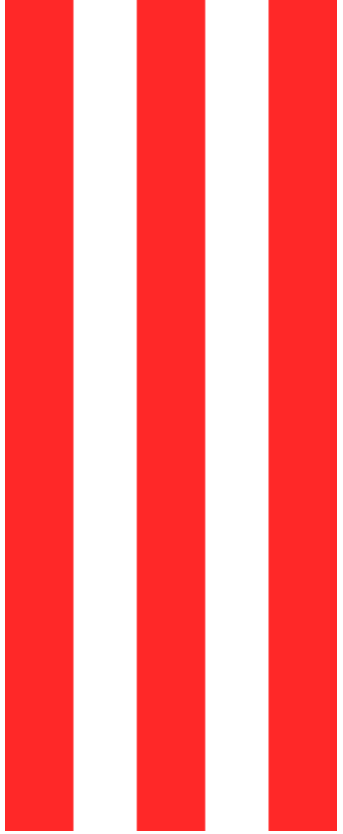
In the name of God



Report of Hematopoietic Stem Cell Transplantation (HSCT) in Bone Marrow Failure of Children &(Rare Hereditary Anemia) in Mofid Children Hospital(1394-1403)

Bibi Shahin Shamsian. MD
Mofid Children Hospital
Shahid Beheshti University of Medical Sciences
10/12/ 1403

HSCT in Bone marrow failure (BMF)

- **Data registry report of BMF patients By EBMT(2024)**
- **Report of HSCT in BMF of children from Mofid Children Hospital**
- **Report of HSCT in rare inherited anemia of children in Mofid Children Hospital**

Transplant Cell Therapy . 2023 Oct;29(10):621
Victor Quintero etal.

Pancytopenia in Children

- **Wide differential & challenging for causes of single Cytopenia or pancytopenia in children; including Bone marrow failure (BMF)**

- **IBMFS(Inherited); 20% of cases, constitutional mutations**

Gene Analysis(Gene screening) in Aplastic Anemia of Children & Adolescents (< 18 Y old).

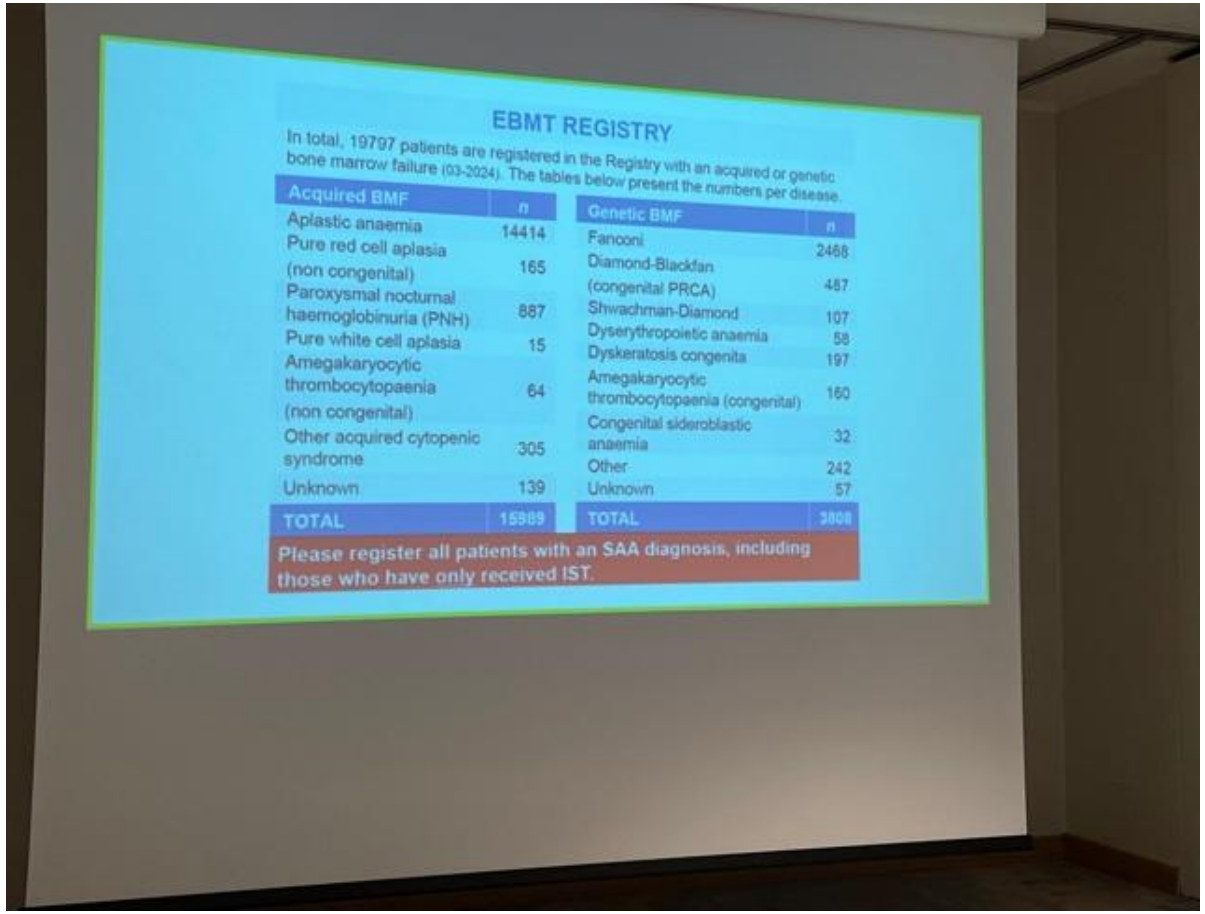
- **WES: 732 patients:17%p….. PID**
- **6.6 % Unrecognized known IBMFS**

EBMT Registry :Severe aplastic anemia working parties

Genova- Italy ; 11-13 Sep 2024 .

2024 : 19797 p ; BMF Acquired(15989) & Genetic(3808)

Severe Aplastic anemia(AA) : 14414 p & Fanconi anemia(FA) : 2468 p

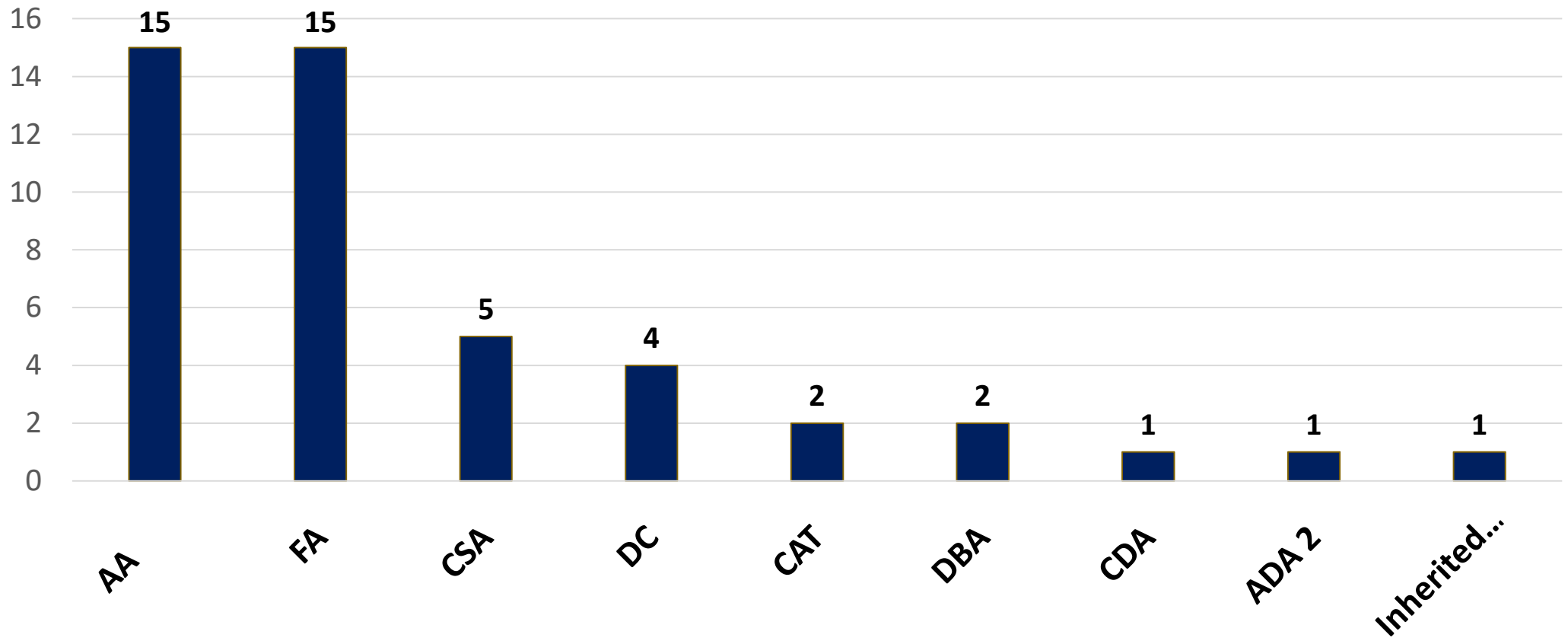


- **Fanconi Anemia (FA) 2468**
- **Diamond Black Fan (PRCA) : 457**
- **Shwachman Diamond : 107**
- **Dyskeratosis Congenita(CDA) : 55**
- **Dys Erythropoietic Anemia ; 58**
- **Congenital Sideroblastic Anemia(CSA) : 32**
- **Congenital Amegacaryocytic Thrombocytopenia(CAT): 160**
- **Other :242**
- **Unknown: 57**

Report :
HSCT in BMF of Children in Mofid Children Hospital
7.1394 – 11.1403

Report of HSCT in BMF of Children.
Mofid Children Hospital: 1394-1403

Total Patients: 46 / 48 HSCT Age :1.4 Y – 16 Y F/ M: 18 / 28



Donors , Sources & Protocols …… in patients of BMF

❑**Donors:**

- **MSD; 16p (1p: 1 MM) MRD : 15 URD: 12(3/12,1 locus MM) Haplo: 2**

❑ **Sources : BM:6 PB : 37 CB :3**

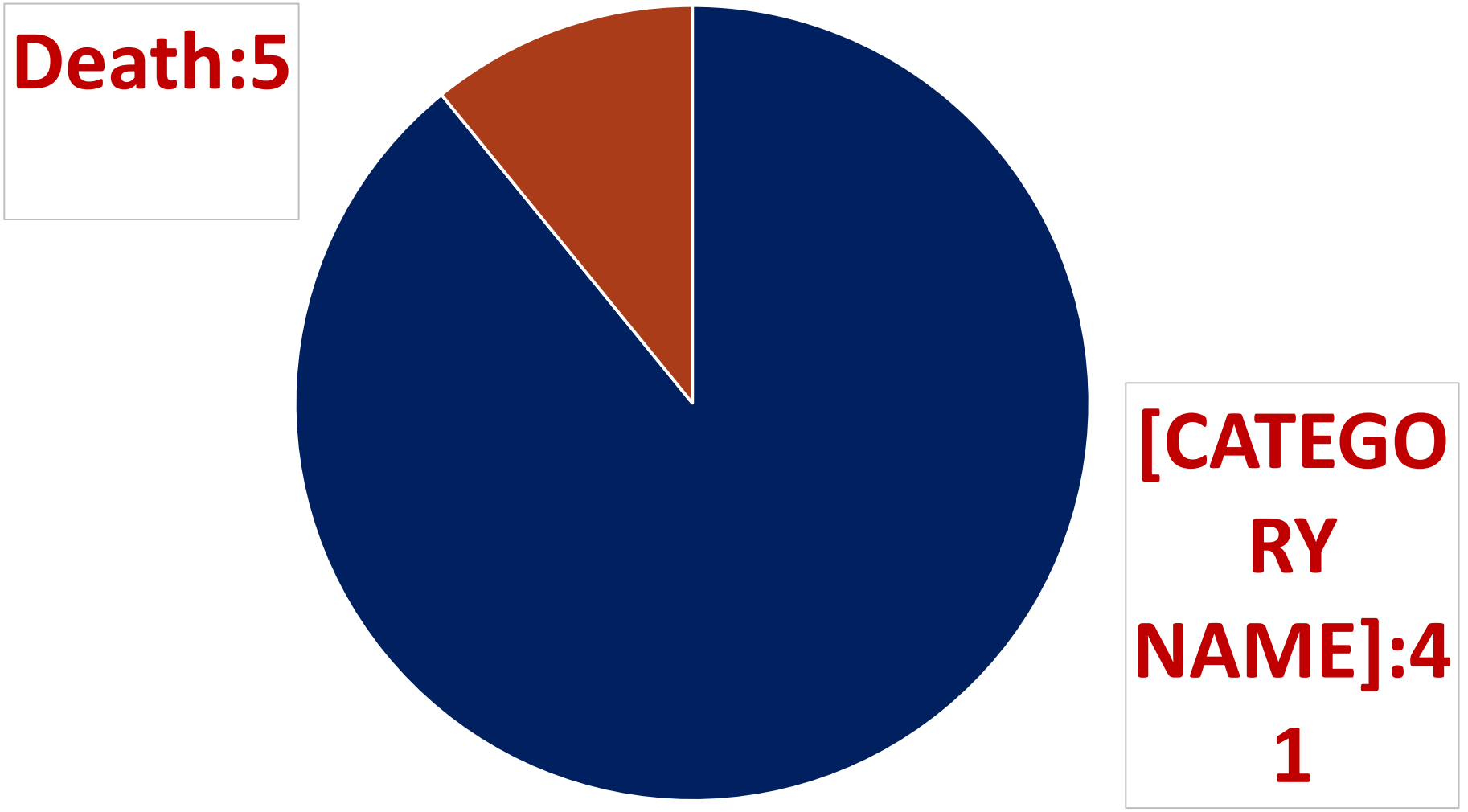
❑**Protocol Conditioning :**

- AA :CY 60 mg kg / day x 2 days + FLU 30mg/m2 / day x 5 days + R-ATG 2.5 mg /kg / day x 3 days
- FA : CY in FA; 30-40mg / kg / day x 2 days+FLU + R ATG
- DBA : Bu x 4 days + x CY x 4 days + R-ATG x 3days
- **ADA 2 Deficiency: RIC ,FLU + MEL, R-ATG**
- CAT : BU x 4 days + Flu x 5 days + R-ATG x 3days
- CAT Haplo (T cell depletion) : BU + FLU + Tiotepa + R- ATG

❑**GVHD - P : Cyclospurine + MTX or/ MMF**

❑**Drugs : Acyclovir , Fluconazole /Voriconazole, Ursodiol + Cotri ……, GCSF & IVIG as protocols**

Total Patients (BMF): 46



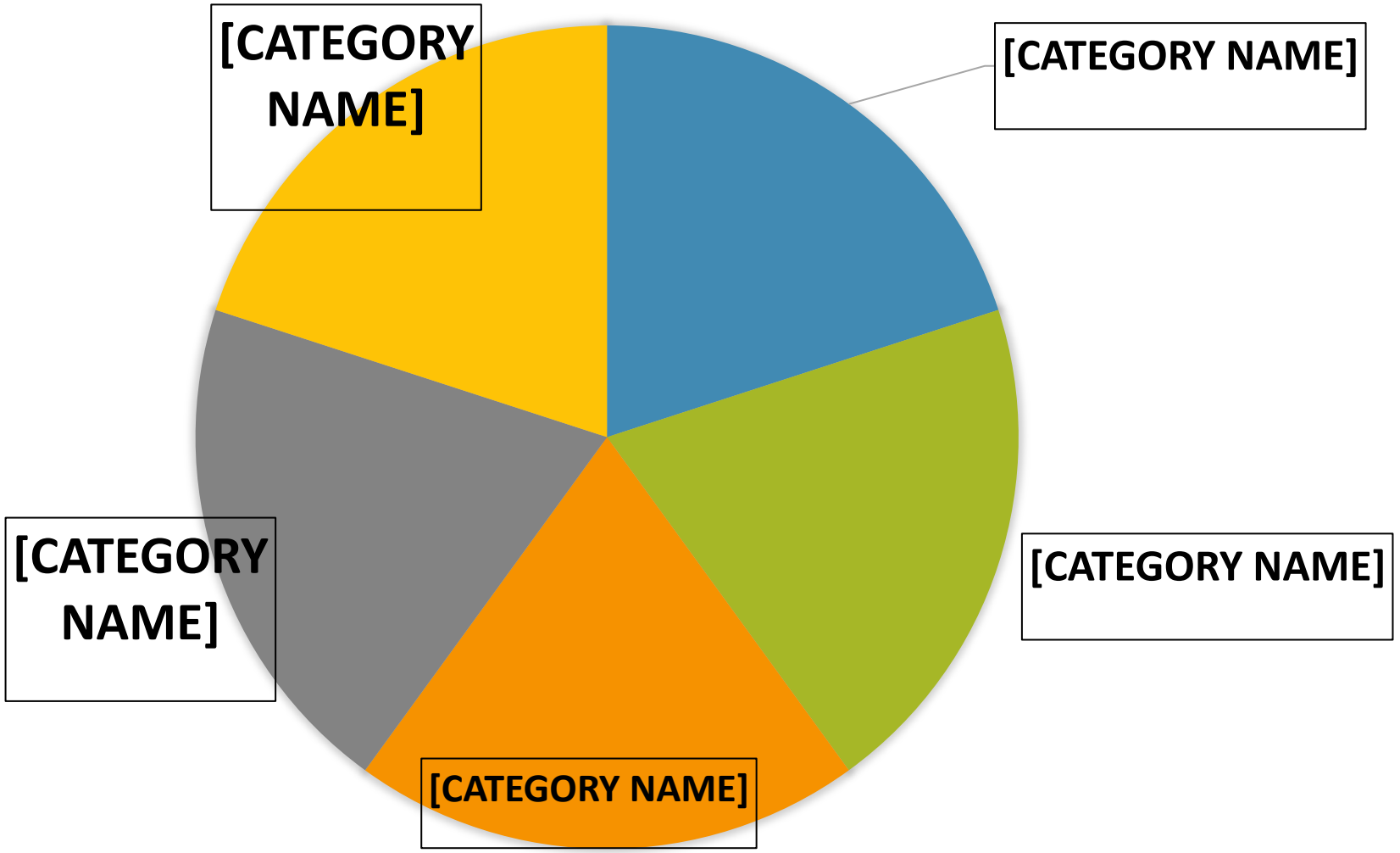
Report of HSCT in Bone Marrow Failure of Children .
Mofid Children Hospital ; 1394-1403

❑3/41 live : Graft Rejection

- **1patient (at 2.5 y old : AA Gene analysis : NL , CB 5/6 - Primary GR ,then on F-up nail dystrophy , Second Gene analysis : DC now candidate for second HSCT)**

- **1patient (8 Y) : FA , PGR, MMURD 9/10, PB**
- **1 Patient AA (7y) , PGF, MMSD 9/10,PB**

Reason of Death in 5 Patients



HSCT in Rare Inherited Anemia of Children

Congenital Sideroblastic Anemia

5 patients ;*SLC25A38* gene mutation

(15% CSA , AR)

Erythroid specific mitochondrial carrier protein

Allo – HSCT (1395-1401)

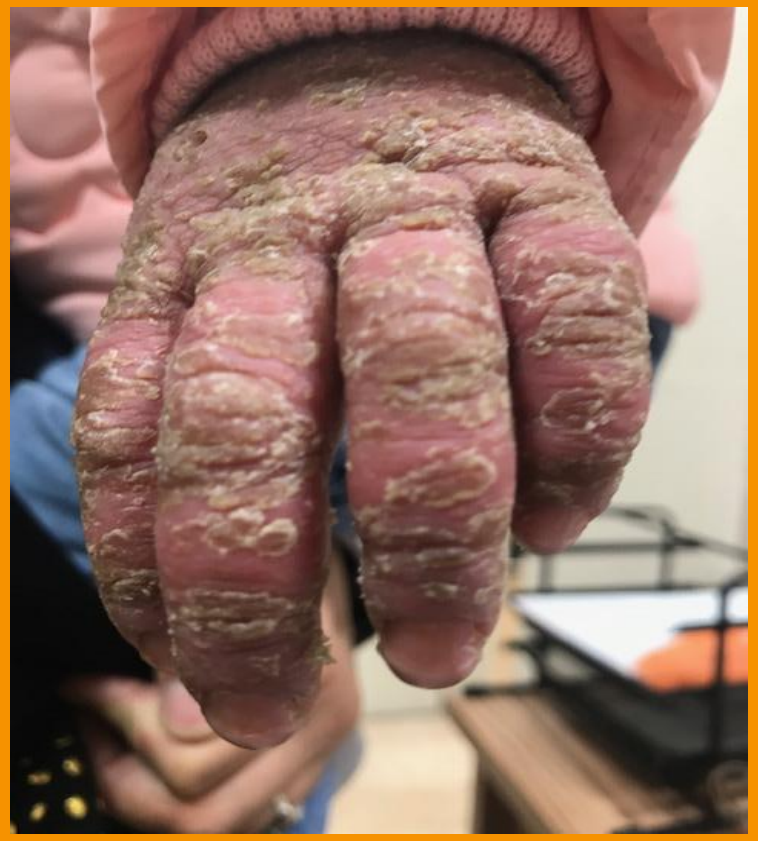
HSCT in Congenital Sideroblastic Anemia
Mofid Children Hospital 1394- 1403 .

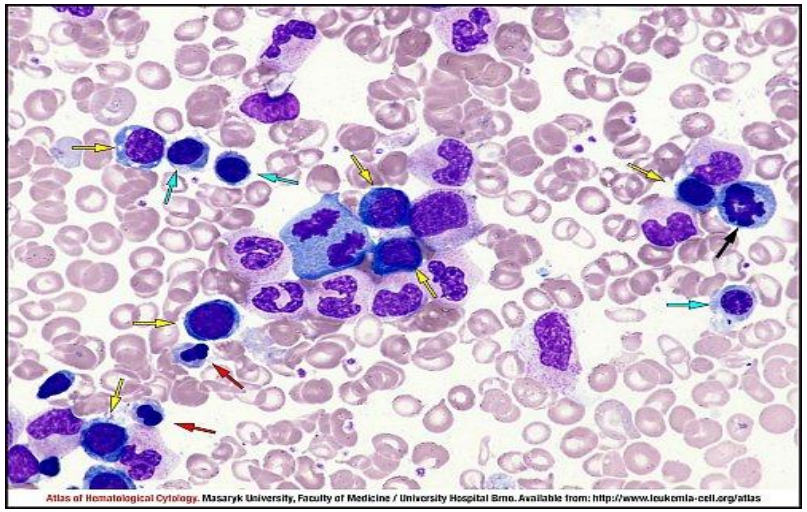
- All 5P : anemia on BT & Iron Chelation since early childhood
- P1 :Male 4 y , MSD : Sister . 9y (BM)
- P2:Female 3 y , MSD -Sister , 12. (BM)
- P3 :Female 2 Y , MRD. Mother .35 y. (PB)
- P4 :Male , 2.5 y , MRD (Aunt, 40 y), (PB)
- P5: Male ,16 y ,MSD(sister,19 y),(PB)
- Ferritin Range (1090- 1700)

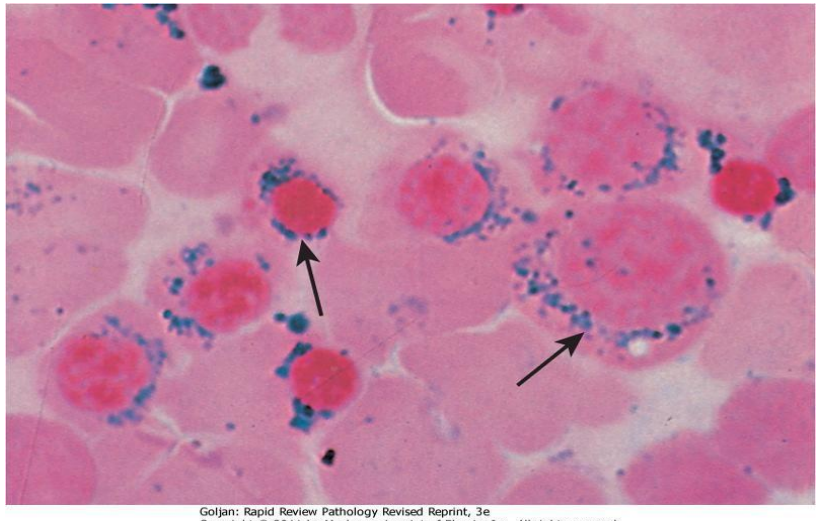
- Age ALLO HSCT :(2.5 y -16 y)
- MAC : BU + CY + R-ATG
- GVHD-P : Cyclospurine + MTX / or MMF

- Complications :
- GVHD skin stage 2-4 (4 /5 p)
- GI GVHD ; 1p
- BK, CMV viral reactivation
- Chimerism All –p ; 95-100%
- (F up 1.5- 7 Y)

Acute skin GVHD in patient (2) of CSA with MSD-HSCT, BM







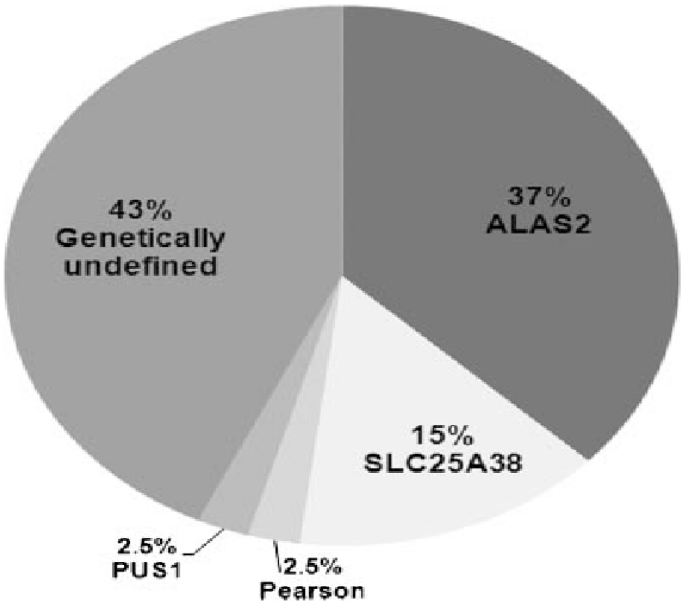
SIDEROBLASTIC ANEMIA

- Heterogen anemia-Ineffective erythropoiesis
- Inherited (X linked , AR , Syndromic or non Syn)
- Acquired (Drugs :INH , chlorampheni…. , linezolide ….)

- BMA & BMB : E hyperplasia+ RING SIDEROBLAST (Iron-laden mitochondria form a ring around the nucleus.
  Ring must encircle a third(1/3) or more of the nucleus & contain 5 or more iron granules
- & Gene analysis

SLC25A38 gene mutation/ AR
congenital sideroblastic anaemias

- **Biallelic mutations in the *SLC25A38* gene, (Ch; 3p22.1),AR,** 15% of CSAs
- **SLC25A38 Gene: mitochondrial carrier protein, Erythropoiesis biosynthesis of heme**
- **Severe anemia ;at birth or in early childhood**
- **Low retic , Ineffective erythropoiesis,Iron overload**
- **Clinical Course ; similar of thalassemia major**
- **Treatment :Regular BT & Iron chelation**
- **Pyridoxine (B6)-refractory**
- **ALLO HSCT : curative therapy**



Review articles of Congenital Sideroblastic Anemia (CSA)

Case Reports › Exp Clin Transplant. 2023 Jan;21(1):70-75. doi: 10.6002/ect.2022.0081.

Allogenic Hematopoietic Stem Cell Transplant in Iranian Patients With Congenital Sideroblastic Anemia: A Single-Center Experience

Bibi Shahin Shamsian [1], Mohammad Reza Jafari, Hassan Abolghasemi, Peyman Eshghi, Mohammad Ali Ehsani, Elham Shahgholi, Maryam Kazemi Aghdam, Atbin Latifi, Mahnaz Jamee

Affiliations + expand

PMID: 36757170 DOI: 10.6002/ect.2022.0081

Free article

› Pediatr Blood Cancer. 2020 Oct;67(10):e28623. doi: 10.1002/pbc.28623. Epub 2020 Aug 13.

Pediatric blood & cancer

Clinical characterization and hematopoietic stem cell transplant outcomes for congenital sideroblastic anemia caused by a novel pathogenic variant in SLC25A38

Kelsey Uminski [1], Donald S Houston [2], Jessica N Hartley [3], Jing Liu [3], Geoffrey D E Cuvelier [4], Sara J Israels [4]

blood®

Volume 136, Supplement 1, 5 November 2020, Pages 45-47

732.Clinical Allogeneic Transplantation: Results

Transplantation for Congenital Sideroblastic Anaemia Is Feasible and Offers Outcomes Comparable to Other Transfusion Dependent Anaemias. a Joint Retrospective Study of the Paediatric Diseases and Severe Aplastic Anaemia Working Parties (PDWP/SAAWP) of EBMT

Josu de la Fuente [1], Dirk-Jan Eikema * [2], Paul Bosman * [3], Robert F Wynn MRCP,MDFRCPath [4], Miguel Díaz * [5], Peter J Shaw MD * [6], Amal Al-Seraihy MD * [7], Muhlis Cem Ar MD PhD * [8], Mohamed Salaheldin Mohamed * [9], Dominique Bron MDPhD [10],

Clinical characterization and hematopoietic stem cell transplant outcomes for congenital sideroblastic anemia caused by a novel pathogenic variant in *SLC25A38*.Kelsey Uminski. PEDIATRIC Blood and cancer .Volume 67, Issue10.Oc 2020.

- **7 p** of Canadian , known or inferred homozygous novel founder missense variant in *SLC25A38*
- Young children (**median age 6 mo**) , severe microcytic, hypochromic anemia ,pretransfusion iron overload, on BT & iron chelation.
- **6p ,pyridoxine supplementation; 2 ; transient partial responses.**
- **3p ALLO (HSCT).**
- **1p with significant iron loading died ,posttransplant sepsis.**
- **The other two individuals remain transfusion-free following HSCT.**

Transplantation for CSA. a Joint Retrospective Study of the Paediatric Diseases and Severe Aplastic Anaemia Working Parties (PDWP/SAAWP) of EBMT.
Josu de la Fuente.*Blood* (2020) 136 (Supplement 1): 45–47.

- **1998 – 2018((20 Y) , 24 Centres**
- **28 patients /Median age at HSCT 7 years of age (3-10 years).**
- **Donors : 15 p MSD , 1p MRD , 1 MURD**
- **sources : BM :20 PB : 4 Cb ; 1 BM+ CB ; 1 unknown : 11**
- **Condition : BU +Cy , BU + FLU FLU +Treosulfan**
- **86% :Serotherapy with ATG or alemtuzumab. F-up ; 31.5 mo**
- **OS at 12 - 24 months : 88% & 82% respectively**
- **EFS at 12 - 24 months was 85%**
- **Graft failure :7% at 12 mo**
- **6p grade II/III incidence of 28%**
- **1 case of limited & 1 of chronic GvHD, giving an incidence of 11% ,at 12 months and 24 months.**

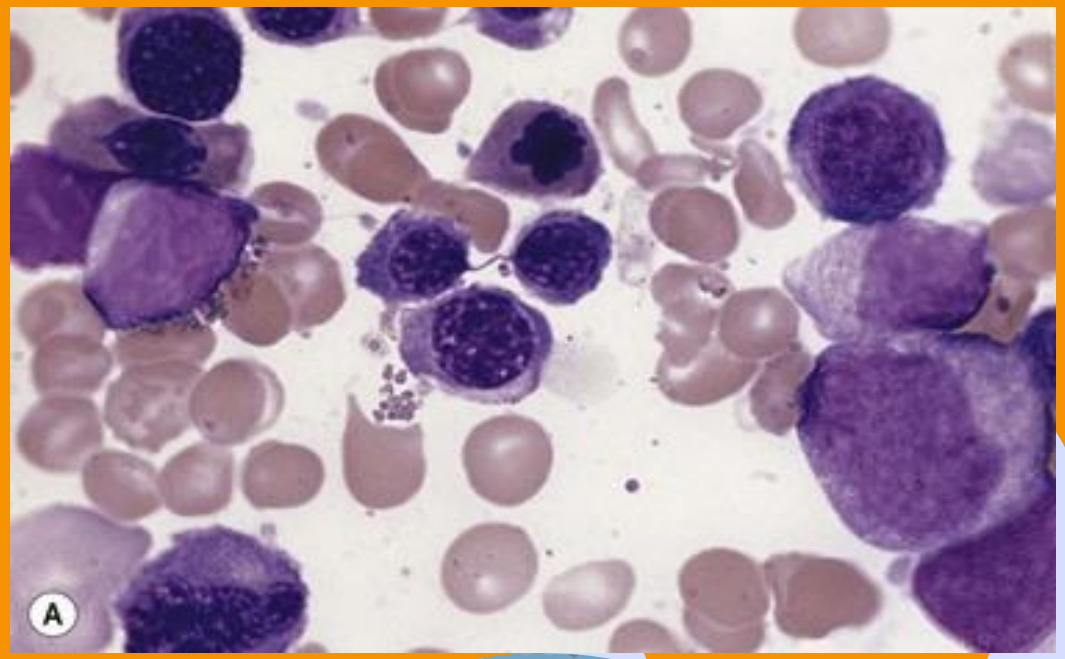
Reduced Toxicity ALLO HSCT for CSA.

Min Hee Kim. Phoenix.USA. Biol Blood Marrow Transplant 22 (2016)

- **Case report : A 4 year old female** ,TD since 2 mo of age
- **CSA caused by SLC25A38 mutation**

- **HSCT& A novel preparative regimen** : **(BU), (FLU), & Alemtuzumab*(improve engraftment & decrease chronic GVHD rates in nonmalignant transplants)**
- **GVHD- p : Tacrolimus + MTX**
- **Phlebotomy :at 1 year post-transplant**

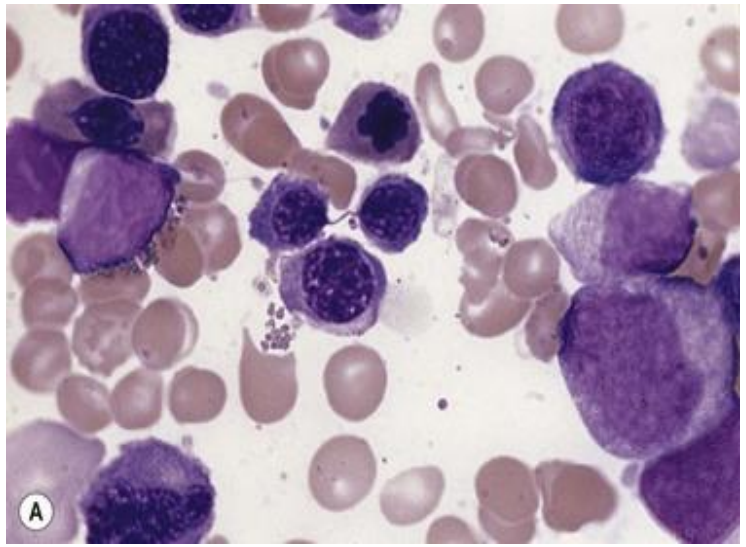
Congenital Dys- Erythropietic Anemia(CDA) type 1



Gene :CDAN1,AR

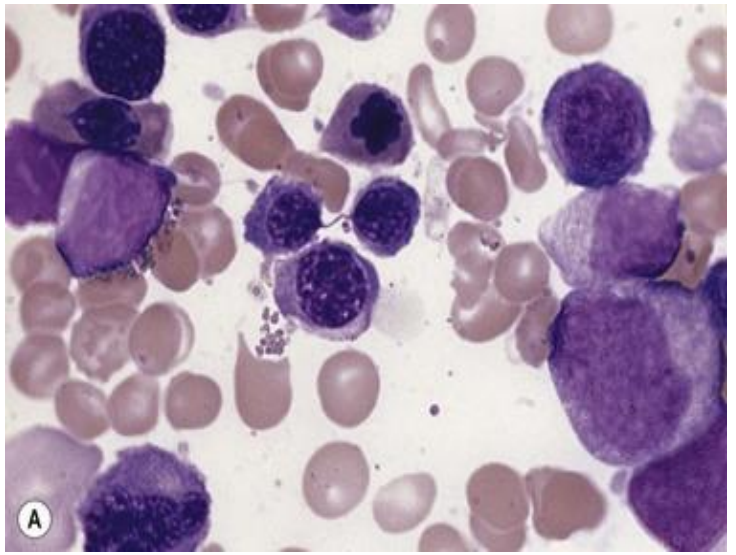
Congenital Dys- Erythropietic Anemia type 1”.(CDA- Type I-CDAN1,AR)

- A 12 Y old boy; anemia, MCV high , low retic , mild jaundice ,splenomegaly & mild macrocephaly
- Parents ; first cousin
- On BT & Iron chelation
- Short period improving but again needs to transfusion
- Evaluation : CBC , Retic…. Ferritin……
- BMA , BMB: (CDA)



"Congenital Dys- Erythropietic Anemia type 1".(CDA- Type I-CDAN1,AR)

- **Gene analysis : CDAN1 ,CDA type 1**
- **Allo HSCT ; MSD ,(Sister, 23 Y old, PB)**
- **Ferritin : 1100**
- **Conditioning, MAC : BU + CY + R ATG**
- **GVHD-P: Cyclospurine + MTX**
- **Chimerism : 100%**
- **Complications ; Skin GVHD stage 2 + Urine BK virus pos ,treatment &improve .**
- **1.5 y after HSCT; on vaccination &F-UP**



“Congenital Dys- Erythropietic Anemia.”

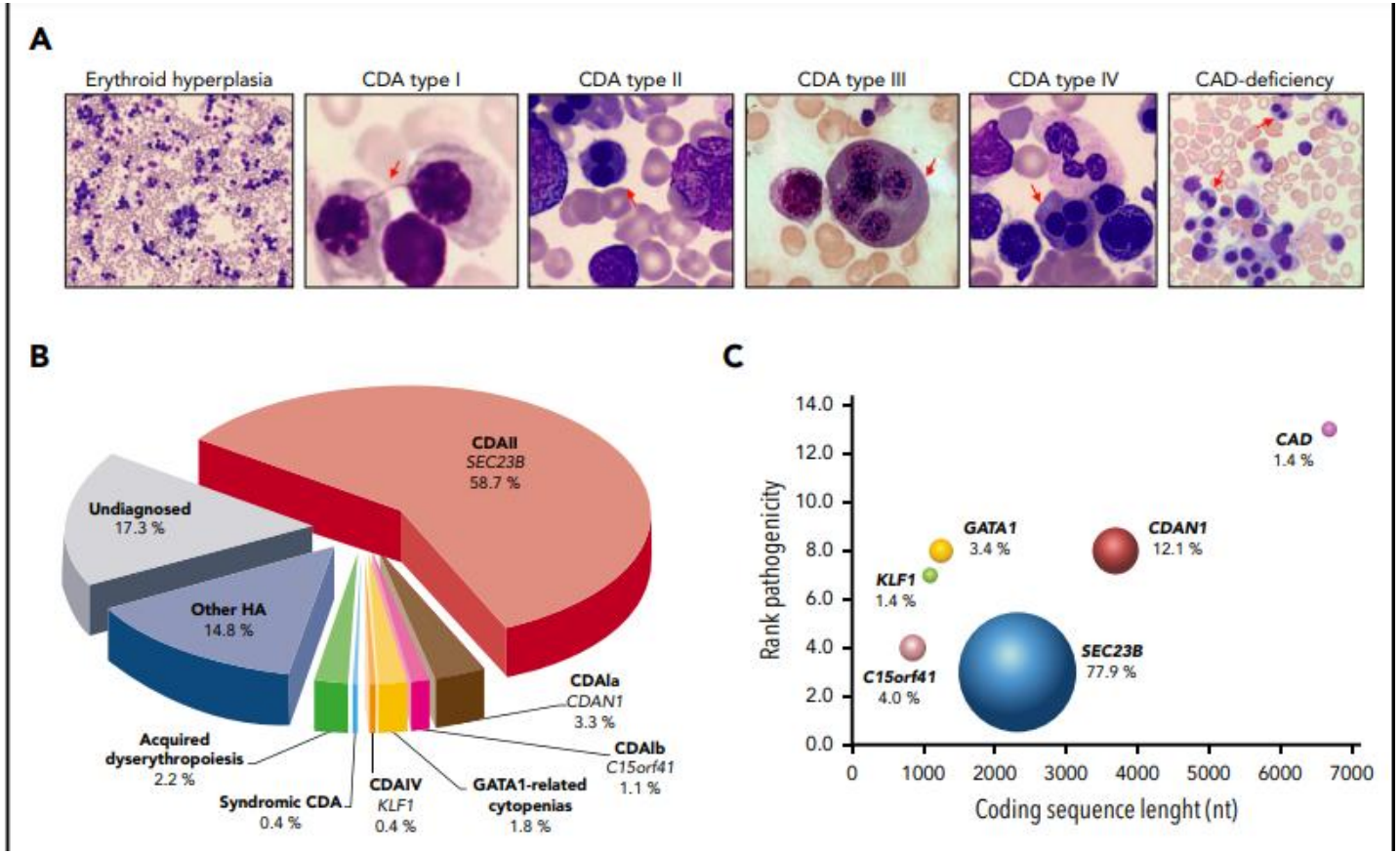
Haematologica 2019; 104:e33. Maurizio Miano. ITALY, EBMT Data

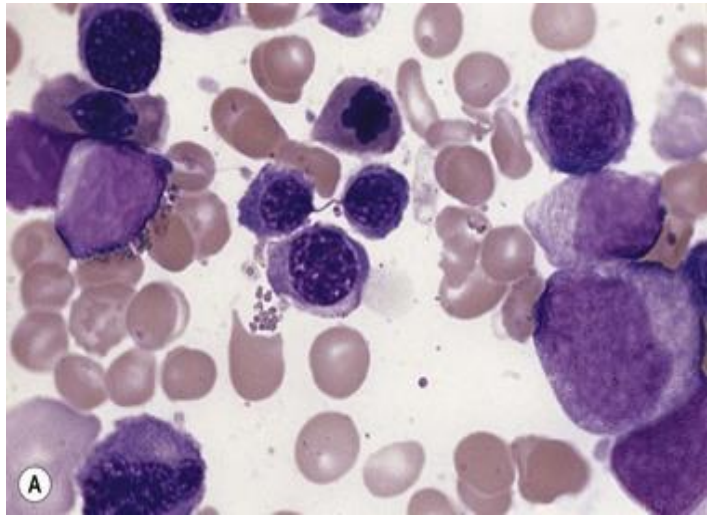
- **A group of heterogeneous of anemia(AR , AD) ,Eneffective erythropoiesis & Iron overload(hemosiderosis)**
- **Somatic abnormalities(skeletal,..)**

CDA Classification :

- **CDA types I (A&B), II, and III,transcription-factor-related CDAs (Type 4), & the CDA variants**
- **Type 2 CDA the most common : > 450 cases**
- **Type 1> 300 cases, Moderate to severe anemia**

Diagnois : BMA & BMB ; Erythroid hyper plasia , morphologic abnormalities in E- series; Bi nuclearity, or Multinuclearity of late erythroblasts , internuclear chromatin bridges between the nuclei pairs …, but ,features are not specific to CDAs . & Molecular Study; NGS





- **Blood transfusion,Iron chelations ,Interferon-α**
- **Allo genic HSCT; Cure**

HSCT for CDA : A Report from the Pediatric Transplant and Cellular Therapy Consortium.G. Rangarajan et al. Transplantation and Cellular Therapy 28 (2022) 329.

- **18 patients , CDA ;Allo HCT ,2002 - 2020**
- (N = 13) CDA type II, ,**CDA type I (n = 2)** or CDA of unknown type (n = 3).
- **Median age /HSCT : 5.5 Y** (range, 0.7 to 26 Y).
- Donors ; HLA-matched (sibling, 4; unrelated, 10) & mismatched (**haploidentical, 1; unrelated, 3).**
- Conditioning : Bu-based MAC(67%) & FluRIC (27%)
- Graft sources :BM 15 P, CB 2 p, or both in 1 P
- Acute & chronic (GVHD) : 33% and 22%, respectively. 4P (22%) :GF
- **Median follow-up :3.2 Y**
- **OS, EFS, and GVHD-free EFS of (2 Y): 88% ,65%.60 unrelateddonor & iron**
- **Un related donors & Iron overload pre HSCT : Risk factors**

BMF & ADA2 Deficiency

- An 11 y old girl , second child , non relative parents
- 9-Y : Fever, chills ,skin lesions ,arthritis, : SJIA
- After 2 y of treatment, progression as .Headache , hemorrhagic stroke, Seizures .& oral ulcer,positive HLA-B5 & HLA-B51; Behcet disease .
- Treatment ; TNF inhibitor (INFLIXIMAB)

- WES mutations ; ADA2/CECR1 Genes

BMF & ADA2 Deficiency

- F- Up : severe Pancytopenia &, low Retic , Coombs neg
- BMA & BMB ; Sever Hypocellular marrow , (2 times)
- FC : Nl Cytogenetic : 46XX EBV & CMV PCR : Neg
- Partial response to CS & Cyclospurine & IVIG,…
- Plan :Allo HSCT : M-MURD , 9/10, PB (1403)
- RIC : Flu + MEL + R- ATG
- GVHD : Cyclos + Celcept
- Engraft: Day + 12 Complications ; EBV & CMV reactivation & Herpes of Genitalia
- Chimerism : 100% 10 Mo pos HSCT

HSCT Cures ADA2 Deficiency: Report on 30 Patients.Hasan Hashem . Journal of Clinical Immunology (2021) 41:1633–1647. Multinational study(EBMT & ESID)

- **Rare Inborn Error of Immunity Disorder(AR - 2014)**
- **30 p DADA2 ;12 countries ;38 HCTs.**
- **Indications HSC:BMF, immune cytopenia, malignancy, or immunodefciency**.
- Median age at HCT 9 y (range: 2–28 years).
- Conditioning R: MAC n=20 **RIC (n=8),** or non-myeloablative (n=2).
- Donors HLA MRD(n=4), HLA-MURD (n=16), **HLA-haploidentical (n=2**), or MMURD(n=8).
- Median F-up of 2 2 (range: 0.5–16 years)
- **2-year OS was 97%, and 2-year GvHD-free relapse-free survival was 73%.**
- Hematological ,immunological phenotypes resolved, & no new vascular events.
- **6p required more than one HCT.**
- **Plasma ADA2 enzyme activity : NL 16/17 p**.
- **HCT is a defnitive cure for DADA2 with>95% survival.**

Rare Inborn Error of Immunity Disorder(AR - 2014)

ADADA2 specific-disease vulnerabilities.

Disease-specific vulnerability	Potential impact of preparative regimen	Agents to be used with caution
Vasculopathy of -small and medium-sized arteries and/or history of strokes/ICH	Peri-transplant and peri-engraftment bleeding	Myeloablation, particularly busulfan-based (PK monitoring can aid in reducing toxicity), TBI
Autoinflammation with fever and elevated inflammatory markers	Peri-transplant inflammation and cytokine storm	Myeloablation, particularly busulfan-based (PK monitoring can aid in reducing toxicity), TBI high-dose cyclophosphamide
Iron overload and red cell alloimmunization	SOS, higher transfusion needs	Myeloablation, particularly busulfan-based (PK monitoring can aid in reducing toxicity), TBI high-dose cyclophosphamide
Liver disease (hepatitis, hepatomegaly, hepatoportal sclerosis, portal HTN, iron accumulation)	SOS	Myeloablation, particularly busulfan-based (PK monitoring can aid in reducing toxicity), TBI high-dose cyclophosphamide
Preexisting infection/severe immunodeficiency and prolonged antibiotics usage	Disruption of mucosal barrier and microbiota dysbiosis	Myeloablation, particularly busulfan-based (PK monitoring can aid in reducing toxicity), TBI high-dose cyclophosphamide
Prolonged severe neutropenia	Susceptibility to fungal infections	Myeloablation, particularly busulfan-based (PK monitoring can aid in reducing toxicity), TBI high-dose cyclophosphamide
Lymphoid aggregates in the bone marrow and autoimmune cytopenias	Graft failure	Reduced intensity conditioning, particularly in absence of serotherapy

ADA 2 Deficiency

➢Diagnosis :

- ❑ Absence or low levels of plasma ADA2 enzymatic activity,
- ❑ Gene analysis :Biallelic loss-of-function mutations of ADA2

➢Biallelic deleterious mutations in the cat eye chromosome region 1 gene (CECR1, subsequently renamed ADA2

➢Treatment plan :

- ❑Vasculopathy & Autoinflammation :Anti-TNF-agents (Etanercept, Infliximab, Adalimumab).
- ❑Hematological & severe immunodeficiency :HSCT

CONCLUSION

- Age is critical factor in D & DD of BMF
- Gene analysis should be considered in evaluations of BMF In age < 18 y old
- HSCT : Cure treatment for some of the rare hereditary anemia of children including : CSA & CDA & ADA2D , CHA & .....

Acknowledgment

- patients & parents
- Collegues (Physicians)
- Genetic& consultant Team
- Dear nursing of

HSCT & Hematology unit in

Mofid Children Hospital

Bone Marrow Transplantation (2025) 60:227 – 236

Jakob R. Passweg, etal . 2022 activity survey data

Utilization of **hematopoietic cell transplantation and cellular therapy** technology in Europe and associated Countries. Using the 2022 activity survey data to correlate with economic and demographic factors.

Annual survey ,EBMT report patients treated NON.2022

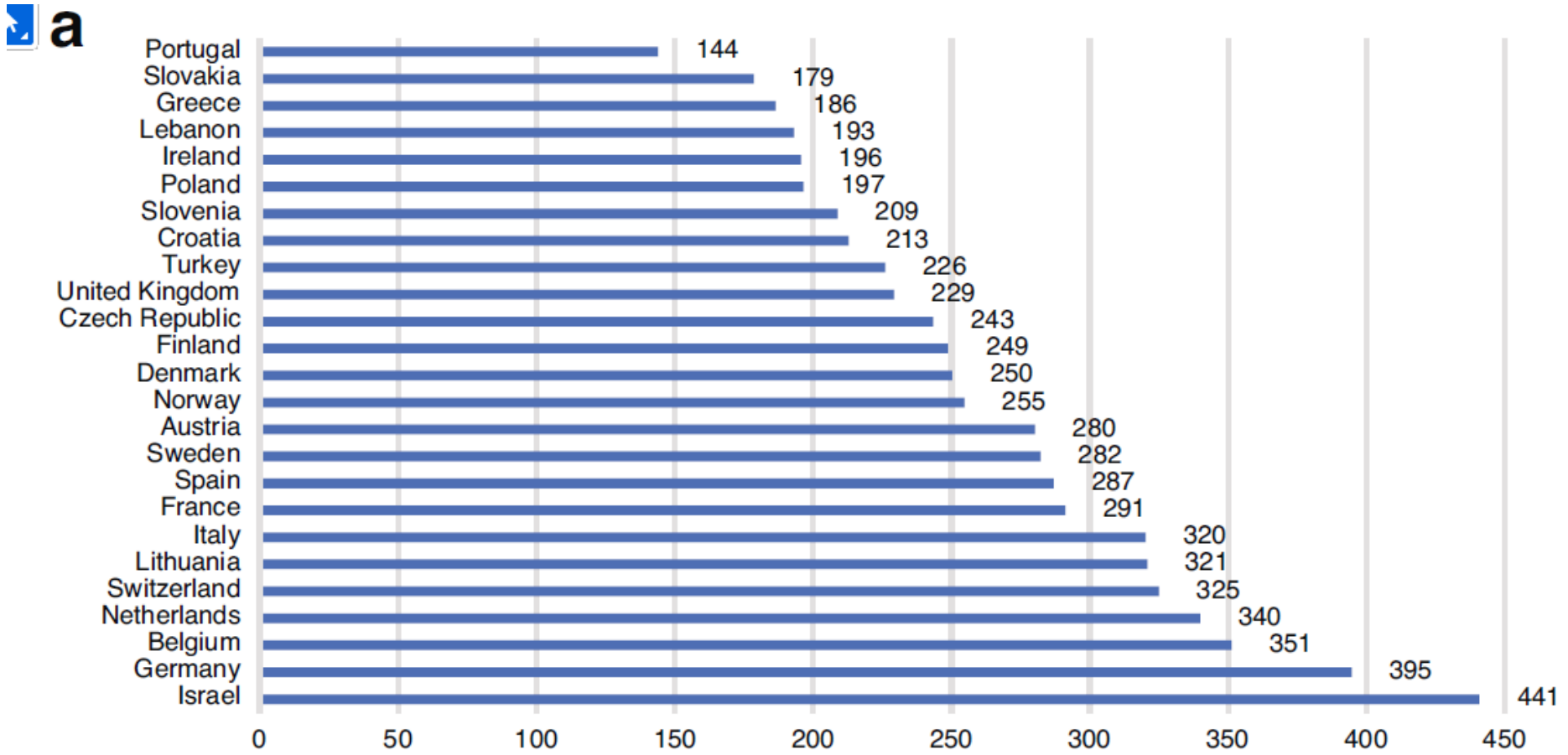
- **46,143 HCTs**
- **19,011 (41.2%); Allogeneic 27,132 (58.8%) ;Autologous**

- **4329 p: advanced cellular therapies**
  - **3205 CART; 214 centers in 28 countries**
  - **2259 (70.5%) were for lymphoma. 470 (14.7%) for myeloma, 380 (11.8%) for ALL and 96 (3%) for other diseases.**

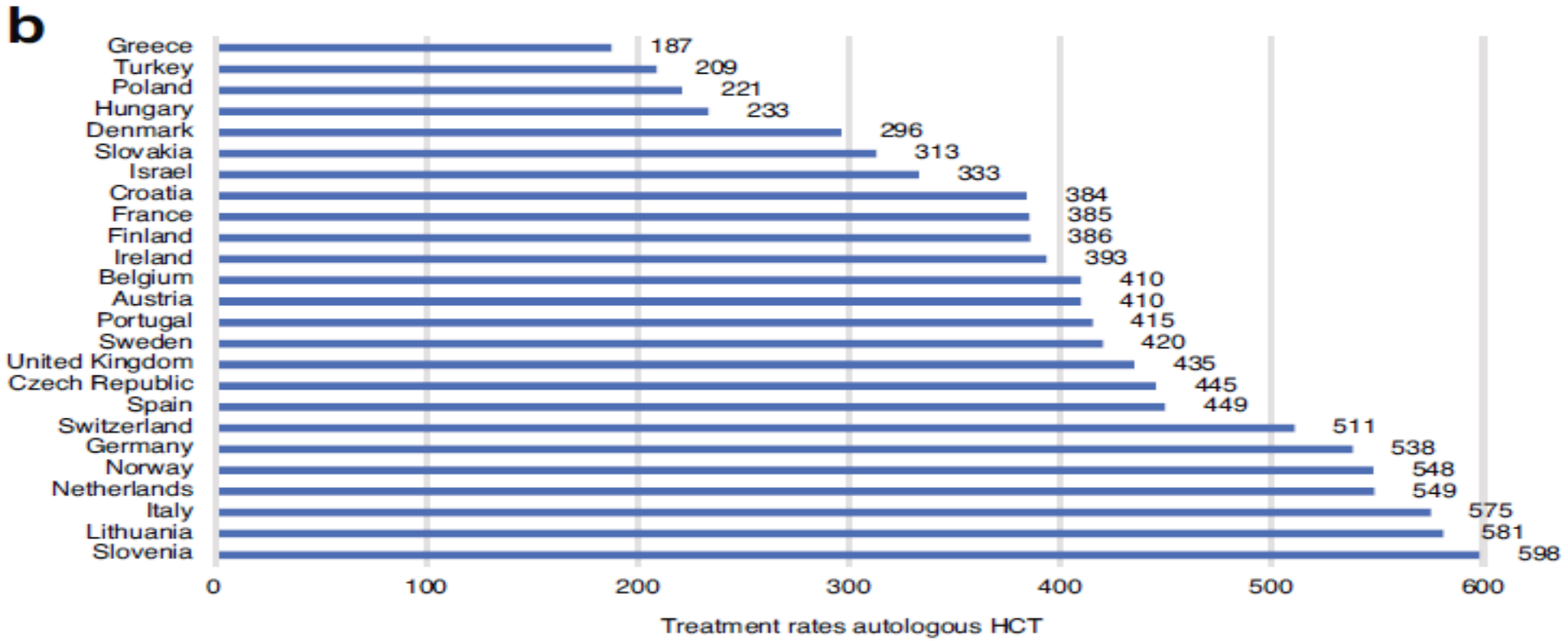
Annual survey ,EBMT report patients treated NON.2022

- **689 /731 centers from 54 countries**
- 44 European **and 10 associated countries**
- **9 collaborating non-European countries in 2022 survey**: Algeria, **Iran**, Iraq, Lebanon, Nigeria, Saudi Arabia, South Africa, Tunisia, & United Arab Emirates.
- **Their data, 2714 HCT in 2601 patients, from 28 actively HSCT center made up 5.9% of the total data set and are included in all analyses.**

Treatment rate per 10 million inhabitants for the top 25 countries by treatment type; allogeneic and autologous HCT and CAR-T,by donor type and by four selected diseases in 2022. a; Allogeneic HCT (all transplants).

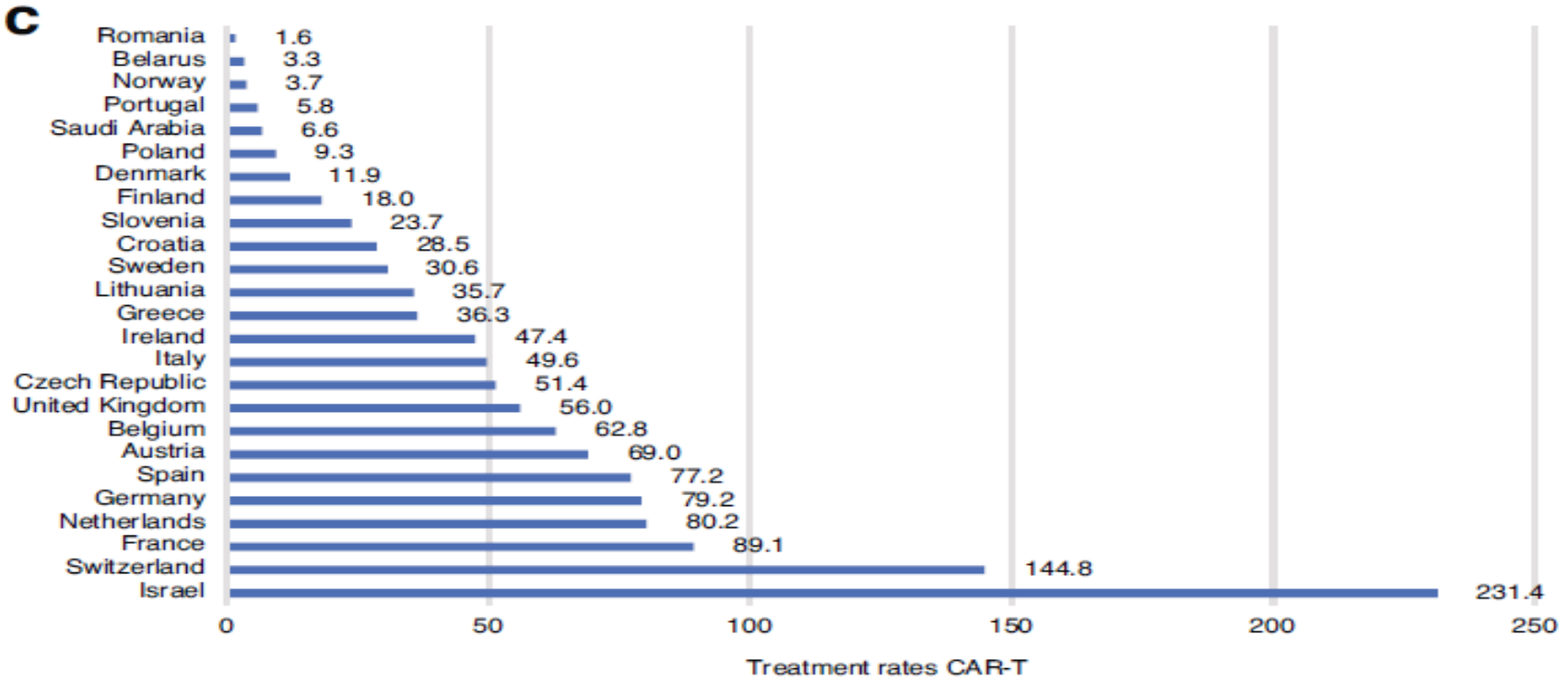


Treatment rate per 10 million inhabitants for the top 25 countries by treatment type; allogeneic and autologous HCT and CAR-T,by donor type & by four selected diseases in 2022. b ;Autologous HCT (all transplants).



Treatment rate per 10 million inhabitants for the top 25 countries by treatment type; allogeneic and autologous HCT and CAR-T,by donor type & by four selected diseases in 2022.

Treatment rates CAR-T



Treatment rate per 10 million inhabitants for the top 25 countries by treatment type; allogeneic and autologous HCT and CAR-T,by donor type and by four selected diseases in 2022. Cord blood HCT all donor types (all transplants). g:Treatment rates cord blood HCT