HSCT Challenges For IEIs Patients

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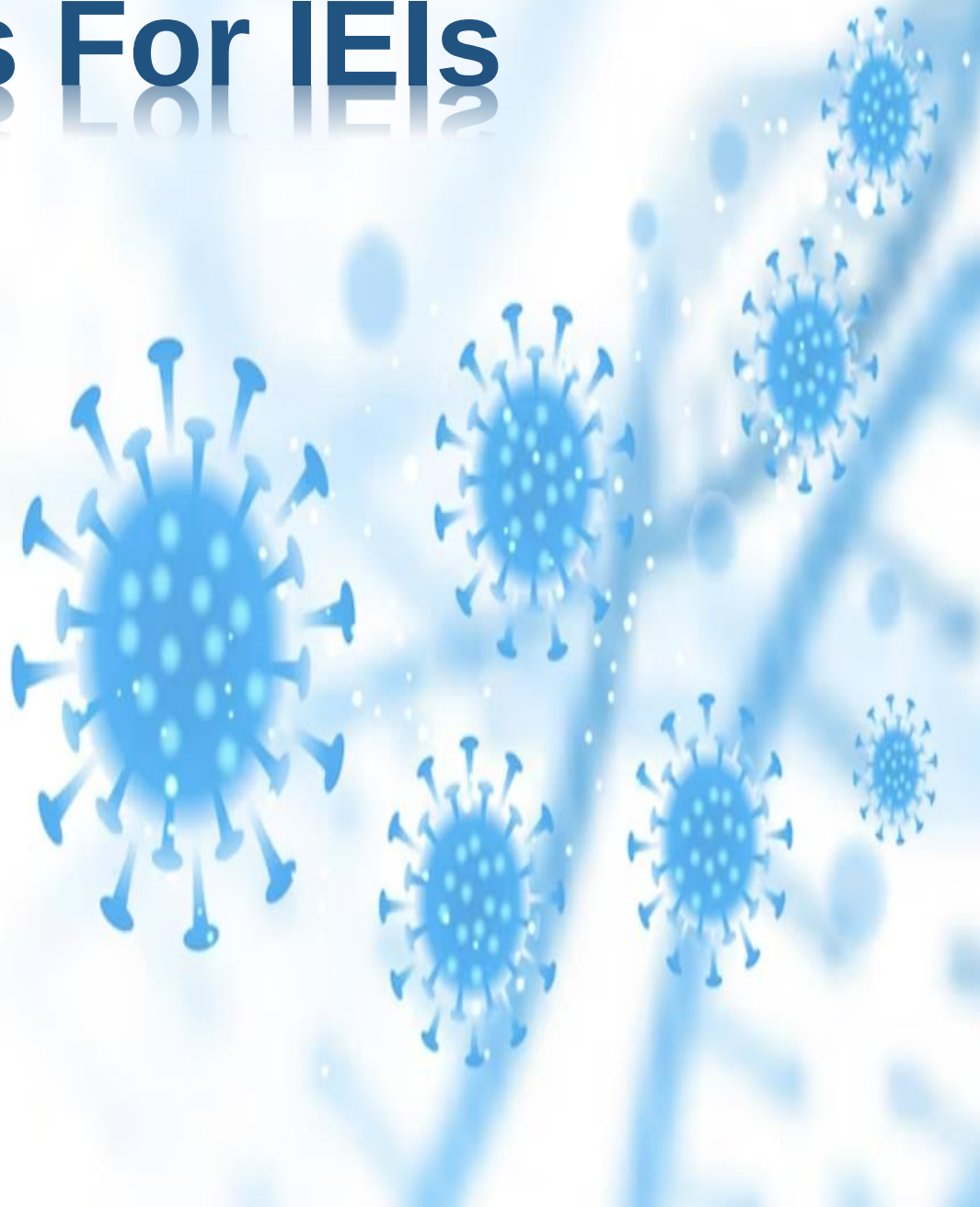


outline

- IEI Introduction
- Challenges Before HSCT
- Challenges Through HSCT
- Our Experience
- Conclusion

Primary Immunodeficiency Diseases

- A **heterogeneous group** of genetic disorders involved in **immune host defense and immunoregulation**, which manifests various combinations of:

The hallmark of nearly all PIDs is being susceptible to recurrent infections.

- Infections
- Autoimmunity
- Lymphoproliferation
- Inflammatory
- Atopy
- Malignancy

https://doi.org/10.3389/fimmu.2020.01923, https://doi.org/10.3389/fped.2019.00295

Primary Immunodeficiency Diseases

- Since the first recognition of primary immunodeficiency (PID) by Bruton in **1952**, **over 450** immunodeficiencies are now described.
- Reports from several PID registries in different countries show **a prevalence of 1:8500 to 1:100000** for **symptomatic patients**.
- The prevalence of PID has been estimated to be around **3.9 per 100000 in the Iranian population**.

https://doi.org/10.1080/1744666X.2020.1801422

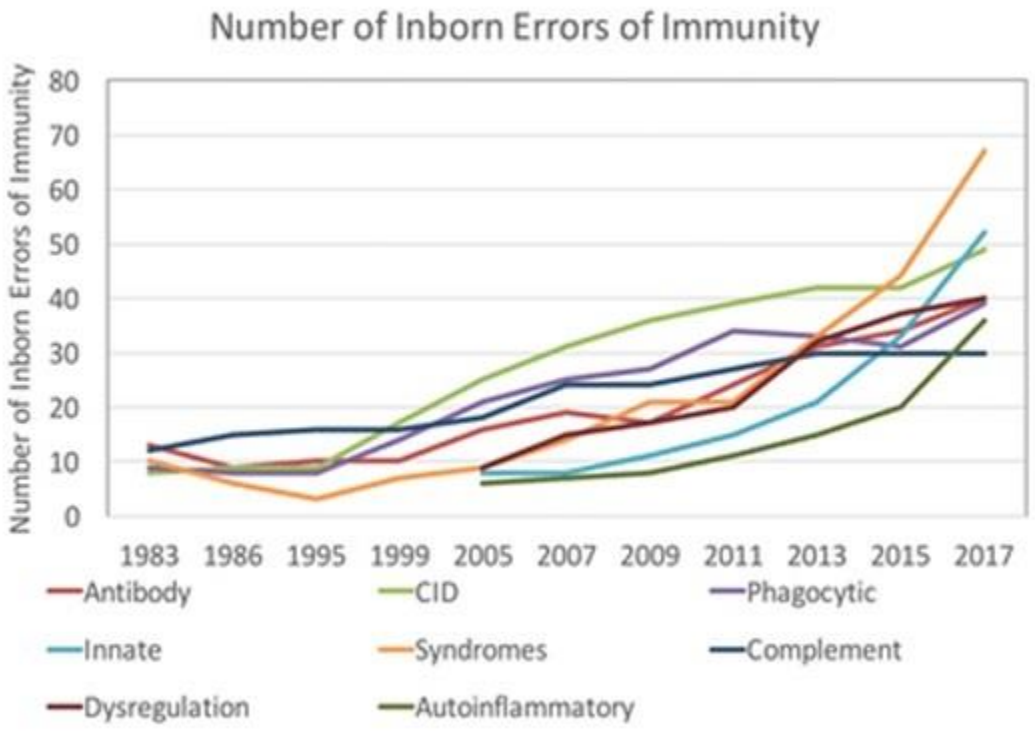
Potential Stem Cell Donors

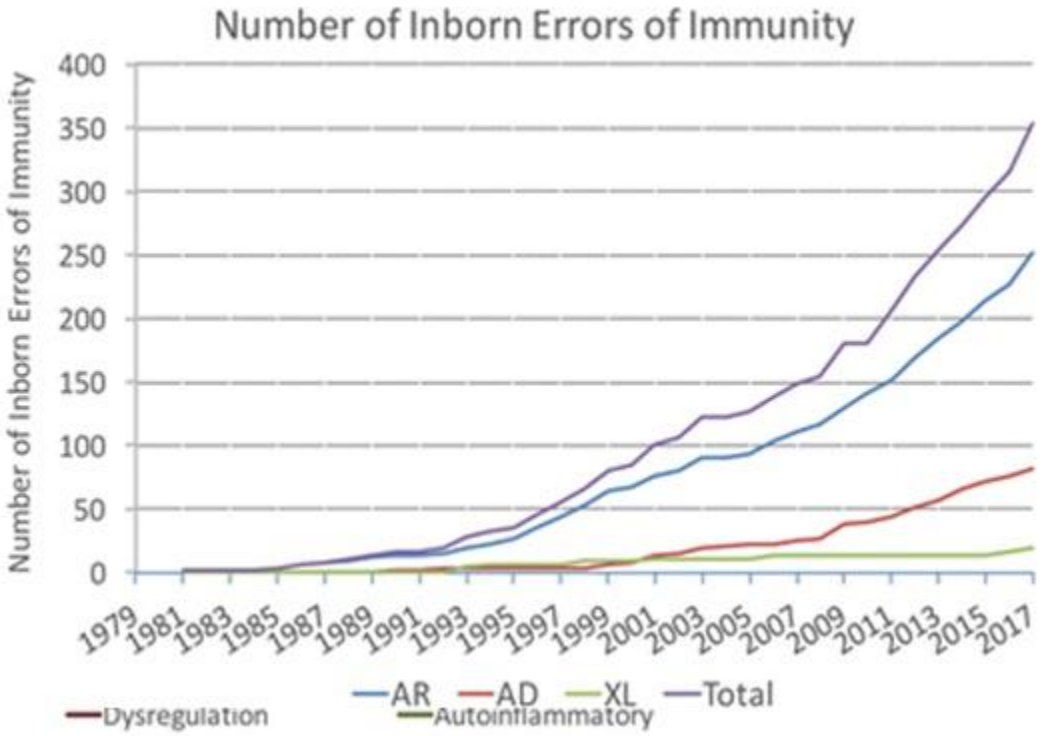
- More than **350 distinct genes** are now associated with clinical immune disorders due to **loss or gain of function** of the implicated protein.

- Presentation of PID varies from potentially **benign forms** such as IgA deficiency to **catastrophic types** such as severe combined immunodeficiency (SCID).

https://doi.org/10.1080/1744666X.2020.1801422, https://doi.org/10.3389/fimmu.2020.01923,https://doi.org/10.3389/fped.2019.00295

Numbers of PIDs





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Current therapeutics modality

- Prophylaxis for bacterial, fungal and viral infection
- IVIG replacement therapy and Steroids
- Enzyme Replacement Therapy (ERT)
- Cytokine therapy or Cytokine Antagonists
- Hematopoietic Stem Cell Transplantation
- Gene Therapy for Specific Immune Deficiencies

https://doi.org/10.3389/fimmu.2017.00937, https://www.ncbi.nlm.nih.gov/books/NBK553955/

PID-HSCT Indications

HSCT curative		HSCT partially curative		HSCT controversial
SCID	CD40 deficiency	Cartilage Hair Hypoplasia	IL-10 Receptor deficiency	CVID
CID^	XLP1, XLP2	PGM3 deficiency	DNA double-strand break repair disorders	Agammaglobulinemia
CGD	APDS	STAT1-GOF		Complement deficiencies (other than C1q deficiency)
DOCK8 deficiency	MHC Class II deficiency	STAT3- GOF		DGS
DOCK2 deficiency	AD Hyper IgE syndrome	Severe congenital neutropenia		IKBA deficiency
IPEX	CTLA4 haploinsufficiency	ADA2 deficiency		NEMO deficiency
WAS	LRBA deficiency	CIQ deficiency		
WIP deficiency	Familial HLH types 1–5	CD25 deficiency		
ARPC1B deficiency	GATA2 deficiency	IL-10 deficiency		
CD40 ligand deficiency	RAB27A deficiency			
	LAD I			
	Reticular Dysgenesis			

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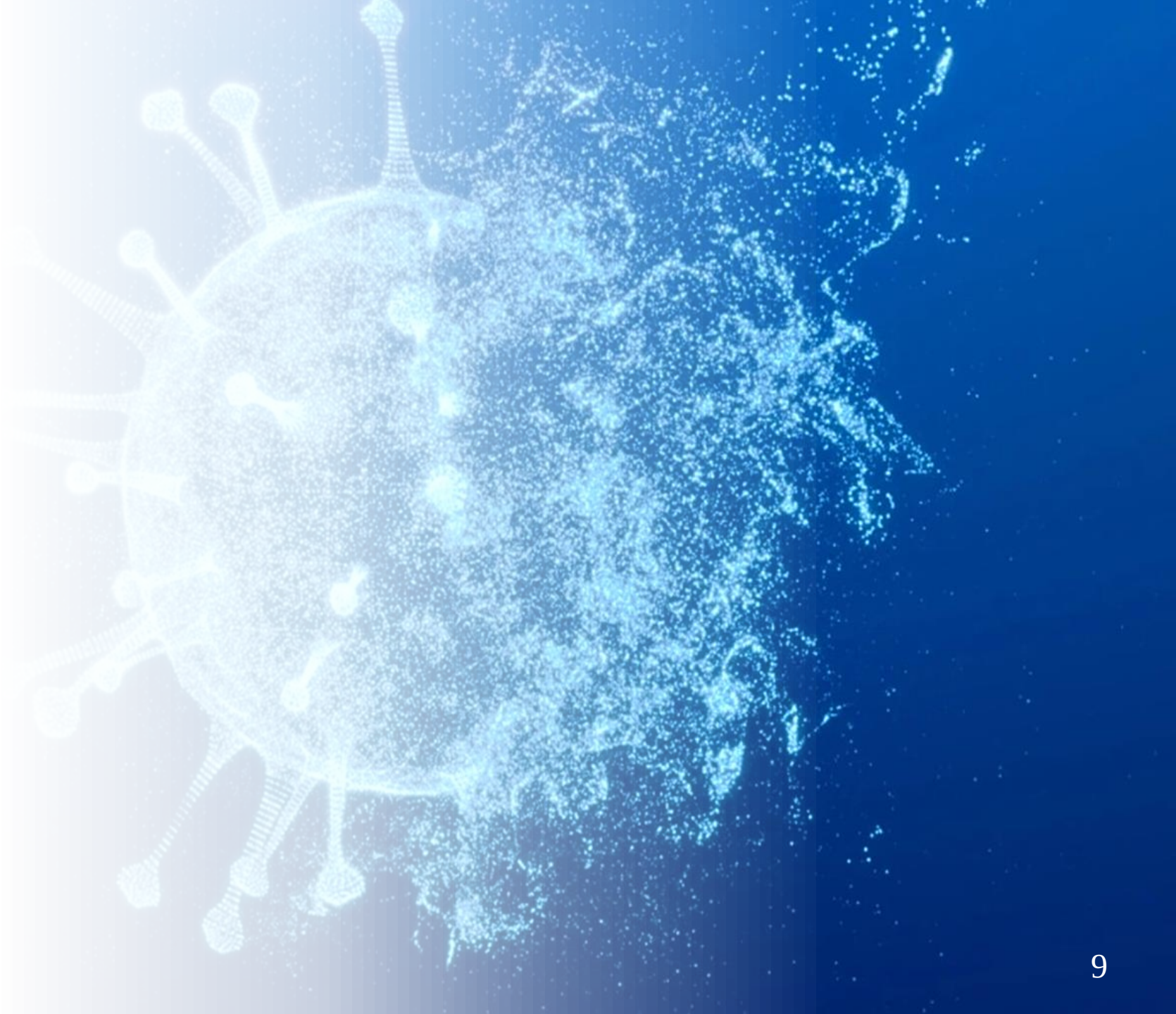
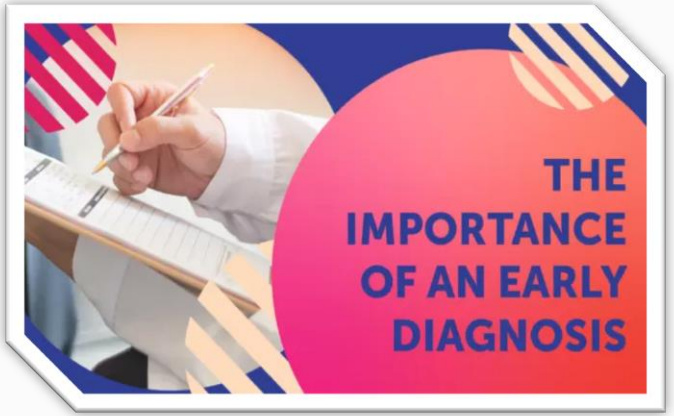
Challenges before HSCT



Early Diagnosis and Optimum time for HSCT

- Many studies have demonstrated that patients transplanted when **young and before they have developed preexisting infection**, **inflammation**, and **end-organ damage** have significantly better survival than older patients who went to transplant with preexisting comorbidities (Especially in SCID patients)
- Patients transplanted before the age of 3 months have a better HSCT outcome.
- For combined immune deficiencies and other PIDs, there may be less urgency to proceed to transplant.
- Particular care should be taken to treat infection, resolve autoimmunity, and enhance nutrition before transplantation.



https://doi.org/10.1093/bmb/ldaa017

Vaccination

Many infants harbor **vaccine-strain** viruses or bacteria, having received live vaccines before diagnosis, which may impact the HSCT outcome.

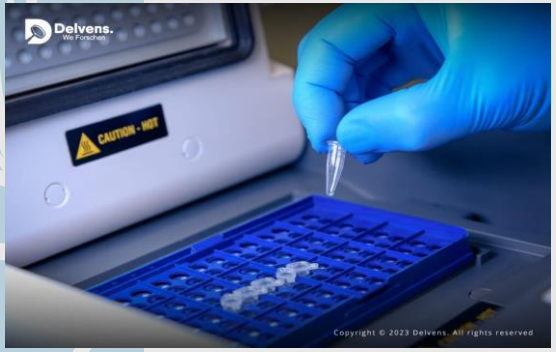
The disseminated form of infection, which is more lethal, is referred to as **“BCGosis”**, whereas the regional form of BCG vaccine complication is called “BCGitis” after BCG vaccination.

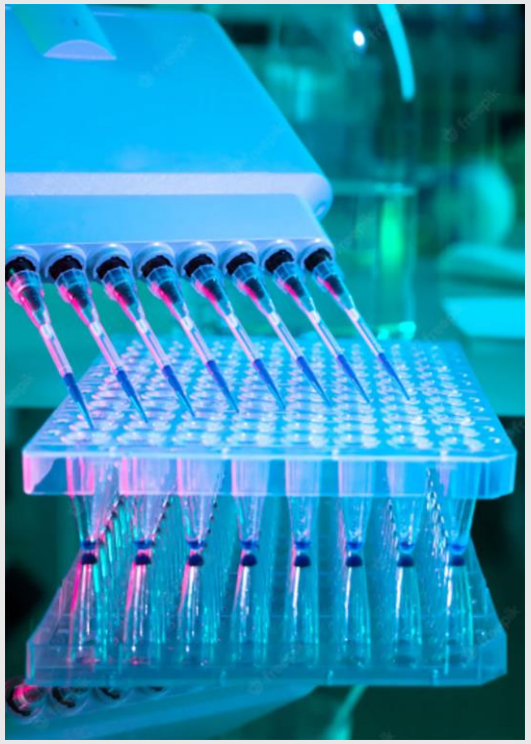
SCID newborn screening was pioneered in the USA but is being introduced in many countries across the world and should change the outcome of HSCT for SCID.

https://priothera.com/hematopoietic-stem-cell-transplantation/

Genetic versus clinical presentations

- As new-generation sequencing becomes more widely available, the dilemma about whether a specific patient requires a transplant becomes more acute.

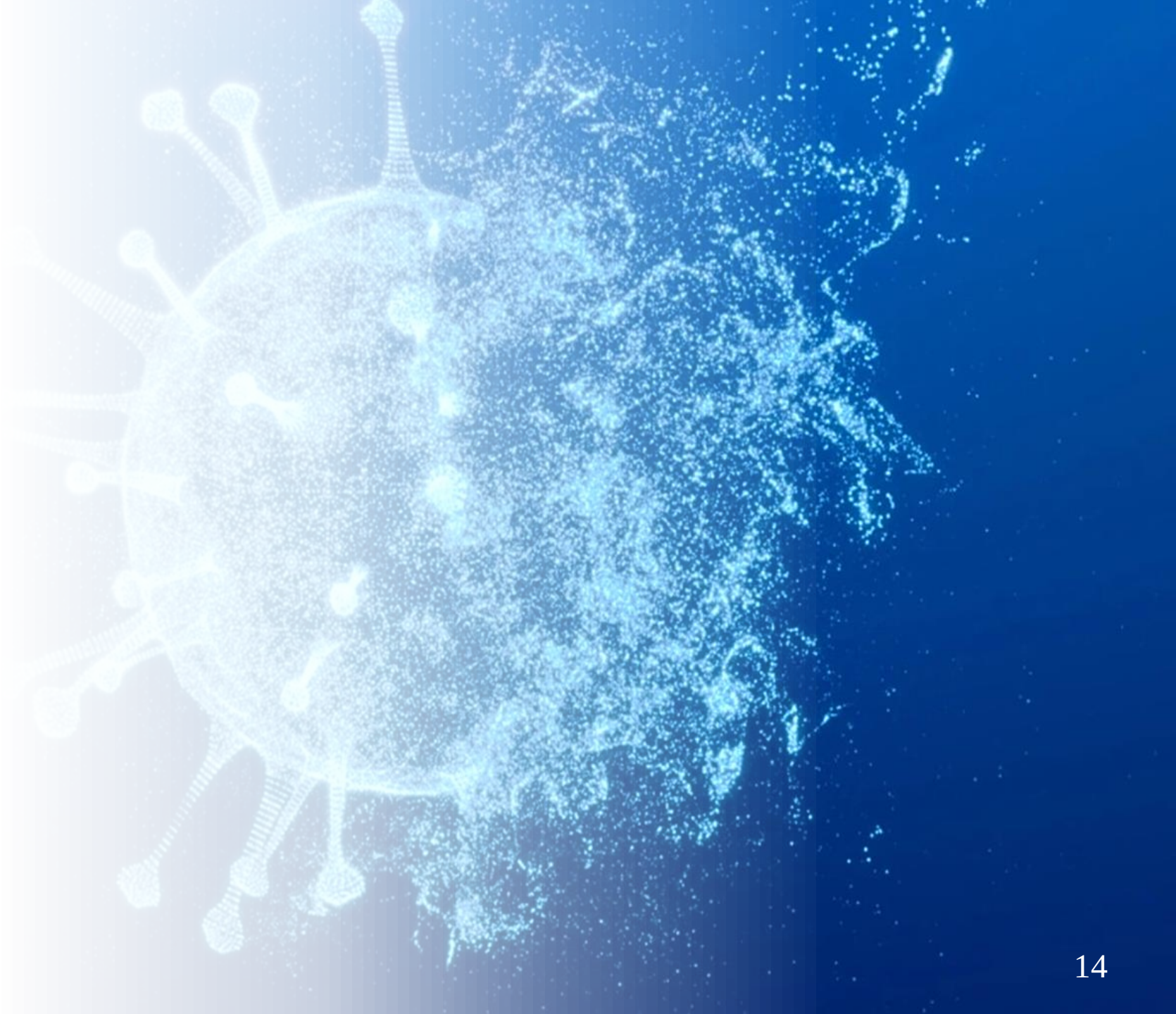




Alternative treatments

- For an increasing number of PIDs, more than one treatment strategy may be available.
  - STAT1 or STAT3 gain of function: JAK inhibitors (such as ruxolitinib)
  - PI3K delta syndrome: Sirolimus or PI3K inhibitors
- The Quality of life of patients on conventional treatment is worse than those who have successfully been transplanted, and they usually experience disease progression.

Challenges Through HSCT



Donor Selection

- Donor selection criteria for patients with PID are broadly the same as for patients undergoing transplantation for other disease.
  - HLA matched sibling
  - Matched related donors
  - Matched unrelated donors
  - Haploidentical related donor

Conditioning Regimen

- Myeloablative Conditioning (MAC)
  - Bu + Flu +/– Alemtuzumab
  - Bu + Flu +/– ATG
- Reduced Intensity Conditioning (RIC)
  - Bu+ Flu +/–Alemtuzumab or ATG
  - Flu + Melphalan +/– Alemtuzumab
  - Treosulphan + Flu +/– Alemtuzumab

Conditioning Regimen

Protocol	Myeloablation
A	Busulfan i.v (AUC = 85–95 mg*h/L) Fludarabine (160 mg/m^2)
B	Treosulfan (30–42 g/m2) Fludarabine (150–160 mg/m^2) Thiotepa (8–10 mg/kg)
C	Busulfan i.v. (AUC = 60–70 mg*h/L) Fludarabine (160–180 mg/m^2)
D	Treosulfan (30–42 g/m^2) Fludarabine (150–160 mg/m^2)
E	Fludarabine (150–160 mg/m^2) Melphalan (140 mg/m^2)
F	Fludarabine (150 mg/m^2) 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.

GVHD Prophylaxis

- **Pharmacotherapy:**
  - Calcineurin inhibitor (Cyc. A or Tacrolimus)
  - Inhibitors of cell proliferation (MMF, MTX, PT-cy)
  - Corticosteroids
  - mTOR inhibitor(sirolimus)

- **Depletion of donor T-lymphocytes**
  - In vivo (ATG, Alemtuzumab)
  - Ex vivo (CD34 selection)

The risk of occurrence of graft-vs.-host-disease (GVHD) is dependent on the **degree of compatibility** between donor and recipient, but also on the **clinical conditions of the recipient**.

Pre-existing viral infections or inflammation related to autoimmunity or immune dysregulation can predispose to onset of early and severe acute GVHD and therefore, effective GVHD prophylaxis is of primary importance. If GVHD occurs, it needs to be aggressively and rapidly treated.

Donor Chimerism

- In many PIDs, **stable mixed donor** chimerism does not lead to graft rejection and may be enough to correct the underlying immunodeficiency.
- Mixed donor chimerism depends on the **underlying disease**.

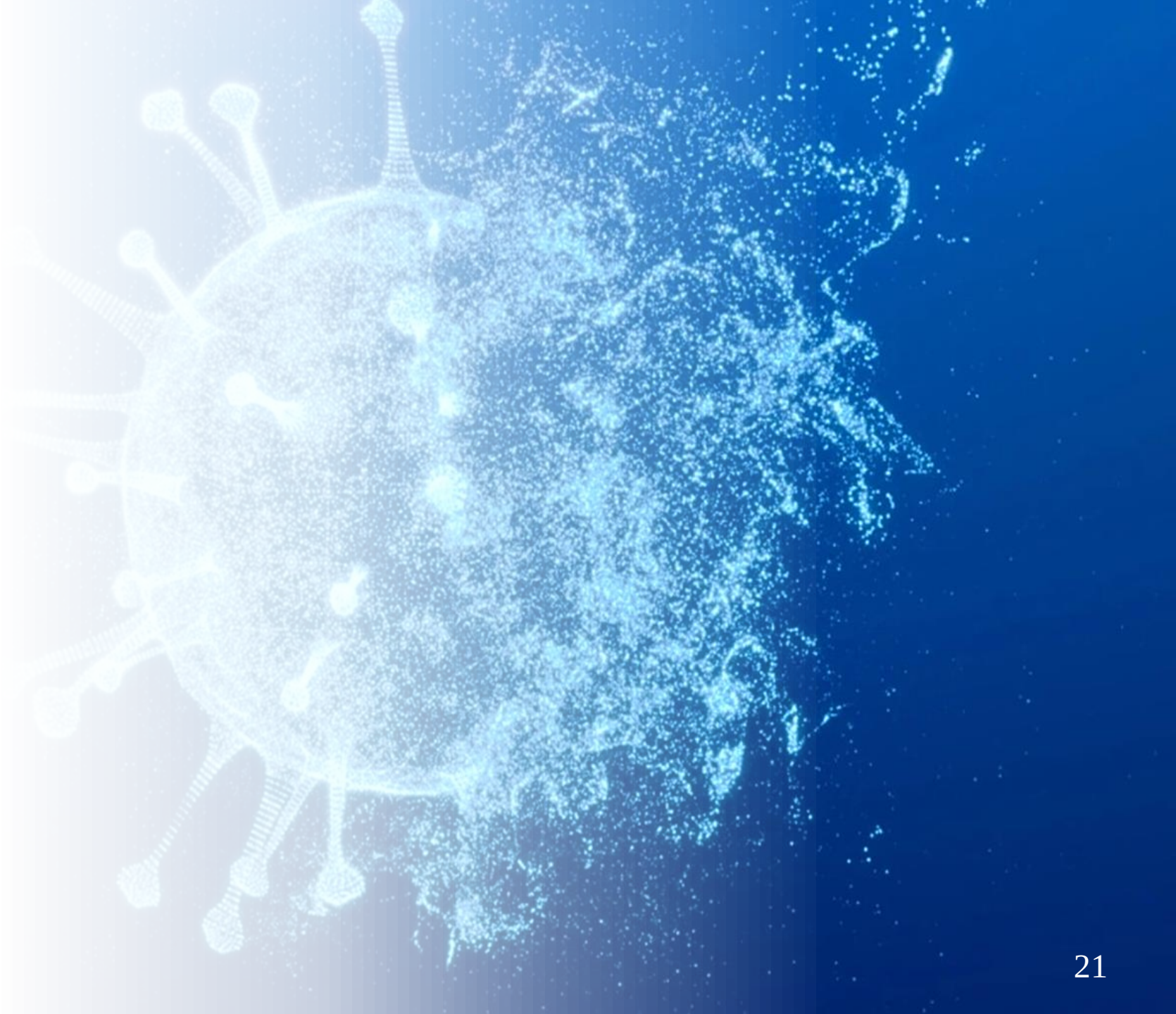
Table 1 Degree of myeloid chimerism required to cure disease

Disease	Low (<20%)	High (~80%)
Severe combined immunodeficiencies	X	
Wiskott Aldrich Syndrome		X
Chronic granulomatous disease		X
MHC Class II deficiency	X	
LRBA deficiency		X
Activated PI3K-δ syndrome		X
CD40L deficiency		X
Purine nucleoside phosphorylase deficiency	X	
STAT1 gain of function		X
IPEX syndrome		X

Complications after HSCT

- Graft rejection
- Infections
- Autoimmune complications(10%)
  - Most commonly hematological cytopenias and thyroid dysfunction
- Post-HSCT malignancy
- Infertility
- Other complications
  - ADA-deficient SCID demonstrate significant central nervous system complications after successful HSCT

Our experience



Transplantation and Cellular Therapy
Volume 29, Issue 3, March 2023, Pages 188.e1-188.e8

ORIGINAL ARTICLE

Long-term outcomes of fludarabine, antithymocyte globulin as reduced-in regimen for allogeneic hematopoietic in children with primary immunodefi prospective single center study

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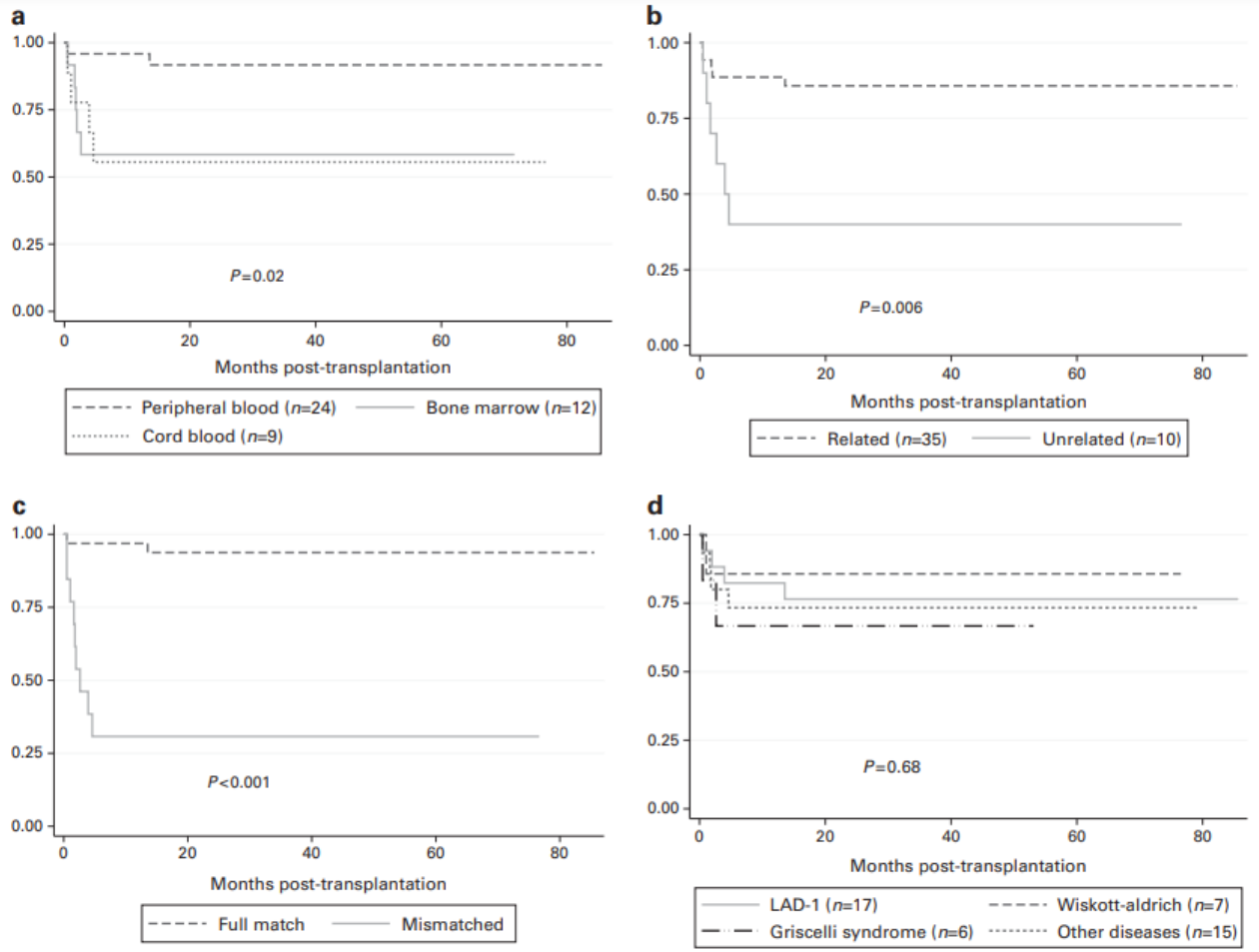
Bone Marrow Transplantation (2016) **51,** 219–226; doi:10.1038/bmt.2015.277; p



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ORIGINAL ARTICLE

Long-term outcomes of fludarabine, melphalan and antithymocyte globulin as reduced-intensity conditioning regimen for allogeneic hematopoietic stem cell transplantation in children with primary immunodeficiency disorders: a prospective single center study

AA Hamidieh[1], M Behfar[1], Z Pourpak[2], S Faghihi-Kashani[1], MR Fazlollahi[2], AS Hosseini[1], M Movahedi[2], M Mozafari[1], M Moin[2] and A Ghavamzadeh[1]

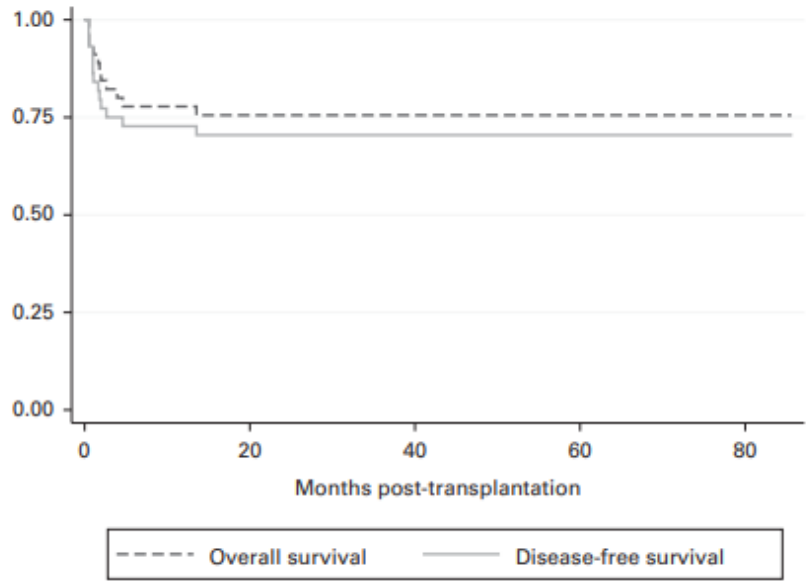
Reduced-intensity conditioning (RIC) has offered many primary immunodeficiency disorder (PID) patients who are ineligible for myeloablative regimens a chance of cure. However, the beneficial role of RIC was questioned following reports suggesting higher chance of rejection and lower symptom resolution rate in mixed chimerism settings. Forty-five children affected by PIDs with a median age of 21 months underwent allogeneic hematopoietic stem cell transplantation in our institute from 2007 to 2013. All patients received an identical RIC regimen. Forty-one patients had successful primary engraftment (91%). Of the successful engraftments, 80% ($n = 33$) had stable full donor chimerism at last contact. Overall, eleven transplant-related mortalities were reported including five patients due to sepsis, three children due to grade IV acute GvHD, two due to chronic GvHD and one patient due to sepsis after primary graft failure. The median post-transplantation follow-up of deceased patients was 55 days. Five-year overall survival and disease-free survival was 75.6% and 68.89%, respectively. All surviving patients with successful engraftment became disease free, regardless of having full or mixed chimerism. Our study suggests that RIC regimen provides satisfactory rates of successful engraftment and full chimerism. Furthermore, patients with mixed chimerism were stable in long-term follow-up and this chimerism status offered the potential to resolve symptoms of immunodeficiency.

Bone Marrow Transplantation (2016) **51,** 219–226; doi:10.1038/bmt.2015.277; published online 23 November 2015

Table 4. Hazard ratios calculated from multivariable Cox regression for risk of mortality.

	Hazard ratio (95% CI)	*P-value*
Unrelated donor	2.19 (0.27–16.77)	0.477
Stem cell source: bone marrow	7.19 (1.02–50.68)	0.048
Stem cell source: cord blood	3.47 (0.26–45.68)	0.343
Age more than 1 year at HSCT	2.70 (0.66–11.07)	0.167
Grade IV acute GvHD	2.44 (0.43–14.01)	0.317

Abbreviations: CI = confidence interval; HSCT = hematopoietic stem cell transplantation.



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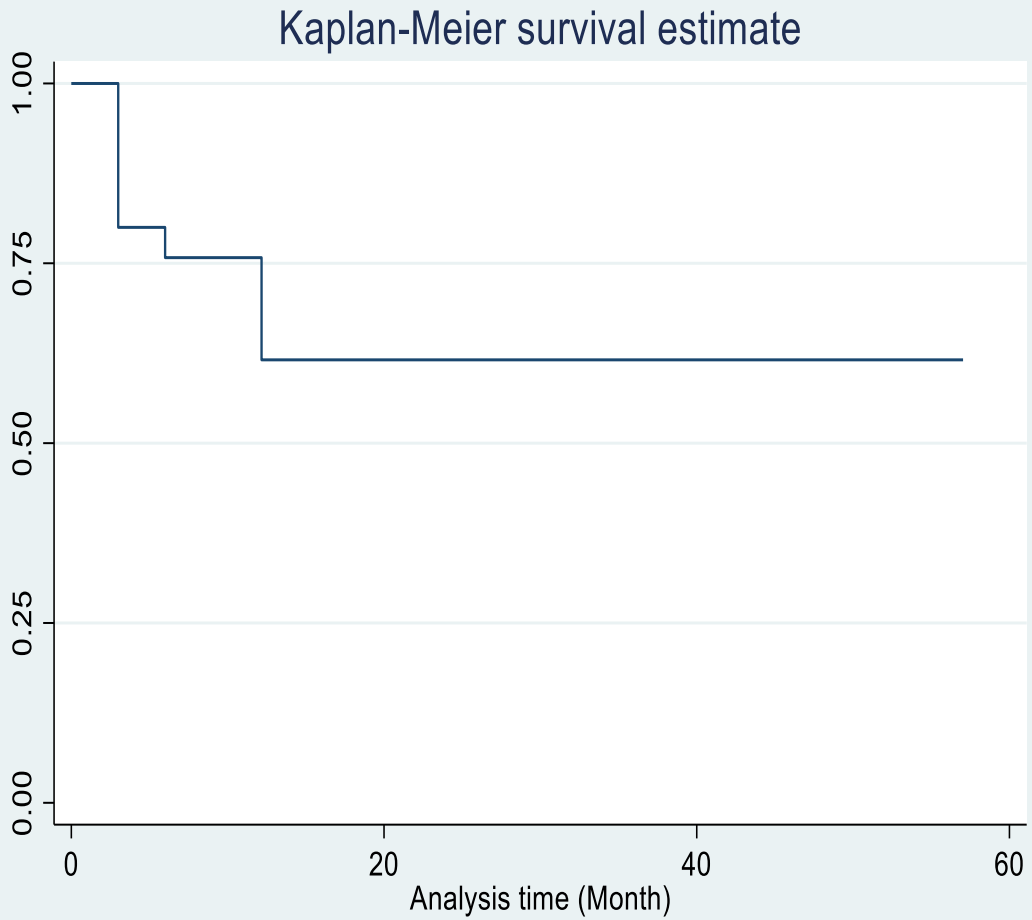
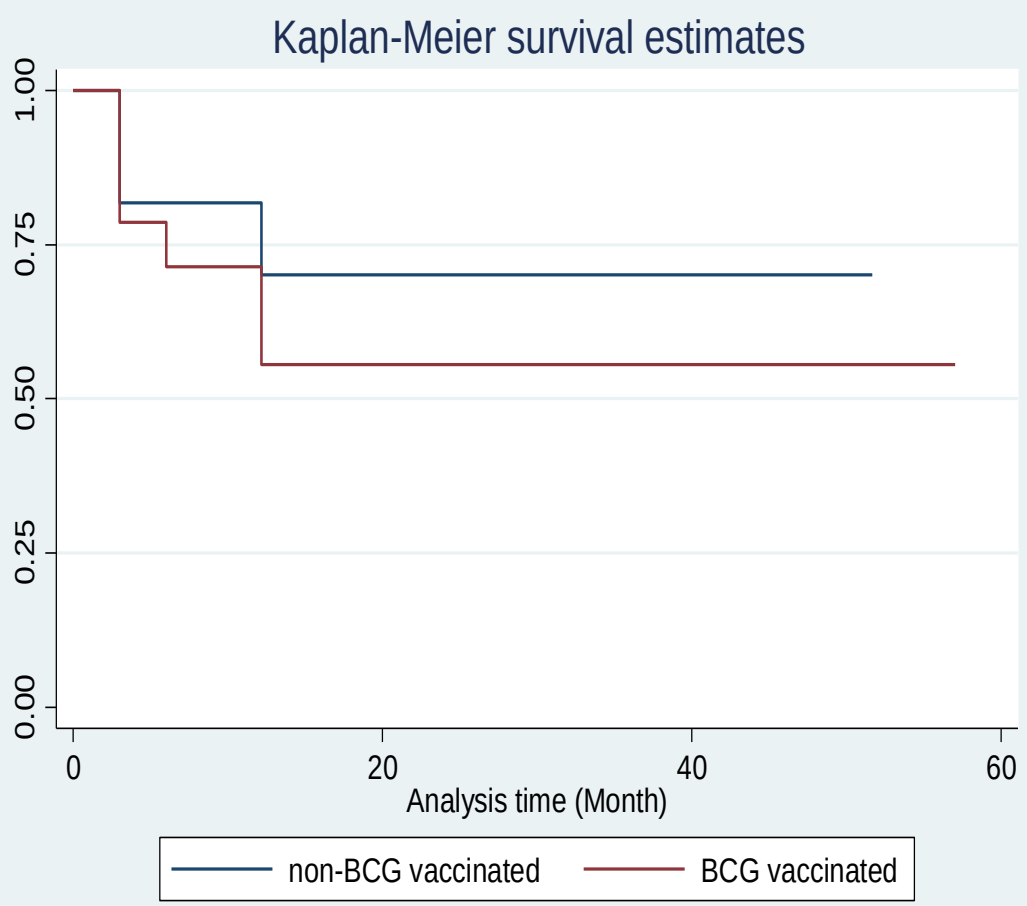
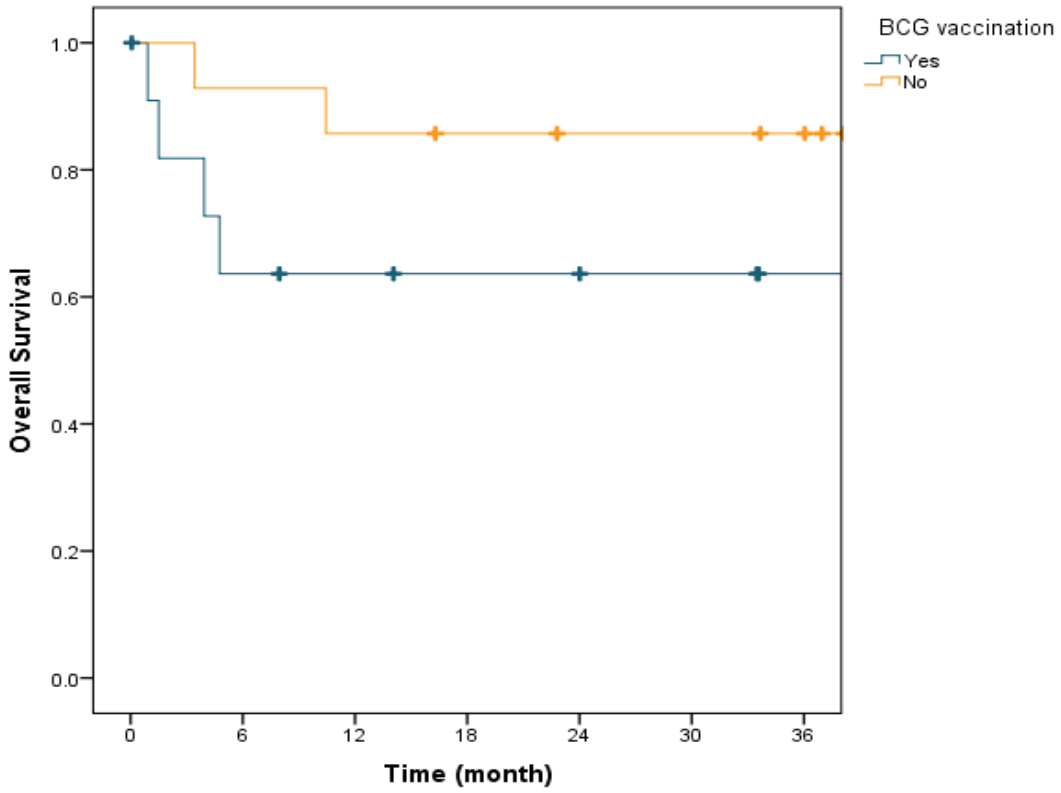




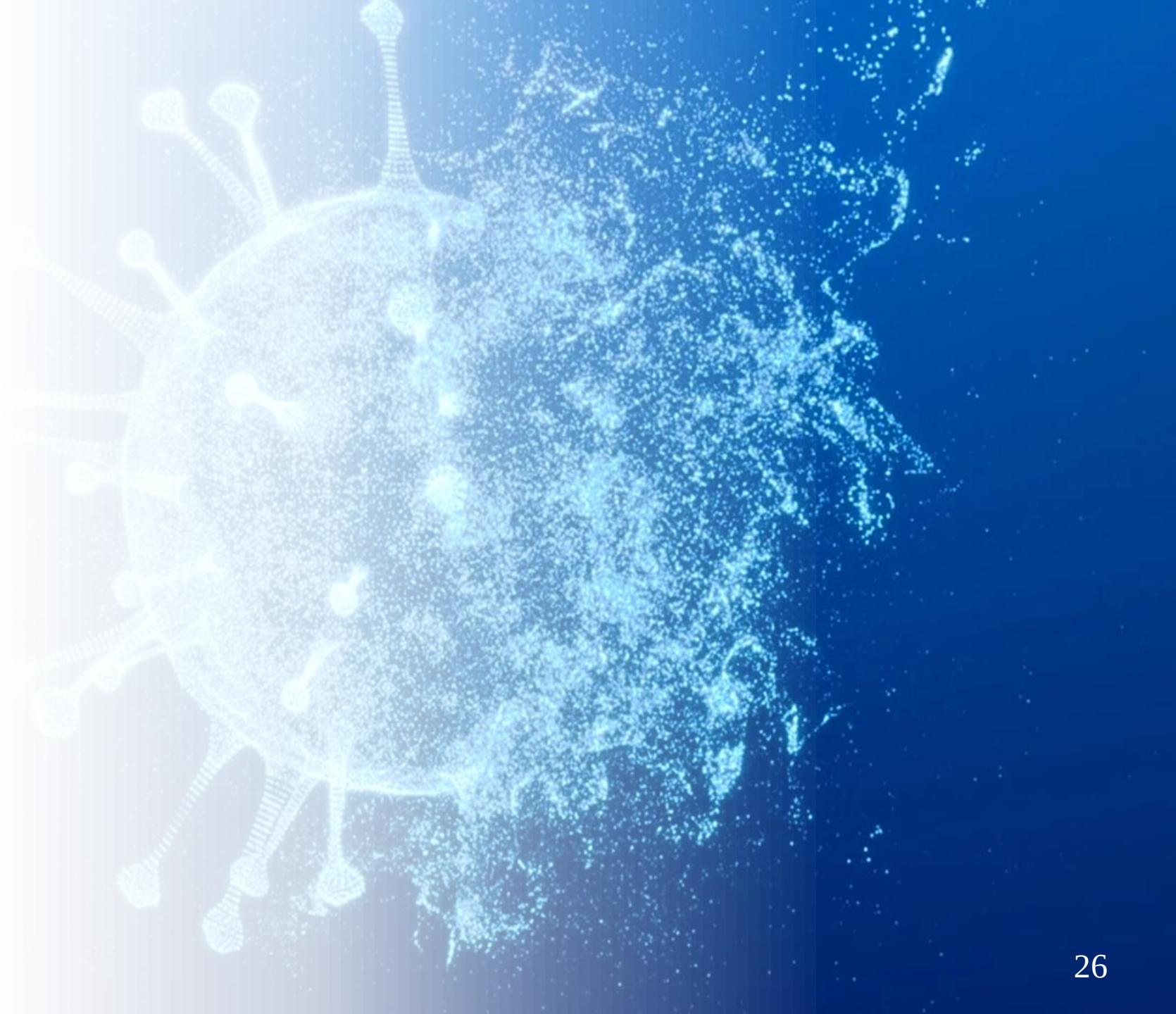
deferred until age 3 months so that APT testing without the interference of maternal antibodies can be performed. However, this study could benefit from a larger cohort to further validate our findings, as the possible reason for some factors not being statistically significant was our small sample size.

Outcome of HSCT in CGD patients (under review)



- 26 pediatric patients
- RIC conditioning Regimen
- Engraftment, chimerism, acute and chronic GVHD were not different between vaccinated and non-vaccinated patients.

Conclusion



Conclusion

- Since 1960, PID-HSCT OS has been constantly increasing.
- The outcomes of challenging HSCT (HID-HSCT, CB-HSCT) are promising.
- The non-TBI preparative regimens seem to have better results.
- RIC preparative regimens result in comparable HSCT outcomes.
- The BCG vaccine challenges transplant outcomes.

Conclusion

- Future perspectives that contribute to improvement of HSCT results in PIDs:
  - Early molecular diagnosis to facilitate early decision of transplantation before development of co-morbidities
  - Tailoring conditioning regimen to reduce toxicity
  - Improving GVHD prophylaxis

- Patients with PIDs present specific challenges when considering HSCT. The best results are obtained when there is close **cooperation between the immunologist and the stem cell transplant specialist**.

https://www.frontiersin.org/articles/10.3389/fped.2019.00552/full

Thank You

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