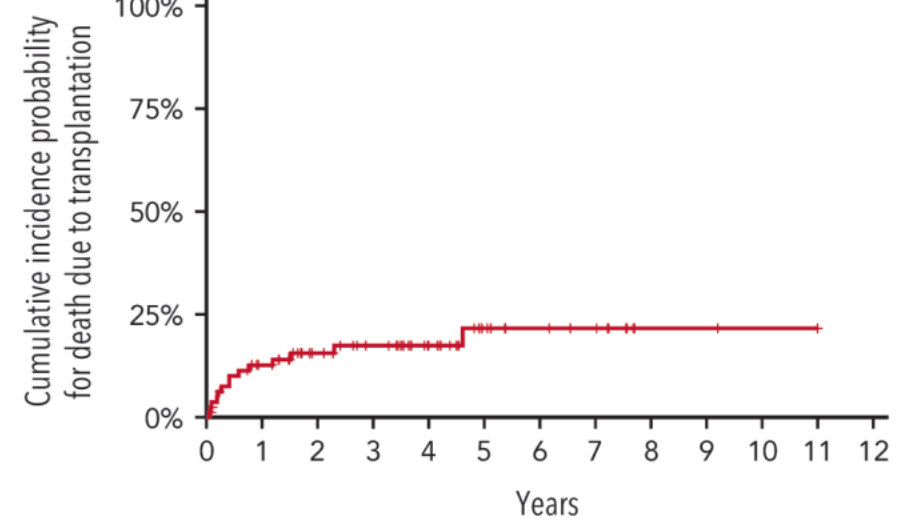
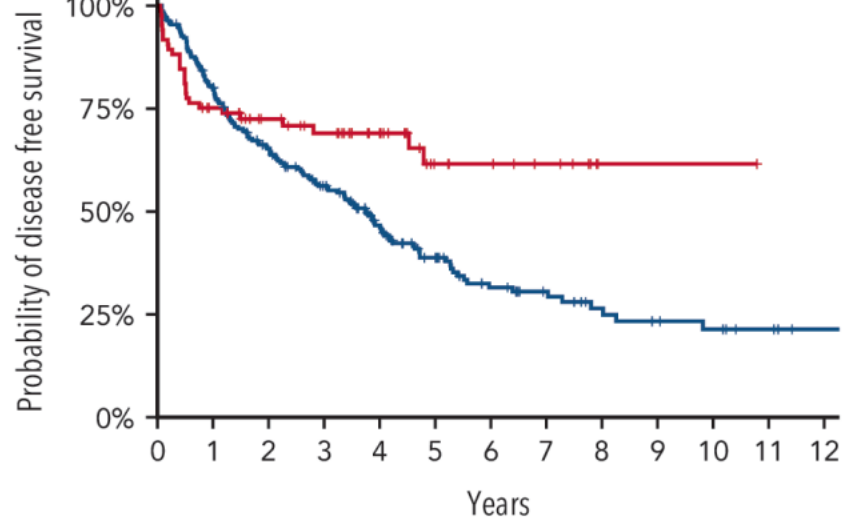
# Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity



## Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity

Transplant indications were mainly lymphoproliferative disease (n=23) or colitis (n=15). Median follow-up was 4.8 years (IQR [2.5-7.2]). One-year TRM was 13%. Estimated DFS at 5 years was higher in transplanted patients (58% vs. 33%, p=0.007). Non-transplanted patients had an ongoing risk of severe events with an increased mean cumulative number of recurrent events compared to transplanted patients.

AlloSCT prevents progressive morbidity associated with IEI in adults, which may outweigh the negative impact of TRM.









No alloSCT	201	194	179	164	141	116	89	67	43	29	23	13	4
AlloSCT	78	62	46	39	27	15	11	9	4	2	1	0	0

**PERSPECTIVE**      **OPEN**



# EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity

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Primary immune deficiencies (PID), or more recently, inborn errors of immunity (IEI), resulting from genetic defects of the immune system may present with **increased susceptibility to infections, persistent inflammation, and autoimmunity.** With recent introduction of next generation sequencing, the number of IEIs increases rapidly, **reaching to 484 in 2022.**

Hematopoietic stem cell transplantation (HSCT) has been used over decades as a **mainstay** of specific treatment modality,

The indication and timing of transplant must be individualized not only on the basis of the **specific PID** but also on the characteristics of the **individual** patient.

For the successful transplant outcome, the **choice of donor** and the optimal pretransplant **conditioning** regimen is important.

## Classical indications for HSCT in PID


### HSCT curative

SCID (severe combined immunodeficiency)  
CID (combine immunodeficiency)\*  
CGD (chronic granulomatous disease)  
DOCK8 (dedicator of cytokinesis) deficiency  
DOCK2 deficiency  
IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked)  
WAS (Wiskott-Aldrich syndrome)  
WIP (WASP interacting protein) deficiency  
ARPC1B (actin related protein 2/3 complex subunit)  
CD40 ligand deficiency  
XLP1,2 (X-linked lymphoproliferative disease)  
APDS (activated PI3K delta syndrome)  
MHC (major histocompatibility complex) class II deficiency  
AD (autosomal dominant) hyper IgE syndrome  
CTLA4 (cytotoxic T-lymphocyte-associated protein) hypoinsufficiency  
LRBA (lipopolysaccharide [LPS]-responsive and Beige-like anchor protein) deficiency  
Familial HLH (hemophagocytic lymphohemophagocytosis) types 1-5  
GATA2 (GATA binding protein) deficiency  
RAB27A (member RAS oncology family) deficiency  
LAD1 (leukocyte adhesion deficiency)  
Reticular dysgenesis




# Classical indications for HSCT in PID

**HSCT  
partially  
curative**



Cartilage hair hypoplasia  
PGM3 (phosphoacetylglucosamine mutase) deficiency  
STAT1 (signal transducer and activator of transcription) - GOF (gain of function)  
STAT3 - GOF  
Severe congenital neutropenia  
ADA2 (adenosine deaminase) deficiency  
C1q deficiency  
CD25 deficiency  
IL-10 deficiency  
IL-10 receptor deficiency  
DNA double-strand break repair disorders

**HSCT  
controversial**



CVID (common variable immunodeficiency)  
Agammaglobulinemia  
Complement deficiencies (other than C1q deficiency)  
DiGeorge syndrome  
NEMO (nuclear factor-kappa B [NF-kB] essential modulator) deficiency  
IKBA (inhibitor of NF-kB alpha) deficiency

Protocol		Myeloablation
A		Busulfan i.v. (AUC=85–95 mg*h/L) Fludarabine (160 mg/m <sup>2</sup> )
B		Treosulfan (30–42 g/m <sup>2</sup> ) Fludarabine (150–160 mg/m <sup>2</sup> ) Thiotepa (8–10 mg/kg)
C		Busulfan i.v. (AUC=60–70 mg*h/L) Fludarabine (160–180 mg/m <sup>2</sup> )
D		Treosulfan (30–42 g/m <sup>2</sup> ) Fludarabine (150–160 mg/m <sup>2</sup> )
E	Fludarabine (150–160 mg/m <sup>2</sup> ) Melphalan (140 mg/m <sup>2</sup> )	
F	Fludarabine (150 mg/m <sup>2</sup> ) Cyclophosphamide (20–40 mg/kg)	

**Protocol A and B:** These are recommended for patients **without severe preexisting organ damage and non-SCID diseases** where a complete donor chimerism is desired for optimal disease correction.

**Protocols C and D:** These are recommended **for patients with preexisting organ damage and/or diseases** where engraftment has been shown to reliably occur with **reduced intensity** conditioning. **Mixed donor chimerism is more likely to occur compared to protocols A and B.**

**Protocol E:** This may be best suited for patients with **preexisting organ damage** and/or diseases where full myeloid engraftment is not absolutely required. Higher degrees of chimerism can be achieved when using PBSC. **DLI may be required in case of mixed chimerism.**

**Protocol F:** To avoid organ toxicity this regimen is **only recommended for patients with DNA repair/radio-sensitivity disorders** (except Artemis deficiency) in which alkylating agents are used in low dose.

Busulfan AUC 90mg\*h/L

Busulfan AUC 60mg\*h/L

Treosulfan 42mg/m<sup>2</sup>

Thiotepa 10mg/kg

Melphalan 140mg/m<sup>2</sup>

Fludarabine 150mg/m<sup>2</sup>

ATG 10mg/kg before d-7

ATG 10mg/kg after d-7

Campath 1mg/kg before d-7

Campath 1mg/kg after d-7

Rituximab 375mg/m<sup>2</sup>

Cyclophosphamide 29mg/kg

INTENSITY

Busulfan AUC 90mg\*h/L

Thiotepa 10mg/kg

Fludarabine 150mg/m<sup>2</sup>

Busulfan AUC 90mg\*h/L

Fludarabine 150mg/m<sup>2</sup>

Treosulfan 42mg/m<sup>2</sup>

Thiotepa 10mg/kg

Fludarabine 150mg/m<sup>2</sup>

Busulfan AUC 60mg\*h/L

Fludarabine 150mg/m<sup>2</sup>

Treosulfan 42mg/m<sup>2</sup>

Fludarabine 150mg/m<sup>2</sup>

**Table 3.** Haploidentical HSCT platforms.

	TCR $\alpha/\beta$ [26, 27, 54]	PT-Cy [24, 25]	CD34 positive selection ( <i>only recommended for some SCID transplants</i> )
Protocols	A, B, C, D	A, B, C, D	C, D
Graft	TCR $\alpha/\beta$ - CD19 depleted PBSC	unmanipulated bone marrow (1st choice) or PBSC <sup>a</sup> (2nd choice)	CD34 positive selected PBSC
Cell dose	10-20 $\times 10^6$ CD34/kg	3–5 $\times 10^8$ TNC/kg	10–20 $\times 10^6$ CD34/kg
Serotherapy	ATG Grafalon: 3 $\times$ 4 mg/kg (d-4 to -2) <sup>b</sup> Rituximab: 200 mg/m <sup>2</sup> (d-1)	Alemtuzumab: 2 $\times$ 0.2 mg/kg (d-10 to -9) If Alemtuzumab is not available: ATG Thymoglobuline 3 $\times$ 2.5 mg/kg (d-10 to -8) <sup>c</sup>	None
GVHD prophylaxis	If $\alpha\beta$ T cells in graft $\geq 10^5$ /kg: add CSA	Cyclophosphamide 50 mg/kg on d + 3 and d + 4 Tacrolimus or CSA from d + 5 until at least d + 100 MMF from d + 5 to d + 35	none

<sup>a</sup>In case PBSC are used, higher rates of cGVHD can be expected and additional or prolonged GvHD prophylaxis may be considered [101].


<sup>b</sup>In case there is no access to ATG-Grafalon alternative serotherapy approaches (i.c. thymoglobulin) may be considered although published recommendations on optimal dose and timing are currently unavailable.

<sup>c</sup>In case of ATG in PT-Cy protocol additional Rituximab may be considered.

ARTICLE



# Curative allogeneic hematopoietic stem cell transplantation following reduced toxicity conditioning in adults with primary immunodeficiency

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The experience on 32 consecutive adult patients with various PID including 17 (53%) with a combined immune deficiency, six (19%) with a disease of immune dysregulation and nine (28%) with a chronic granulomatous disease (CGD) who underwent an allo-HSCT between 2011 and 2020.

The median age at transplant was 27 years (17–41).

The majority of patients received a **fludarabine-Busulfan (FB) based regimen (FB2-3 in 16, FB4 in 12).**

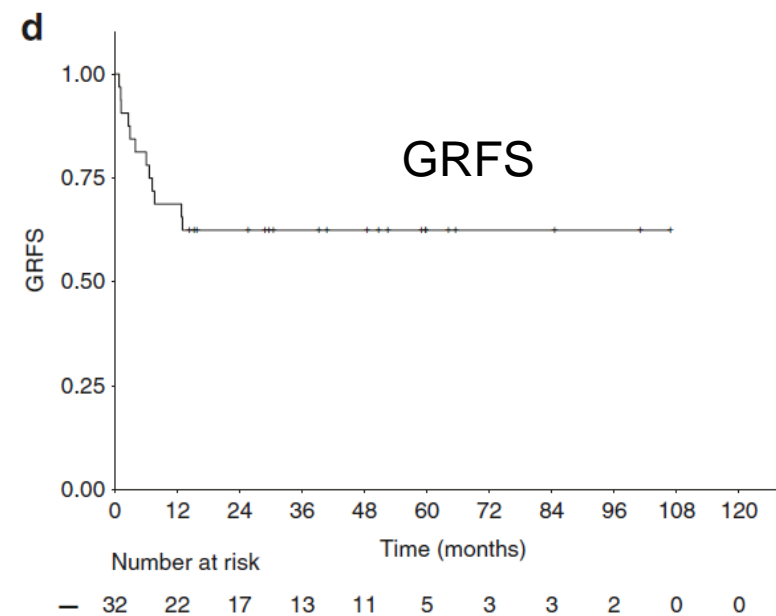
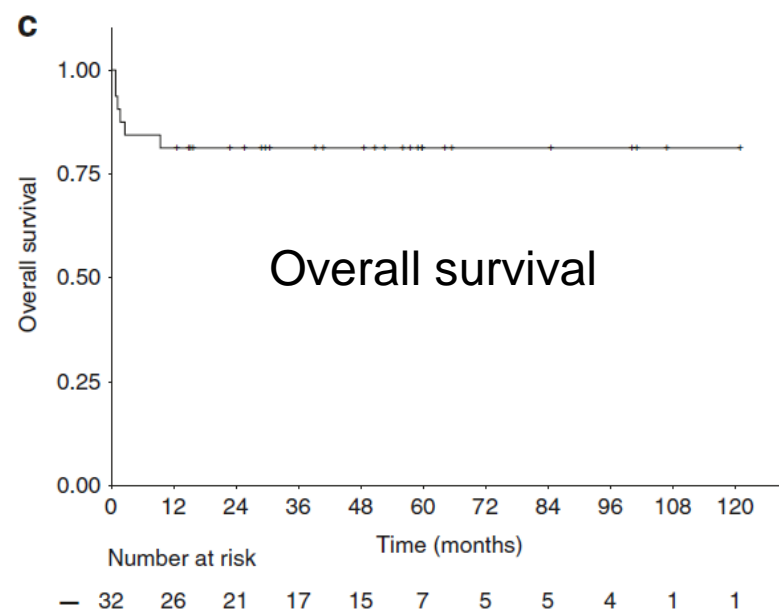
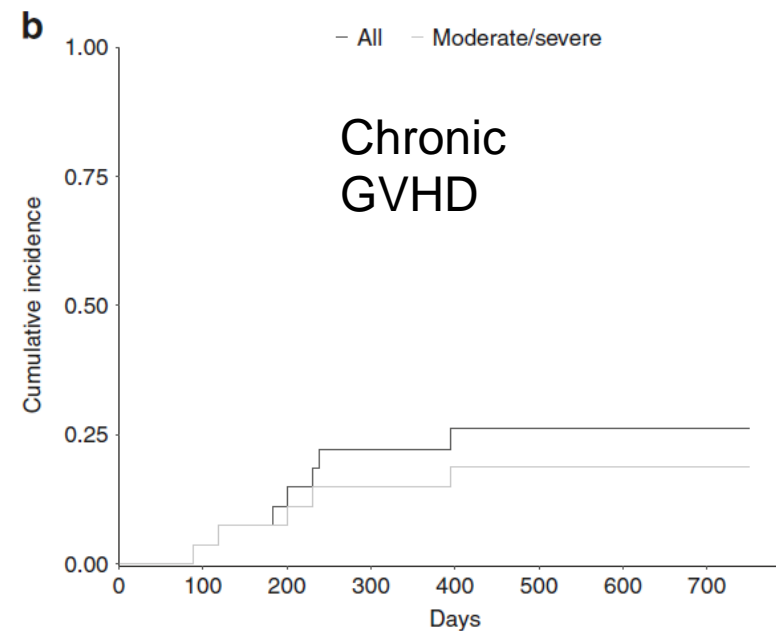
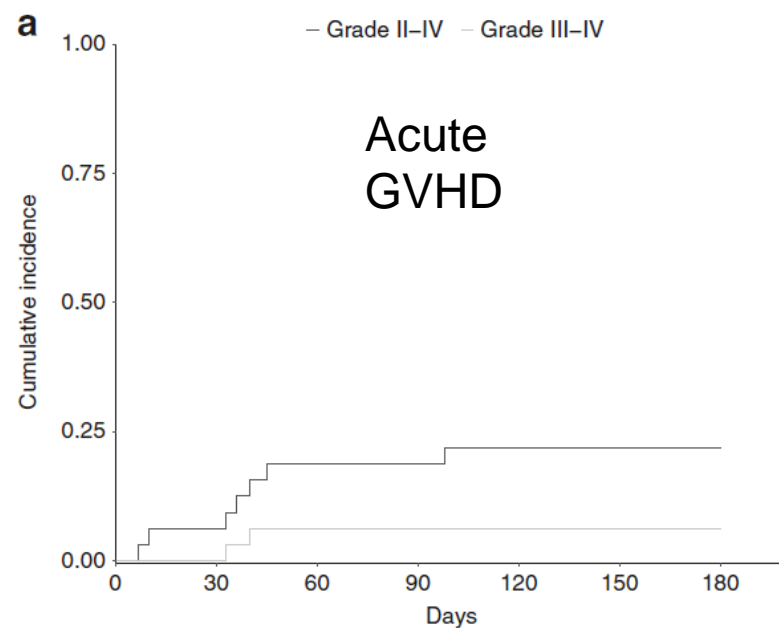
**Overall survival (OS) was 80.4%** (100% for CGD and 74% for other PID patients) at 9 months and beyond (median follow-up 51.6 months).

Cumulative incidences of grade II–IV acute GVHD/chronic GVHD were 18%/22%.

Stem cell source, GVHD prophylaxis and conditioning intensity had no impact on OS.


**Allo-HSCT is effective in young adults PID patients with an acceptable toxicity and should be discussed in case of life-threatening PID.**







# A fludarabine and melphalan reduced-intensity conditioning regimen for HSCT in fifteen chronic granulomatous disease patients and a literature review

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Mohammad Reza Fazlollahi<sup>4</sup>  · Zahra Pourpak<sup>4</sup> · Mohsen Badalzadeh<sup>4</sup> · Shaghayegh Tajik<sup>4</sup> ·  
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## Main points discussed in the paper (Vaezi et al):

- ✓ Chronic granulomatous disease (CGD) is a life-threatening immunodeficiency condition.
- ✓ Hematopoietic stem cell transplantation (HSCT) is the only curative modality for CGD.
- ✓ Fifteen CGD patients underwent HSCT with **fludarabine and melphalan plus anti-thymocyte globulin** (ATG).
- ✓ Most of the donors were fully matched siblings.
- ✓ Cyclosporine A and methylprednisolone were used for graft-versus-host disease (GVHD) prophylaxis.
- ✓ Eleven patients achieved full donor chimerism, two had stable mixed chimerisms with no sign of the underlying disease, and two experienced secondary graft failure.

Table 3 Survival probabilities in adults and children

Authors	Mean OS (95% CI) months	3 years OS	Mean EFS (95% CI)months	3 years EFS	Mean GVHD-FS (95% CI)	3 years GVHD- FS	Mean TRM (95% CI)months	3 years TRM
<i>Pediatrics</i>	41.0 (25.8 – 56.2)	75%	28.4 (10.8–45.9)	50%	38.9 (21.7–56.2)	70%	46.3 (33.6–58.8)	14.3%
<i>Adult</i>	41.6 (23.5 – 59.6)	71.4%	24.4 (4.9–43.8)	42.9%	24.4 (4.9–43.8)	42.9%	37.4 (18–56.4)	33.3%
<i>Total</i>	42.6(30.6 – 54.7)	73.3%	26.8 (13.6–40.0)	46.7%	35.7 (19.2–46.2)	57.8%	42.7 (31.2–54)	23.1%

# Allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency

**Emma C. Morris**

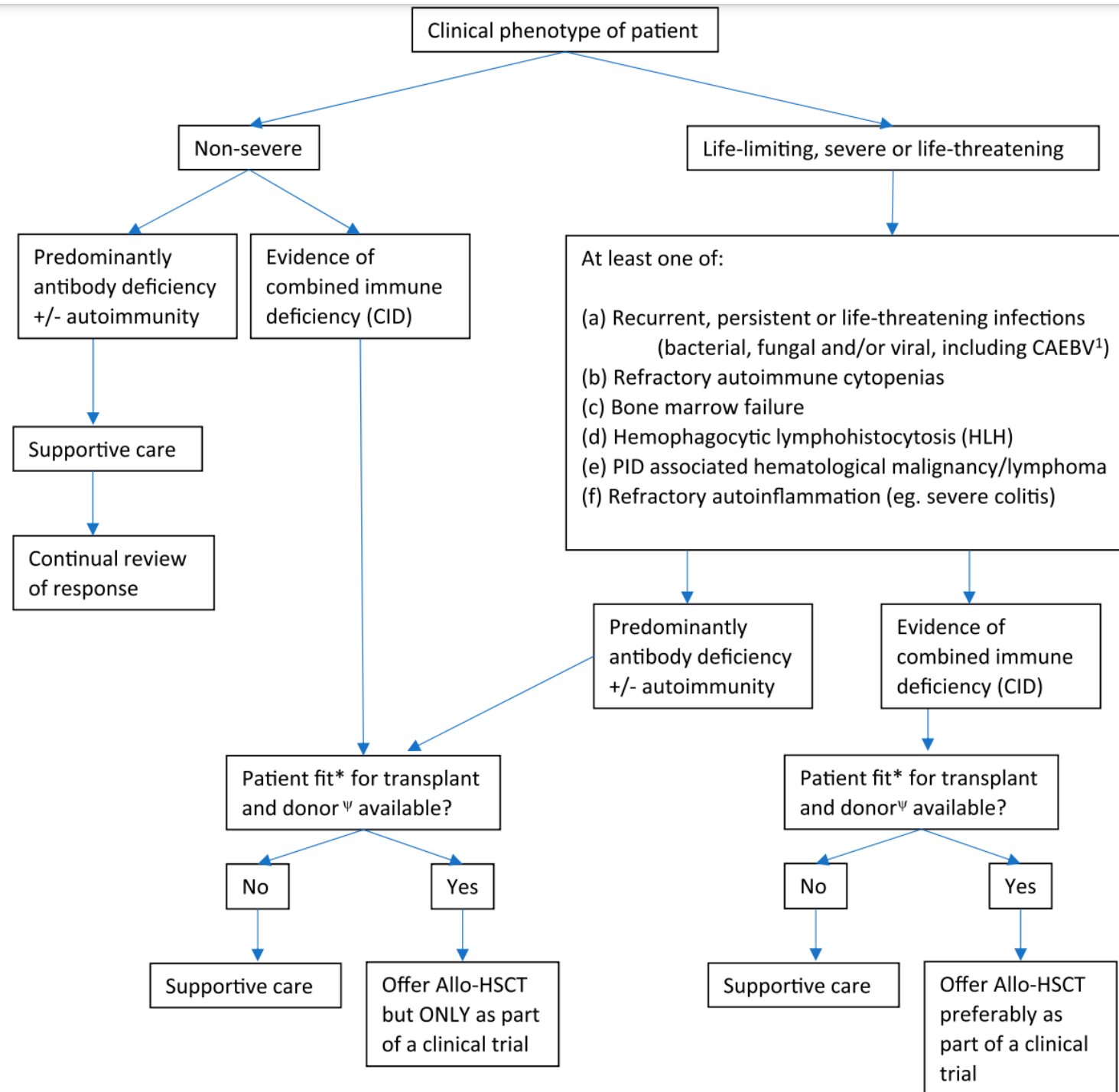
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With recent advances in genetic sequencing and its widespread adoption for clinical diagnostics, the identification of a primary immunodeficiency (PID) as the underlying cause of diseases presenting to hematologists including refractory autoimmunity, cytopenias, immune dysregulation, and hematologic malignancy, is increasing, particularly in the adult population. Where the pathogenic genetic variants are restricted to the hematopoietic system, selected patients may benefit from allogeneic hematopoietic stem cell transplantation (allo-HSCT). Although it is generally accepted that *early* allo-HSCT (ie, in infancy or childhood) for PID is preferable, this is not always possible. The clinical phenotype of non-severe combined immune deficiency forms of PID can be very heterogeneous, in part because of the high number of genetic and functional defects affecting T, B, and natural killer cells, neutrophils, and/or antigen presentation. As a result, some patients have less severe disease manifestations in childhood and/or a later de novo presentation. For others, a delayed diagnosis, lack of a genetic diagnosis, or a previous lack of a suitable donor has precluded prior allo-HSCT. Specific issues which make transplantation for adult PID patients particularly challenging are discussed, including understanding the natural history of rare diseases and predicting outcome with conservative management alone; indications for and optimal timing of transplant; donor selection; conditioning regimens; and PID-specific transplant management. The role of gene therapy approaches as an alternative to allo-HSCT in high-risk monogenic PID is also discussed.

One of the biggest challenges for hematologists and immunologists looking after adults with PID is knowing **which patient and when to refer for consideration of allo-HSCT.**

The clinical decision is straightforward if the underlying condition is known to be life-threatening or life-limiting, and the patient has a predicted poor prognosis with conservative management alone.

Decision flowchart for  
adult PID patients  
**without a genetic  
diagnosis** referred for  
allogeneic HSCT



Decision flowchart for adult PID patients with **known genetic diagnosis** referred for allogeneic HSCT

