Hematopoietic Stem Cell Transplantation In Phagocytic Disorders

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Update on the Classifcation from the International Union of Immunological Societies Expert Committee (2022)

Congenital defects of phagocyte number or function(table 5)

- 1. Congenital Neutropenias
- 2. Defects of Motility (LAD1,…)
- 3.Defects of Respiratory Burst(CGD,…)

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Table 1. Indications for HSCT in PID, based on IUIS classification [1] and modification by Westhafen International BMT group [3] and British Society of Blood and Marrow Transplantation (www.bsbmt.org).

I. Combined Immunodeficiency (CID)	
SCID	ADA, reticular dysgenesis, RAG 1/2, DCLRE1C, Cernunnos, DNA Ligase 4, DNA PKcs, X-linked, Jak 3 kinase, IL7Rα, CD3γδε, CD45, Zap70 kinase, Coronin 1A
CID	CD40 ligand deficiency, CD4 lymphopaenia, MHC Class II, PNP, Omenn syndrome, Leaky SCID, MALT1, LCK, STK4, CTPS1
II. CID with associated features	
WAS, DiGeorge, CHARGE, Cartilage Hair Hypoplasia with CID, Nijmegen breakage syndrome*, DOCK 8, Tyk2, ICF, DKC, PI3Kδ activating mutant, LRBA, ORAI 1, STIM1	
III. Antibody Deficiencies	
CVID, *MDS with hypogammaglobulinaemia*	
IV. Immune Dysregulation	
Hemophagocytic disorders	Familial HLH with genetic diagnosis (PRF1, UNC13D, MUNC 18-2, STX11); HLH without genetic diagnosis but with recurrent/refractory disease, affected sibling, absent NK function, CNS disease; Griscelli syndrome type 2 (RAB27A); Chediak Higashi syndrome (LYST)
Lymphoproliferative disorders*	XLP1 (SH2D1A) and 2 (XIAP), Chronic active EBV (with or without lymphoma or HLH)*, ITK, CD27, MAGT1
Autoimmune	ALPS (homozygotes) STAT3 GOF, CTLA4, JIA, SLE, SS, Evans
Intractable Colitis	IPEX syndrome, IL-10, IL-10 receptor, immune deficiency with multiple intestinal atresias (TTC7a)
V. Phagocytic cell disorders	
Immunodeficiency with partial albinism, severe congenital neutropaenia, Schwachman-Diamond syndrome, LAD 1-3, X-linked CGD, AR CGD, GATA2	
VI. Innate Defects	
NEMO, STAT1, STAT5, IFN-γ receptor, IL-12 receptor	

- The decision about the indication and the correct timing of HSCT indication for a patient diagnosed with a PID(IEIs) :

it should be individualized and based not only on the specific PID, but also on each patient’s characteristics

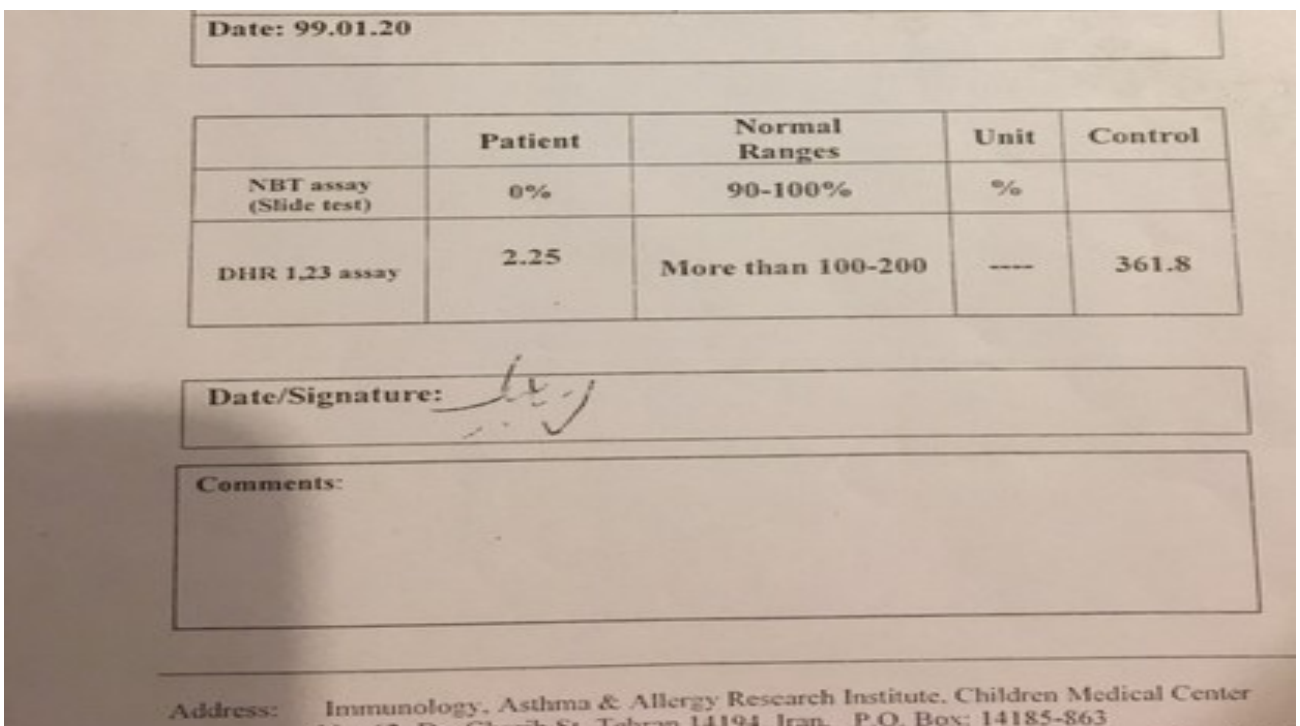
CGD

- CGD is a genetically heterogeneous disease, with an X-linked recessive (XL) form caused by hemizygous mutations of the *CYBB* gene encoding the gp91^{phox} protein, and an autosomal recessive (AR) form caused by biallelic mutations of the *CYBA*, *NCF1*, *NCF2*, *NCF4*, and *CYBC1* genes encoding p22^{phox}, p47^{phox}, p67^{phox}, p40^{phox}, and EROS, respectively

case

- A 20-months-old boy, was referred to our center for investigations regarding history of hospital admission for sepsis which was occurred approximately 1 years ago.
- Her height and weight were at the 25th-50th percentile and the 50th-75th percentile for her age respectively.
- Routine vaccination has been done without complications.
- He is the only child from non-consanguineous parents ,however his family history related to primary immunodeficiency is positive and his cousin has CGD

- He was diagnosed as CGD due to NBT and dihydrorhodamin test.



Date: 99.01.20

	Patient	Normal Ranges	Unit	Control
NBT assay (Slide test)	0%	90-100%	%	
DHR 1,23 assay	2.25	More than 100-200	----	361.8

Date/Signature:

Comments:

Address: Immunology, Asthma & Allergy Research Institute, Children Medical Center
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I A A R I

Date: **99.05.04**

Sample:

Blood ■ Muscle ☐ CVS ☐ Amniotic fluid ☐

Techniques are used in this investigation:

PCR ■ PCR-RFLP ☐ ARMS ☐ Southern Blot ☐

Western Blot ☐ Sequencing ■

Result:

Exon 9 of *CYBB* gene was investigated. The mutation NM_000397.3(*CYBB*):c.1016C>A (p.Pro339His) was found as hemizygous. This mutation has been previously reported in ClinVar as pathogenic.

- What is your decision about HSCT ?

Which patients with CGD should undergo transplantation?(past)

- Survival of stem cell transplantation for CGD has increased from approximately 85% to 90%.
- HSCT is generally considered for:
- X-CGD
- AR-CGD patients who have an HLA genoidentical donor and one or more of the following complications:
- non-availability of specialist medical care
- non-compliance with long term antimicrobial prophylaxis
- at least one life-threatening infection
- severe granulomatous disease with progressive organ dysfunction (e.g. lung restriction)
- steroid-dependent granulomatous disease (e.g. colitis)
- ongoing therapy-refractory infection (e.g. aspergillosis)

Which patients with CGD should undergo transplantation?

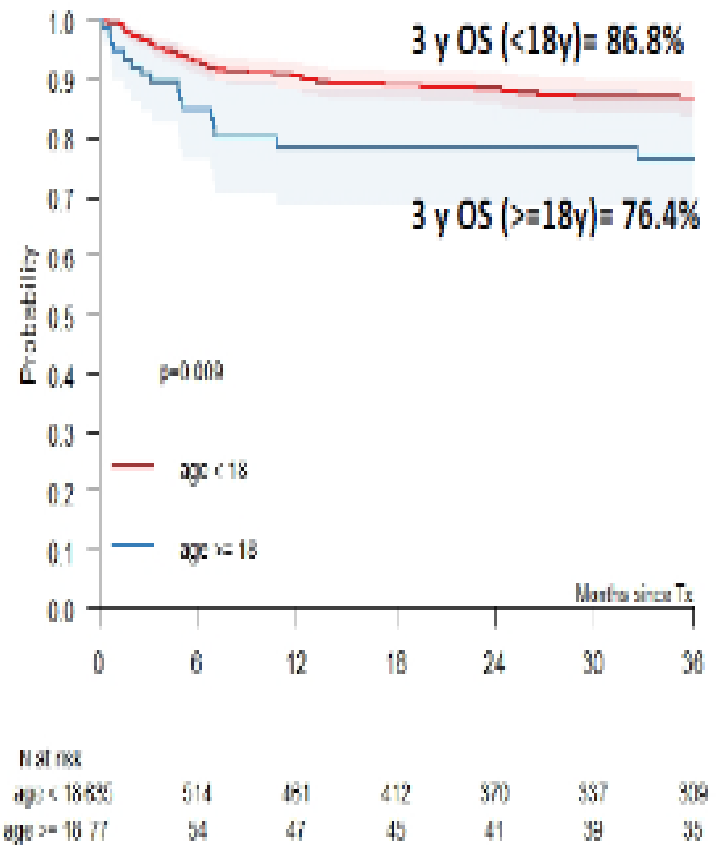
- Very low superoxide production(DHR↓↓↓)
- An increased alkaline phosphatase level
- A history of liver abscesses
- Decrease in platelet count reflecting portal hypertension
- Specific mutation ?

Chronic granulomatous disease: Overview and hematopoietic stem cell transplantation (J AllergyClin Immunol 2011;127:1319-26.)

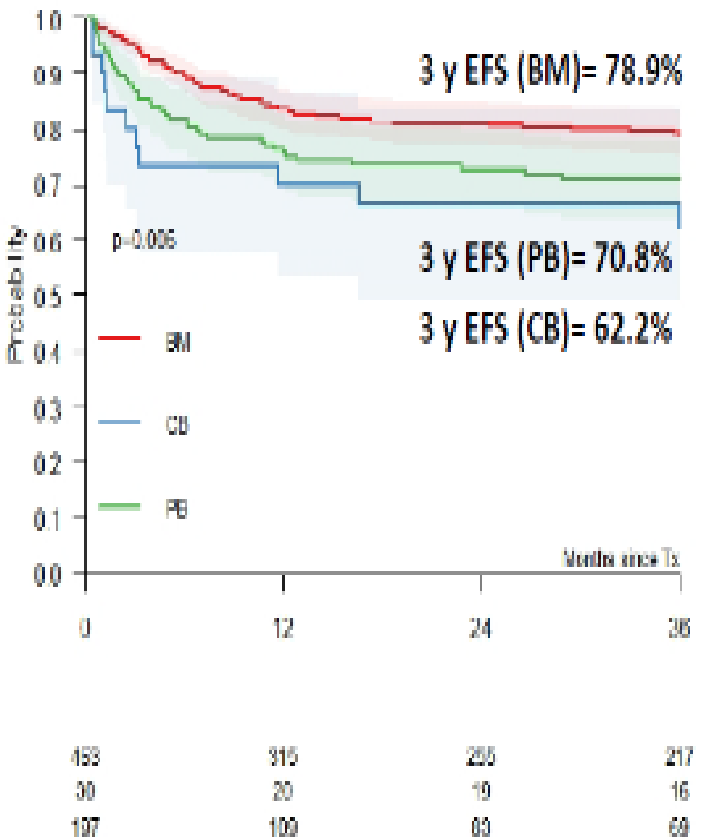
- Allogeneic HCT can be challenging in patients with CGD due to the presence of refractory fungal or other microbial infections or preexisting pulmonary, liver, or gastrointestinal disease, all of which are more common in patients with an older age at diagnosis or HCT.
- A large collaborative allogeneic HCT study of 712 patients observed three-year overall and event-free survival of 86 and 76 percent, respectively.
- Patients transplanted after age 18 years or with HLA-mismatched donors had inferior outcomes.
- Choice of conditioning regimen did not influence OS or EFS.

blood,2020 Sep 3;136(10):1201-1211. doi: 10.1182/blood.2020005

- Overall Survival by Age



D - Event-free Survival by Stem Cell Source



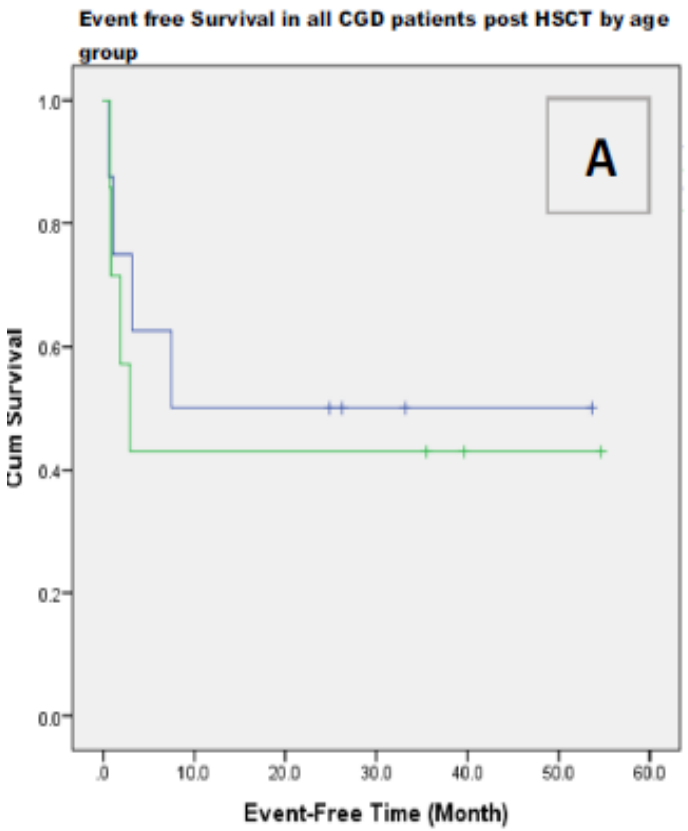
Blood. 2020 Sep 3;136(10):1201-1211.

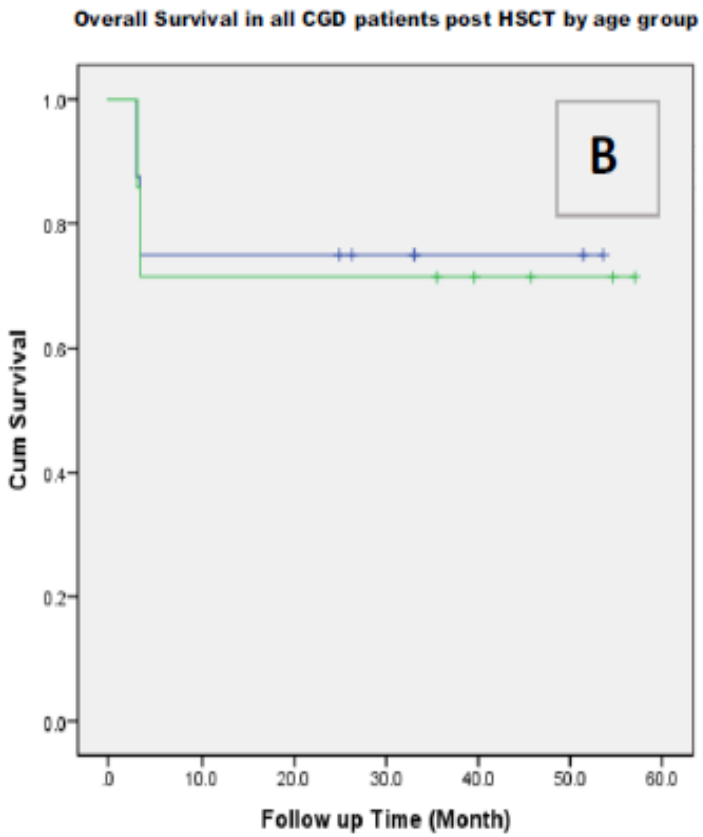
A fludarabine and melphalan reduced-intensity conditioning regimen for HSCT in fifteen chronic granulomatous disease patients and a literature review

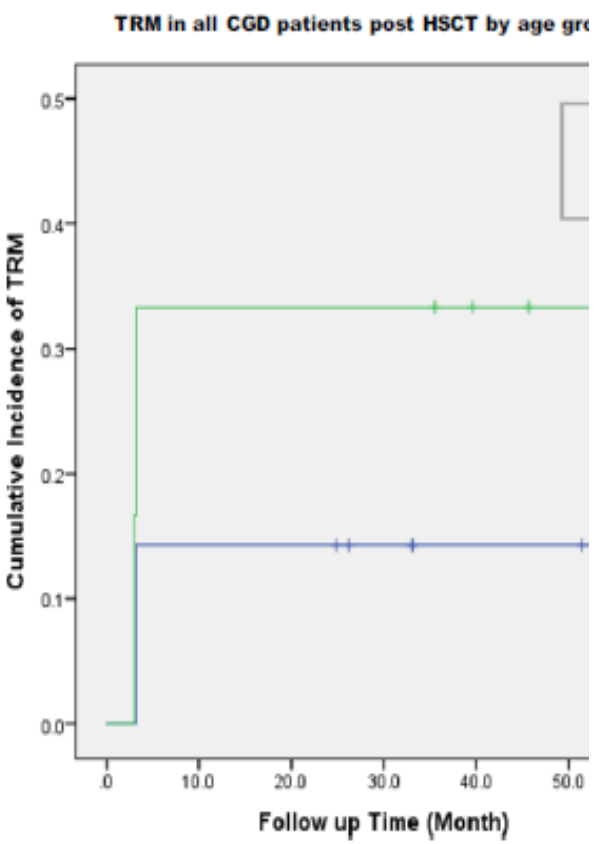
- We prospectively studied the outcomes of fifteen CGD patients undergoing HSCT with fludarabine and melphalan plus anti-thymocyte globulin (ATG).
- The three-year overall survival (OS) and event-free survival (EFS) rates were 73.3% and 46.7%, respectively.
- Three years GVHD-FS (free survival) was 57.8% in all patients and it was 70% and 42.9% in children and adults, respectively.

Vaezi, M., Souri, M., Setarehdan, S.A. Hamidieh A.A.
Fazlollahi et al. Ann Hematol **101**, 869–880 (2022)

Event-free survival (A), overall survival (B), and TRM (C) in adult and pediatric groups

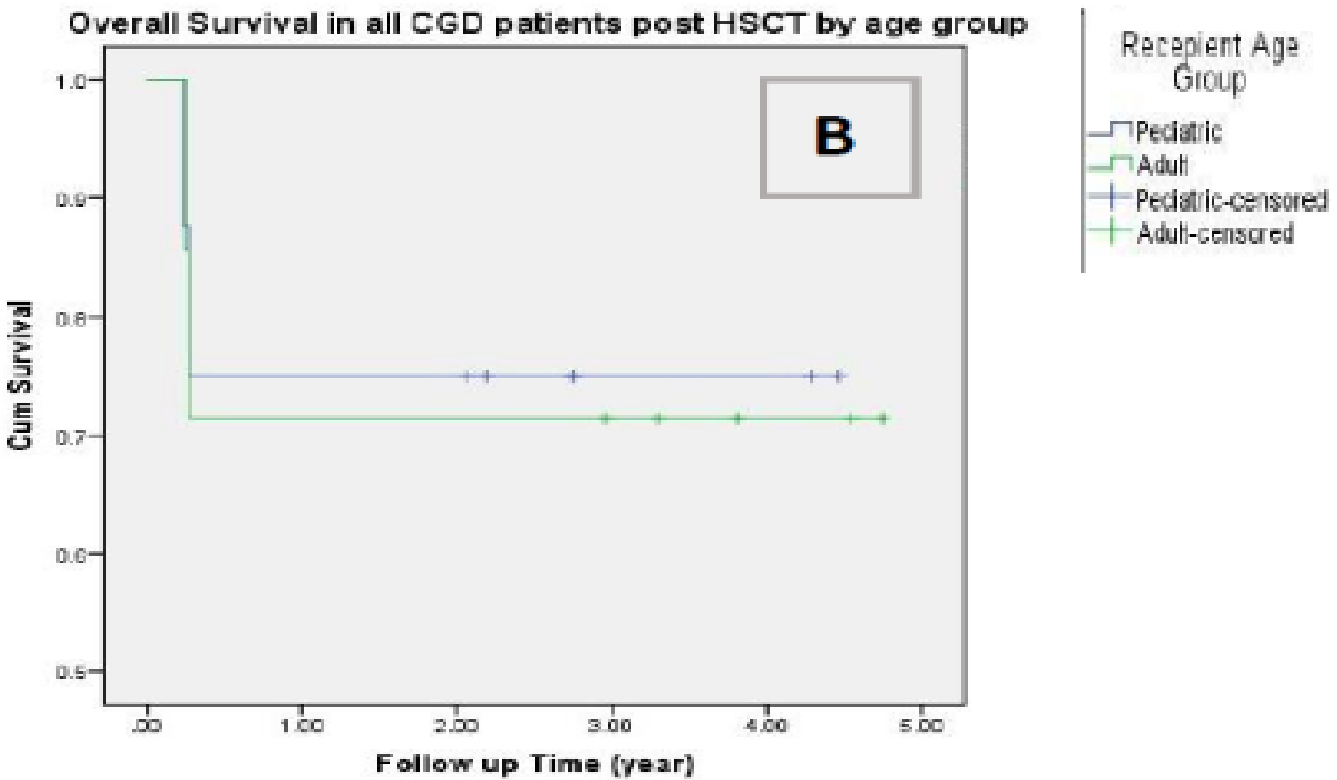


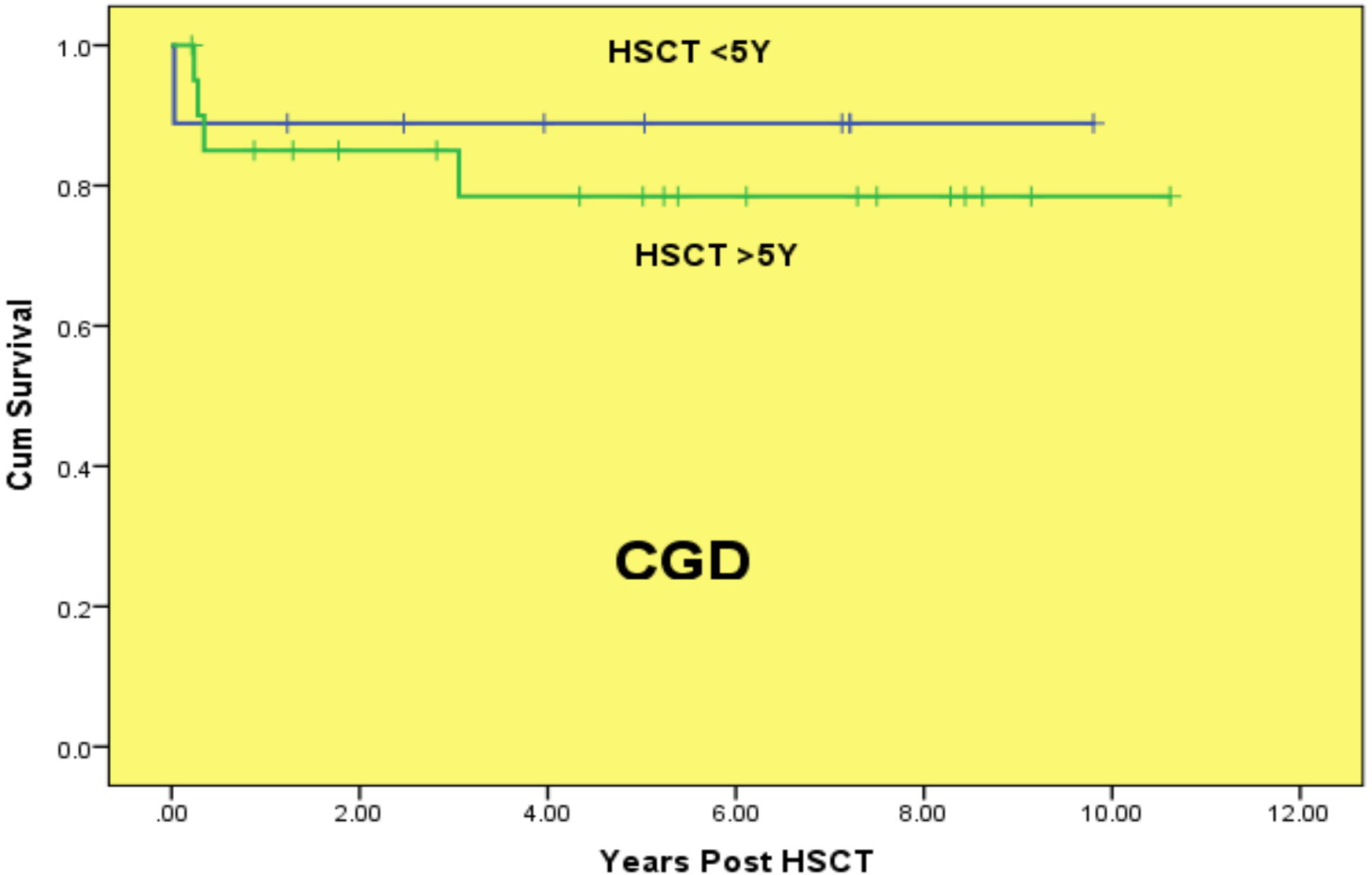




A prospective report of fludarabine and melphalan reduced-intensity conditioning regimen for HSCT in fifteen chronic granulomatous disease patients :

Overall Survival=73%




HSCT <5Y
HSCT >5Y
CGD
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
2.00
4.00
6.00
8.00
10.00
12.00
Years Post HSCT

Recent Update

- Survival following HSCT has increased from approximately 85% before 2000 to greater than 90% in recent reports. Children who undergo HSCT are also healthier with better QoL than those managed conservatively.
- As such, HSCT should be considered for all patients with CGD regardless of sex, genetic mutation, and clinical manifestations.
- It is preferable to perform HCT as early as possible

(https://doi.org/10.1007/s10875-019-00635-2)doi: 10.1007/s12325-017-0636-2

Severe congenital neutropenia

- More than 90% of congenital neutropenia(CN) patients respond to G-CSF with an increase in ANC > 1000, and require fewer antibiotics and reduced hospitalization
- All CN patients are at risk of developing myelodysplasia (MDS) or AML, but the risks of malignant transformation and septic death appear higher in less responsive patients.
- Some studies demonstrate elevated risk with mutations in the G-CSF receptor gene and a specific mutation in the ELANE gene. (Gly185Arg mutation)
- SCT from an HLA-identical donor is therefore beneficial for CN patients refractory to G-CSF. Outcome of transplantation after the development of frank leukemia in CN is poor.

Stem cell transplantation in severe congenital neutropenia

- HSCT is the only curative treatment of severe congenital neutropenia .
- Outcome of 136 SCN patients who underwent HSCT between 1990 and 2012 in European and Middle East centers.
- The 3-year overall survival (OS) was 82%, and transplant-related mortality (TRM) was 17%.

HSCT IN Severe congenital neutropenia(SCN)

- The absolute indications for HSCT in SCN are a failure to respond to G-CSF or the development of MDS/leukemia.
- High-risk patients that should strongly be considered for HCT include patients who require high doses of G-CSF (> 8 μg/kg/d) with poor response in neutrophil counts.

doi: 10.1097/MOH.0b013e32834da96e

Leukocyte adhesion deficiency (LAD)

- Complete absence of CD11/CD18 leads to a severe phenotype of LAD and often leading to death within the first 5 years of life
- Good results have been achieved with genotypically identical and related HLA-mismatched donors (70%).This is in contradiction to most other non-SCID patients in whom HLA-mismatched transplants tend to do less well.

- The severe forms of LAD are usually treated with allogeneic HCT.
- A variety of conditioning approaches have been used. Three-year survival among a large cohort of 84 patients with LAD type I and type III was 83 percent, and transplant before 13 months of age and receipt of a MSD graft were associated with superior outcomes

Clinical and immunological characteristics of 69 leukocyte adhesion deficiency-I patients

- Sixty-nine patients (40 females and 29 males) with LAD-I
- The diagnosis median age of the patients was 6 months.
- The median diagnostic delay time was 4 months (min–max: 0–82 months).
- Forty-six patients (66.7%) were categorized as severe (CD18 and/or CD11a: below 2%); while 23 children (33.3%) were in moderate category (CD18 and/or CD11a: 2%–30%).
- The overall survival of patients with(31 patients) and without hematopoietic stem cell transplantation was 79.3% and 55.6%, respectively

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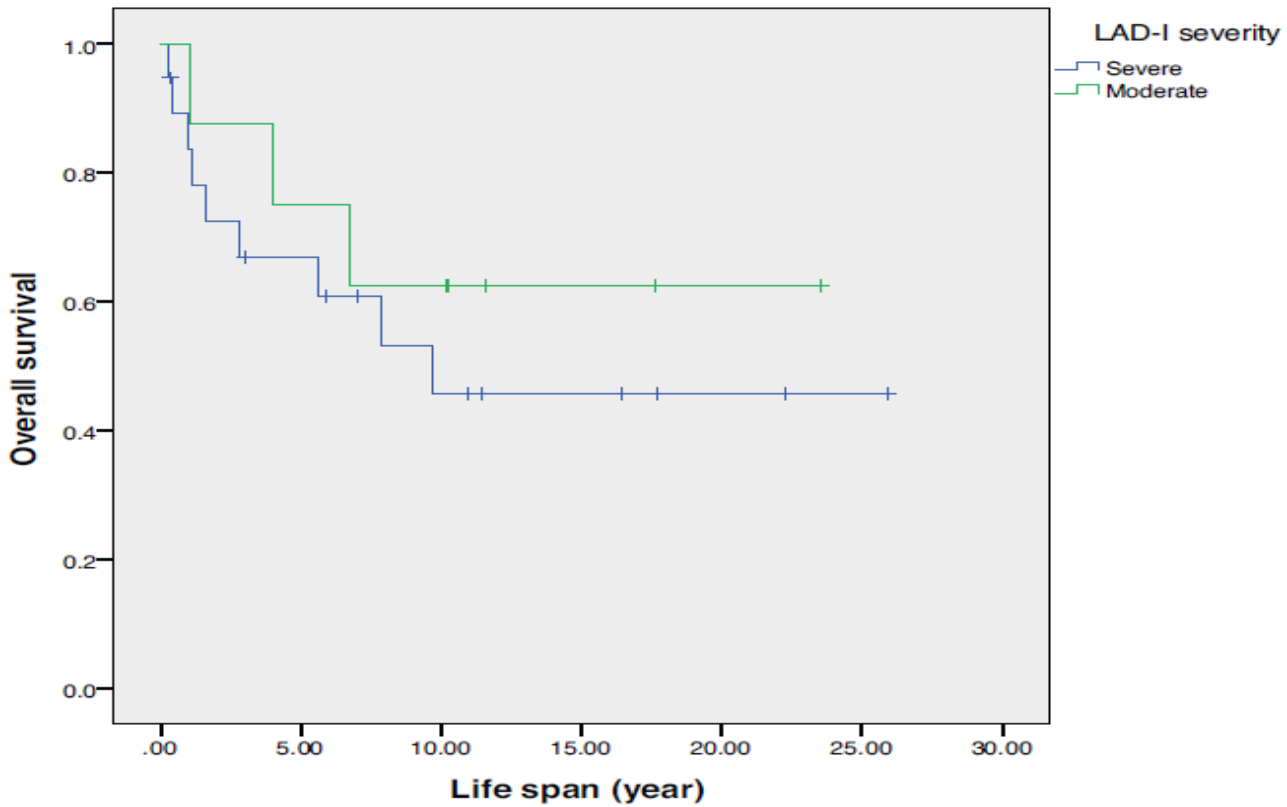
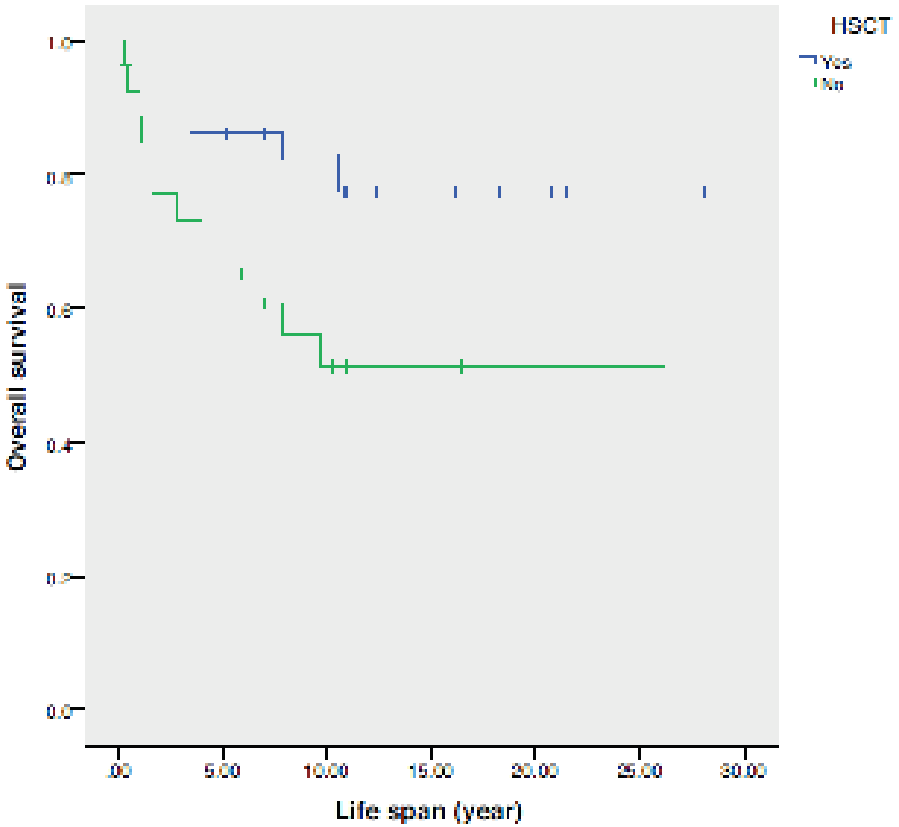
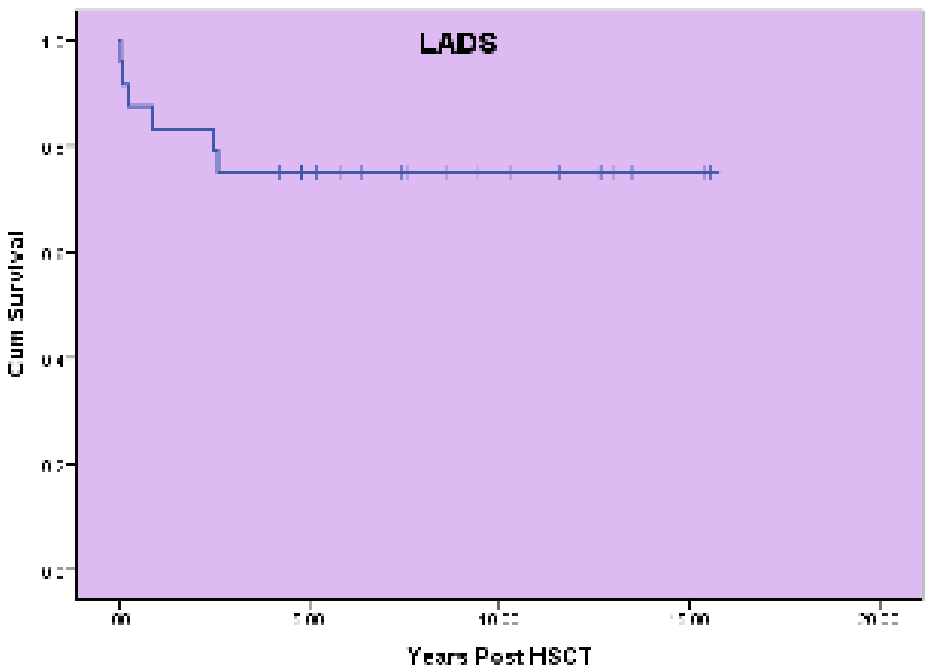
The overall survival of patients with LAD-I without HSCT according to the severity classification (severe and moderate).



The overall survival of patients with LAD-I in two groups (with HSCT and without HSCT)





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- These results highlight the importance of timely diagnosis and treatment with HSCT at the early childhood in severe cases. Moreover, similar results were obtained in our patients with moderate LAD-I. Considering the progressive course of this disease, even in its moderate form, treatment with HSCT should be considered for patients with this type.

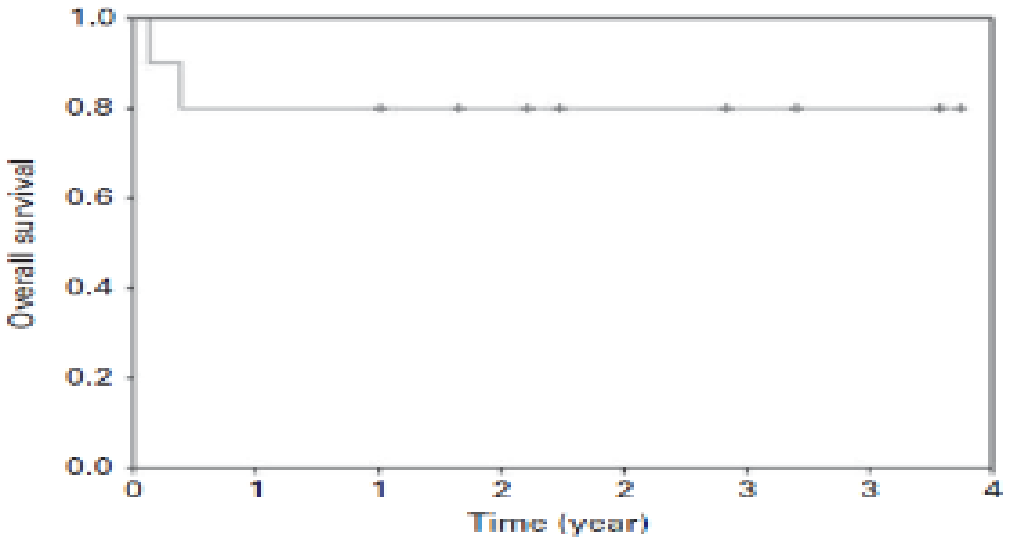

Figure 1 Cumulative OS of LAD-1 patients treated with the RIC regimen and allogeneic transplantation.

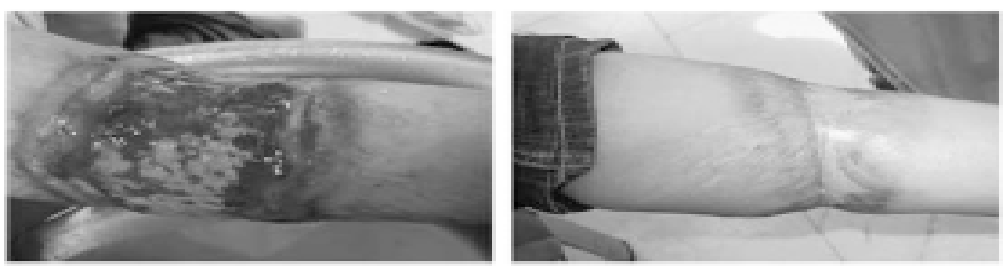

Figure 2 14-year-old girl diagnosed with moderate LAD and leg ulcer showing improvement after 4 months.

Hamidieh AA, Pourpak Z, Hosseinzadeh M, Fazlollahi MR, et al Bone Marrow Transplant. 2012 May;47(5): 646-50

.Reduced-intensity conditioning hematopoietic SCT for pediatric patients with LAD-1: clinical efficacy and importance of chimerism.