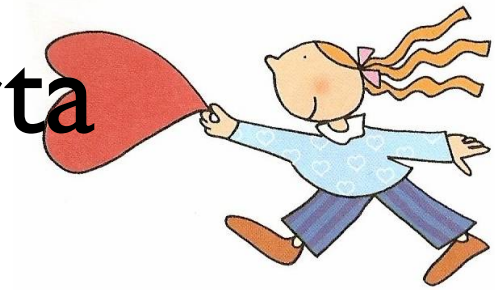
IL TRAPIANTO NELLE IMMUNODEFICIENZE PRIMITIVE

24 Gennaio 2017

Dott. Fulvio Porta



U.O. Oncoematologia Pediatrica e Trapianto Midollo Osseo

Ospedale dei Bambini, Spedali Civili, Brescia

J Clin Immunol
DOI 10.1007/s10875-015-0198-5

ORIGINAL RESEARCH

The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies

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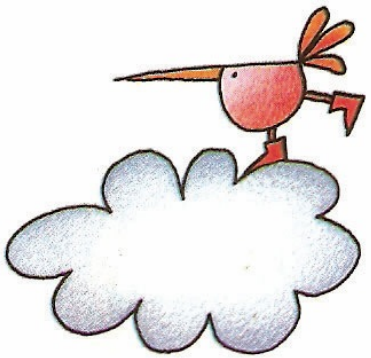

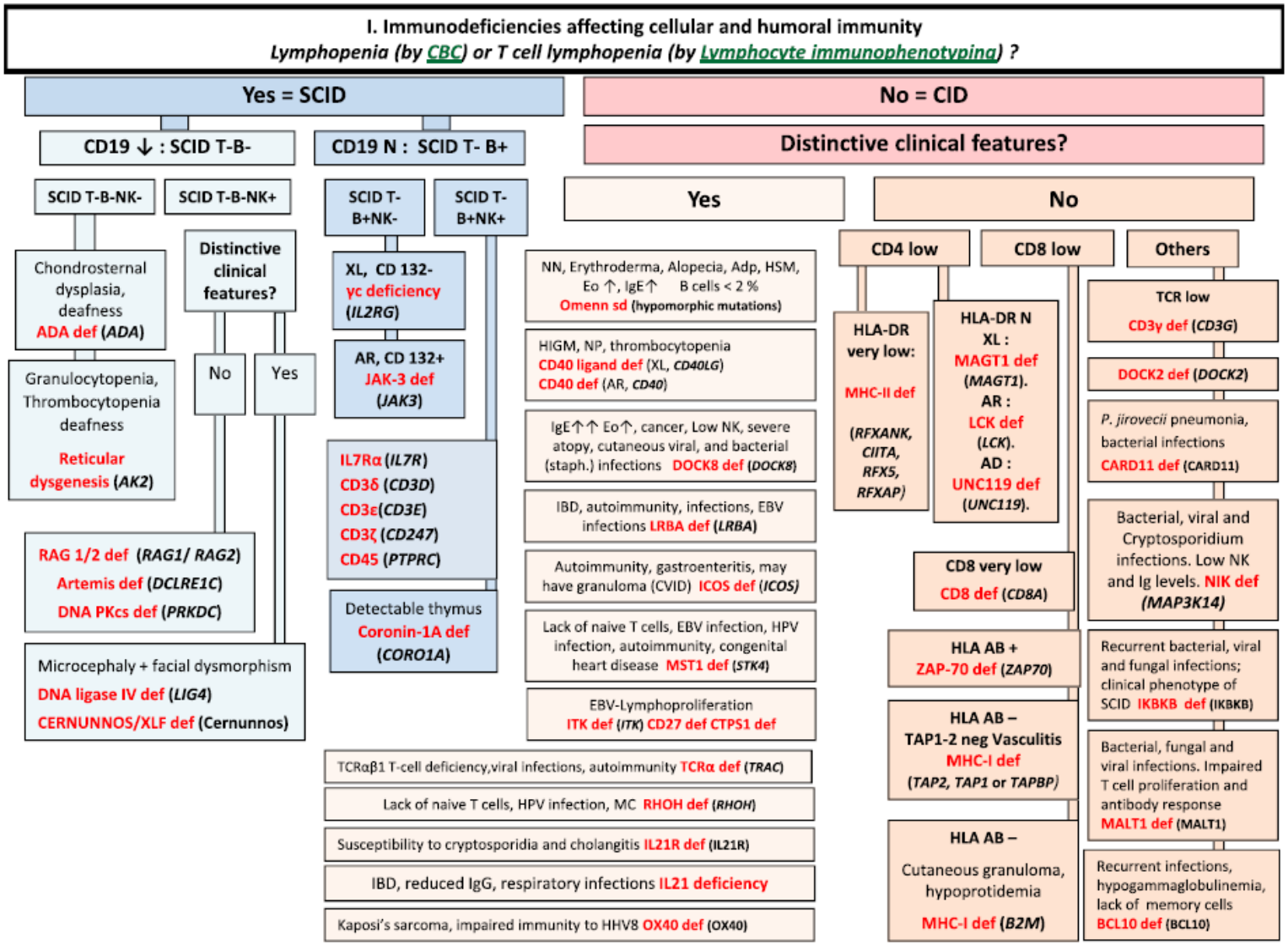

Fig. 1 Immunodeficiencies affecting cellular and humoral immunity. *ADA* Adenosine Deaminase, *Adp* adenopathy, *AR* Autosomal Recessive inheritance, *CBC* Complete Blood Count, *CD* Cluster of Differentiation, *CID* Combined Immunodeficiency, *EBV* Epstein-Barr Virus, *EO* Eosinophils, *HHV8* Human Herpes virus type 8, *HIGM* Hyper IgM syndrome, *HLA* Human Leukocyte Antigen, *HSM* Hepatosplenomegaly, *HPV* Human papilloma virus, *IBD* Inflammatory bowel disease, *Ig* Immunoglobulin, *MC* Molluscum contagiosum, *N* Normal, not low, *NK* Natural Killer, *NN* Neonatal, *NP* Neutropenia, *SCID* Severe Combined ImmunoDeficiency, *Staph Staphylococcus sp.*, *TCR* T-Cell Receptor, *XL* X-Linked

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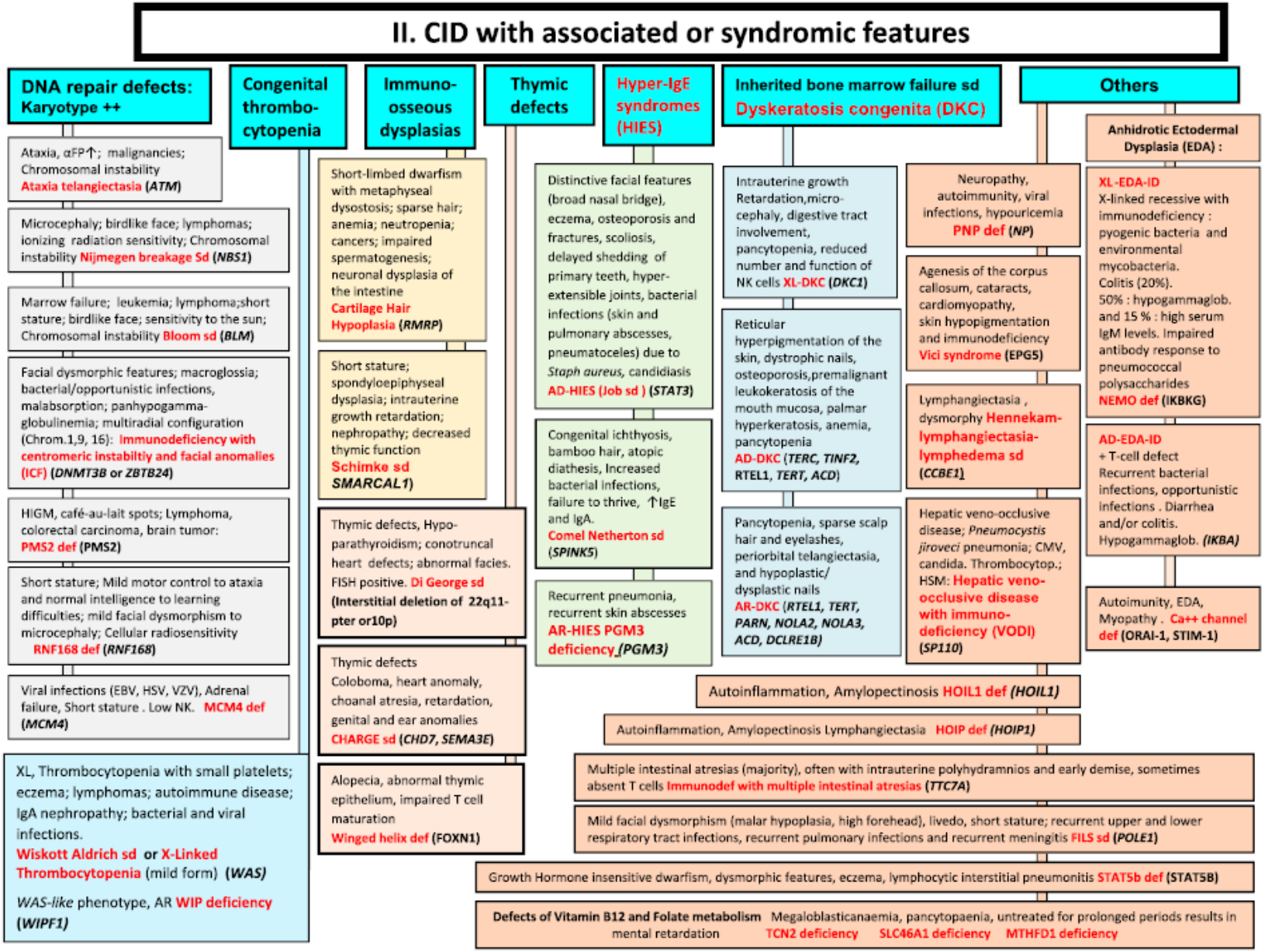

Fig. 2 CID with associated or syndromic features. These syndromes are generally associated with T-cell immunodeficiency. *αFP* alpha-fetoprotein, *AD* Autosomal Dominant inheritance, *AR* Autosomal Recessive inheritance, *CMF* Flow cytometry available, *EDA* Anhidrotic ectodermal dysplasia, *EDA-ID* Anhidrotic Ectodermal Dysplasia with Immunodeficiency, *FILS* Facial dysmorphism, immunodeficiency, livedo, and short stature, *FISH* Fluorescence in situ Hybridization, *HSM* Hepatosplenomegaly, *HSV* Herpes simplex virus, *Ig* Immunoglobulin, *VZV* Varicella Zoster virus, *WAS* Wiskott-Aldrich syndrome, *XL* X-Linked inheritance

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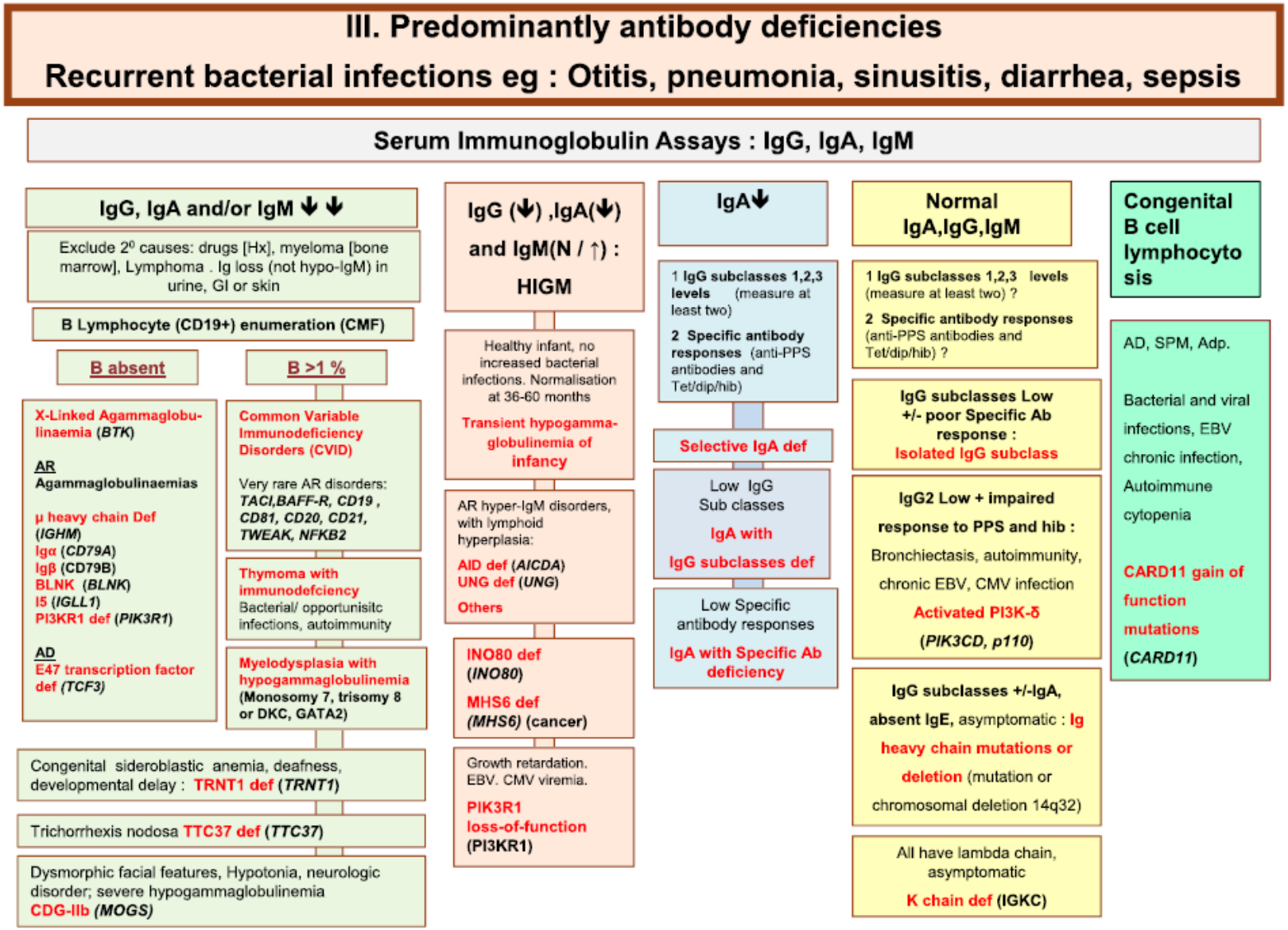

Fig. 3 Predominantly Antibody deficiencies. *Ab* Antibody, *Adp* adenopathy, *Anti PPS* Anti- pneumococcus Antibody, *AR* Autosomal Recessive inheritance, *CD* Cluster of Differentiation, *CDG-IIb* Congenital disorder of glycosylation, type IIb, *CMV* Cytomegalovirus, *CT* Computed Tomography, *EBV* Epstein-Barr Virus, *Dip* Diphtheria, *GI* Gastrointestinal, *Hib Haemophilus influenzae* serotype b, *Hx* medical history, *Ig* Immunoglobulin, *SPM* Splenomegaly, *subcl* subclass, *Tet* Tetanus, *XL* X-Linked inheritance

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Severe Primary Immunodeficiency in Infancy

The Diagnostic Challenge

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Primary immunodeficiencies (PID) are rare disorders, and by the time the diagnosis is made the child is too ill to benefit from curative treatment. Sadly whilst paediatricians often think of other rare diagnoses, PIDs are often not considered. This is no longer acceptable as for many of these conditions there is an 80% or higher chance of cure using the latest treatments.

The serious life threatening PIDs seen in infancy include:

- Severe Combined Immunodeficiency SCID
- Omenn's Syndrome
- Immune dysregulation Polyendocrinopathy Enteropathy X-linked IPEX
- Wiskott Aldrich Syndrome WAS
- Haemophagocytic Lymphohistiocytosis HLH
- Leucocyte Adhesion Deficiency LAD
- Chronic Granulomatous Disease CGD
- Severe Congenital Neutropaenia SCN

Remember the serious primary immune deficiency of infancy or "immunological emergencies" that require urgent action!

This booklet describes their key presenting features and highlights the abnormal results found in first and second line investigations.

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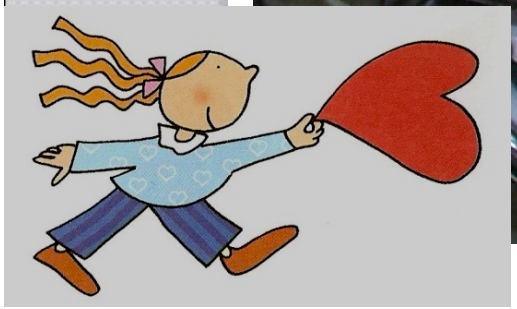

Consequences of Missed or Delayed Diagnosis

- It is often more difficult to diagnose mild forms of PIDs in comparison with severe forms of PIDs

- Severe forms of PIDs are characterized by:

  - absent/non functional T cells
  - absent/non functional NK cells
  - syndromes with profound T def.

- All patients present symptoms and require hospital admission before the second decade of life

- These patients are candidates for bone marrow transplantation

Consequences of Missed or Delayed Diagnosis

- Mild form of PIDs are characterized by:

  - absent/non functional B cells
  - absent/non functional aspecific defences
  - syndromes without profound T def.

- Patients can present symptoms and require hospital admission, but sometime are undiagnosed until adulthood

ASSOCIAZIONE IMMUNODEFICIENZE PRIMITIVE ONLUS

ipinet
italian primary immunodeficiencies network

ESID

116 XLA

230 CVID

105 CGD

118 WAS

DECEMBER 28, 1968 ORIGINAL ARTICLES THE LANCET

IMMUNOLOGICAL RECONSTITUTION OF SEX-LINKED LYMPHOPENIC IMMUNOLOGICAL DEFICIENCY

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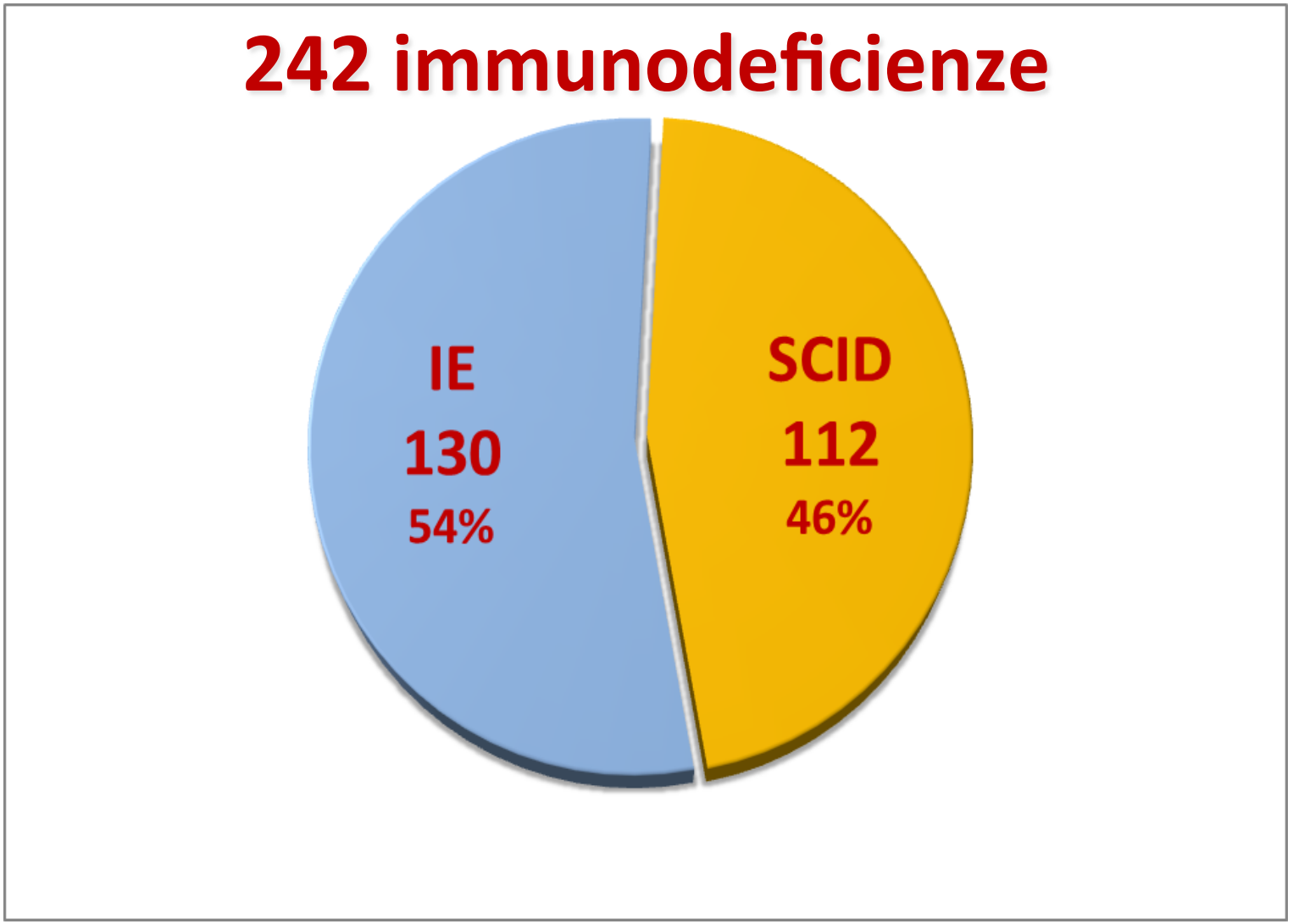
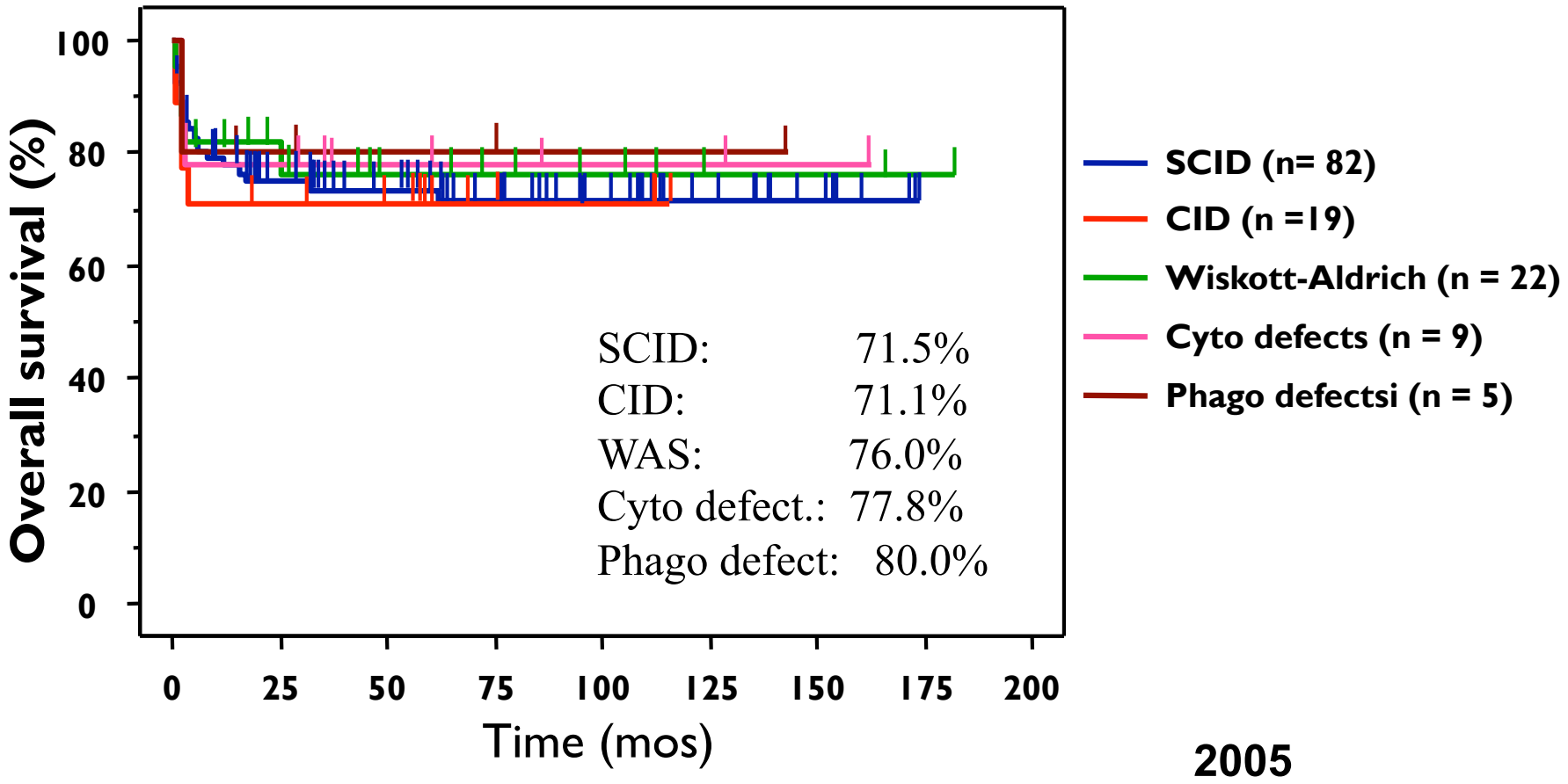
BMT ACTIVITY (1990-2015)



Event free survival in 137 children affected by PID

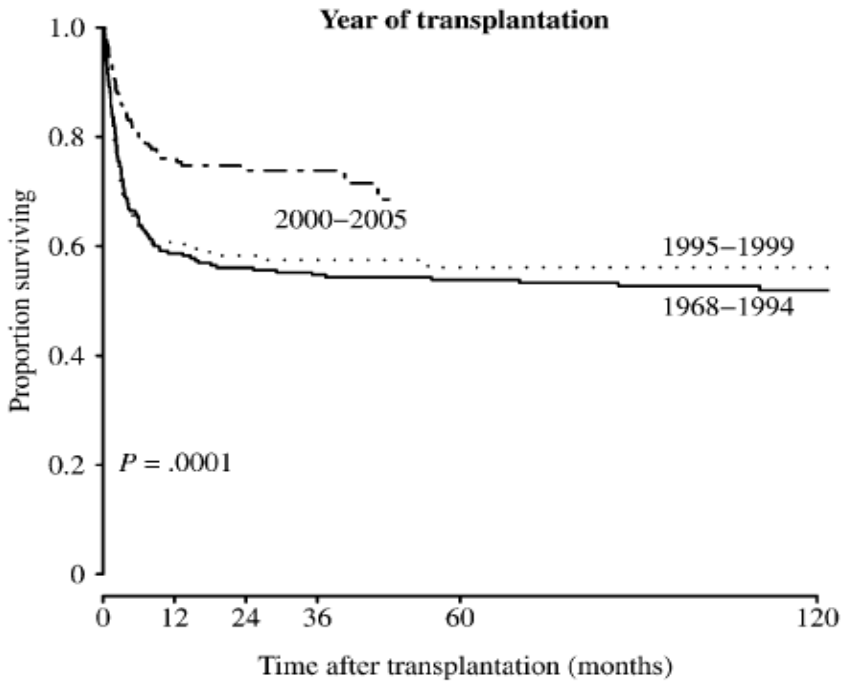


2005

Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better?

Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, Amrolia PJ, Gaspar HB, Davies EG, Friedrich W, Hoenig M, Porta F, et al.

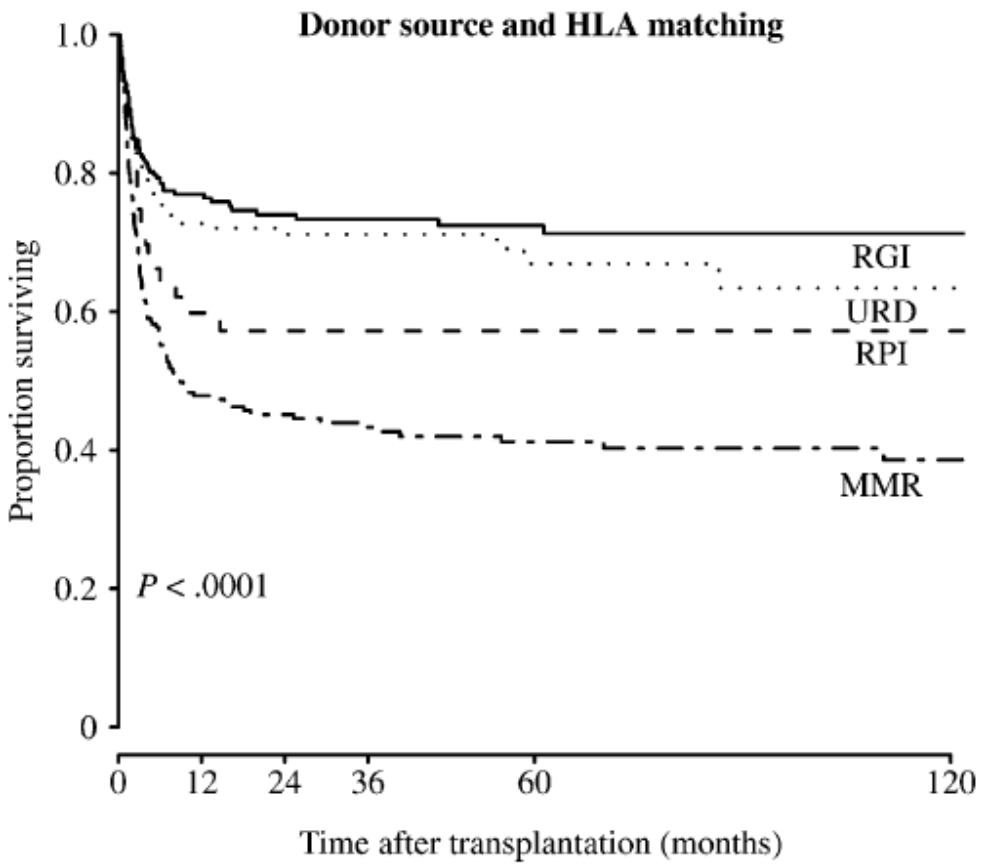
J ALLERGY CLIN IMMUNOL
SEPTEMBER 2010



Months	0	6	12	24	36	60	120
Number at risk							
1968–1994	278	179	135	129	125	114	52
1995–1999	238	137	109	79	61	36	5
2000–2005	267	185	123	79	44	0	0

Key messages

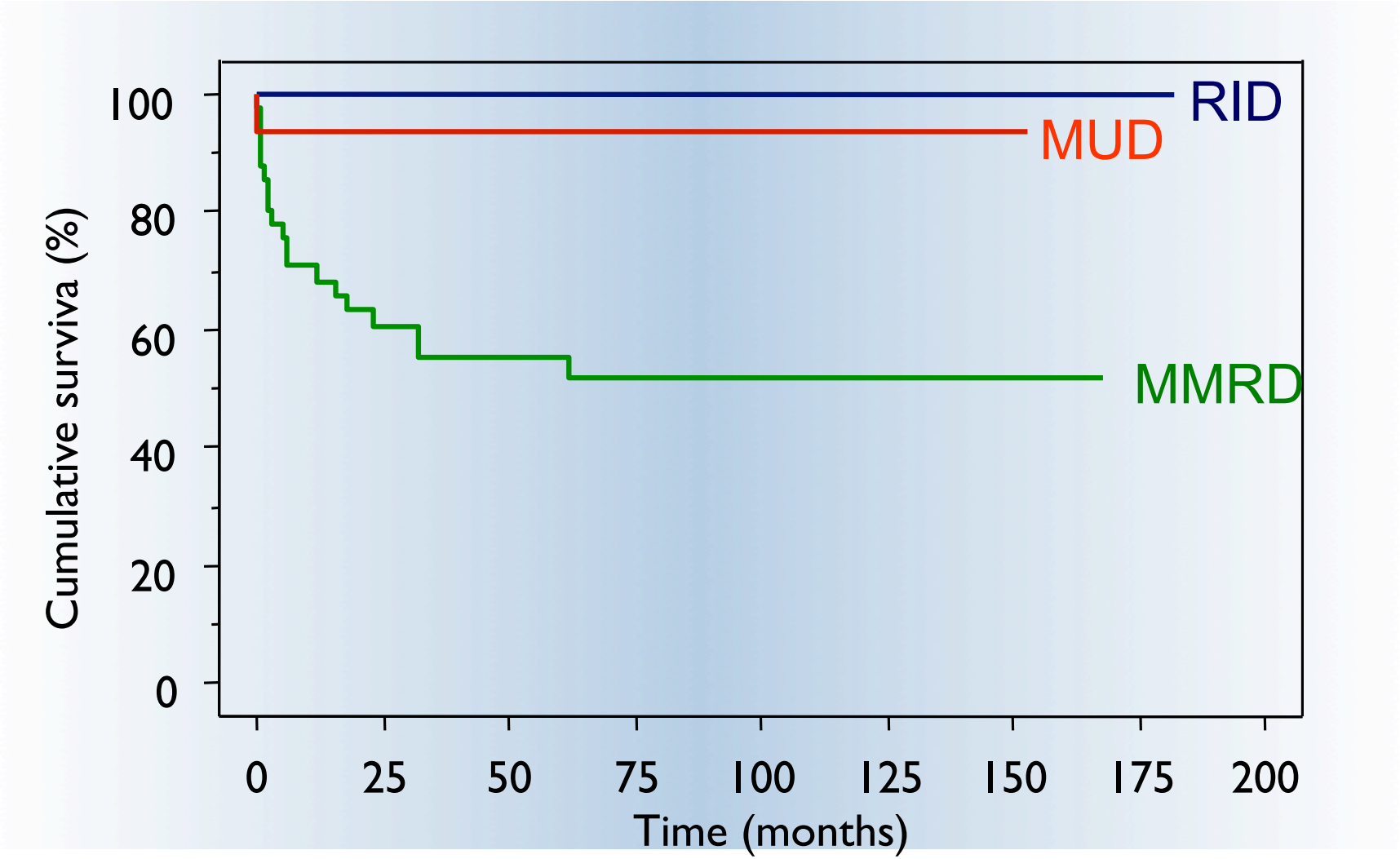
- Transplantation for primary immunodeficiency before 6 months of age is associated with improved outcome and supports the use of newborn screening programs to facilitate the early diagnosis of SCID.
- Prognosis after HSCT for PID is multifactorial, including molecular defect, disease status, donor, stem cell source, and conditioning regimen, and it is important now to analyze the long-term outcome for disease-specific groups.



Months	0	6	12	24	36	60	120
Number at risk							
RGI	251	186	138	110	90	67	29
RPI	65	36	25	18	13	9	2
URD	224	151	110	81	60	31	9
MMR	243	128	94	78	67	51	17

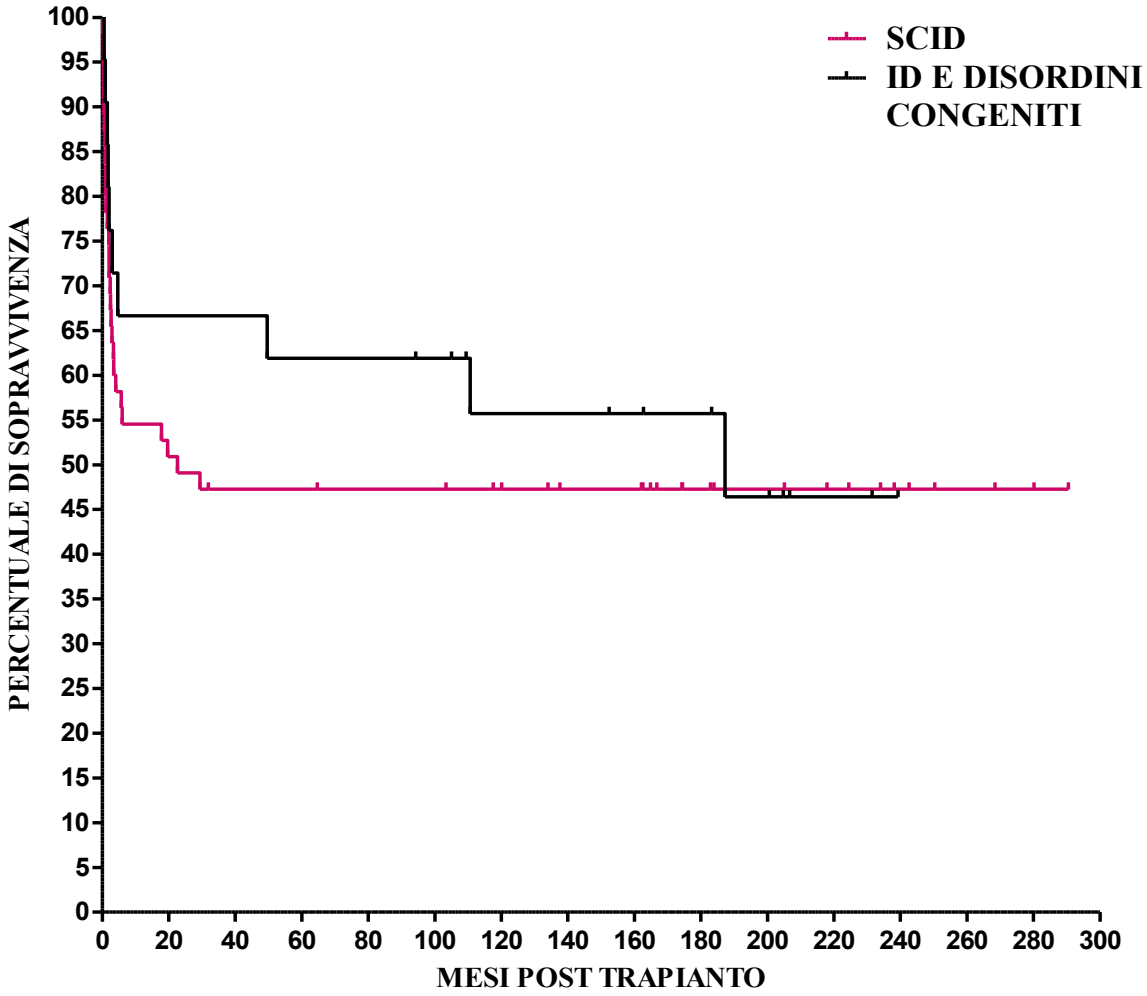
FIG 3. Cumulative probability of survival in patients with non-SCID PID after HSCT according to the period in which transplanted, donor source (related or URD), and HLA matching and type of immunodeficiency through all periods. *MMR,* Mismatched related; *RGI,* related genoidentical; *RPI,* related phenoidentical.

Survival following HSCT for PID



Brescia, April 2009

SOPRAVVIVENZA PAZIENTI TRAPIANTATI CON DONATORE APLOIDENTICO DAL 1991 AL 2016



Novel Conditioning

EBMT IEWP Chairmen: H.B.Gaspar, F.Porta

Donor/stem cell source	Serotherapy	Chemotherapy	GVHD prophylaxis	Diseases
		Reduced Intensity		
UD PBPCs	Camp 1mg/kg	Fludarabine 150 mg/ m^2 Melphalan 140 mg/m^2	CYA/MMF	T cell deficiency, HLH, LAD, XLP, CD40 ligand def
UD PBPCs	Camp 1mg/kg	Treosulphan 42 g/m^2 Fludarabine 150 mg/ m^2	CYA/MMF	WAS, SCID, gut disorders (CGD)
		Modified Ablative		
Any	ATG / Campath	Busulphan (IV) (wt or AUC dosing) Fludarabine 160 mg/ m^2	CYA/(MMF)	CGD, all

Avoid Melphalan 140mg/m^2 < 1 year of age unless HLH.
Consider dropping Campath dose to 0.6 mg/kg if Bone Marrow
Treosulphan 36mg/m^2 < 1 year of age

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ORIGINAL RESEARCH

Diagnosis, Treatment and Long-Term Follow Up of Patients with ADA Deficiency: a Single-Center Experience

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Table 1 Characteristics of ADA patients

Patient #	Gender (*M* = male, *F* = female)	Geographical origin	Age at the symptoms onset (*d* = day, *m* = months)	Age at diagnosis (months)	Lymphopenia	Severe respiratory infection	Failure to thrive	Hyperpyrexia	Candidiasis	Diarrhea
1	F	Tuscany, Italy	1 m	4.4	x	x	x	–	–	–
2	M	Romani	1 m–2 m	3.7	x	x	x	x	–	–
3	F	Apulia, Italy	1 m–6 m	6.8	x	x	x	x	x	–
4	M	Lombardy, Italy	3 d–3 m	3.8	x	–	–	x	–	–
5	F	Ukraine	NA	10.6	x	x	x	–	x	x
6	F	Calabria, Italy	–	prenatal	x	–	–	–	–	–
7	M	Tuscany, Italy	1 m	2.1	x	x	–	–	–	–
8	F	Apulia, Italy	10 d–24 d	1.2	x	x	x	–	–	–
9	M	Lombardy/Calabria, Italy	1 m	1.7	x	x	–	–	–	–
10	M	Romani	1 m	3.7	x	x	x	x	–	–
11	F	Romani	6 m	6.1	x	x	x	x	x	x
12	M	Romani	3 m	3.2	x	x	x	–	–	–
13	F	Apulia, Italy	1 m	2.7	x	x	x	x	–	–
14	F	Tunisia, Africa	1 m	2.1	x	x	–	–	–	x
15	M	Campania, Italy	NA	13	x	x	x	–	x	–
16	F	Apulia, Italy	3 m	3	x	x	x	–	–	–
17	M	Senegal, Africa	NA	1	x	–	–	–	–	–
18	M	Romani	15 d	2	–	x	–	x	–	x
19	F	Lombardy, Italy	NA	4	–	–	NA	–	–	–
20	F	Bulgaria	NA	6	x	x	–	x	x	x
21	M	Lazio, Italy	NA	24	x	x	–	–	–	–
22	F	Lazio, Italy	NA	3	–	–	–	–	–	–
23	M	Lazio, Italy	36 m	36	x	–	–	–	x	–
24	F	Macedonia	2 m–3 m	6.3	x	–	x	–	x	x
25	M	Romani	NA	3	–	–	NA	–	–	–
26	M	Serbia	NA	4	–	–	NA	–	–	–
27	F	Bulgaria/Campania, Italy	1 m–7 m	8.5	x	x	–	–	–	–

Patient #	Hypotonia	Bronchitis	Hepatomegaly	Dermatitis	Hypotrophy	Tremors	ADA activity in RBC at diagnosis U/g Hb	Therapies
1	x	–	–	–	–	–	0.20	HSCT
2	x	–	–	–	x	–	0	PEG-ADA/PEG-ADA*
3	x	–	x	x	x	–	0.34	HSCT
4	–	–	–	–	x	x	0.19	HSCT
5	–	–	–	–	–	–	0.39	HSCT
6	–	–	–	–	–	–	0.16	PEG-ADA
7	–	–	–	–	–	–	0.26	PEG-ADA/PEG-ADA*
8	–	–	–	–	x	–	0.17	PEG-ADA/GT*/HSCT
9	–	–	–	–	–	–	0	PEG-ADA
10	–	–	x	–	–	–	0.17	HSCT
11	x	–	–	–	–	–	0	PEG-ADA
12	–	–	x	–	–	–	0	PEG-ADA
13	x	–	–	–	–	–	transfused	PEG-ADA/GT*

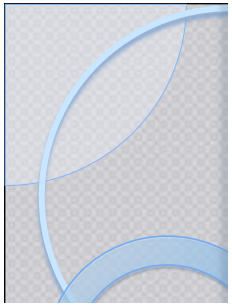

Table 1 (continued)

Patient #	Hypotonia	Bronchitis	Hepatomegaly	Dermatitis	Hypotrophy	Tremors	ADA activity in RBC at diagnosis U/g Hb	Therapies
14	–	–	–	x	–	–	0.54	PEG-ADA/HSCT
15	–	–	x	–	–	–	0.11	PEG-ADA*/GT*
16	x	x	x	–	–	–	0	PEG-ADA*/GT*
17	–	x	–	–	–	–	0.32	HSCT*
18	–	–	–	–	–	–	transfused	HSCT
19	–	–	–	–	–	–	transfused	HSCT*
20	–	–	–	x	–	–	ND	PEG-ADA
21	–	–	–	–	–	–	ND	PEG-ADA*
22	–	–	–	–	–	–	ND	PEG-ADA*
23	–	x	–	–	–	–	ND	PEG-ADA*
24	–	x	–	–	–	–	transfused	PEG-ADA/HSCT
25	–	–	–	–	–	–	0.13	HSCT*
26	–	–	–	–	–	–	0.32	PEG-ADA*
27	–	x	–	x	–	–	transfused	HSCT

GT gene therapy; *Hb* hemoglobin; *HSCT* hematopoietic stem cell transplantation; *NA* not available; *ND* not done; *RBC* red blood cells; * performed or followed in another center; − absence of the clinical feature; x presence of the clinical feature

Table 2 HSCT characteristics and outcomes

Patients	Age at HSCT (months)	Donor	Type of conditioning	$CD34^+$/ Kg × 10^6	$CD3^+$/ Kg × 10^6	Clinical complication	Post-HSCT follow up (months)	Latest lymphocyte values (μL)	Latest engraftment	Last RBC ADA activity (U gHb)	Ig replacement duration (months)	Post-HSCT vaccination beginning (months)	Vaccination responses
#1	4.5	sister	no	8.6	42.8	cutaneous GVHD grade I	123	1498	$CD3^+$: 100 % $CD19^+$: 94.8 %	1.45	43	53	yes
#3	7.2	brother	no	7.6	52	no	212	1545	$CD3^+$: 100 % $CD19^+$: 100 % PMN: 27.3 %	0.93	33	33	yes
#4	7.4	MUD[a] (9/10)	busulfan, cyclophosphamid, anti-thymocyte globulin	12.6	23	no	137	1434	$CD3^+$: 100 % $CD19^+$: 100 % PMN: 19.3 %	0.74	69	73	yes
#5	19.9	MUD (10/10)	busulfan, cyclophosphamid, anti-thymocyte globulin	9	50	no	91	3335	$CD3^+$: 100 % $CD19^+$: 100 % PMN: 100 %	1.20	18	20	yes
#8	105.5	sister	no	3.8	16.9	no	42	930	$CD3^+$: 100 % $CD19^+$: 100 % PMN: 100 %	1	2	12	yes
#10	4.8	brother	no	8	75	no	144	2070	$CD3^+$: 96.1 % $CD19^+$: 81.7 % PMN: 63.2 %	1.17	30	36	yes
#14	27.2	MUD (10/10)	no	17.6	64	no	64	1307	$CD3^+$: 100 % $CD19^+$: 100 % PMN: 100 %	1.27	25	27	yes
#18	2.6	sister	no	14.7	104.3	died 1 week after HSCT	0.1	NA	NA	NA	NA	NA	NA
#24	21.1	brother	no	18.3	47.5	no	32	2190	$CD3^+$: 89.9 %	1.37	ongoing	NA	NA
#27	11.8	MUD (10/10)	busulfan, fludarabine, anti-thymocyte globulin	10.5	75.5	hemolytic anemia, hepatic GVHD grade II	18	351	$CD3^+$: 100 % $CD19^+$: 100 % PMN: 100 %	ND	ongoing	NA	NA

GVHD Graft Versus Host Disease; *MUD* Matched Unrelated Donor; *NA* not applicable; *ND* not done; *PMN* Polymorphonuclear cells

[a] For MUD donors, HLA matching is reported

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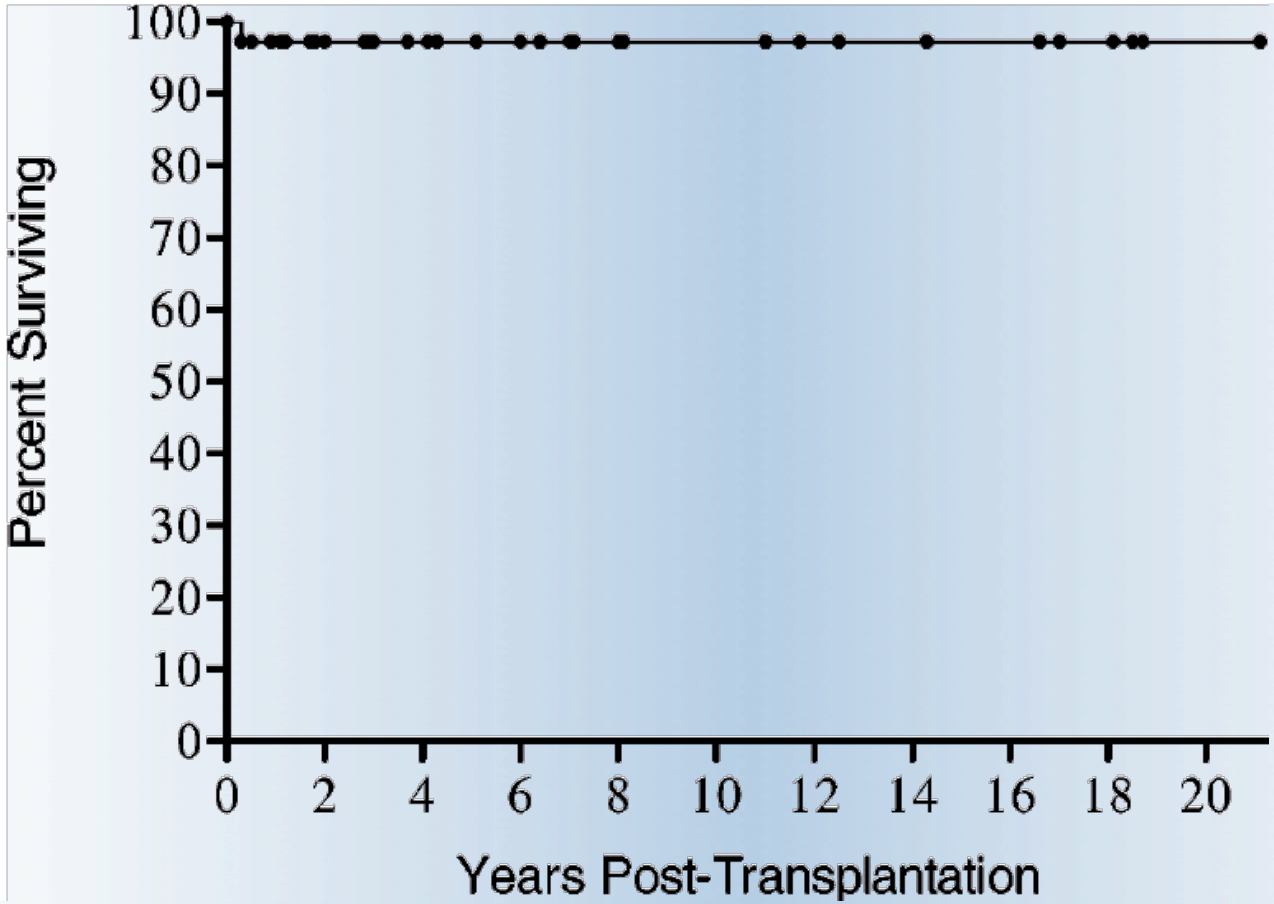

Figure 7 Kaplan Meier plot of 36 SCID infants transplanted in the first 3.5 months of life. Thirty-five survive from 3 months to 21.3 years post-transplantation; only 5 had HLA-identical donors.

(Buckley, 2004)

SEMINARS IN PERINATOLOGY 39 (2015) 194–205

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History and current status of newborn screening for severe combined immunodeficiency

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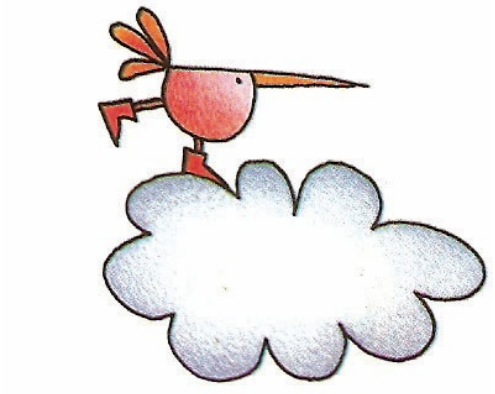
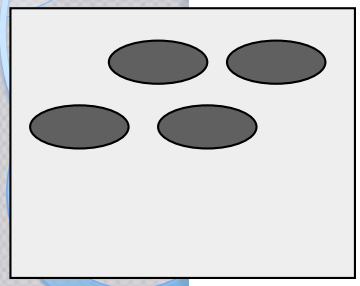
Department of Pediatrics, UCSF Benioff Children's Hospital, University of California San Francisco, Box 0519, 513 Parnassus Ave, HSE 301A, San Francisco, CA 94143-0519



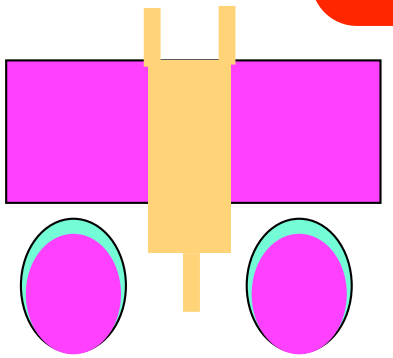


SSCP

Anti CD34

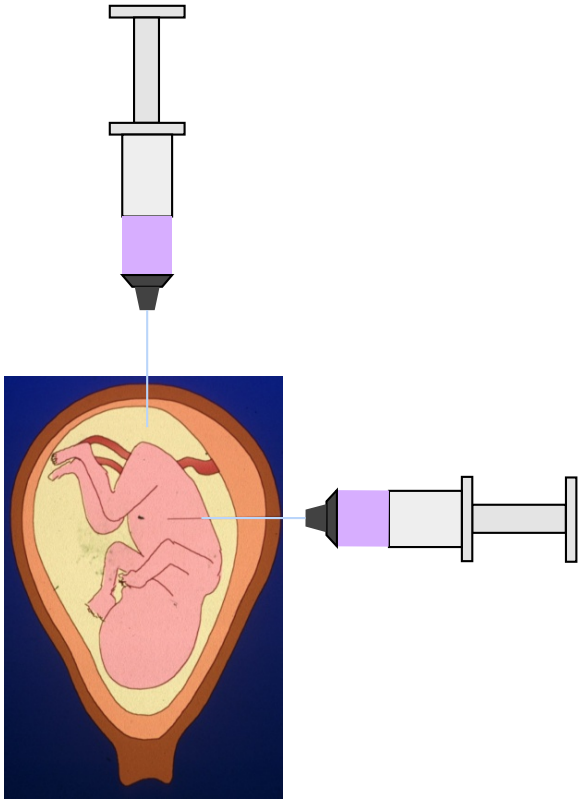
Midollo osseo paterno

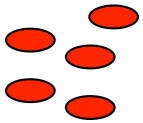
DNA

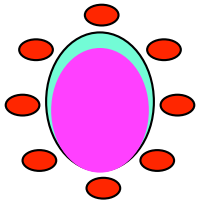


CD34 CD2

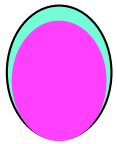
Deplezione T linfociti





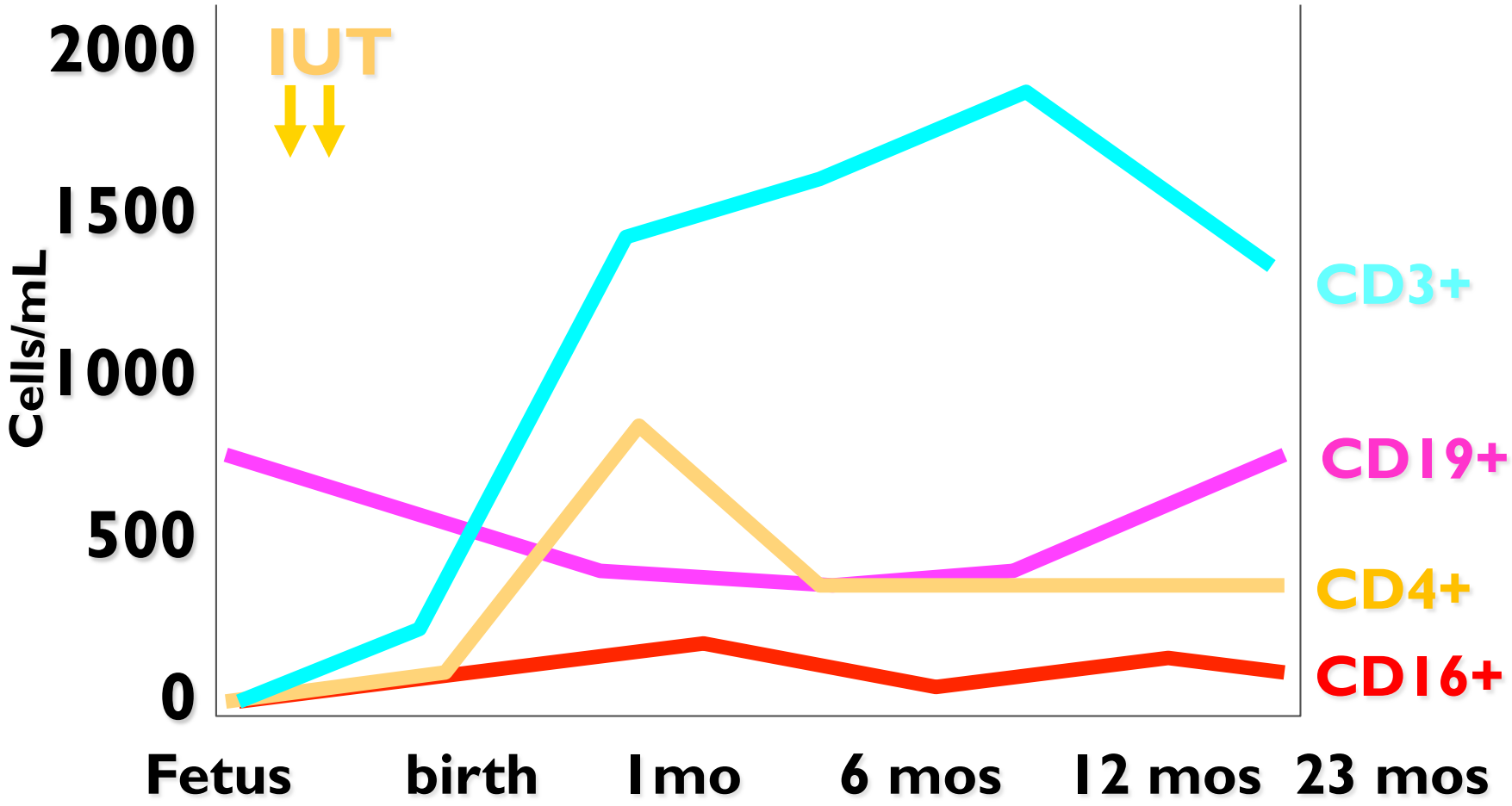


CD2

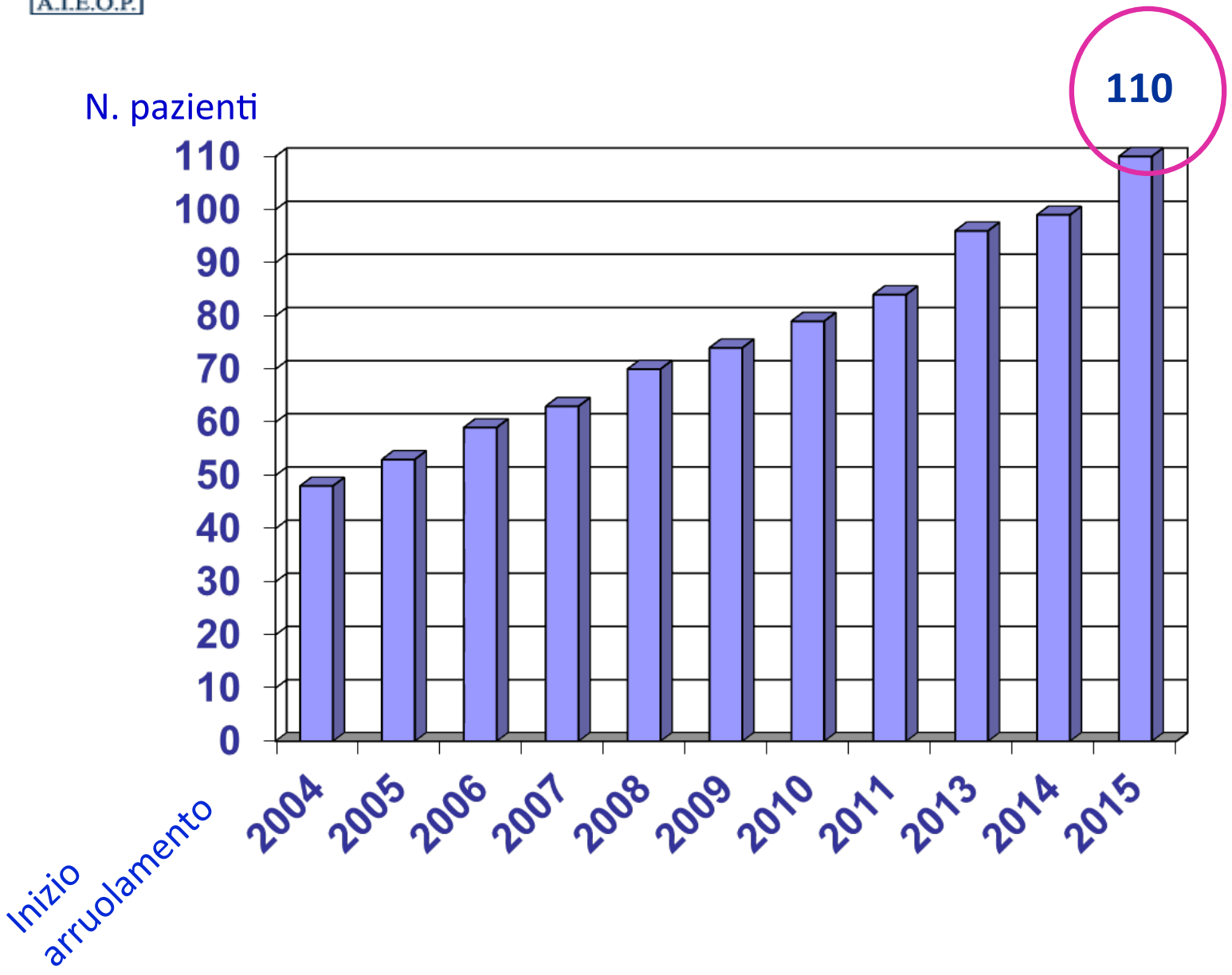


CD34

Immunological reconstitution following IUT in a fetus with SCIDX1 (fetus#1)

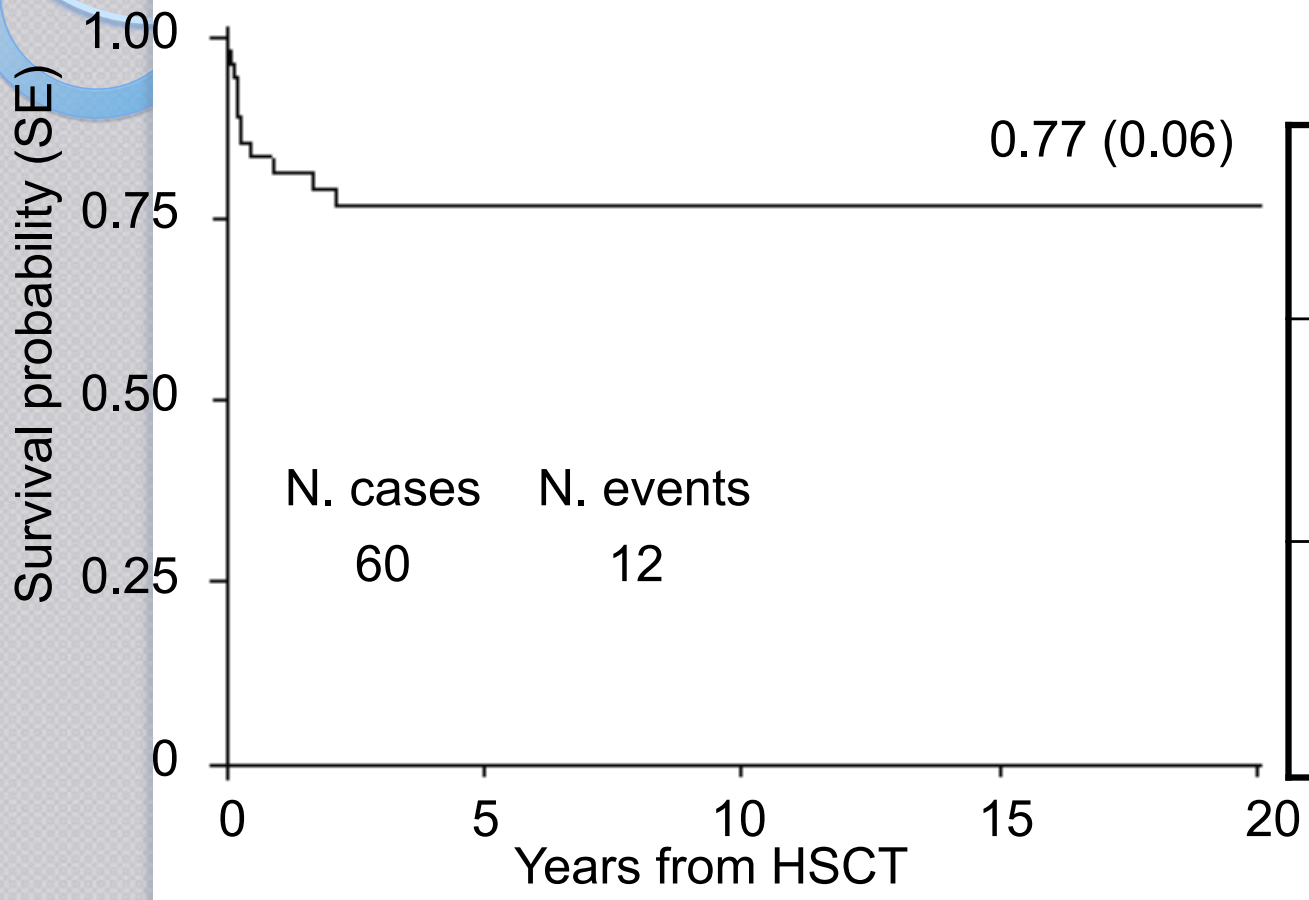


AIEOP WAS-XLT



Settembre 2015

AIEOP WAS
Curva di sopravvivenza dopo TCSE



Number of cases at risk:

60 28 19 9 4

	Mediana (min-max)
Età al TCSE	21 mesi (4,8m- 8 aa)
Tempo tra diagnosi-TCSE	10 mesi (16gg – 7 aa)

Maggio 2014

Malattia granulomatosa cronica (CGD)

Malattia da immunodeficienza congenita provocata da un'alterazione del gene che codifica una componente dell'enzima NADPH ossidasi

frequenza: **circa 1/200.000 nati vivi**

genetica:
- **X-recessiva (60% dei casi)**
- **autosomica recessiva**

esordio nei primi mesi di vita

infezioni ricorrenti fungine (*Aspergillus species, Candida species*) e batteriche (*Staphilococcus aureus, Serratia marcescens, Pseudomonas*) accompagnate da risposte cellulo-mediate croniche ed evoluzione granulomatosa delle lesioni: polmonite, linfoadenite, osteomielite, ascessi epatici, infezioni SNC.

COMITATO STRATEGICO E DI STUDIO IMMUNODEFICIENZE

ASSOCIAZIONE ITALIANA DI EMATOLOGIA ED ONCOLOGIA PEDIATRICA

MALATTIA GRANULOMATOSA CRONICA
RACCOMANDAZIONI PER LA DIAGNOSI E LA TERAPIA

Versione definitiva: Dicembre 2000

Versione aggiornata: Dicembre 2007

3.5. Trapianto di Midollo Osseo

Malgrado i progressi realizzati negli ultimi anni nella profilassi e nella terapia delle infezioni, questa malattia resta caratterizzata da una bassa qualità di vita e da una elevata prevalenza di mortalità. Le cause possono essere ascritte a

- ridotta compliance alla profilassi farmacologica per tutta la vita;
- difficoltà a prevenire le sequele infiammatorie croniche e danni d'organo permanenti;
- lunghe e frequenti ospedalizzazioni.

Studi internazionali multicentrici dimostrano che il rate di sopravvivenza in terza decade si attesta intorno al 50% e non è variato in maniera significativa nel corso dell'ultima decade.
Il Registro Americano stima una mortalità annua per malattia tra il 2% per le forme AR e il 5% per le forme X recessive.
Allo stato attuale l'unica possibilità di guarigione definitiva è offerta dal Trapianto di Midollo Osseo. La recente esperienza internazionale del TMO da donatore HLA identico nella CGD dimostra che le percentuali di successo sono sovrapponibili a quelle di altre malattie ematologiche (es. thalassemia) sottoposte a trapianto, e aumentano se questo viene eseguito prima della adolescenza e, comunque, prima dell'instaurarsi di complicanze infiammatorie croniche e/o danni d'organo permanenti. Sulla base di queste osservazioni, il CSS AIEOP delle ID riunitosi a Firenze il 10 e 11 Dicembre 2004 ha deciso di modificare le precedenti indicazioni relative al trapianto di Midollo osseo nella CGD.

Si raccomanda pertanto di :

- informare e discutere con la famiglia della possibilità di cura di questa malattia tramite trapianto di midollo osseo, già al momento della diagnosi.
- avviare la ricerca di un donatore HLA identico familiare o non consanguineo

TRAPIANTI E FOLLOW UP PAZIENTI CGD

Patient ID	Age at HSCT (months)	Donor*	Type of conditioning	Source and manipulation	$CD34^+$ /Kg $x10^6$	$CD3^+$ /Kg $x10^5$	Hematological engraftment (days post HSCT)	% of donor chimerism	Clinical complication	Post-HSCT follow up
P1	16	MUD 10/10	Busulfan+thiotepa+ cy+atg	HPC-M - MNC	4.27	ND	+21	PBL 100% PMN 100% after 5 years	Cutaneous, hepatic and intestinal aGvHD grade II	Alive after 18 years
P2	7	Father HLA ID	Busulfan+ mabcampath+cy	HPC-M – $CD34^+$ positive selection and buffy coat	27.26	505.62	+26	PMN 87.7% after 61 days	Hepatic and intestinal aGvHD grade II; CVC sepsis; TTP; Adenovirus	/
P2 II	10	Father HLA ID	None	HPC-A – $CD34^+$ positive selection	28.1	0,000	+15	PMN 0% after 7 years	EBV-associated lymphoproliferative disorders	Alive after 9.6 years
P3	22	Sister HLA ID	Busulfan+cy+ melphalan+atg	HPC-M – Unmanipulated	9.2	423.00	+23	PMN 100% after 2 months	TTP; CMV reactivation	Death after 3,1 months
P4	43	MUD 10/10	Busulfan+thiotepa+ cy+atg	HPC-M – Buffy coat	1.79	318.00	+20	PBL 100% PMN 100% after 22 days	Central nervous system complications; Aspergillus	Death after 1,6 months
P5	37	MUD 10/10	Busulfan+fludarabin + mabcampath	HPC-M – $CD34^+$ positive selection, buffy coat, MNC	8.97	175.69	+21	CD3+ 93.1% CD19+ 100% CD15+ 100% after 4 years	Cutaneous aGvHD grade I; CMV reactivation	Alive after 5.6 years
P6	120	MUD 10/10	Busulfan+atg+ campath	HPC-A - $CD34^+$ positive selection and negative fraction	33.48	150.91	+20	PBL 88.7% PMN 85.7% after 6 months	None	Death after 6,4 months
P7	19	Brother HLA ID	Busulfan+ fludarabin+atg	HPC-M - Unmanipulated	11.24	23.25	+21	PBL 73.1% PMN 84.5% after 2 years	EBV-associated lymphoproliferative disorders	Alive after 2.9 years
P8	56	MUD 10/10	Busulfan+ fludarabin+atg	HPC-M – $CD34^+$ positive selection and MNC from negative fraction	6.3	249.31	None	PBL 0% PMN 0% after 20 days	Fever; rising inflammatory markers; Aspergillus; CMV reactivation	/
P8 II	57	MUD 10/10	Treosulfan+cy+atg	HPC-A - $CD34^+$ positive selection and negative fraction	17,26	297,7	+12	PBL 100% PMN 100% after 15 days	Cutaneous rash; cough; polipnea; Aspergillus; CMV reactivation	Death after 3,4 months

* for MUD donors, HLA matching is reported.

aGvHD: acute Graft versus Host Disease; ATG: Anti-thymocyte globulin; CMV: Citomegalovirus; CY: Cyclofosfamide; HPC-A: Hematopoietic Progenitor Cell-Apheresis; HPC-M: Hematopoietic Progenitor Cell-bone marrow; MNC: Mononuclear cells; MUD: Matched Unrelated Donor; ND: not done; TTP: Thrombotic Thrombocytopenic Purpura; PMN: Polymorphonuclear cells; PBL: Peripheral Blood Lhymphocytes; II: second transplant

Bone Marrow Transplantation (2015), 1–3

www.nature.com/bmt

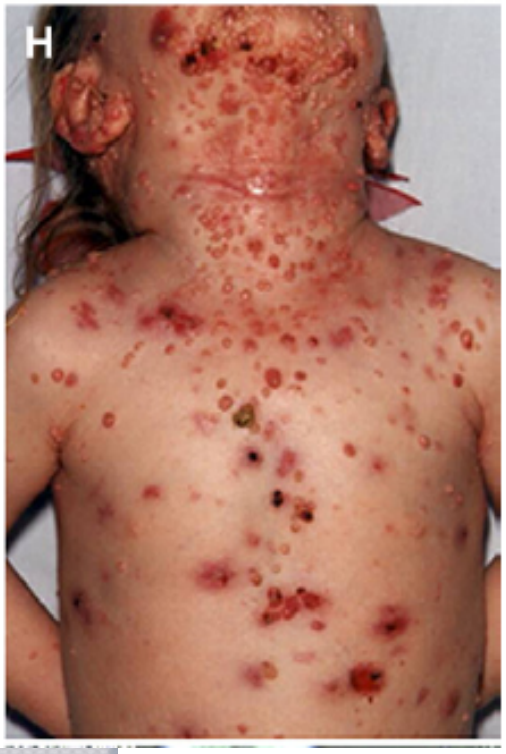
Letter to the Editor

Bone Marrow Transplantation advance online publication 14 September 2015; doi: 10.1038/bmt.2015.201

Partial depletion of TCR alpha/beta$^+$/ CD19$^+$ cells in matched unrelated transplantation of three patients with osteopetrosis

F Porta[1], S Cavagnini[1], L Imberti[2], A Sottini[2], F Bolda[3], A Beghin[3], A Caruso[3,4] and A Lanfranchi[3]

[1]Oncohaematology and Bone Marrow Transplantation Unit, Children's Hospital, Brescia, Italy
[2]Centro Ricerca Emato-oncologica AIL (CREA), Diagnostics Department, Spedali Civili of Brescia, Brescia, Italy
[3]Section of Haematology and Coagulation, Stem Cell Lab, Spedali Civili of Brescia, Brescia, Italy
[4]Section of Microbiology, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy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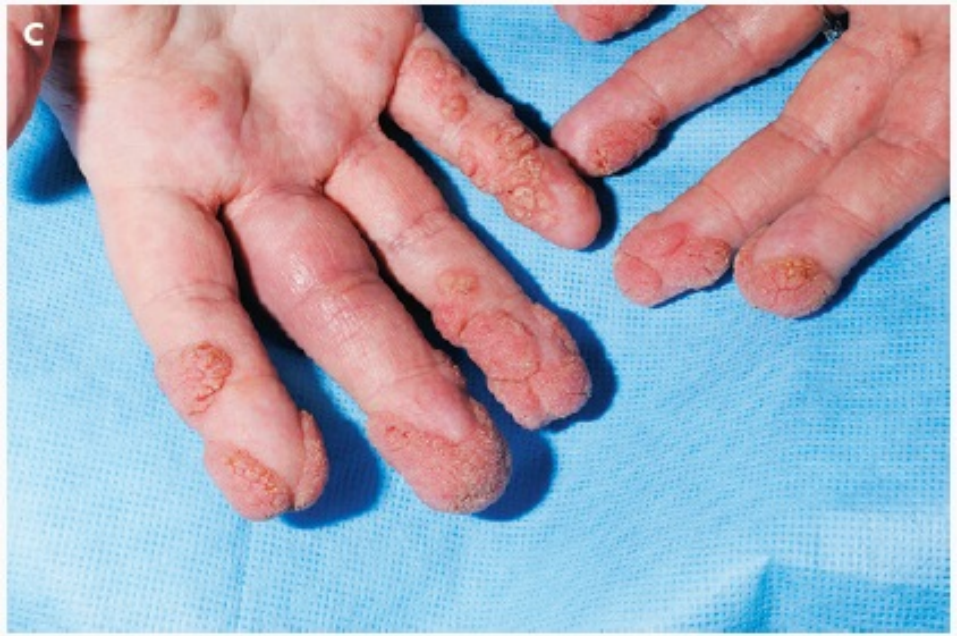
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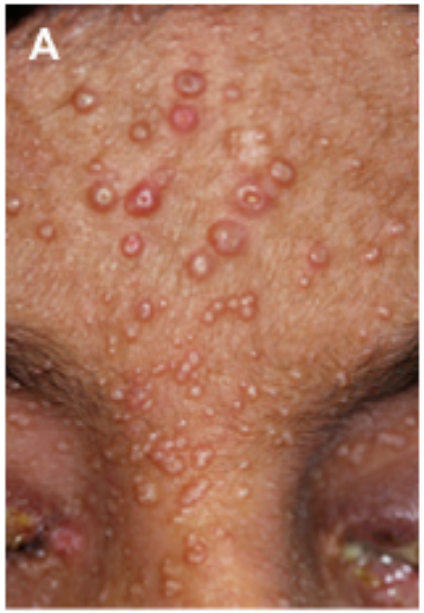
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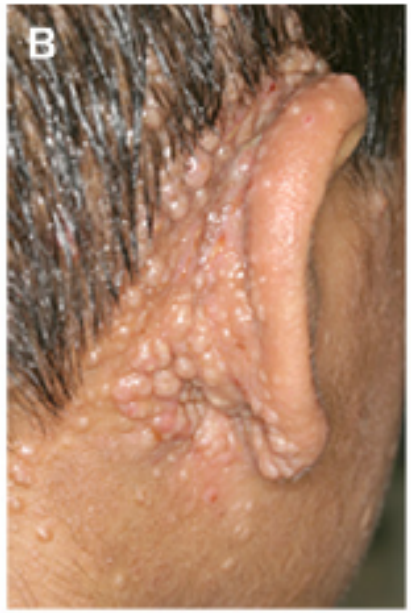
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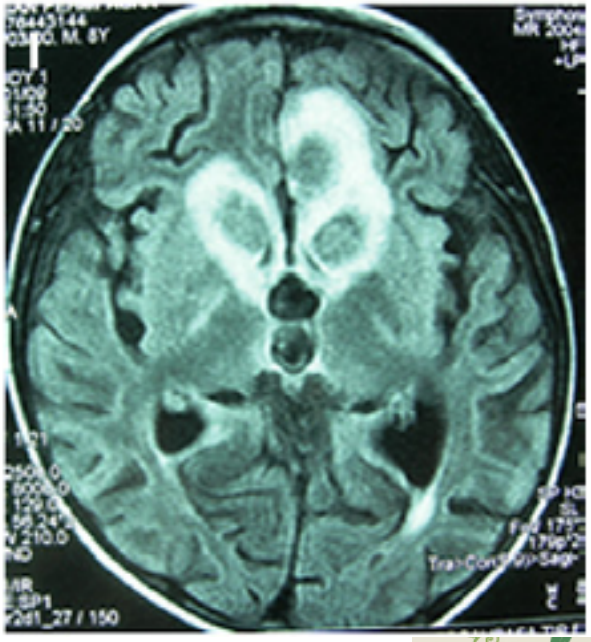


Sindrome da Iper IgE

Table 1

A classification of HIES

HIES type	Inheritance	Discriminant clinical findings
Type 1	Sporadic (more than 90% of cas Familial with autosomal dominant	
Type 2	Familial with autosomal recessive	

Current Opinion in Immunology 2009, 21:487–492

Table 3. Relative Frequency of Features of *DOCK8* Deficiency vs Job's Syndrome

Feature	*DOCK8* Deficiency	Job's Syndrome
Eczematous dermatitis	++++	++++
Newborn rash	+	+++
Coarse facies	–	+++
Retention of primary teeth	+	++++
Joint hyperextensibility	+	+++
Minimal trauma fractures	+	+++
Elevated serum IgE levels	++++	++++
Eosinophilia	++++	++++
Asthma	+++	+
Allergies	+++	++
Skin abscesses	++	+++
Mucocutaneous viral infections	++++	+
Mucocutaneous candidiasis	++	+++
Sinopulmonary infections	++++	++++
Squamous cell carcinoma	++	–
Lymphoma	+	+

AZIENDA OSPEDALIERA SPEDALI CIVILI - BRESCIA

U.O. Laboratorio di Analisi Chimico Cliniche - Spedali Civili

Cattedra di Biochimica Clinica e Biologia Molecolare Clinica - Università di Brescia

Responsabile: Prof. Luigi Caimi

Sistema Qualità Certificato ISO 9001:2008

Id.: **93039616** Sig.ra O.B.A

Data Nascita: 07/04/2009 Età: 5 Anni Sesso: F Codice Sanitario: 740MT280

Medico:

Destinazione referto: **037 Ambulatori Pediatrici**

Richiesta: **04291153** Del: **29/04/2014** Ore: 08:00 Routine

Esame	Risultato	Unità di misura	Valori di riferimento
ESAME EMOCROMOCITOMETRICO			
Globuli Bianchi (WBC)	**4.87**	x10^3/uL	4.50 - 17.00
Globuli Rossi (RBC)	**4.72**	x10^6/uL	4.00 - 5.00
Emoglobina (Hb)	**11.3**	g/dL	10.5 - 15.5
Ematocrito (HCT)	**35.3** L	%	37.0 - 47.0
Volume Globulare medio (MCV)	**74.8** L	fl	75.0 - 95.0
Contenuto Emoglobin. medio (MCH)	**23.9** L	pg	27.0 - 31.0
Conc. cellulare media di Hb (MCHC)	**32.0**	g/dL	32.0 - 37.0
Distrib. volumi eritrocitari (RDW)	**19.1** H	%	12.0 - 17.0
Piastrine (PLT)	**433** H	x10^3/uL	100 - 400
FORMULA LEUCOCITARIA			
Neutrofili	**43.7**	%	40.0 - 74.0
Linfociti	**39.9**	%	20.0 - 45.0
Monociti	**11.4** H	%	3.40 - 9.00
Eosinofili	**4.7**	%	0.00 - 8.00
Basofili	**0.3**	%	0.00 - 1.50
Neutrofili	**2.13**	x10^3/uL	1.30 - 8.50
Linfociti	**1.94**	x10^3/uL	1.30 - 8.50
Monociti	**0.55**	x10^3/uL	0.10 - 1.00
Eosinofili	**0.23**	x10^3/uL	0.10 - 0.60
Basofili	**0.02**	x10^3/uL	0.00 - 0.20
CHIMICA CLINICA			
P-Glucosio	**80**	mg/dL	60 - 100
P-Creatinina	**0.36**	mg/dL	0.30 - 0.90
P-Bilirubina totale	**0.24** L	mg/dL	0.30 - 1.20
P-Bilirubina diretta	**<0.10**	mg/dL	< 0.30
P-Bilirubina indiretta	**0.14** L	mg/dL	0.20 - 0.90
P-Sodio	**139**	mmol/L	138 - 144
P-Potassio	**4.1**	mmol/L	3.3 - 4.7

segue

Referto firmato digitalmente in data 29/04/2014 15:30:32 da dott.
secondo la normativa vigente.

AZIENDA OSPEDALIERA SPEDALI CIVILI - BRESCIA

U.O. Laboratorio di Reumatologia e Immunologia Clinica
Cattedra di Reumatologia - Università di Brescia
Direttore: Prof.ssa Angela Tincani

Sistema Qualità Certificato ISO 9001:2008

Id.: **93039616** Sig.ra O.B.A
Data Nascita: 07/04/2009 Età: 5 Anni Sesso: F Codice Sanitario: 740MT280
Medico:

Destinazione referto: **037 Ambulatori Pediatrici**

Richiesta: **04291153** Del: **29/04/2014** Ore: 08:00 Routine

Esame	Risultato	Unità di misura	Valori di riferimento
Complemento			
Attivita' emolitica totale (CH50)	**101.92**	%	94.00 - 184.00
Tipizzazioni linfocitarie			
Immunofenotipizzazione estesa delle cellule ematiche			
CD3+ Linfociti totali	**31.6** L	%	52.0 - 83.0
CD3+ conta assoluta	**667** L	Cell/uL	770 - 1 880
CD3+ CD4+ Linfociti T Helper	**18.2** L	%	31.0 - 58.0
CD3+ CD4+ conta assoluta	**384** L	Cell/uL	470 - 1 240
CD3+ CD8+ Linfociti T Suppressor	**3.7** L	%	16.0 - 40.0
CD3+ CD8+ conta assoluta	**78** L	Cell/uL	215 - 730
CD4+ / CD8+ rapporto	**4.9** H		0.8 - 3.6
CD19+ Linfociti B	**40.8** H	%	5.0 - 18.0
CD19+ conta assoluta	**861** H	Cell/uL	100 - 390
CD16+ Linfociti NK	**24.4**	%	5.0 - 27.0
CD16+ conta assoluta	**515**	Cell/uL	70 - 550
HLA-DR+	**43.0** H	%	2.0 - 21.0

(i valori di riferimento sono validi per una popolazione adulta)

Si consiglia di interpretare i risultati contenuti nel presente referto con il proprio medico di fiducia.

Referto firmato digitalmente in data 02/05/2014 18:00:01 da dott.
secondo la normativa vigente.

O.B.A. (dn 07/04/09) 4

Risposta proliferativa ai mitogeni (09/05/14):

CD3 (200 ng/ml): pz 18 x 10.000 cpm,
controllo sano 86 x 10.000 cpm

CD3+ (200 ng/ml) + IL2 (20 U/ml): pz 67 x 10.000 cpm,
controllo sano 87 x 10.000 cpm

PHA (25 microgra/ml): pz 25 x 10.000 cpm,
controllo sano 133 x 10.000 cpm

PMA (5 ng/ml) + ionomicina: pz 129 x 10.000 cpm,
controllo sano 121 x 10.000 cpm

IL2 (200 U/ml): pz 6,2 x 10.000 cpm,
controllo sano 6 x 10.000 cpm

Non stimolato: pz 0,6 x 10.000,
controllo sano 1 x 10.000 cpm

Risposta ai limiti della norma

O.B.A. (dn 07/04/09) 2

-benessere fino all'inizio della scuola materna

-infezioni riccorenti delle alte vie aeree (tosse/febbre 1 episodio al mese circa)

-a marzo 2013 ricovero presso altro Presidio per BPN dx con scissurite

-da maggio 2013 ad aprile 2014 9 episodio di flogosi delle alte vie aeree (bronchiti, otiti)

-marzo 2014 sospetta mastoidite (non conferma ORL) trattata con amoxicillina+acido clavulanico

-aprile 2014 BPN dx

-giugno 2014: ricovero in Pediatria Ovest per BPN dx a lenta, alle indagini colturali aspirato naso-faringeo positivo per Haemophilus influenzae e virus parainfluenzale 3

-settembre 2014: bronchite

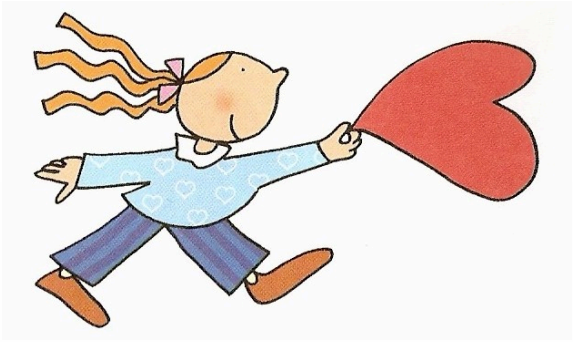
-ottobre 2014: BPN iloperilare dx e basale

-novembre 2014: ricovero in Pediatria per probabile infezione fungina

-dicembre 2014: ricovero in Pediatria per BPN da verosimile infezione fungina

-dicembre 2014: ricovero in Pediatria per BPN da verosimile origine fungina

-**gennaio 2015: peggioramento quadro respiratorio e radiologico polmonare: agobiopsia polmonare che risulta compatibile con linfoma di Hodgkin B a grandi cellule EBV correlato (granulomatosi linfomatoide di grado 3)**



Pediatr Blood Cancer 2015;62:1782–1789

Non-Hodgkin Lymphoma in Children With an Associated Inherited Condition: A Retrospective Analysis of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)

Maurizio Aricò, MD,[1]* Lara Mussolin, PhD,[2] Elisa Carraro, BS,[3] Salvatore Buffardi, MD,[4] Nicola Santoro, MD,[5] Paolo D'Angelo, MD,[6] Alessandra Lombardi, MD,[7] Paolo Pierani, MD,[8] Eugenia Giraldi, MD,[9] Rossella Mura, MD,[10] Alessandra Sala, MD,[11] Alberto Garaventa, MD,[12] Annalisa Tondo, MD,[13] Matilde Piglione, MD,[14] Luca Lo Nigro, MD,[15] Simone Cesaro, MD,[16] Katia Perruccio, MD,[17] Angelo Rosolen, MD,[3,†] Giuseppe Basso, MD,[3] Marta Pillon, MD,[3] and On behalf of the NHL-Committee of the Italian Association of Pediatric Hematology Oncology (AIEOP)

Background. Inherited conditions affecting genetic aberration, viral oncogenesis, reduced immune surveillance, and long-lasting antigen stimulation may build the way to lymphomagenesis in humans. ***Methods.*** We extracted from the database of 4 consecutive trials for pediatric non-Hodgkin lymphoma (NHL) all cases with an associated genetic disease. ***Results.*** Among 1,430 patients, 34 (2.4%) had an associated inherited condition and a mature B-lineage (n = 28), anaplastic large cell lymphoma (n = 4), or T-lineage (n = 2) NHL. Their median age at the diagnosis was 9.3 years (range, 2.6–17.8 years). In 14 cases (41%) the underlying condition was considered to be a potential cause for undue toxicity if the expected therapy was applied. Thus, treatment modification had been planned in advance. The overall survival was 89% (standard error [SE] 1%), 73% (SE 10%), and 73% (SE 23%) at 3 years for registered patients with no inherited condition associated, with genetic abnormalities and with underlying condition causing an immune deficiency, respectively ($P = 0.003$). ***Conclusion.*** In our cohort, patients with NHL with an underlying constitutional condition represent the 2.4% of the cases. In the subset of patients with primary immune deficiency, which may have contributed to lymphomagenesis, allogeneic hematopoietic stem cell transplantation may be required. In the remaining patients, the association with lymphoma remains apparently unexplained and could be not causative. Detailed reporting of such cases may contribute to disclose even rare and fully unexpected association, which may have implications for research in the field of lymphomagenesis. Pediatr Blood Cancer 2015;62:1782–1789.

Key words: associated genetic condition; ataxia-telangiectasia; childhood; non-Hodgkin lymphoma; treatment

TABLE III. List of the Risk Group and Treatment Protocol Applied in 11 Patients With Childhood NHL and Associated Condition, in Whom Chemotherapy was Significantly Modified Due to the Associated Condition

Associated condition	NHL Stage/Risk group	Treatment protocol, modifications	Events (in bold) and current status
With immune deficiency			
Down Syndrome[a]	III/R2	AIEOP LNH-97 (4 courses), MTX[b] 500 mg/m^2 50% reduction, Ara-C[c] and Etoposide 30% reduction; 4 doses of Rituximab	Matched unrelated donor HSCT[d]; disease free 1 years
Leaky Severe Combined Immune Deficiency (SCID)	II/R2	AIEOP LNH-97 (4 courses), MTX[b] 500 mg/m^2 50% reduction, Ara-C[c] and Etoposide 30% reduction; 4 doses of Rituximab	Matched unrelated cord blood HSCT[d]; dead of multi-organ failure at 7 months
Immunodeficiency with Hyper-IgM, Type 1	III/R2	AIEOP LNH-97 (4 courses), CPM[e] at Pre-phase 50% reduction, MTX[b] 500 mg/m^2 50% reduction	Relapse at 3 years; disease free at 5 years
Waardenburg syndrome with common variable immune deficiency (CVID)	III/R3	AIEOP LNH-97 (6 courses), TIT[f] omitted in Prephase; 4 doses of Rituximab	Autologous HSCT[d]; dead of progressive disease at 1 years
X-linked Lymphoproliferative Syndrome; XLP1	III/R2	AIEOP LNH-97 (6 courses), MTX[b] 500 mg/m^2 50% reduction, Ara-C[c] and Etoposide 30% reduction; 4 doses of Rituximab	Matched unrelated donor HSCT[d]; disease free 3 years

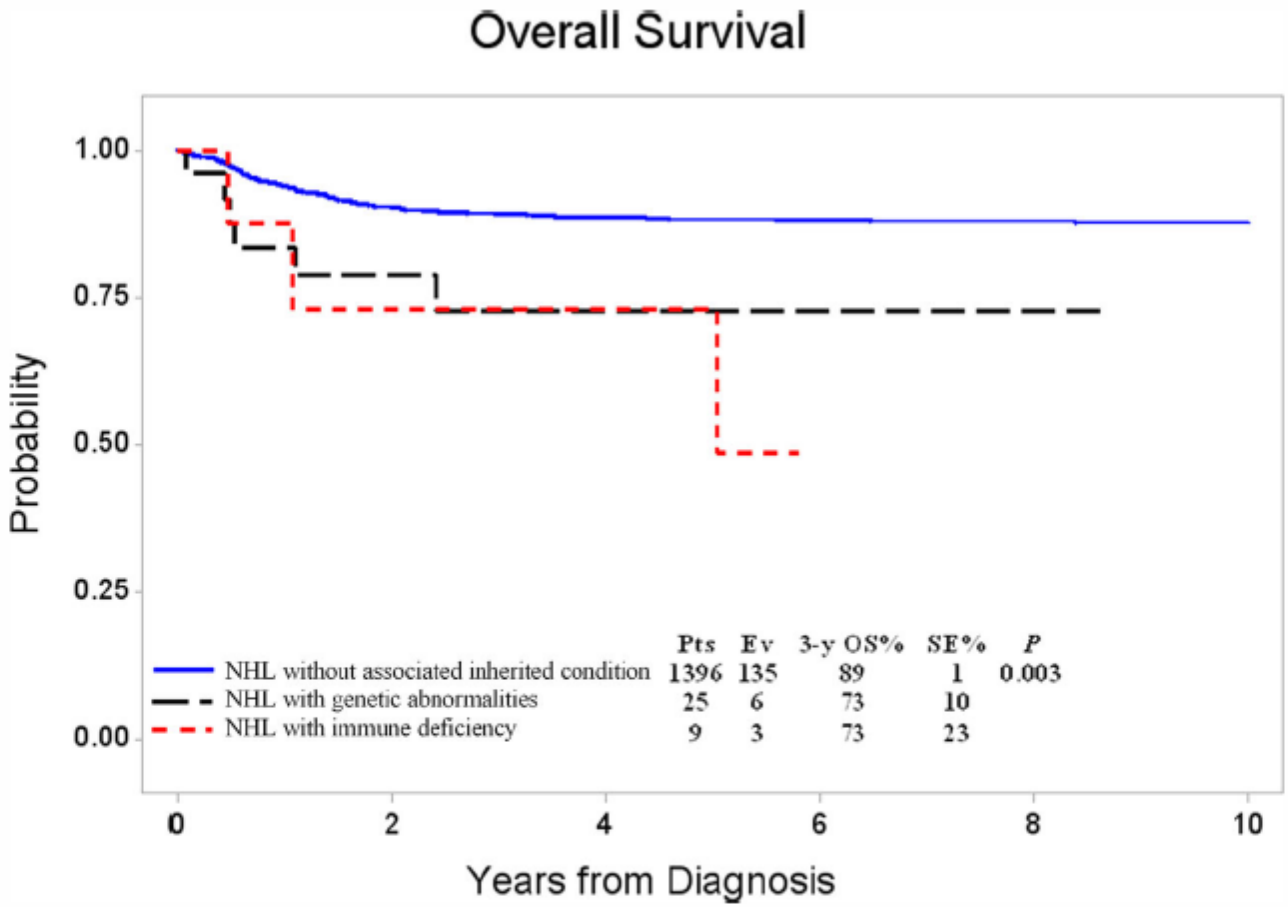


Fig. 1. Overall survival of the whole cohort stratified by no inherited condition associated, with genetic abnormalities and with underlying condition causing an immune deficiency.

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Table 2 – Classification of infants with low TRECs and low T cells found by SCID NBS.

Category	Definition of condition[a]
Typical SCID	<300 autologous T cells/μL, <10% of normal proliferation to PHA, frequently with maternal T-cell engraftment and deleterious defect(s) in a known SCID gene
Leaky SCID	300–1499 autologous T cells/μL (or higher numbers of oligoclonal T cells), reduced proliferation to PHA, no maternal engraftment, generally with incomplete defect(s) in a known SCID gene
Omenn syndrome	Similar to leaky SCID, but also with oligoclonal T cells, erythroderma, hepatosplenomegaly, eosinophilia, and elevated serum IgE levels
Syndrome with low T cells	Recognized genetic syndrome that includes low T cells within its spectrum of clinical findings
Secondary low T cells	Congenital malformation or disease process without intrinsic immunodeficiency that results in low circulating T cells
Preterm birth alone	Preterm infants with low T cells early in life that become normal over time
Idiopathic T-cell lymphopenia	Persistently low T cells (300–1499/μL), functional T-cell and/or B-cell impairment, no defect in a typical SCID gene; etiology and clinical course undetermined[b]

PHA, phytohemagglutinin.

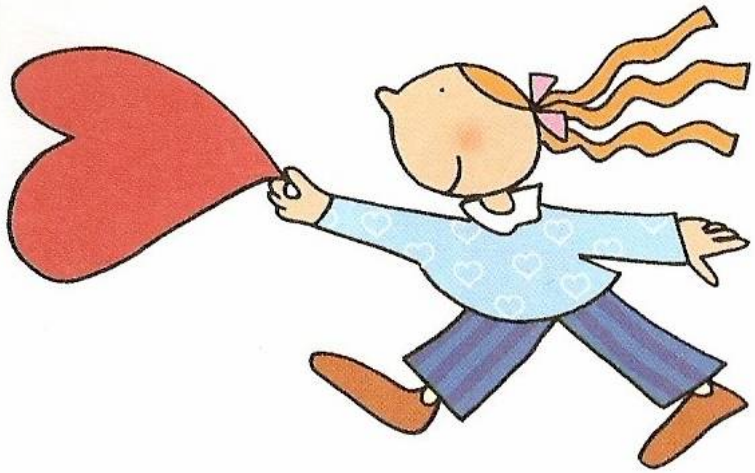
[a] Definitions used by Region 4 Stork (R4S) Laboratory Performance Database and Primary Immunodeficiency Treatment Consortium (PIDTC).

[b] When or if an etiology for low T cells is discovered, the affected individual is moved to the appropriate category.

La storia di Sara

- Nasce il 3 Ottobre 2016
- Al nido, per alopecia e linfocitopenia il collega neonatologo sospetta una immunodeficienza primitiva. Inizia profilassi.
- In quinta giornata viene traferita a Brescia e posta in flusso laminare
- Le sottopolazioni mostrano assenza di T linfociti.
- Radiologicamente assenza del timo
- Quadro compatibile con def. FOXN1
- In assenza del timo, non indicazione a TMO.

- Il 2 Dicembre 2016, in collaborazione con GOSH, trapianto di timo da donatore vivente. Primo trapianto in Europa, terzo nel mondo per questa patologia.
- La bimba sta bene a 50 giorni dal trapianto



GRAZIE