Hematopoietic Cell Transplantation for Inborn Errors of Immunity: Sharing experiences from different world regions

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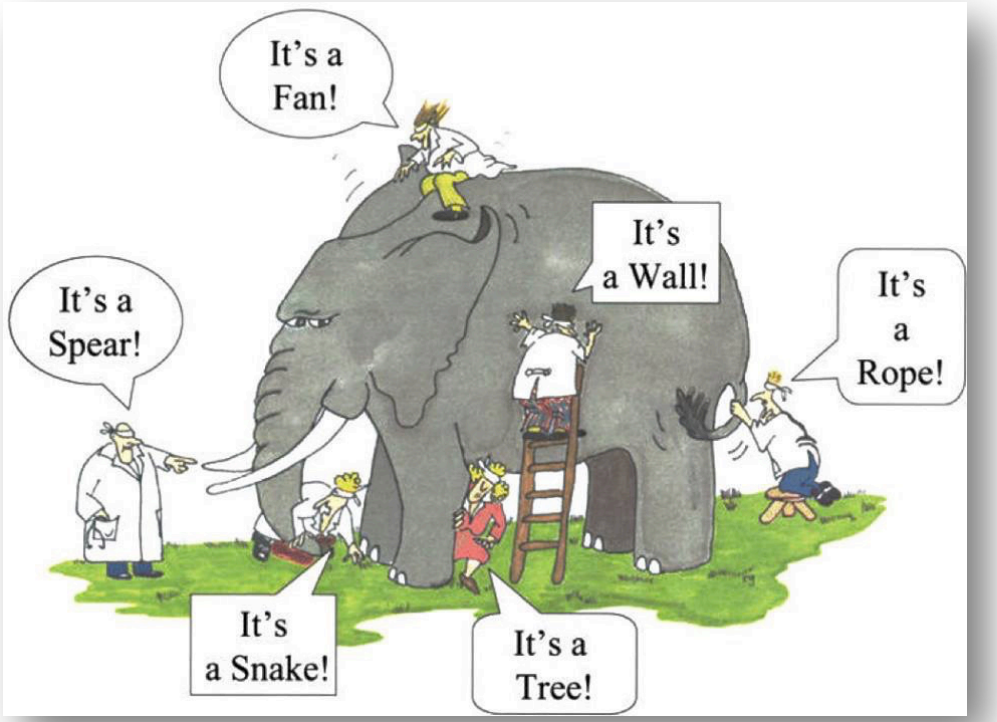
Introduction

- Inborn errors of immunity (IEI) are rare inherited disorders affecting immune function and can be life-threatening if not treated.
- More than 400 monogenetic IEI have been identified and a genetic diagnosis can be made in an increasing number of patients.
- Various combinations of recurrent infections, autoimmunity, lymphoproliferation, inflammatory manifestations, atopy, and malignancy.
- Most IEI are due to genetic defects that are intrinsic to HSC and treatment by HSCT can be offered with success to many patients.

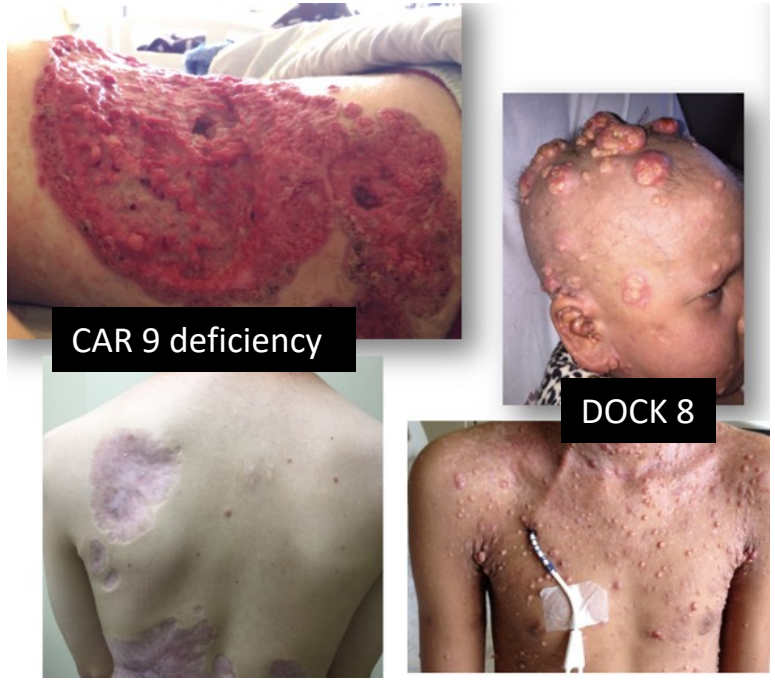


MULTIDISCIPLINARY TEAM

Castagnoli et al 2019; Lankester et al 2021

Hematopoietic Cell Transplantation for IEI

HSCT curative	HSCT partially curative	HSCT controversial
SCID; WAS; CGD	CHH	CVID
DOCK8, CD40L	STAT1-GOF; STAT3-GOF	IKBA def
HLH, Griscelli	IL-10 def	NEMO def
CTLA4; LRBA, IPEX	P13K def	
GATA2 def	CD25 def	
LAD, reticular dysgenesis	Chediak-Higashi	
Kostmann	DNA repair disorders	
XLP, XIAP, MHC class II def		*Castagnoli et al 2019*



- Increasing complexity of these diseases
  - ⇢ Challenge to decide which disease, who and when to transplant.
- Early diagnosis and improved supportive care
  - ⇢ Increase survival rates and improve quality of life.

HSCT for IEI : not just for children

- Early HSCT outcomes in adults were poor, resulting in extremely limited use worldwide.
- Recently published HSCT outcomes for adults with IEIs have been comparable with pediatric data, making HSCT an important option for correction of clinically severe IEIs in adulthood.

Appropriate indication for allo-HSCT	Specific indication for allo-HSCT?	Biopsy proven, severe, refractory colitis (consistent with CGD histology and infectious causes excluded). No history of aspergillosis, abscesses or significant infection.
	Evidence for effectiveness of allo-HSCT?	Yes: Clear published evidence for the role of HSCT in X-CGD including cure of CGD-associated colitis. Case reports only of X-CGD carriers having undergone HSCT.
	Predicted poor prognosis with conservative management?	Unclear: Patient failed numerous disease modifying drugs. Gastroenterology team considering total colectomy and stoma – although disease not limited to large bowel.

Allo-HSCT planning	Appropriate donor identified?	No siblings. But likely good MUD. 5 potential 10/10 matched unrelated donors identified.
	Fit for transplant?	Probably: Normal pulmonary function and HRCT; Malnourished with BMI <18; incidental hydronephrosis on CT scan under investigation (EDTA-GFR normal); no active infection; HCT-CI score <3.
	Management plan agreed at specialist MDT	Yes: Agreed to proceed to 10/10 MUD, CMV-matched if patient declines or fails surgical intervention. If proceeds to allo-HSCT conditioning with Flu/Bu (AUC 60-70) based regimen recommended.

Initial assessment of adult PID patient	Functional immune deficiency confirmed?	Yes: Manifesting female carrier of X-CGD with 7-9% neutrophils with normal oxidative burst and severe refractory colitis.[72]
	Natural history known?	Unclear: Few manifesting carriers described but can assume severe colitis will be chronic and likely difficult to treat based on male patients with X-CGD.
	Pathogenesis/Genetics understood?	Yes: Confirmed pathogenic mutation in *CYBB* with less than 10% normal neutrophil function.

Alternative therapy options	Conservative Therapy	No: Patient failed to respond to multiple other immunosuppressive agents including azathioprine and mycophenolate mofetil.
	Targeted drugs	Unclear: Patient failed to respond to biologics including Humira, Infliximab, Vedolizumab and Ustekinumab. Not yet had a trial of GCSF +/– IFNg (considered experimental).
	Gene Therapy	No: Gene therapy for X-CGD patients available as part of phase I/II clinical trial, but not currently recruiting carriers.

Siobhan Burns, Emma Morris; Blood nov 2021

EBMT/ESID inborn errors working party guidelines for HSCT for inborn errors of immunity

A. C. Lankester , M. H. Albert , C. Booth, A. R. Gennery, T. Güngor, M. Hönig , E. C. Morris, D. Moshous, B. Neven, A. Schulz , M. Slatter, P. Veys and on behalf of the Inborn Errors Working Party of the EBMT and the ESID, and European Reference Network on Rare Primary Immunodeficiency Autoinflammatory Autoimmune diseases (RITA)

- Wide clinical heterogeneity of patients.
- Outcome data are based on observational rather than prospective studies.

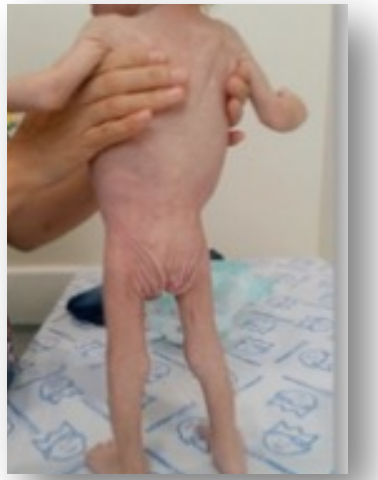
⇢ Not yet possible to recommend strictly defined protocols for transplanting IEI patients.

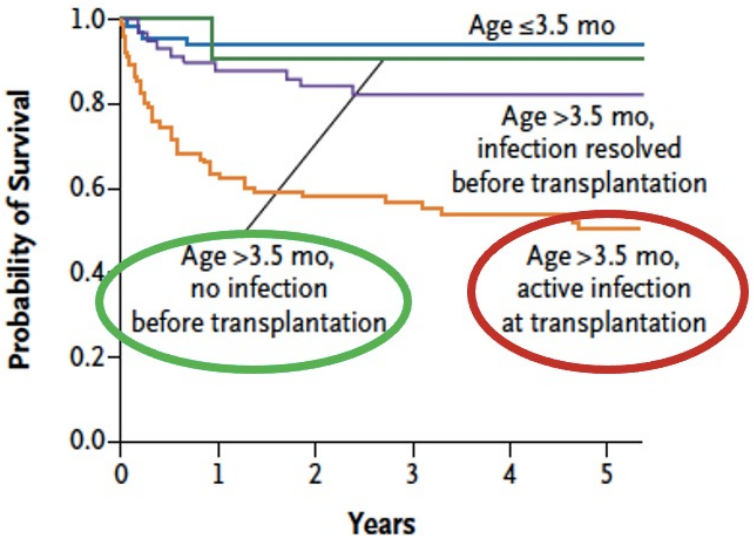
- Standardize pre transplant evaluation as well as supportive care, conditioning regimens, GvHD protocols and LTFU care.
- Retrospective and prospective studies with European and world-wide data.
- International collaborative studies: may help to adapt these protocols in developing countries.

Bone Marrow Transplantation (2021) 56:2052–2062

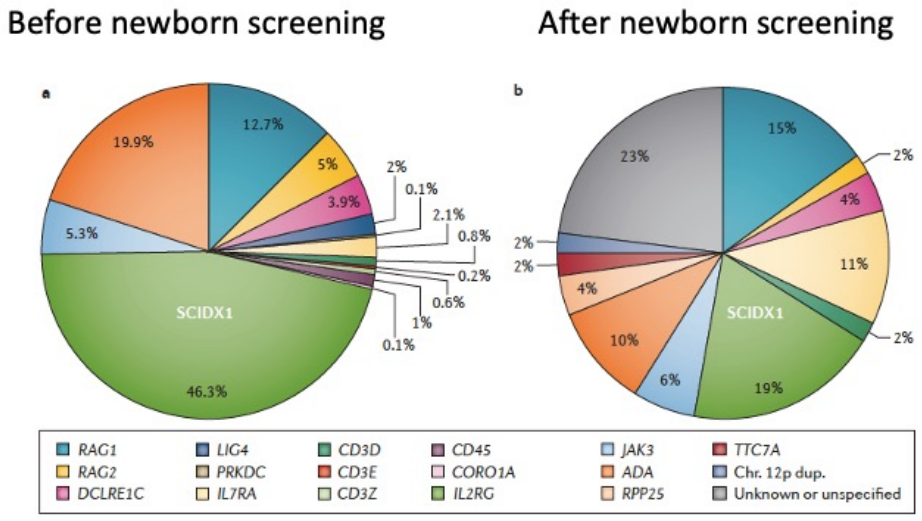
SCID is a pediatric emergency and HCT is the only curative treatment in most countries around the world

- Ideally, HCT should be performed before live vaccines (rotavirus, BCG), non-irradiated blood products are given and before the development of severe infections.
- Better outcomes after HCT: younger age, absence of active infections at the time of transplant and adequate immune recovery
- Newborn screening changed the outcome of SCID patients





Pai S.Y., et al. NEJM, 2014

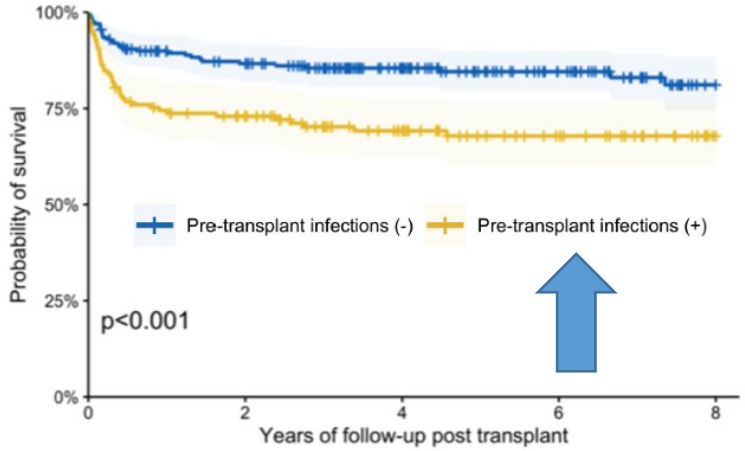


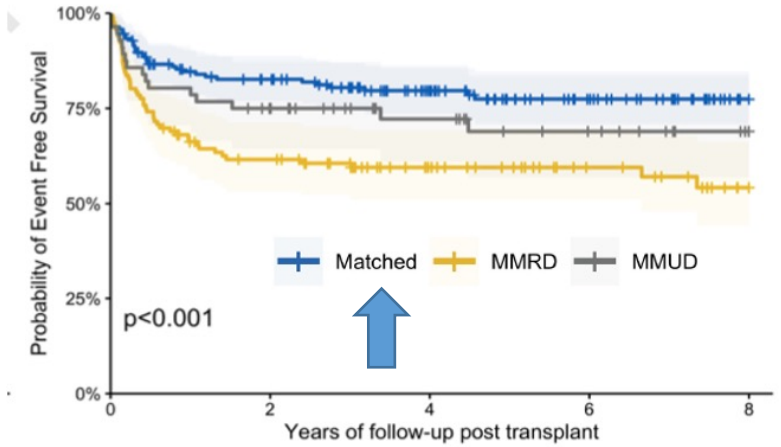
Fischer et al Nature Rev Disease Primers 2015

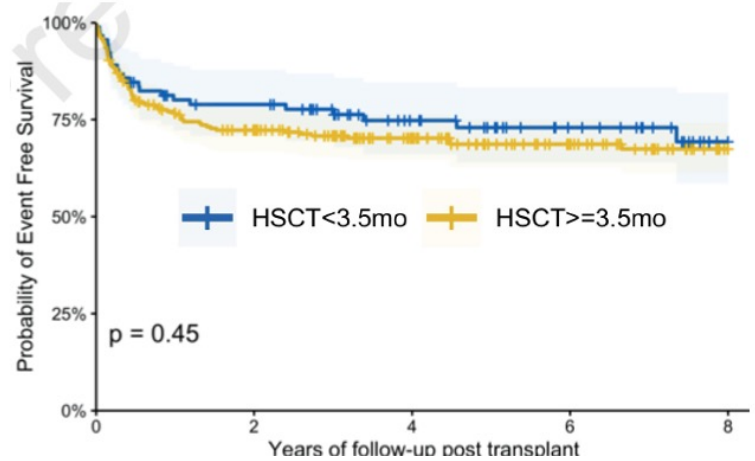
HSCT in SCID: the SCETIDE 2006-2014 European cohort

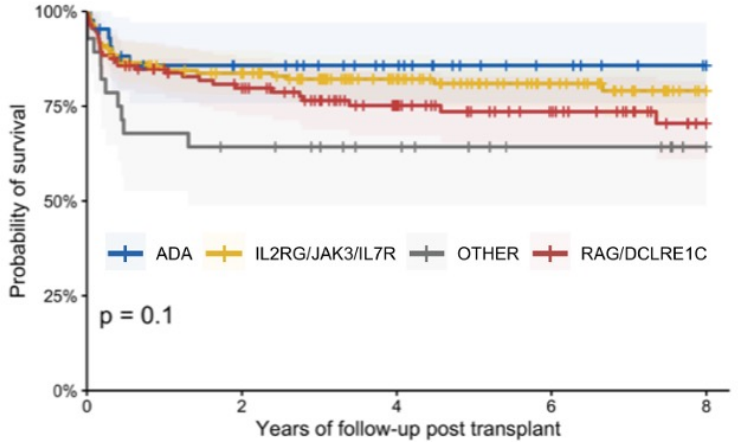
Lankester et al Journal of Allergy and Clinical Immunology 2021

- Period: 2006 – 2014
- Reported to the SCETIDE registry
- 43 HCT centers, 338 patients (80% of SCIDs reported in this same period)
- None diagnosed by newborn screening
- CD4 > 500/ul at 1-year: better outcome and IGG independency

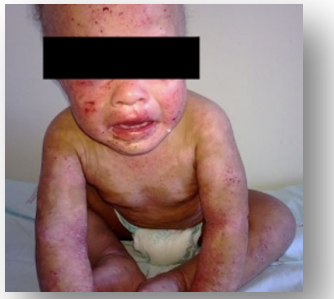








- All typical SCIDs (Omenn excluded, other SCIDs included if CD3 <300/ul and HCT below the age of 15 months



Wiskott Aldrich Syndrome

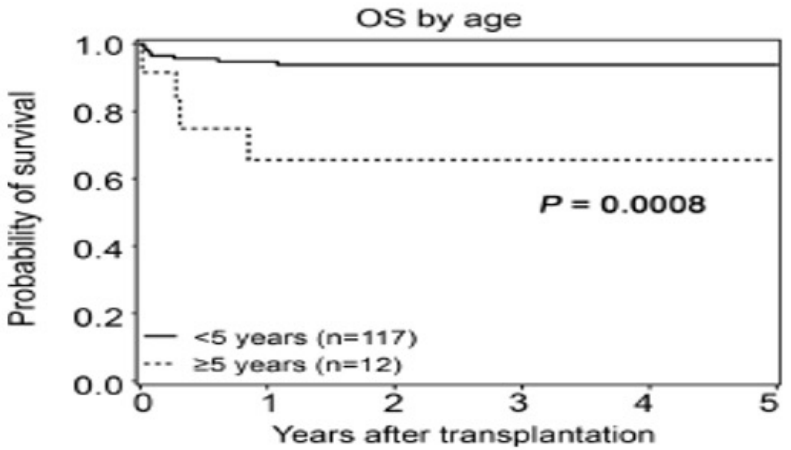
- WAS is an X-linked disease caused by mutations in the WAS gene, leading to thrombocytopenia, eczema, recurrent infections, autoimmune disease, and malignancy.
- Younger age and MAC regimens are associated with a better myeloid and lymphoid engraftment and excellent outcome .

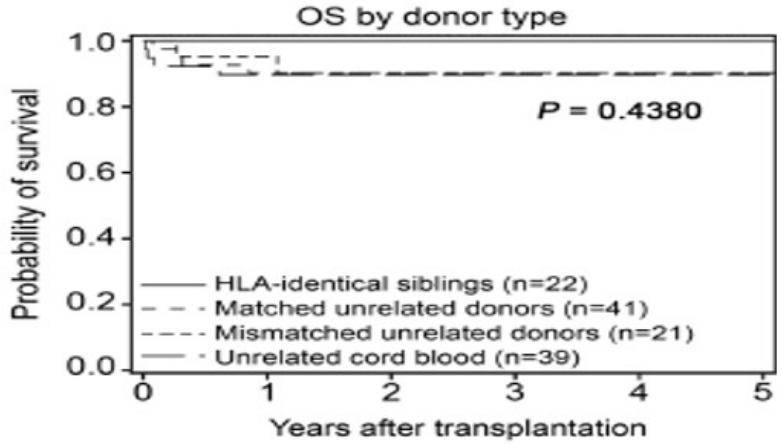
Table 1 Scoring System to Define Clinical Phenotypes Associated with Mutations in the *WAS* Gene

Clinical Phenotype	XLN	iXLT	XLT.		Classic WAS		
Score	**0**	**<1**	**1**	**2**	**3**	**4**	**5**
Clinical/laboratory findings							
Thrombocytopenia	–	–/+	+	+	+	+	+
Small platelets	–	+	+	+	+	+	+
Eczema	–	–	–	(+)	+	++	–/(+)/+/++
Immunodeficiency	–/(+)	–	–/(+)	(+)	+	+	(+)/+
Infections	–/(+)	–	–	(+)	+	+/++	–/(+)/+/++
Autoimmunity and/or malignancy	–	–	–	–	–	–	+
Congenital neutropenia	+	–	–	–	–	–	–
Myelodysplasia	–/+	–	–	–	–	–	–

Mallhi et al 2021; Albert et al 2011

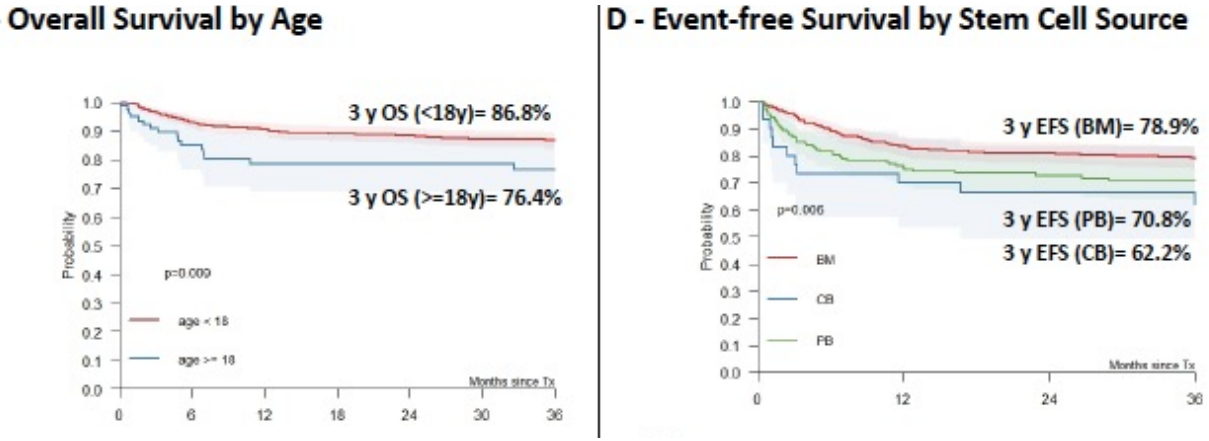
PIDTC – 129 patients





Burroughs et al 2020

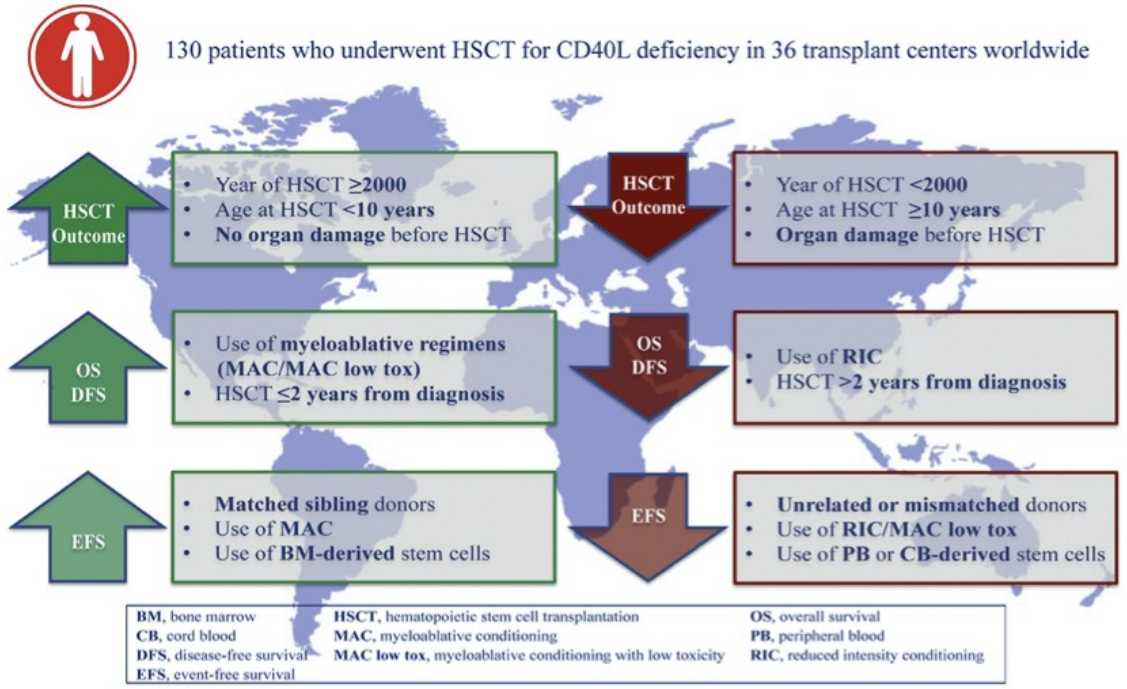
HSCT in Chronic Granulomatous Disease (CGD): a study of 712 children and adults IEWP - EBMT



- Excellent outcome after HCT in 712 pts with CGD, with a low incidence of graft failure and mortality.
- Older pts and recipients of 1-antigen-mismatched grafts had a less favorable outcome.
- HSCT for CGD should strongly be considered at a young age particularly in the presence of a well-matched donor

Chiesa et al Blood 2020

HSCT for CD40 ligand deficiency: Results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study

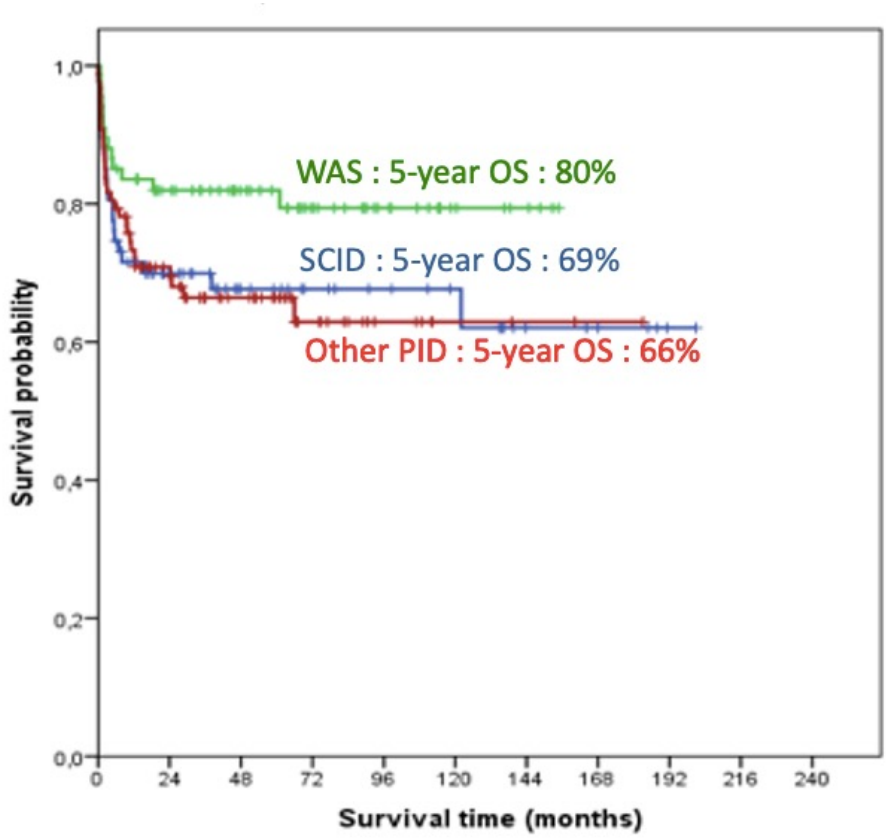


- Best outcome after HCT:
  - Pts < 10 years of age and without organ damage
  - Matched donors, MAC regimens and bone marrow as the stem cell source

Ferrua et al ; Journal Allergy Clin Immunol 2019

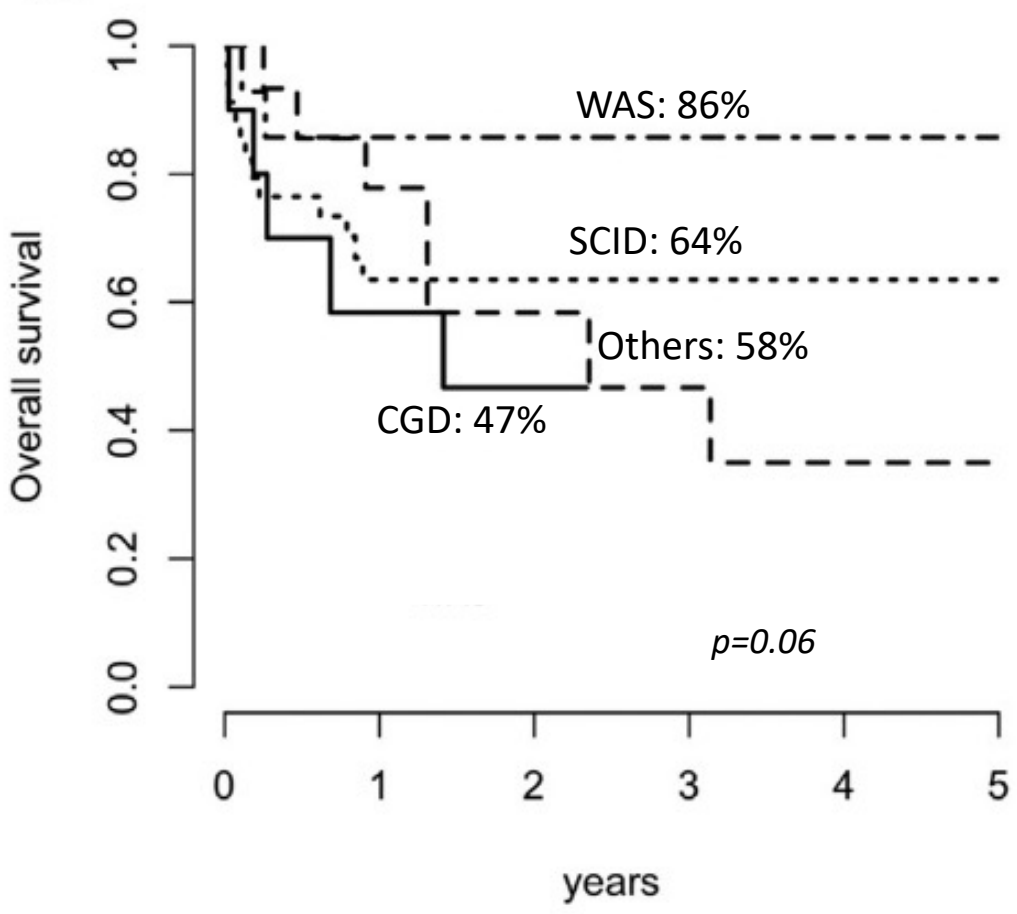
HSCT for Inborn Errors of Immunity in Brazil

- 1st report of HSCT for PID in Brazil showing the development and results in this field.
- Period: July 1990 to December 2015.
- Number: 221 pts transplanted in 11 BMT centers
- The median age at transplant was 22 months and the most frequent diagnosis were SCID (n = 67) and WAS (n= 67).
- Only 15 pts received unconditioned infusions.
- Most deaths (n=53) occurred in the first year after HSCT mainly due to infection (55%) and GVHD (13%).



Fernandes et al JoCI 2019

Outcomes after Haploidentical Cell Transplantation with PT-CY in Patients with PID in Brazil: 73 patients



- Median Follow-up : 24 months

- Multicenter, retrospective survey
- June 2012 - May 2019
- Median age – 1.6 years
- 55 first transplants and 18 salvage transplants
- 68% had active infections

Outcome	SCID Group (N = 34)	Non-SCID Group (N = 39)
Neutrophil recovery, n (%)	30 (88)	33 (84)
aGVHD grade II-IV, n (%)	10 (29)	14 (36)
Chronic GVHD, n (%)	2 (6)	8 (17)
CMV reactivation, n (%)	13 (39)	15 (36)
2-year OS, n (%)	22 (64)	26 (65)

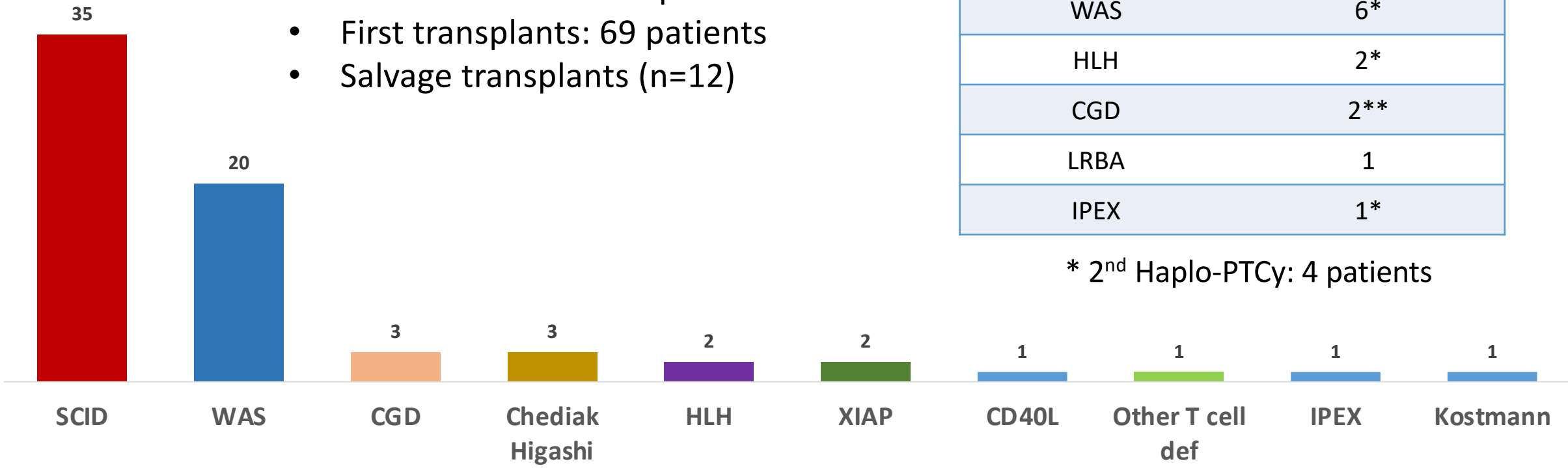
Fernandes et al, BBMT 2020

Haplo-PTCy for Inborn Errors of Immunity
Data from Curitiba: 81 transplants in 77 patients

- Period: Jan 2015 – Sept 2021
- First transplants: 69 patients
- Salvage transplants (n=12)

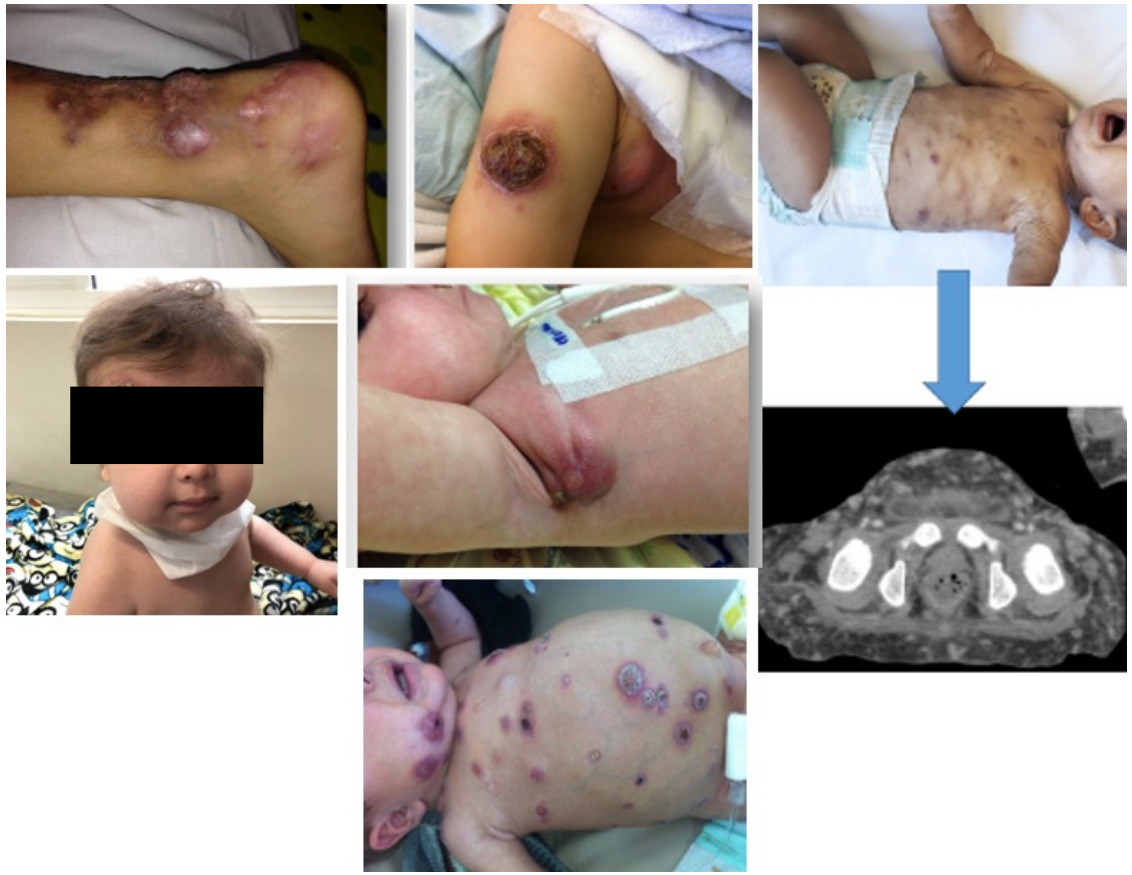
Salvage procedures	No of HCT n=12
WAS	6*
HLH	2*
CGD	2**
LRBA	1
IPEX	1*

* 2nd Haplo-PTCy: 4 patients

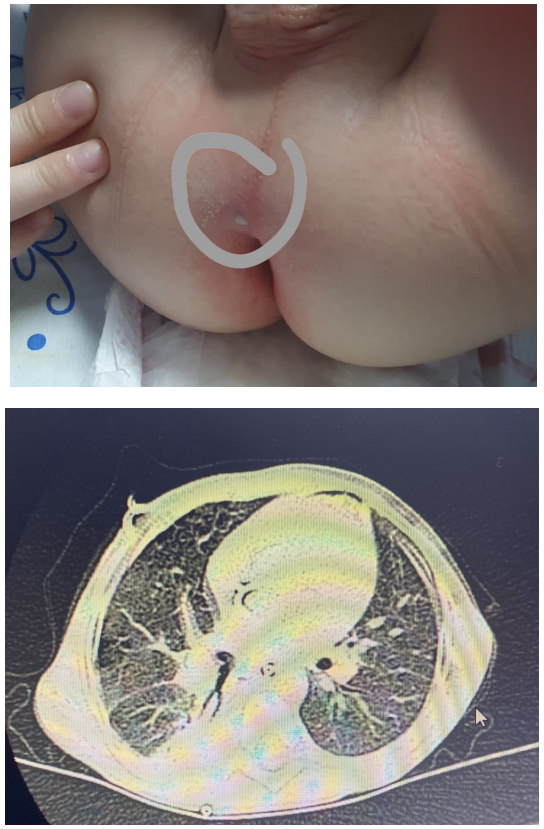


Data from Curitiba 2021– not published

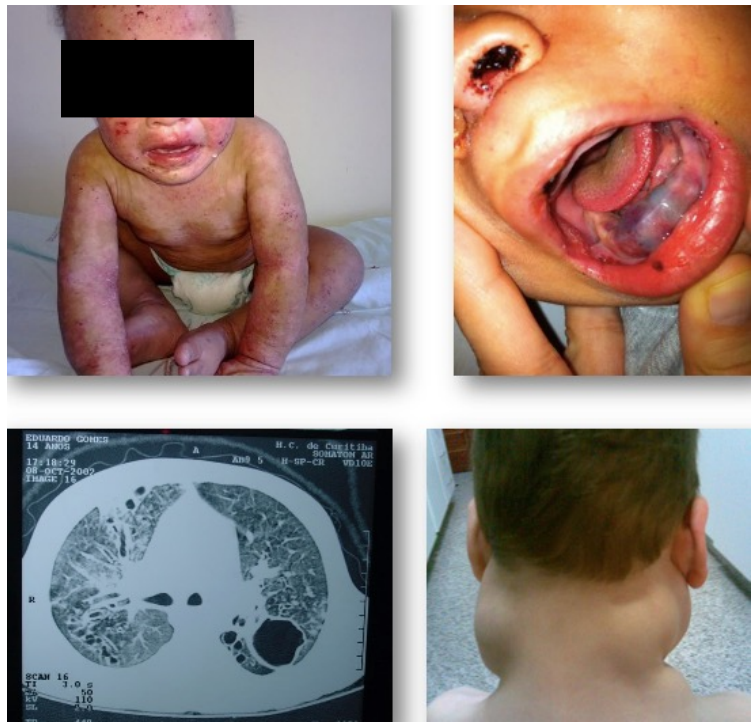
SCID and non-SCID patients: Role of pre transplant infections, nutrition and other co morbidities



SCID and BCGitis

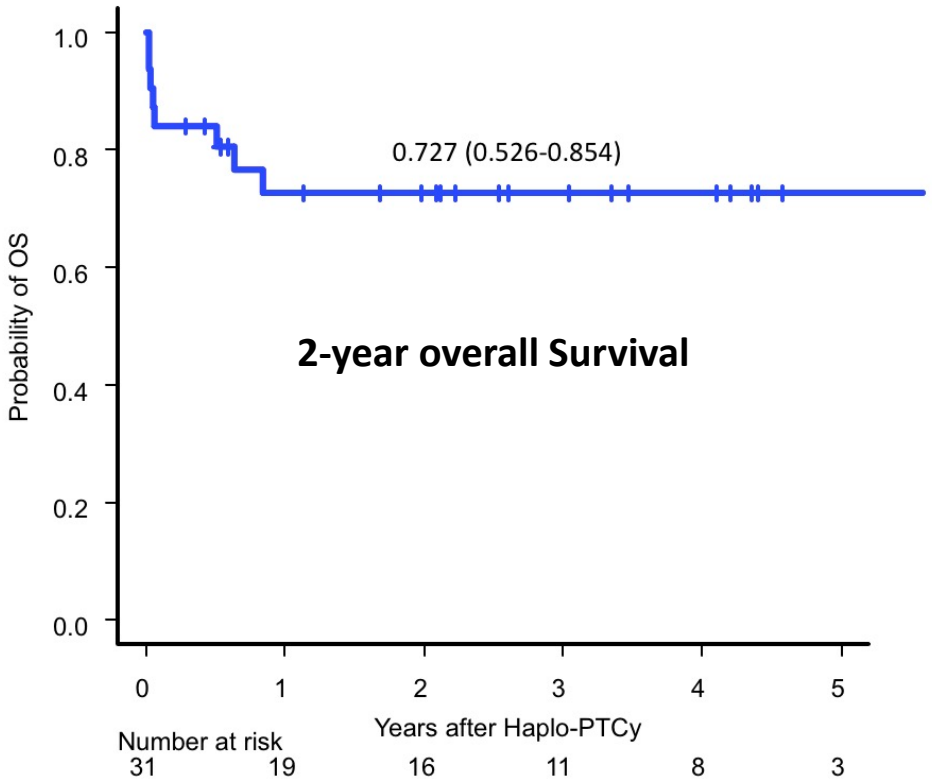


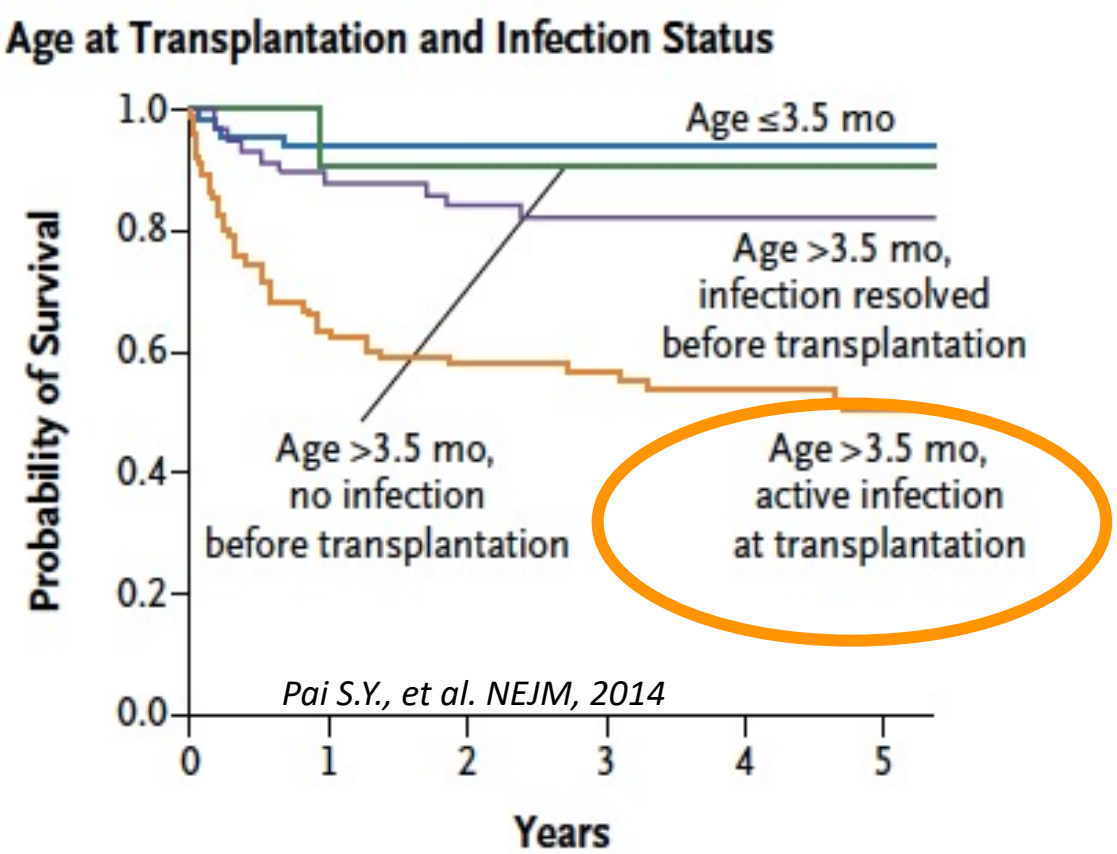
CGD : GI fistulae and fungal disease



WAS: viral complications and bleeding

Overall Survival after Haplo-PTCY for SCID : Curitiba data





- Eight pts died at a median of 19 days after HCT (range 8-308), with 5 very-early deaths (median survival of 11 days), four due to bacterial infection and one due to SOS.

Data from Curitiba 2021– updated from 2020 publication

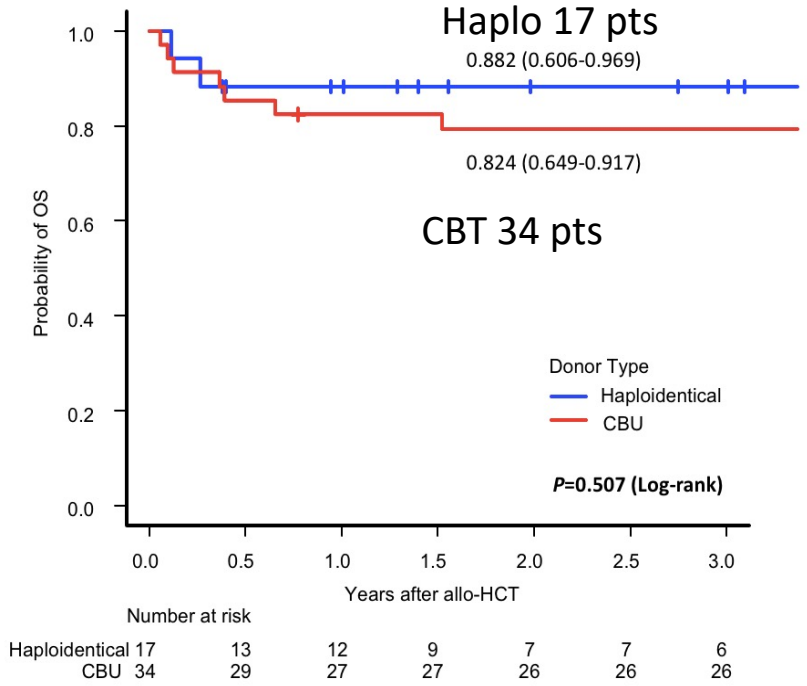
The "excellent group" : Wiskott Aldrich Syndrome 26 transplants in 25 patients (Haplo-PTCY)

- Period: June 2013 – August 2021
- Median age: 2.7 years (range; 9 m – 12,8 years)
- All received BM and the father was the most frequent donor
  - ✓ Upfront: 20 patients (21 transplants)
  - ✓ Rescued after primary or secondary GF: 5 patients

Upfront transplants: 20 patients

- First 3 pts received a RIC regimen (Johns Hopkins protocol)
  - 2pts died: Aspergillosis(n=1); Secondary GF/CMV(n=1)
  - One alive after 2nd Haplo PTCY transplant (secondary GF)
- **The next 17 pts: MAC regimen with BU/FLU/ATG.**
  - All alive and well (3 pts with < 6m FU)
  - 1 patient: Mixed chimerism + refractory AIHA and ITP, successfully treated with a 2nd URD MMUD BMT

Upfront transplants



Data from Curitiba 2021– updated from the 2020 publication – not published

Outcomes of HLA-mismatched HSCT in patients with IEI following *in vitro* T-cell depletion with CD3+TCRαβ/CD19 depleted PBSC or *in vivo* T-cell depleted HSCT with post-transplant cyclophosphamide – EBMT/ESID IEWP

- **Study design:** *Retrospective study*
- **Study period: Jan 2010 – Dec 2018**

Inclusion criteria:

1. IEI or autoimmune or autoinflammatory disorders
2. 1st HCT with either **TCRαβ/CD19 depletion** or **PTCY**
3. Mismatched donors: haplo or or ≤9/10 mismatched donor

	Entire cohort n=363 n (%)	TCR a/b n =227 (62.5%) n (%)	PTCy n=136 (37.5%) n (%)	*p*-value
Sex				
Male	250 (68.9)	157 (69.2)	93 (68.4)	0.069
Female	113 (31.1)	70 (30.8)	43 (31.6)	
Diagnosis				
SCID	101 (27.8)	59 (26.0)	42 (30.9)	**0.007**
non-SCID	228 (62.8)	154 (67.8)	74 (54.4)	
HLH	34 (9.4)	14 (6.2)	20 (14.7)	
Age at HSCT (years)				
Median (range)	1.6 (0.1 -19.6)	1.8 (0.1-18.0)	1.5 (0.2-19.6)	0.398
Infection	248 (74.3)	144 (68.2)	104 (84.6)	**0.002**
Organ damage	134 (39.2)	67 (30.0)	67 (56.3)	**< 0.001**

Primary outcomes:

- OS and EFS (death, graft failure and GVHD)

Secondary outcomes:

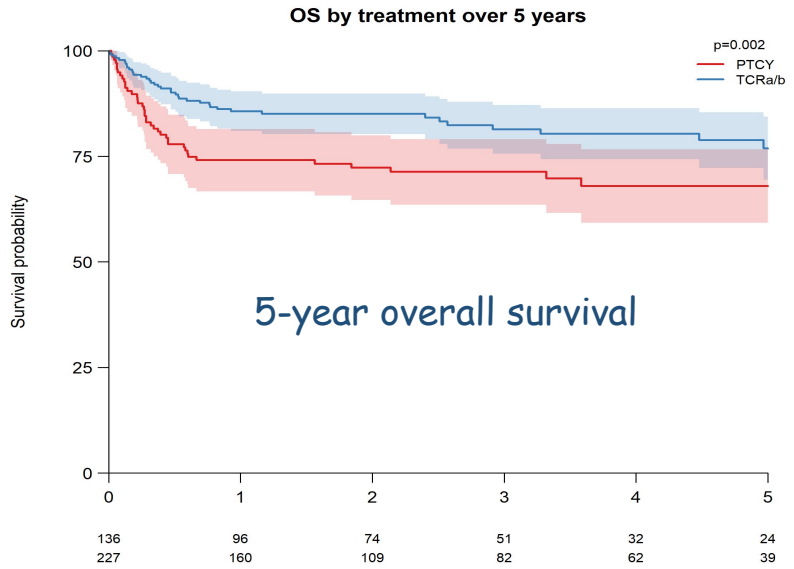
- Early toxicities, immune recovery, infections, chimerism, post-transplant auto-immunity and freedom from IVIG replacement

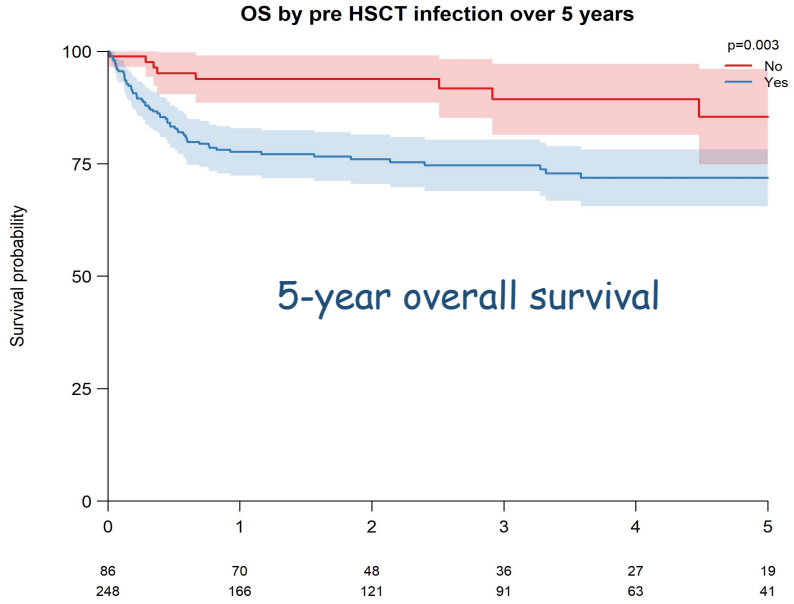
Courtesy Mary Slatter , data not published

Preliminary results

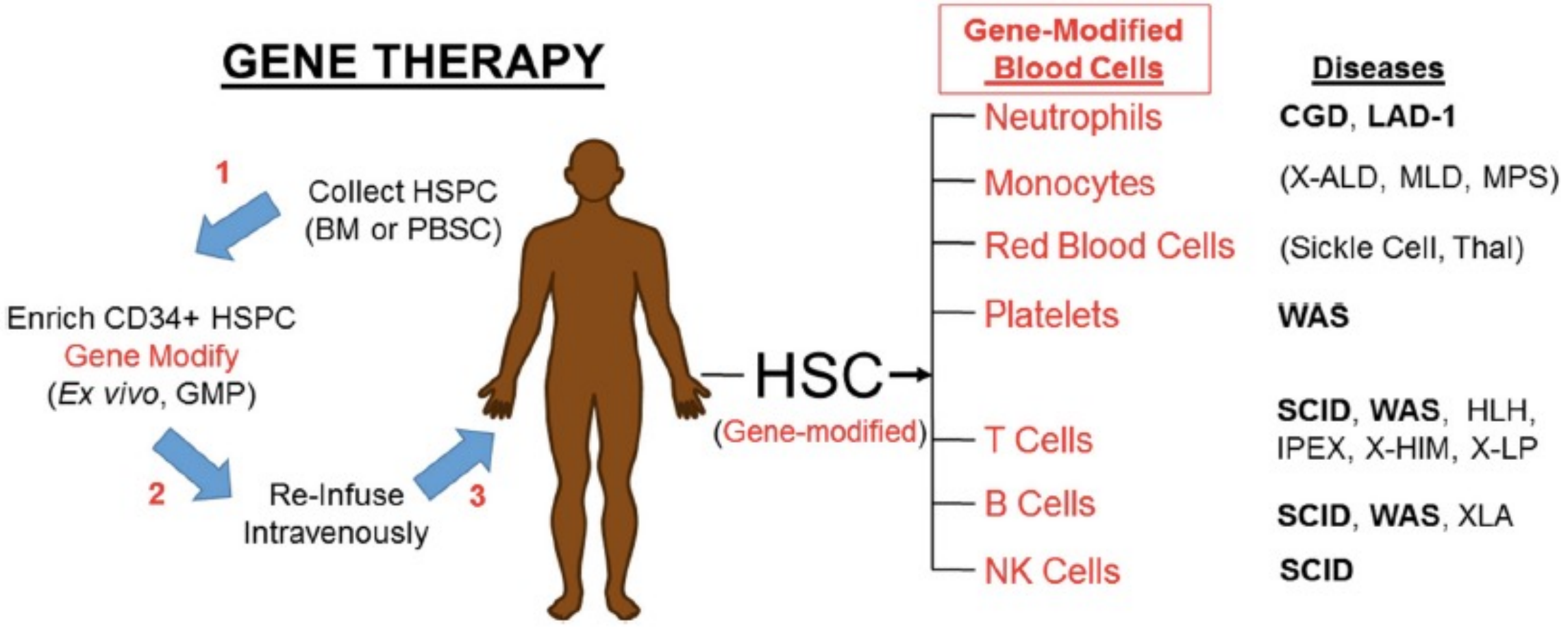
- In vitro T-cell depletion with CD3+ TCRαβ/CD19+ depletion and in vivo T-depleted HSCT with PTCY have proven efficacy in patients with IEI
- Numbers of transplants using these methods are rapidly increasing
- Early results suggest that 5 year OS using CD3+ TCRαβ/CD19+ depletion is superior to the use of PTCY, but differences in patient characteristics may account for this
- Further work to be done on differences between the groups, immune reconstitution and chimerism

Courtesy Mary Slatter , data not published





Gene therapy: The future is here, but how many will benefit?



Lisa A. Kohn and Donald B. Kohn 2021

Summary and Conclusions

- HSCT can cure many IEI, and results have improved in the past decades:
  - ⇢ Early diagnosis, time to transplant, supportive care and recent transplant approaches
- **Rare diseases:** International collaboration is the best way to move the field forward
  - For newly described IEI, decisions regarding the time to transplant must carefully consider the risks of HCT against other treatments.
- In countries with restricted resources, patients are still referred with severe infections and multiple comorbidities. The use of haploidentical donors using PTCY allows immediate treatment, and there is no need for graft manipulation.
- Newborn screening programs may allow these children to be diagnosed with better clinical conditions and have superior outcomes (law approved in Brazil).
- Strongly recommended to register your patients (national and international registries), and collect regional data.

HOSPITAL DE CLÍNICAS
UNIVERSIDADE FEDERAL DO PARANÁ

Muito obrigada!!!

transplante de medula óssea pequeno príncipe

Instituto Pasquini

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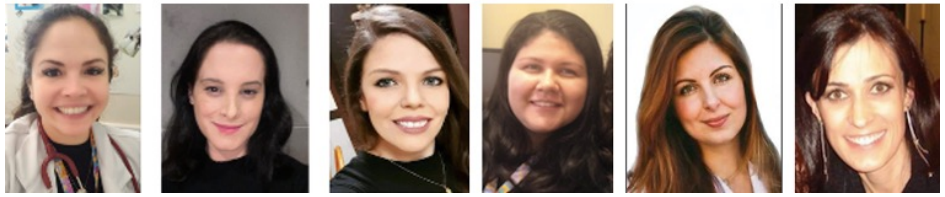
Thanks to Dr Ricardo Pasquini and the wonderful BMT teams from Hospital de Clínicas, Hospital Pequeno Príncipe, Hospital Nossa Senhora das Graças in Curitiba- Brazil
Thanks to families and patients



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