



ISBMT

Indian Society for Blood & Marrow Transplantation

BMT MASTER CLASS

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HSCT for Inborn Errors of Immunity

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Terminology - what is it now..

INBORN ERRORS OF IMMUNITY - IEI



IUIS - Updates every 2 years - 2024 recent classification

HSCT for IEI

- First successful HSCT in PID included SCID and WAS - 1967
- HSCT is Curative - reaching survival >80-90%
- Pathological basis and advancement in NGS and diagnostic techniques
- Advances in HSCT and cellular therapy
- Immunologists + Transplant physicians - Team work
- Indications and Timing of Transplant - Crucial Decision to successful outcomes

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HSCT for IEI - Indian Scenario



Hematopoietic Stem Cell Transplantation for Primary Immunodeficiency Disorders: Experience from a Referral Center in India

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Received: November 18, 2017;
Initial review: March 08, 2018;
Accepted: May 23, 2018.

Objective: To share experience of over 15 years in hematopoietic stem cell transplantation in children with primary immunodeficiency disorders.

Design: Medical record review.

Setting: A referral center for pediatric hemato-oncological disorders.

Participants: Children (<18 y) diagnosed to have primary immune deficiencies who underwent hematopoietic stem cell transplantation between 2002 and August 2017.

Main outcome measures: Disease-free survival, morbidity and mortality.

Results: 85 primary immunodeficiency disorder transplants were performed with engraftment noted in 80 (94%) transplants and an overall survival of 67%. The conditioning regimen was individualized based on the underlying immune defect. Mixed chimerism was noted in 20% children with 56% (9/16) remaining disease-free. Graft versus host disease was noted in 33 (39.2%) children with most seen in children with chronic granulomatous disease. Severe combined immune deficiency transplants were mainly complicated by infections. Immune cytopenias complicated Wiskott Aldrich syndrome and Hemophagocytic lymphohistiocytosis transplants. 29.4% (25/85) children underwent haploidentical transplant in our cohort with a survival of 70% in this group. Infectious complications were the most common cause of death.

Conclusion: Primary immunodeficiency disorders are curable in India when transplanted in centers with experienced and trained pediatric transplant physicians and intensivists.

Keywords: Immunity, Management, Outcome, Prognosis, Stem cell therapy.

Multicenter Outcome of Hematopoietic Stem Cell Transplantation for Primary Immune Deficiency Disorders in India

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Background: Hematopoietic stem cell transplantation (HSCT) is the curative option for many primary immune deficiency disorders (PID). In the last 5 years, increased awareness, availability of diagnostics based on flow cytometry, genetic testing, improved supportive care, use of reduced toxicity conditioning, and success of haploidentical donor HSCT have improved access to HSCT for children with PID in India. We present results on children with PID who underwent HSCT across India and the factors that influenced outcome.

Patients and Methods: We collected retrospective data on the outcome of HSCT for PID from seven centers. We analyzed the impact of the type of PID, conditioning regimen, time period of HSCT - before or after January 2016, graft versus host disease prophylaxis, cause of mortality and overall survival.

Results: A total of 228 children underwent HSCT for PID at a median age of 12 months (range, 1 to 220 months) with a median follow up of 14.4 months. Infants accounted for 51.3% of the cohort and the male female ratio was 3:1. SCID (25%) and HLH (25%) were the more frequent diagnoses. Matched family donor was available in 36.4% and 44.3% children had a haploidentical HSCT. Reduced and myeloablative conditioning regimens were used with 64% children receiving a treosulfan based conditioning regimen. Peripheral blood stem cells were the predominant graft source at 69.3%. The survival in infants (60.2%) was inferior to children aged over 1 year (75.7% p value = 0.01). Children with Wiskott Aldrich syndrome (74.3%) and chronic granulomatous disease (82.6%) had the best outcomes. The survival was superior in children receiving HSCT from a matched sibling (78%) versus an alternate donor HSCT (61% p value = 0.04). In the cohort

transplanted after January 2016 survival improved from 26.8% to 77.5% (p value = 0.00). Infection remains the main cause of mortality at in over 50% children. The 5-year overall survival rate was 68%.

Conclusion: Survival of children with PID undergoing HSCT in India has improved dramatically in last 5 years. Alternate donor HSCT is now feasible and has made a therapeutic option accessible to all children with PID.

Keywords: hematopoietic stem cell transplant, primary immune deficiency, conditioning, India, haploidentical

Human inborn errors of immunity: 2024 Update on the classification from the International Union of Immunological Societies Expert Committee

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TABLE 1 | Classification of PID according to IUIS Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity (1, 2).

I. Immunodeficiencies affecting cellular and humoral immunity			
a. Severe Combined Immunodeficiency (SCID) defined by CD3 ⁺ T cell lymphopenia			
T- B+ NK-	T- B+ NK+	T- B- NK-	T- B- NK+
<i>IL2RG</i> (SCID-XL)	<i>IL7R</i>	<i>ADA</i>	<i>LIG4</i>
<i>JAK3</i>	<i>CD3δ</i>	<i>AK2</i> (Reticular dysgenesis)	<i>RAG1</i>
	<i>CD3ε</i>		<i>RAG2</i>
	<i>CD3ζ</i>		<i>DCLRE1C</i> (Artemis deficiency)
	<i>CORO1A</i>		<i>NHEJ1</i> (Cernunnos XLF)
	<i>PTPRC</i> (CD45 deficiency)		<i>PRKDC</i> (DNA-PKcs deficiency)
	<i>FOXN1</i>		
b. Combined Immunodeficiencies (CID) generally less profound than SCID			
II. CID with associated or syndromic features			
III. Predominantly antibody deficiencies			
a. Hypogammaglobulinemia			
b. Other antibody deficiencies			
IV. Diseases of immune dysregulation			
a. Hemophagocytic Lymphohistiocytosis (HLH)			
b. EBV susceptibility			
c. Syndromes with autoimmunity			
d. Immune dysregulation with colitis			
V. Congenital defects of phagocyte number, function or both			
a. Neutropenia			
b. Functional defects			
VI. Defects in intrinsic and innate immunity			
a. Predisposition to invasive bacterial infections (pyogenes)			
b. Predisposition to parasitic and fungal infections			
c. Mendelian susceptibility to mycobacterial disease (MSMD)			
d. Predominant susceptibility to viral infection			
VII. Auto-inflammatory disorders			
VIII. Complement deficiencies			
IX. Phenocopies of PID			

IL2RG, interleukin 2 receptor subunit gamma; *JAK3*, Janus kinase 3; *IL7R*, interleukin 7 receptor; *CD3δ*, CD3δ molecule; *CD3ε*, CD3ε molecule; *CD3ζ*, CD3ζ molecule; *CORO1A*, cor 1A; *PTPRC*, protein tyrosine phosphatase, receptor type C; *FOXN1*, Forkhead box N1; *ADA*, adenosine deaminase; *AK2*, adenylyate kinase 2; *LIG4*, DNA ligase 4; *RAG1*, recombination activating 1; *RAG2*, recombination activating 2; *DCLRE1C*, DNA cross-link repair 1C; *NHEJ1*, non-homologous end joining factor 1; *PRKDC*, protein kinase, DNA-activated, catalytic subunit.

Indications for HSCT

- Wide range of diseases
- Diseases with Thymic stromal defect - not amenable for HSCT

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

Case Vignette

- 6 Month girl with very severe pneumonia/ ARDS
- Child born of 2nd degree consanguineous parents with
- H/O elder sibling death due to recurrent infections

Investigation	Observed Value	Unit	Biological Reference Interval
Immunoglobulin Profile IgG, IgM and IgA, Serum (Serum, immunoturbidimetric)			
IgG Total	12.00	mg/dL	232-1411
Medical Remarks: (Rechecked) Please Correlate clinically.			
IgA Total	5.10	mg/dL	00-83
IgM total	29.00	mg/dL	0-145
Interpretation :			
1. Decreased levels are seen in primary immunodeficiency conditions and in secondary immune insufficiencies like advanced malignant tumours, lymphatic leukemias, multiple myeloma and Waldenstrom's disease.			
2. Increased concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferations seen in hepatic disease, acute/chronic infections and autoimmune disease.			

FLOW CYTOMETRY (PHERPERAL BLOOD/BONE MARROW)

LAB NO: SC 058/2021

MARKER	RESULT	REFERENCE RANGE
CD3+ (T CELLS)	1.62	55 – 73%
CD3+ (Absolute count)	31	2187 – 6352 cells/μL
CD3+ CD4+ (Helper cells)	0.14	30 – 63%
CD3+ CD4+ (Absolute count)	3	1327 – 4455 cells/μL
CD3+ CD8+ (Cytotoxic cells)	0.59	11 - 18%
CD3+ CD8+ (Absolute count)	11	593 – 1517 cells/μL
CD3-/CD19+ (B Cells)	97.45	11 –45%
CD3-/CD19+ (Absolute count)	1859	571 – 3680 cells/μL
CD3-/CD56+ (NK Cells)	0.05	4 – 17%
CD3-/CD56+ (NK cells Absolute count)	1	130– 720 cells/μL

Clinical exome sequencing done showed **JAK3 exon 19 mutation.**

MEDICAL EMERGENCY – EMERGENCY REFERRAL AND SHIFTING

Management

- Medical emergency
 - IVIG replacement
 - Antifungal/antiviral/ HR and PCP prophylaxis + appropriate antibiotics
 - Irradiated Blood products
 - URGENT HSCT planning
 - Genetic counselling
- No 10/10 family or unrelated donors
- Father - 5/10
Mother - 7/10
- Haplo-identical HSCT from father as donor
- TCR alpha beta depleted

Conditioning

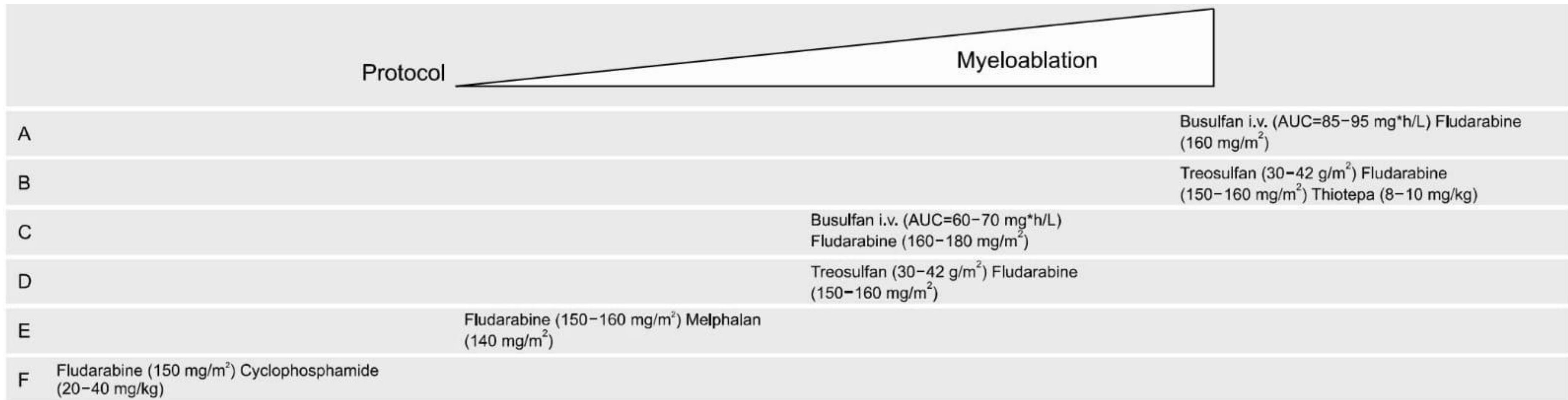


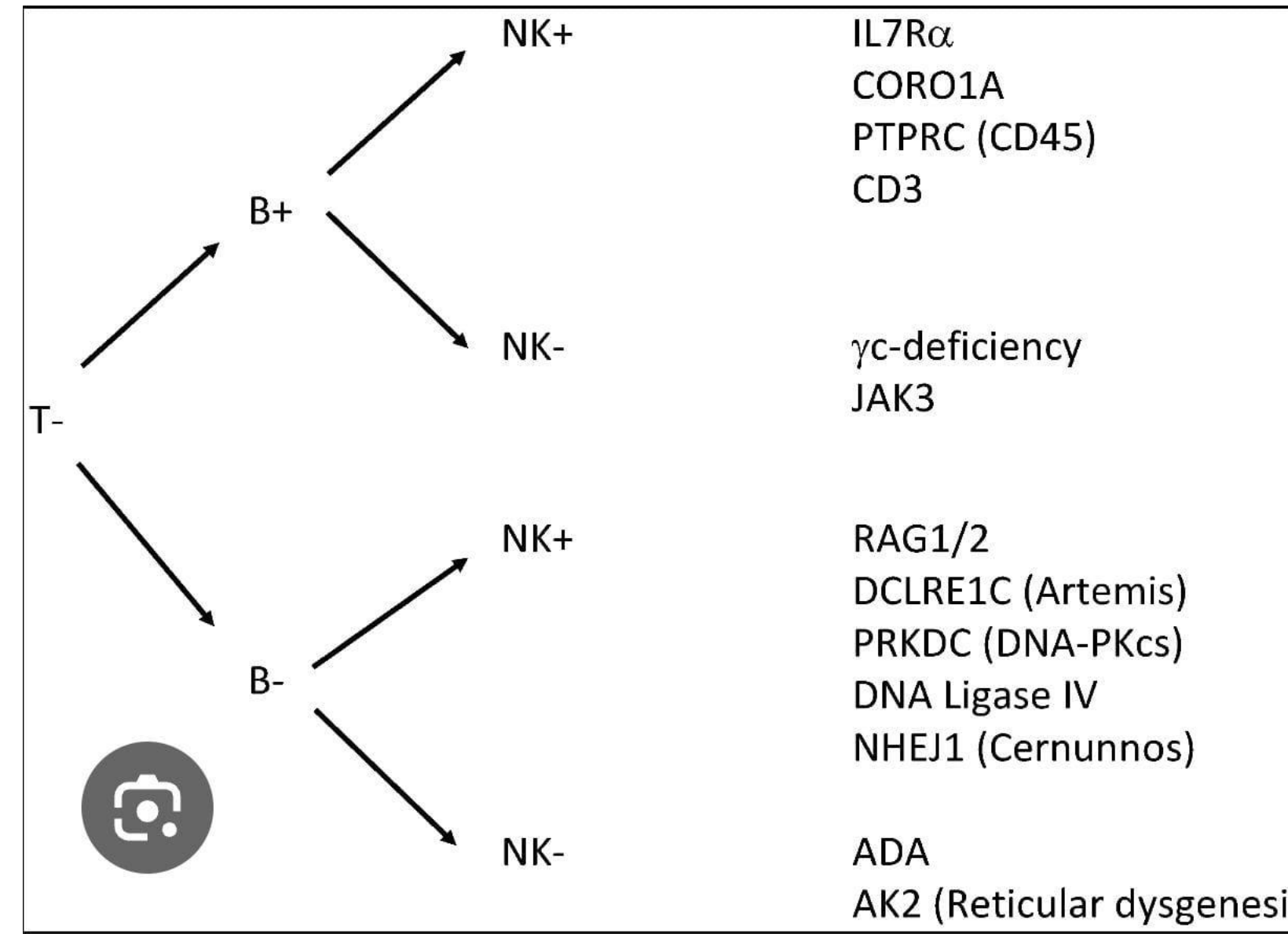
Fig. 1. Conditioning regimens for PID recommended by EBMT/ESID inborn errors working party [14]. Protocol A and B: These are

Conditioning regimen - greatly dependent on underlying disease and comorbidity/ clinical status of the child

SCID -HSCT planning

- Heterogenous group of disorders
- NGS - very important for patient and donor screening
- HSCT - Without conditioning
- Matched family donor
- NK negative SCID
- Sick child
- T cell reconstitution - universal
- B-cell reconstitution - doubtful - might need IVIG/ later on HSCT with conditioning.

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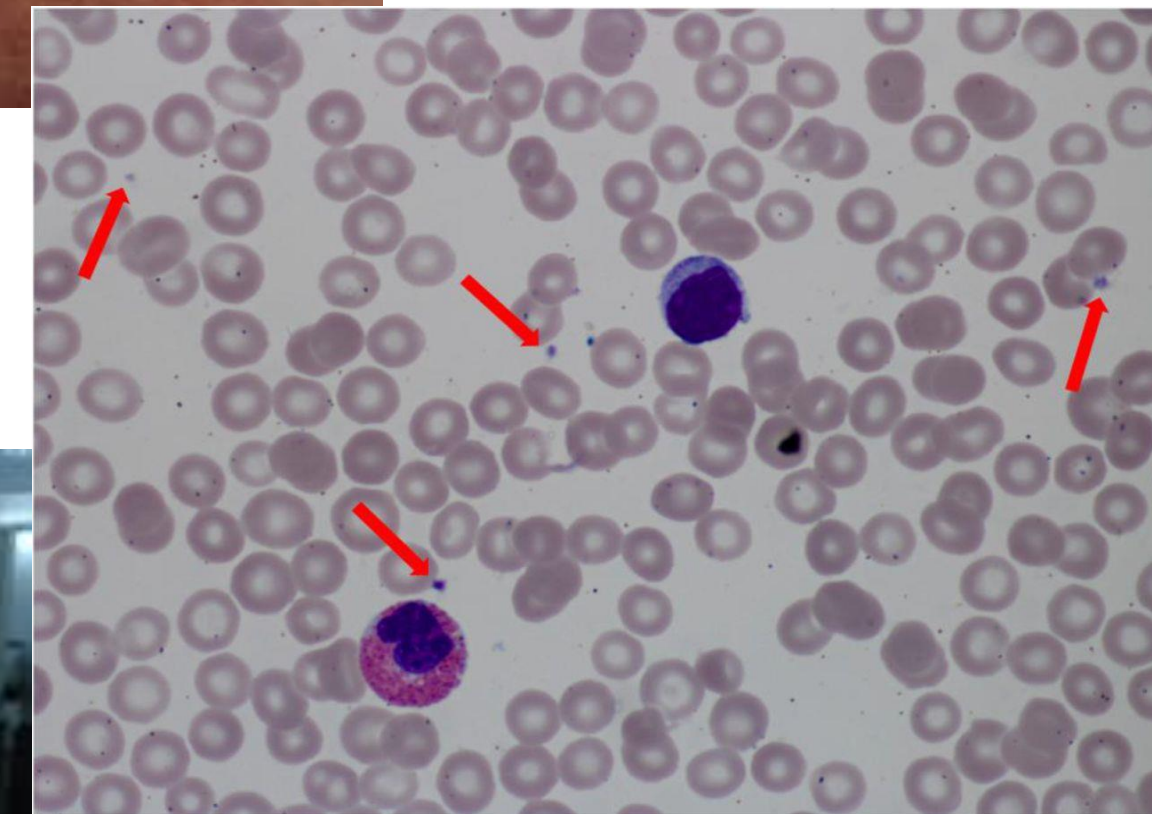
Remember in SCID.....

- DCLREC1C/Artemis SCID - use of alkylating agents associated with microdontia/ shorter height and renal impairment
- Omenn syndrome - skin rash, hepatosplenomegaly, hypereosinophilia, elevated IgE - Leaky SCID - Steroids/ cyclosporine/ Alemtuzumab
- Conditioning is mandatory - endothelial toxicities are anticipated
- Radiosensitive SCID - DNA ligase 4 deficiency, NBS and Cernunnos XLF deficiency - predisposition to BM failure/MDS/ autoimmunity
- RIC regimen
- Reduced dose of cyclophosphamide
- Avoiding the radiation exposure



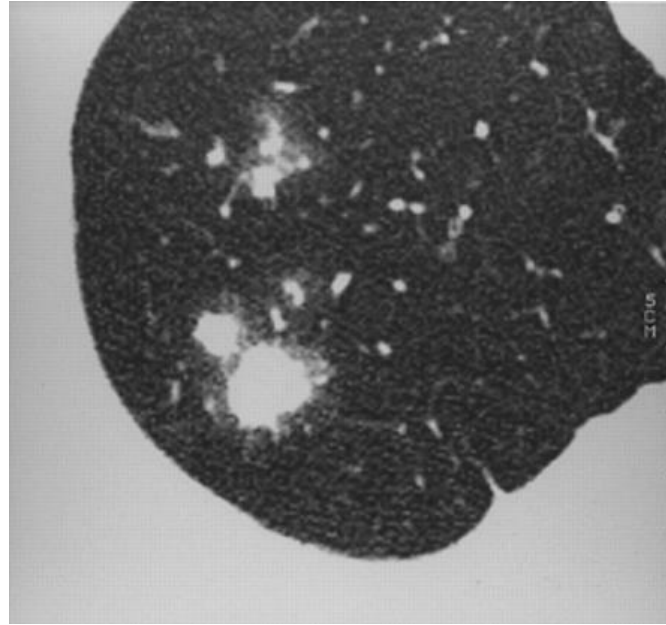
Other CID.....

- Only immunodeficiency - CD40 ligand defect, Bare lymphocyte syndrome, DOCK 8 deficiency
- Associated syndromic features - WAS, Anhidrotic ectodermal dysplasia with Immunodeficiency
- Protocols B/ C and D - suggested - reduced toxicity
- Sustainable donor engraftment and T-cell immunity - myeloablation is necessary
- Control of autoimmunity/ vasculitis - important



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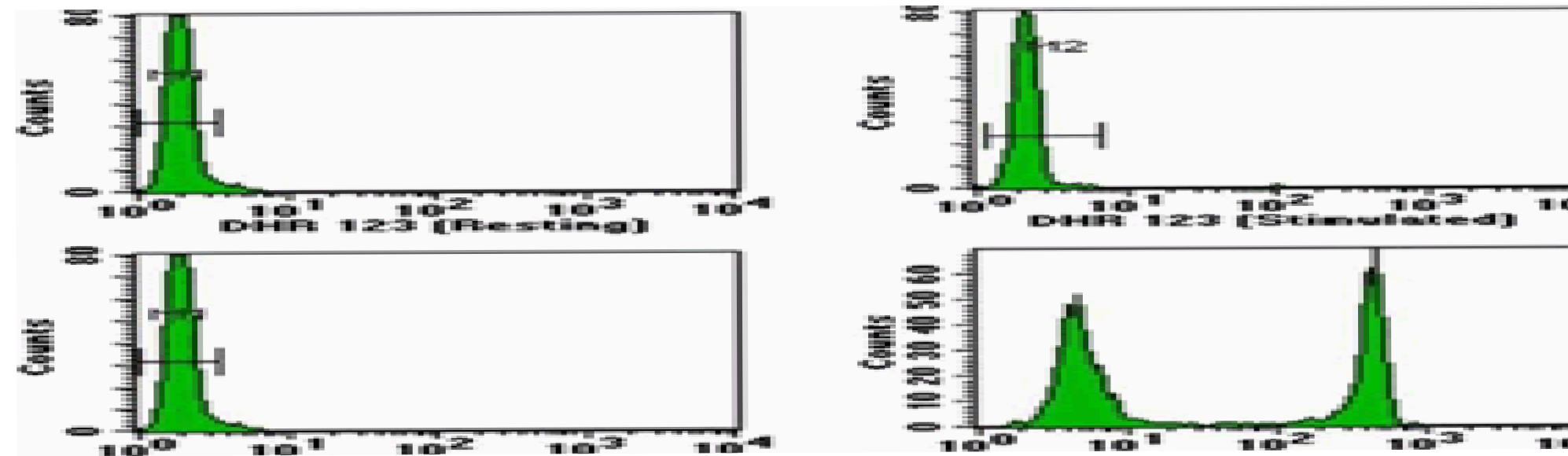
CASE Vignette



- 5-year-old child admitted for prolonged fever and cough
- At the age of 4 weeks, he developed an axillary abscess which healed spontaneously, followed by a staphylococcal abscess of the chest wall, requiring surgical incision and a course of cloxacillin
- Cervical lymphadenitis - recurrent
- Empirically treated with ATT - no response

INVESTIGATIONS

- Total white-cell count of $45 \times 10^9/l$
- Differential count: 90% were neutrophils
- *Quantitative serum immunoglobulins (g/l)*
 - IgG 17.8 [5.5-10.0]
 - IgA 4.8 [0.3-0.8]
 - IgM 2.0 [0.4-1.8]
- T and B markers normal



Phagocyte disorders

- Only curative option - HSCT
- CGD - non-infectious colitis/ inflammatory granulomas - common
- Control of inflammation pre HSCT crucial
- Warrants myeloablative conditioning for sustained myeloid engraftment
- >20% myeloid chimerism - sufficient for functional outcomes post HSCT
- Serotherapy with ATG/ Alemtuzumab - indicated even in sibling allograft

Donor screening - important to detect pre-symptomatic carriers

Carriers might manifest autoimmune / inflammatory symptoms

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Case Vignette

- 1.5 year old girl
- 3 months of age - BCGosis - treated with INH for 6 months and stopped
- Recurrent lymphadenitis after 1 month of stopping ATT - evaluated
- Recovering well on ATT
- Well thriving
- Contemplating the role and timing of HSCT...
- On 4th month of ATT - presented with neck stiffness and irritability

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Test Name	Result	Unit	Normal Range
Memory B cells (CD19+CD27)	15.33	%	7-24.3
CLASS SWITCHED MEMORY B CELL (CD19+CD27+IgM-IgD-)	4.44	%	0.8-4.2


Naive T Cell

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Test Name	Result	Unit	Normal Range
Naive helper T cells (CD3+CD4+CD27+CD45RA+)	39.39	%	56-100
Naive cytotoxic T Cells (CD3+CD8+CD27+CD45RA+)	9.74	%	10-100

Remark: Patient monocytes showed 100% IFNGR1 expression with an SI of 12.6 as compared to healthy controls SI of 4.3. The patient pSTAT1 expression on monocytes is 28% as compared to healthy control. These features suggest the possibility of partial dominant IFNGR1.

Checked By: Aparna Dalvi **Approved By:** Dr Umair Bargir  **Director**

Test Results and Interpretation

HETEROZYGOUS LIKELY PATHOGENIC VARIANT CONSISTENT WITH PHENOTYPE DETECTED.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygoty	Classification	OMIM Phenotype	Inheritance
IFNGR1 (NM_000416.3)	Exon 6	c.814A>T p.Lys272Ter [20x / 46x]	Heterozygous	Likely pathogenic	Immunodeficiency 27B, mycobacteriosis, AD, Immunodeficiency 27A, mycobacteriosis, AR	Autosomal dominant Autosomal recessive

Case Vignette

- Meningitis!!
- MRI Brain - Skull base Osteomyelitis with erosion of odontoid process

Treated with broad spectrum antibiotics for 6 weeks + HRE and Levofloxacin was added

Microbiological diagnosis - could not be achieved

Haplo-identical HSCT from father as donor

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Test Name	Result	Unit	Normal Range
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Checked By: Aparna Dalvi **Approved By:** Dr Umair Bargir 

Investigations: GL - MTB detected

Director

Test Results and Interpretation

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Case Vignette

- Pre-transplant Immunosuppression - Flu/Dex - 2 cycles
- High IFN gamma levels - higher the rejection - Plasma exchange prior to HSCT
- Flu/Treo/thiotepa/ATG/ Rituximab + PBSC + TCR alpha beta and CD45 RA depletion

- D+21 - chimerism 55% (T cells 23%)
- Cyclosporine stopped
- D+28 - chimerism 83%

- Stem cell Boost/ DLI based on repeat chimerism ...

- Functional assays...

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CASE Vignette

- At 3.5 months of age, child presented to us with fever for 2 week duration
- Bruises noticed over trunk and abdomen distension – 2 days
- Irritable child with poor feeding
- No significant associated symptoms
- No significant past history

Pallor

Ecchymosis

Hepatosplenomegaly

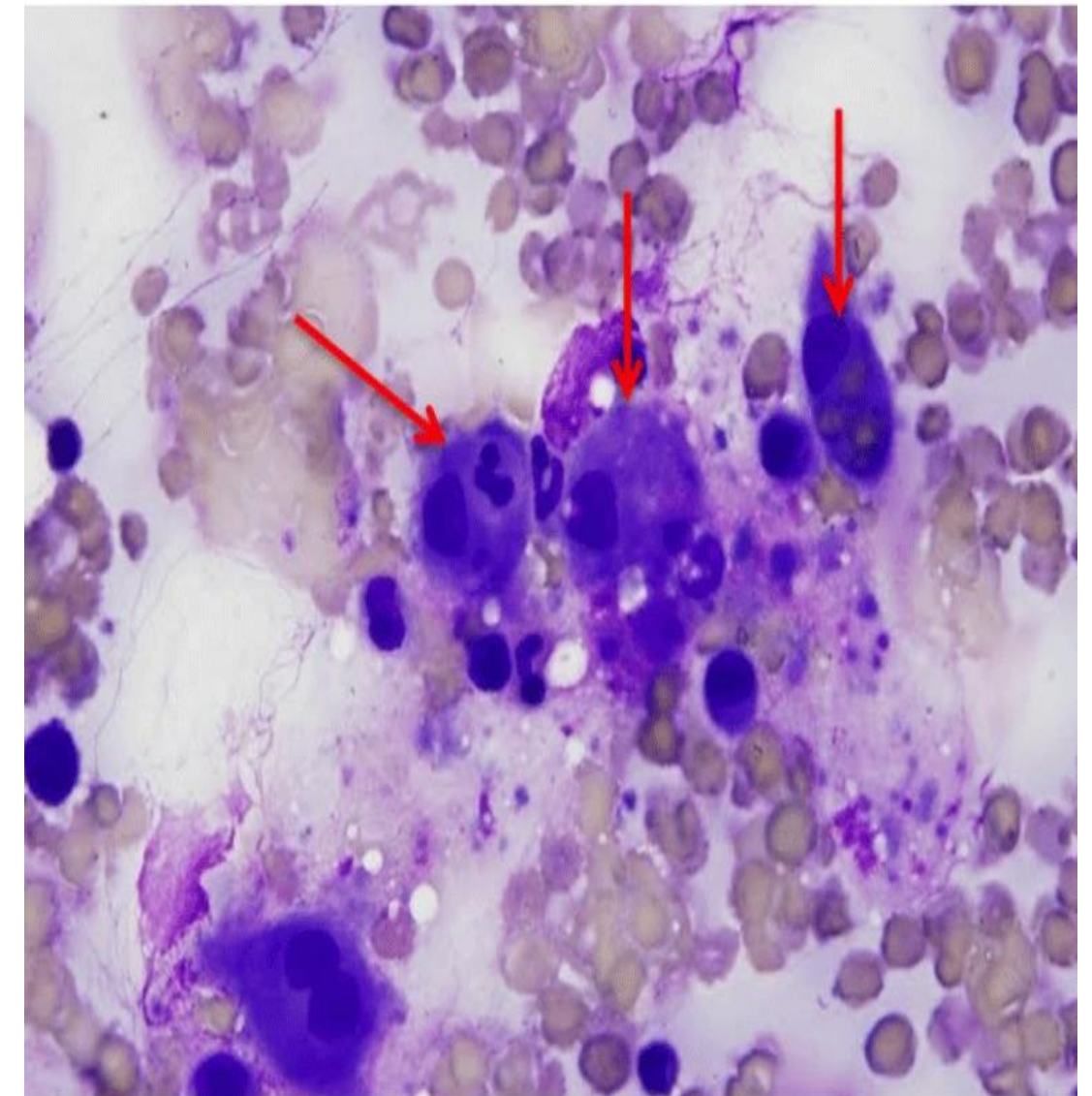
Irritability - no bulging AF or focal deficits

LAB INVESTIGATIONS

CBC – Anemia (5.3gm/dL)
Thrombocytopenia (37000 cumm/L)
WBC – 4400; N – 19; L-66

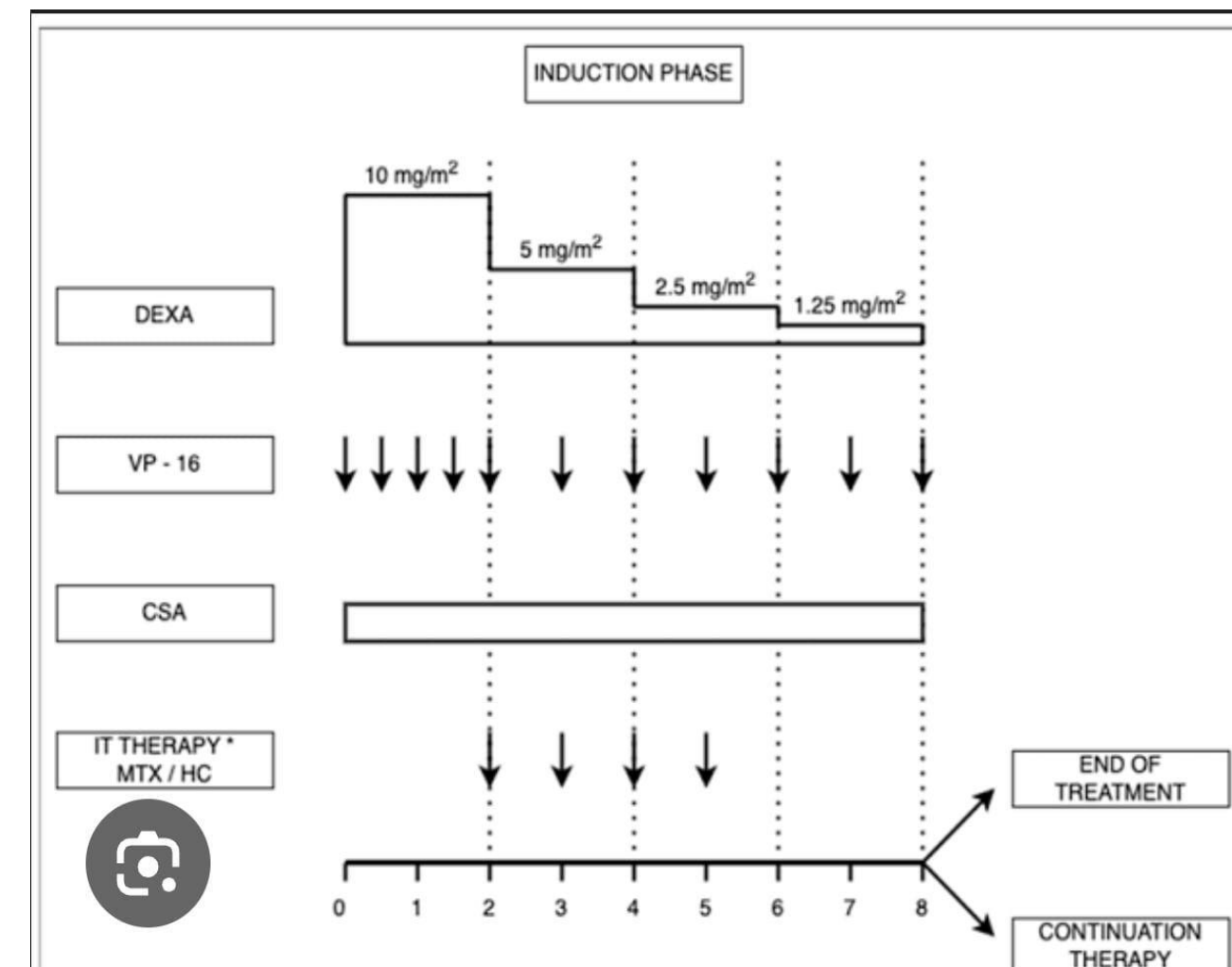
LFT – Transaminitis (SGOT – 60IU/L, SGPT – 83IU/L)
Hypoalbuminemia (2.8g/dL)
Blood glucose - normal

Sr. Ferritin – 9786 ng/ml;
Triglycerides – 550mg%;
Fibrinogen – 49mg%



Primary Immune Dysregulation Disorders

- HLH protocol - IVIG/Dexamethasone/ Cyclosporine/ Etoposide
 - CNS prophylaxis - mandatory
 - Disease in complete remission - >70% outcomes
 - Active disease/ partial remission - significantly reduced OS
 - Drugs to control HLH in case of PR - Ruxolitinib/ Serotherapy - better remission in refractory cases
- 22
- Warrants myeloablative conditioning for sustained myeloid engraftment
 - >30% T-cell chimerism - sufficient for functional outcomes post HSCT



Primary Immune Dysregulation Disorders - HLH

- Myeloablative conditioning/ Reduced toxicity - Thiotepa/ Fludarabine/ Treo - comparable outcomes
- More prone for VOD during HSCT - prophylaxis/ monitoring very important
- XIAP deficient patients with HLH - Particularly sensitive to alkylating agents and suffer more GVHD compared to other types

Primary Immune Dysregulation Disorders

- IPEX syndrome
- CTLA 4 deficiency
- ZAP 70 deficiency

- Increasing role of HSCT

Time to answer QUIZ

- 4 month old boy with persistent diarrhea since day 10 of life, occasional blood in stools
 - Feed intolerance - Failure to thrive
 - Elder sibling - girl - had similar complaints and died at 8 months of age
 - She was operated for perianal fistula once and died later due to sepsis
 - Weight 3.7kg
 - No dysmorphism / lymphadenopathy/ organomegaly; Perianal rash and fissures+
- 25
- CBC, T and B lymphocyte subsets normal; Immunoglobulins - normal

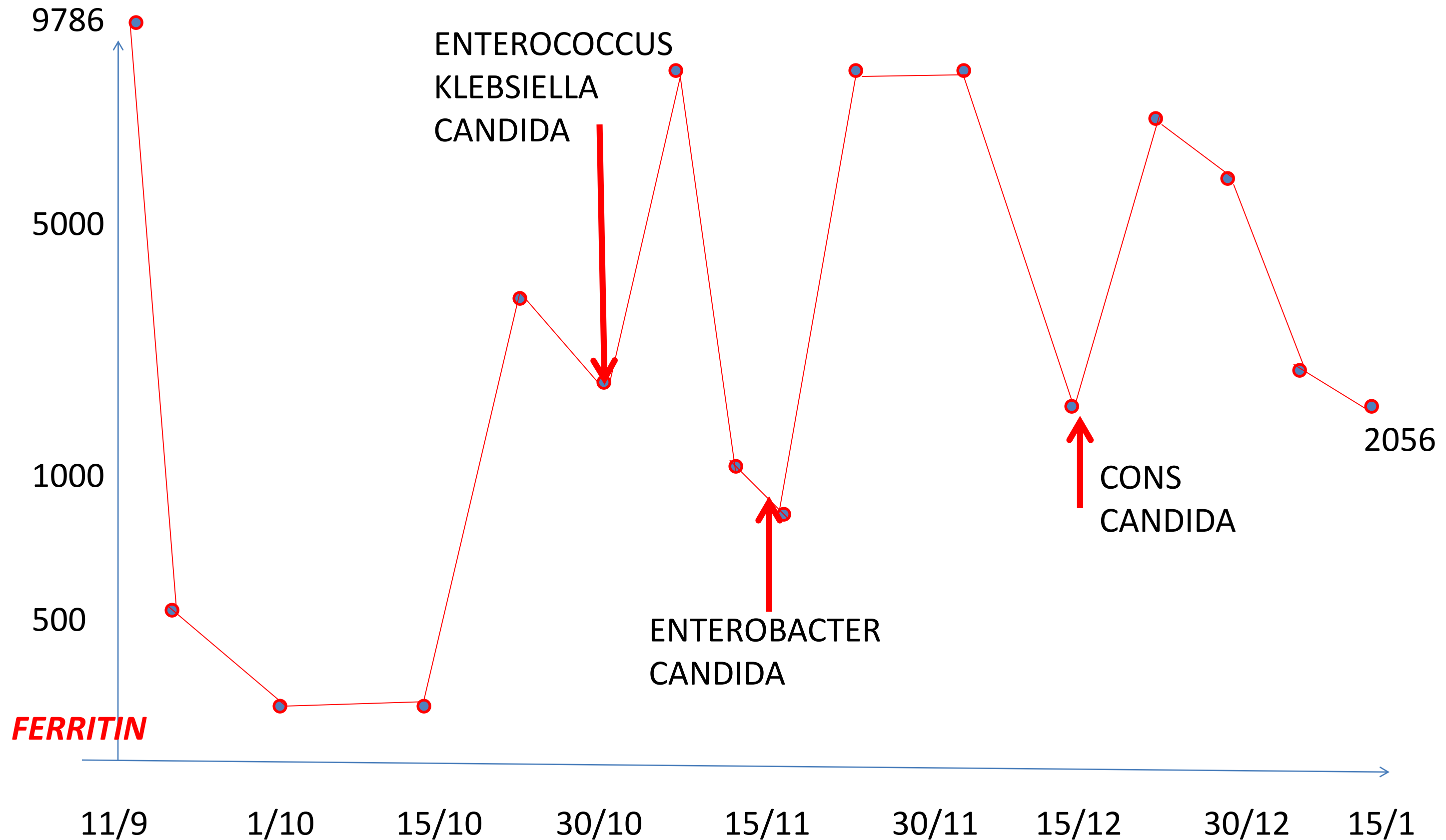
What are we dealing with??

Treatment of choice??

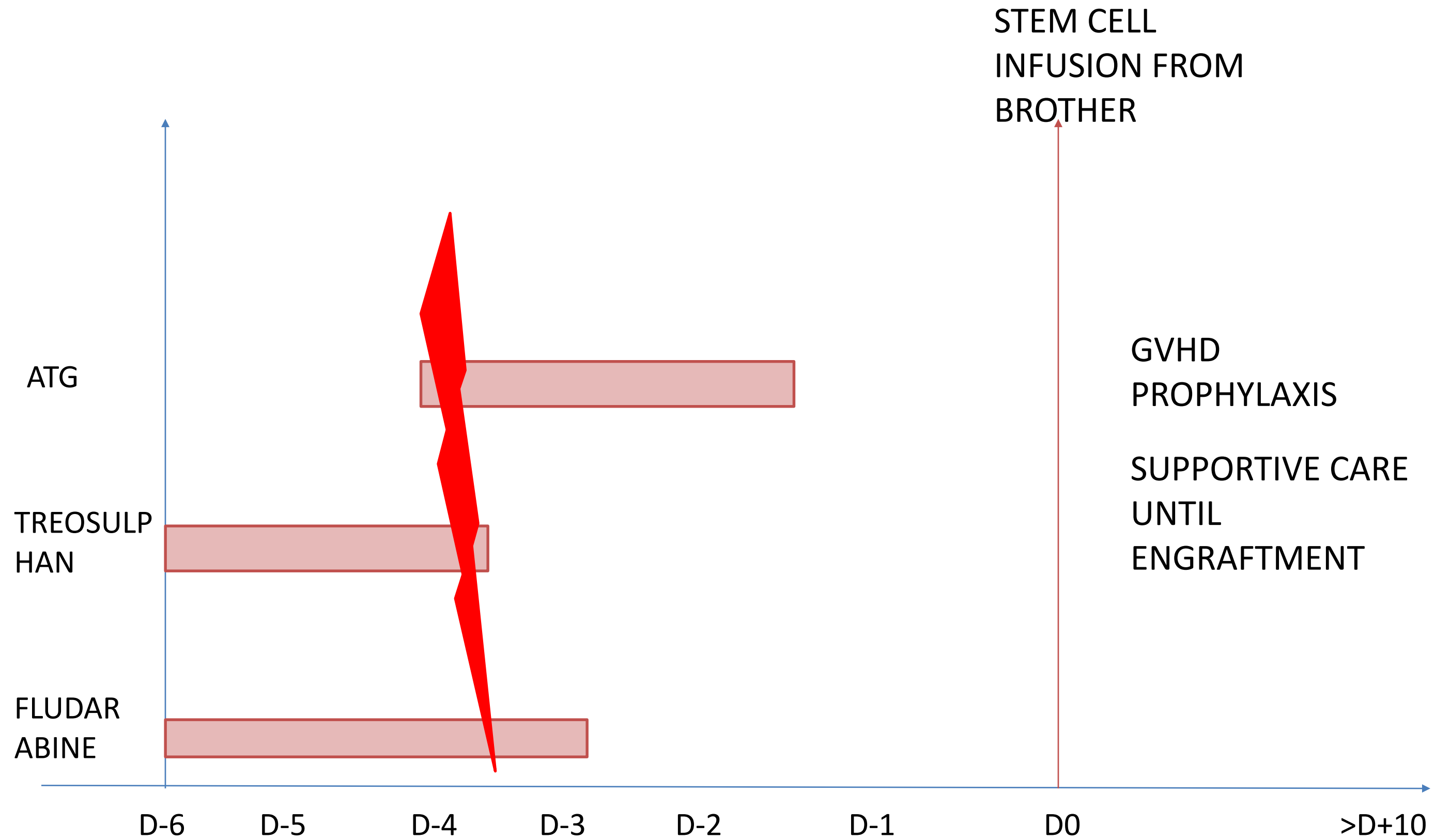
Time to answer QUIZ

- Successful non HSCT treatment outcomes have been documented in a variant of SCID
- **Which variant?**
- **What is the treatment?**

HLH COURSE PRE-TRANSPLANT



HSCT PROTOCOL - INTENDED

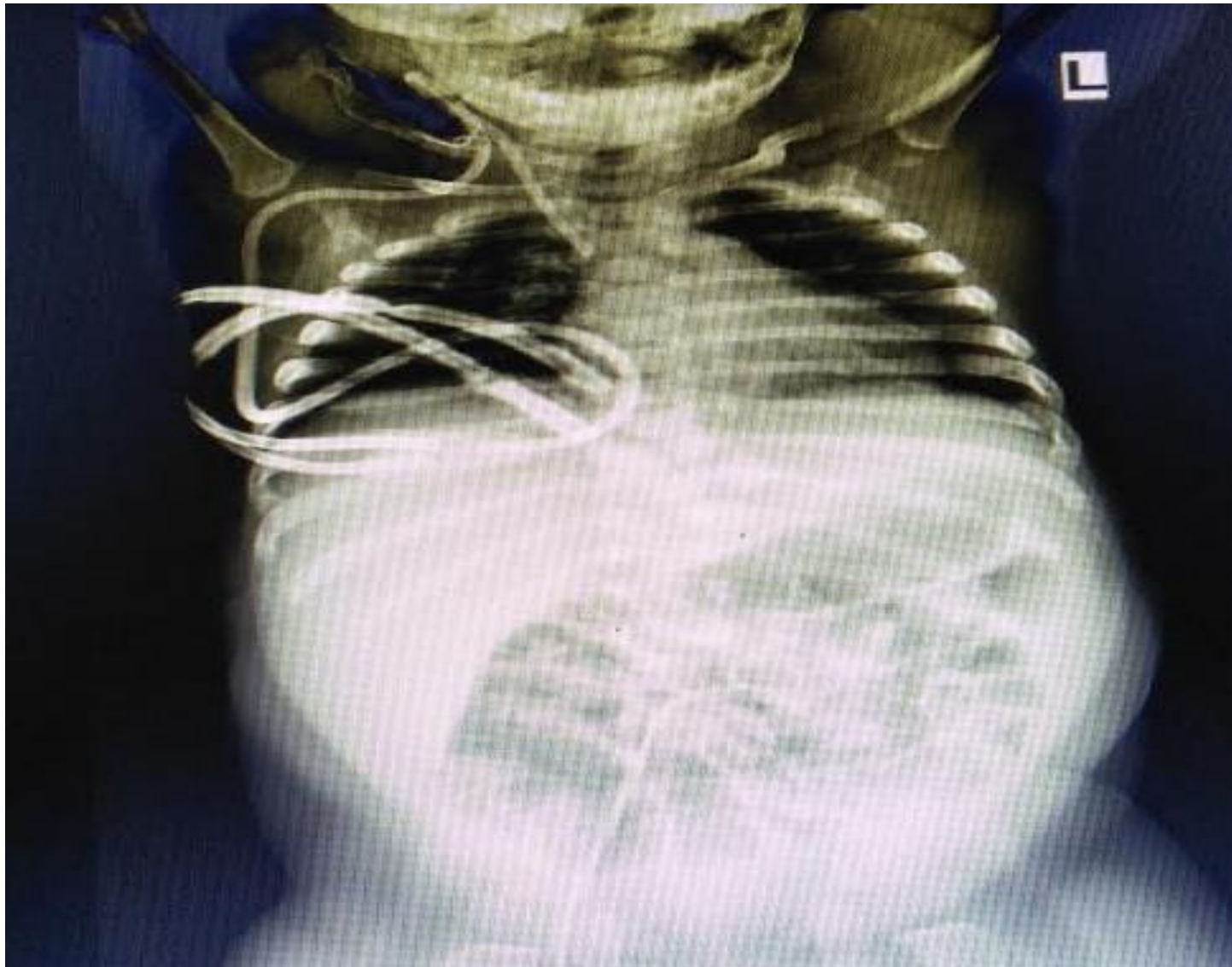


HSCT

3 days intensive chemo given, Day 3 after chemo, before ATG



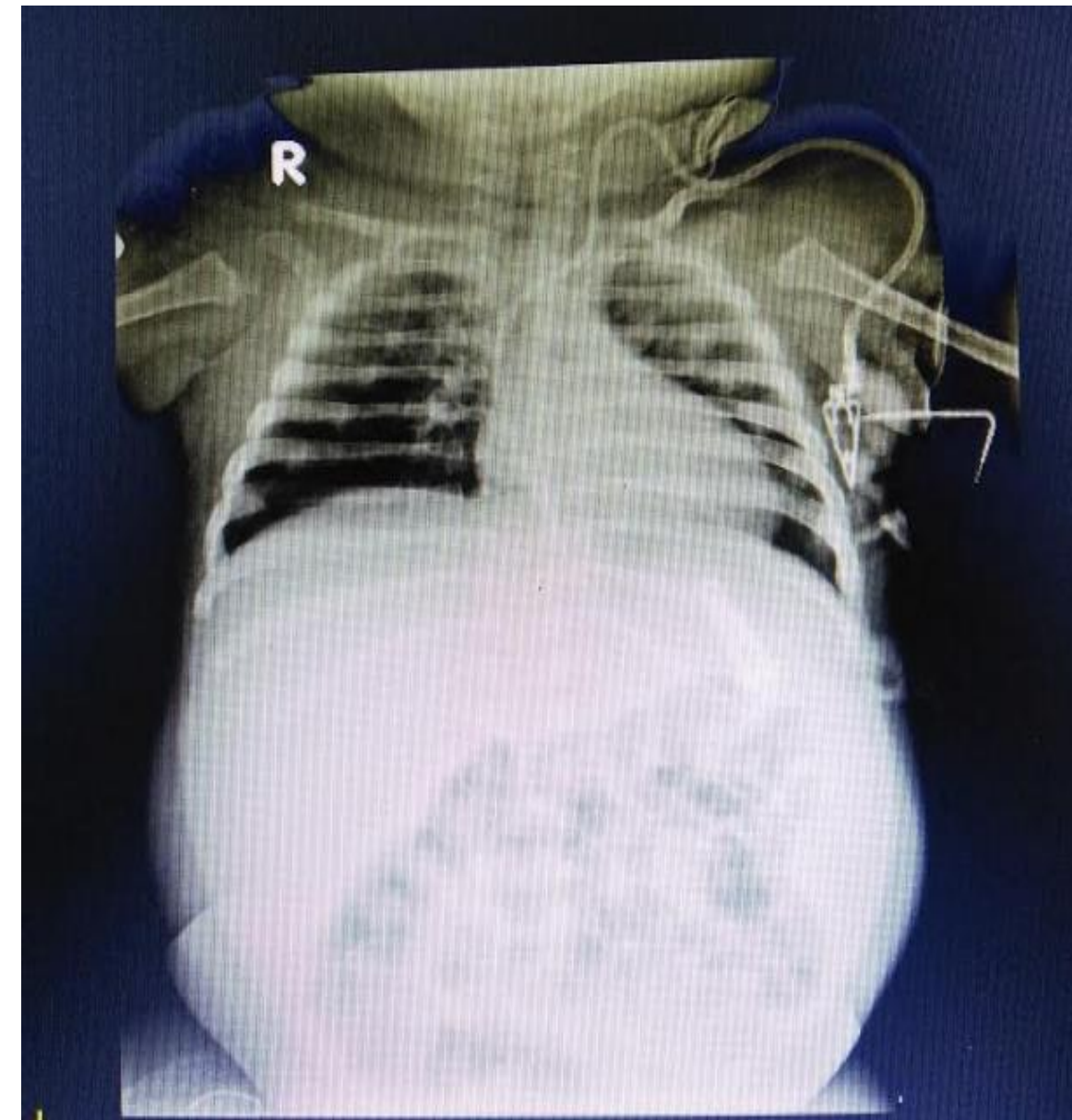
HICKMANN LINE



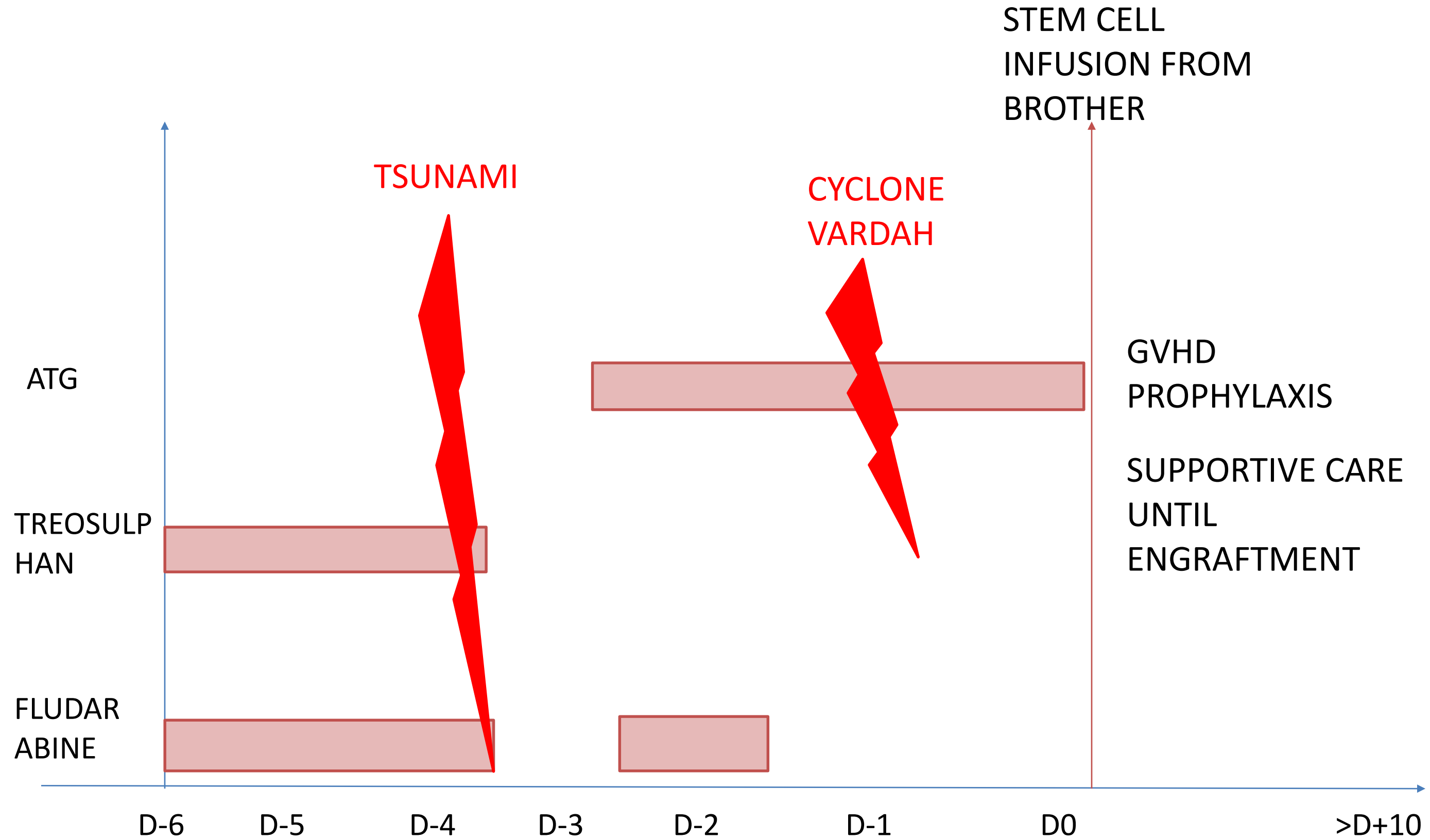
FEMORAL AND NECK LINES - UNDER GA COULDN'T BE ESTABLISHED

URGENT CHEMOPORT.....

- HIGH RISK CONSENT INCLUDING DEATH ON TABLE;
- PLATELET COUNT - 40000
- PROTOCOL INTERRUPTION
- ALREADY ACCESSED MAJOR VEINS – VERY LESS OPTIONS LEFT



HSCT PROTOCOL – INTERRUPTED



HSCT - CHALLENGES

- Day prior to infusion- fever and massive splenomegaly
- Total WBC – 100/cubic.mm
- Elevated ferritin level - >75000 U/L - ?? REACTIVATION
SECONDARY TO STRESS

- Treated with Dexamethasone, IVIG
- ICU Monitoring,
- Meropenem and teicoplanin
- Increased platelet transfusion

**SIGNIFICANT INCREASE IN CHANCES OF GRAFT REJECTION AND
COST OF CARE!!!!**

HSCT – CALM AFTER STORM!!

- Sibling donated ABO matched stem cell – CD34 9×10^6 kg/body weight (increased stem cell dose)
- Supportive care – leucodepleted and irradiated transfusions, IV antibiotics + Dexamethasone
- Serum ferritin – D+4 – 7500 U/L
- WBC engraftment – D+12 (PBSC source)



Financial Stress

- Govt schemes and Insurance
-
- Crowd funding
-
- NGOs support
-
- Drugs available at compassionate basis
-
-
-

Take Home Messages

- Need to think beyond infections - immune dysregulation is very much a part of PID/~~IEI~~
- IEI - One size Does Not Fit All - case to case discussion with the institutional multidisciplinary board, clinical immunologists and experts in challenging situations do help
- Detailed evaluation of the genotype/ phenotype, family screening for the asymptomatic states before HSCT and addressing the other comorbidities - very important

THANK YOU...



Organising team

Mentors

NGO/Schemes

Patient and Families