Update on Congenital and Acquired neutropenia

EHA-ISHBT Hematology Tutorial

March 1-3, 2024
Hyderabad, India

F Fioredda
Unita' di Ematologia
IRCCS
Istituto G Gaslini

European Reference Network

My disclosures
X4 Pharmaceutic Advisory board

LEARNING GOALS

Recognize and approach children and adults with low neutrophils to define the diagnosis

Adopt management strategies for neutropenia patients

Design appropriate follow-up according to the neutropenia type

NEUTROPENIA THRESHOLD

From 14 days to 1 year	**< 1.0 x 10^9/L**
Children > 1 year to adulthood	**< 1.5 x 10^9/L**
Adult	**<1.8 x 10^9/L**

Mild 1.0 - 1.5 (or 1.8 for adults) × 10^9/L
Moderate 0.5 -1.0×10^9/L
Severe <0.5 × 10^9/L

Agranulocytosis <0.2×10^9/L usually associated with a high risk of severe, life-threatening infections
Acute <3months
Chronic>3months

Fioredda F, Haemasphere 2023

NEUTROPENIA *definition & classification*

CHRONIC
benign
NEUTROPENIA
SEVERE
Congenital
IDIOPATHIC
acute
AUTOIMMUNE
PRIMARY
ISOLATED
SECONDARY

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According the criteria of degree, persistence, presence of extra-hematological signs

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Guideline Article – Consensus based

Open Access

The European Guidelines on Diagnosis and Management of Neutropenia in Adults and Children: A Consensus Between the European Hematology Association and the EuNet-INNOCHRON COST Action

Francesca Fioredda[1], Julia Skokowa[2], Hannah Tamary[3,4], Michail Spanoudakis[5], Piero Farruggia[6], Antonio Almeida[7,8], Daniela Guardo[1], Petter Höglund[9,10,11], Peter E. Newburger[12], Jan Palmblad[10,11], Ivo P. Touw[13], Cornelia Zeidler[14], Alan J. Warren[15,16,17], David C. Dale[18], Karl Welte[19], Carlo Dufour[1], Helen A. Papadaki[20,21]

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CLASSIFICATION of chronic neutropenias

CONGENITAL

- Isolated
- Associated with various extrahematological manifestations
- Associated with immunodeficiency/immune dysregulation
- Associated with metabolic disorders and nutritional deficiency
- Associated with bone marrow failure

ACQUIRED

- Primary or Idiopathic
  - ✓Antibody-mediated
  - ✓Non-antibody mediated
- Secondary due to
  - ✓Hypersplenism
  - ✓Infections
  - ✓Autoimmune diseases
  - ✓Nutritional deficiencies
  - ✓Hematologic diseases
  - ✓Drug-induced

LIKELY ACQUIRED

In children/adolescents, young adults

Late-onset/Long lasting

Fioredda F Haemasphere 2023

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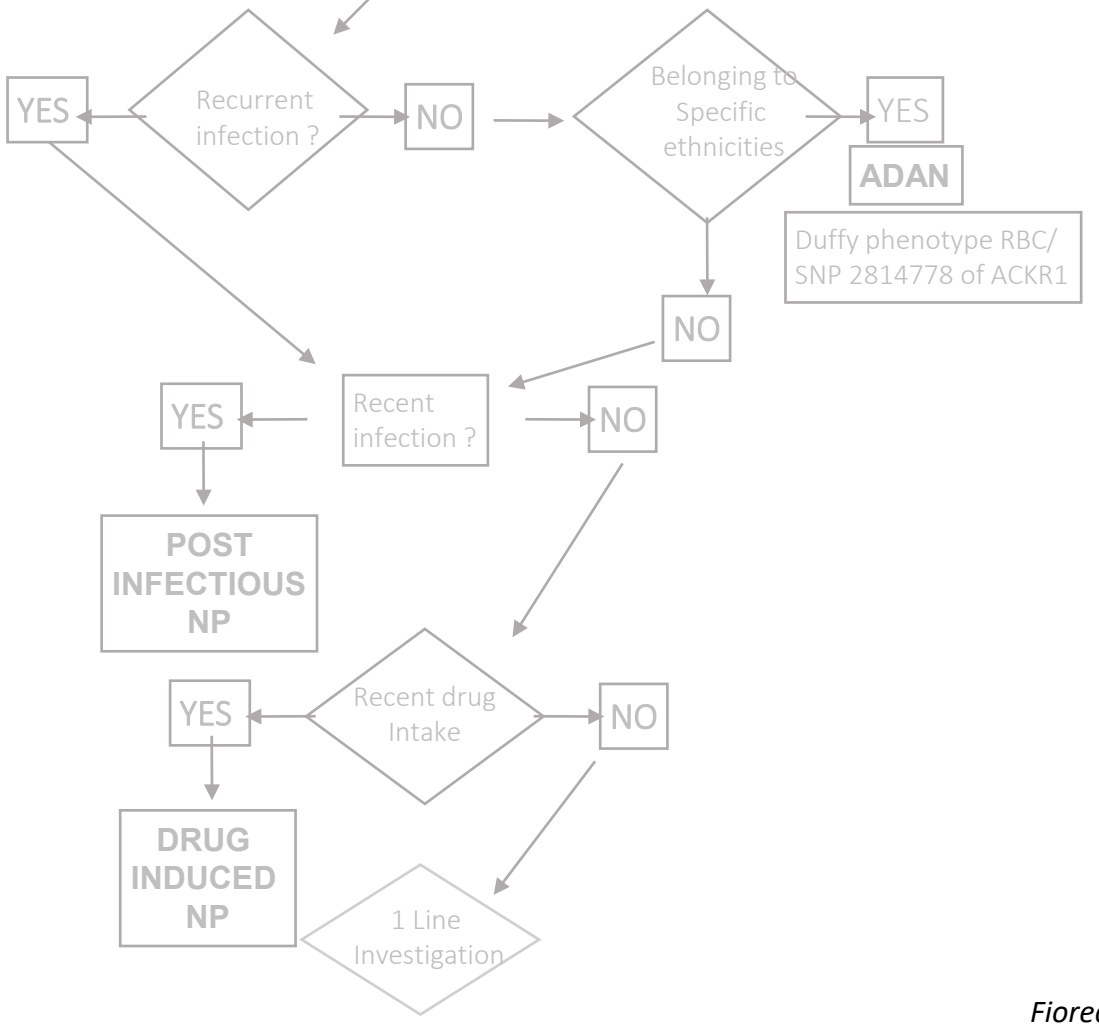
DIAGNOSTIC ALGORYTHM 1

Isolated chronic neutropenia with/without extra-hematological **symptoms/signs suggestive of an underlying congenital neutropenia syndrome**



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Fioredda F, Haemasphere 2023

Symptoms/signs suggestive of an underlying congenital neutropenia syndrome

FAMILY HISTORY

Consanguineity
Malformations
Neutropenic relatives & unexplained infant death or miscarriages
Infections type and time

CLINICAL EXAMINATION

Failure to thrive
Cognitive impairment
Developmental delay
Dysmorphism (mainly skeletal)
Nail, hair or skin abnormalities (i.e. superficial veins)
Signs of bronchiectasis
Organ enlargment or malformation (liver , spleen , heart, genitourinaryjoint symptoms)
and finally signs of photophobia, nystagmus, oculocutaneous albinism, and neuropathy.

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Symptoms/signs suggestive of an underlying congenital neutropenia syndrome

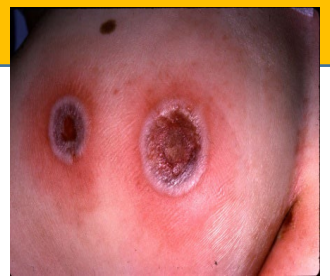
PERSONAL & FAMILY HISTORY

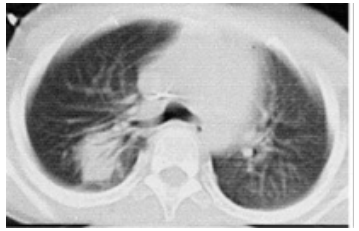
Consanguinity

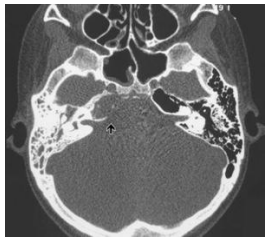
Malformations

Neutropenic relatives & unexplained infant death or miscarriages

Infections type and time

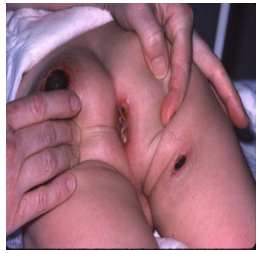


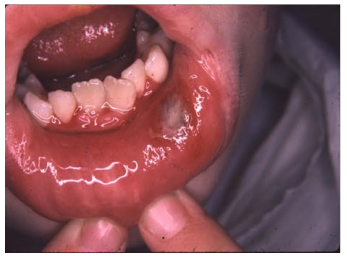


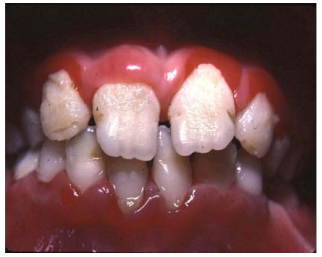


>>Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Streptococcus pyogenes

<< Candida spp & Aspergillus spp







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NP DIAGNOSIS in children

Significative elements to produce a score

key informations needed to make a diagnosis of congenital neutropenia

Family history/**consanguinity**
Any associated morbidity
Severe infections (Cellulitis; pneumonitis; any sepsis; any deep bacterial infections)
Stomatitis or gingivitis
Monocytes >1.5 × 10^9/l
Hemoglobin <90 g/l or platelets <150 × 10^9/l

Bejjani N, Ped Blood and Cancer 2017

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DIAGNOSTIC FAST TRACK

Severe neutropenia (either isolated or associated to any signs of complex syndromes)

Severe infections (sepsis, meningitis, osteomyelitis,deep abscesses/flemmons or pneumonia) or recurrent/torpid infections (i.e. otitis, masthoiditis, skin abscesses, urinary tract infections, enteritis)

Early infancy

First level investigations & bone marrow examination

Targeted genes analysis

Sanger tecnique

ELANE, HAX1

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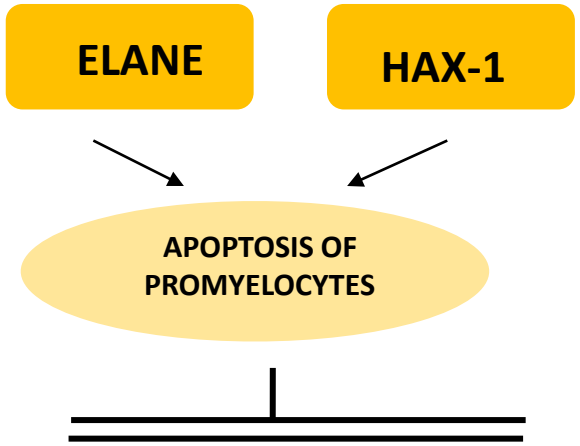
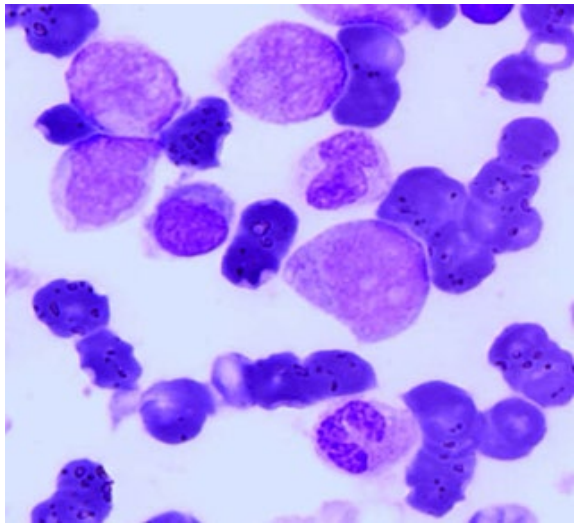
PATHOGENETIC MECHANISMS



Block in the bone marrow



LEF1 e CEBP αlfa
HYPOESPRESSION
Block at Promyelocytes

PU1 Hyperespression
Monocytes proliferation

JAK2 e STAT5 activation
Prolypherative stimulus

Skokowa J Hematol Oncol Clin N Am 2013

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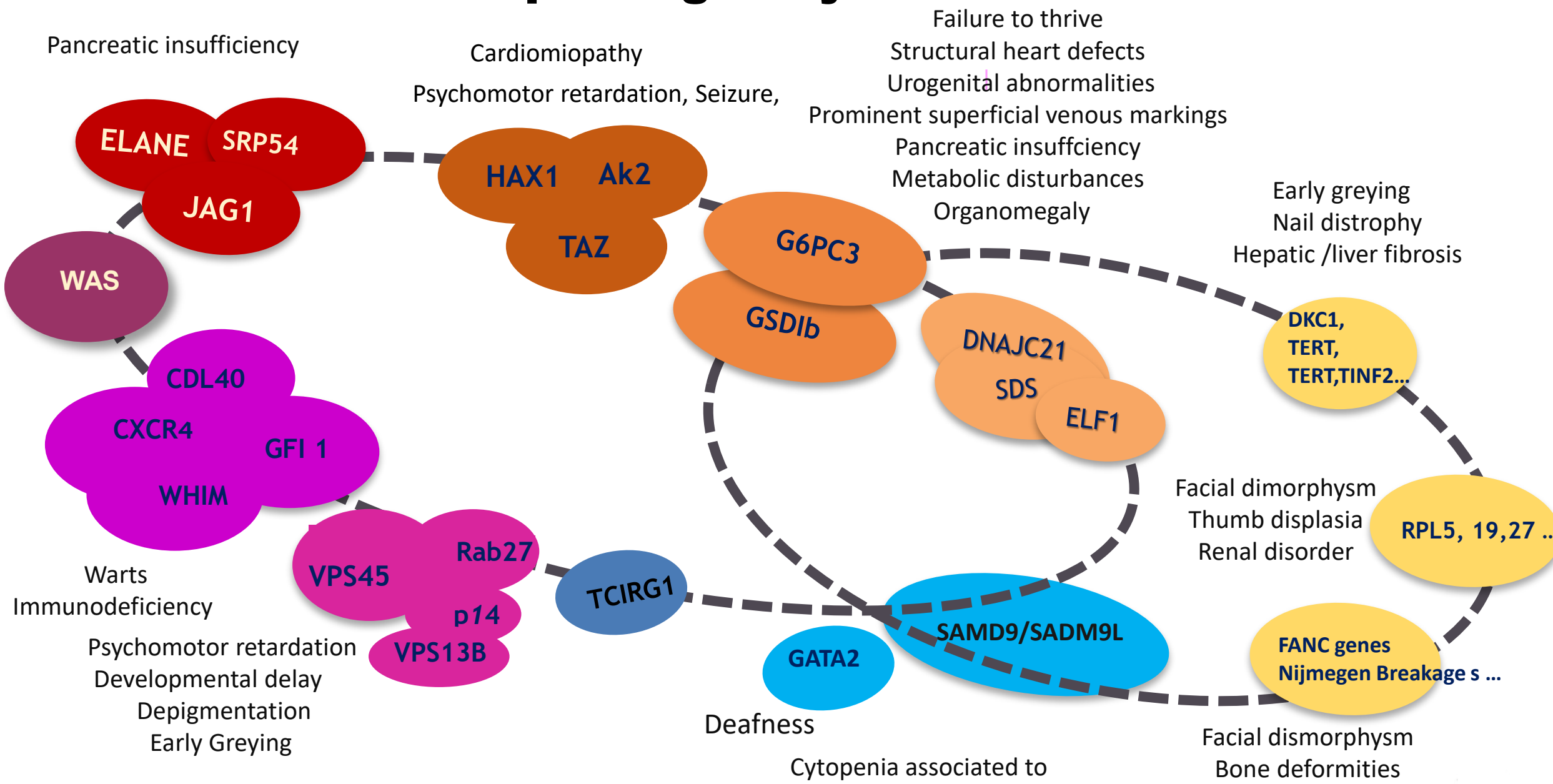
Neutropenia galaxy



Bluteau O, Blood 2018, Blanche A, Hematology Am Soc Hematol Educ Program 2007 Boztug and Klein, 2009

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Genetic variants -SCN

ISOLATED SCN

ELANE
CSF3R
CXCR2
WAS GOF

SCN ASSOCIATED TO

Various extra-haematological sign

HAX1
G6PC3
GFI1
TAZ
VPS13, VPS45
COH1
SMARCAL1
JAGN1
DNM2
TCGIR1
DNMT3
SEC61A1
HYOU1
LAMTOR2
SMARCD2
CEBPE
EIF2AK

Immunodeficiency/dysregulation

CD40L
ADA2
FAS, FASL, CASP10
AK2
AP3B1
CLBP
RAB27A
PRF1-UNC13D-STX11-STXBP2
RMRP
LYST
STK4
CXCR4
GATA2
WAS LOF

Metabolic diseases

TCN2
SLC37A /G6PT1(Glicogenosi1b)
PCCA-PCCB (Propionico-aciduria)
MMUT-MMAA-MMAB-MCEE-MMADHC
IVD Tyrosinemia
GBA

Bone Marrow Failure

FANC genes
RPS19,RPL5,RPS26,RPL11,
GATA1
TSR2
HEAT3
RMRP
SAMD9,SAMD9L
SBDS,EFL1, DNAJC21
SRP54
hTR,TERT,TINF2,DKC1, ACD,TERC
NOPO10,WRAP53,NOLA3,
TCBI,RTEL1, CTC1,PARN, USB1

Unknown genes (25%)

Fioredda F, Haemasphere 2023

Genetic tests: choice of technique

Sanger (single gene) when strong evidence (inheritance, clinical findings, bone marrow appearance i.e. block at the promyelocyte stage) for a specific gene mutation.

- ✓ ***ELANE maturation arrest***
- ✓ ***TAZ cardiomiopathy***
- ✓ ***G6PC3 cardiomiopathy***
- ✓ ***SDS malabsorption, fatty stools, bone anomalies***

NGS/WES

- ✓ **Congenital neutropenia without evidence for a specific gene**
- ✓ ***Consider inclusion in NGS panels of PID/PIRD,BFM, metabolic genes***
- ✓ ***Trios and functional studies for VUS***

WGS/and RNA seq ***If a genetic cause is not identified by the above methods***

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Fioredda F, Haemasphere 2023

Last discovered genes

CLBP *apoptosis of myeloid progenitor related to mitochondrial dysfunction*

Warren JT, Blood 20

CXCR2 *impaired neutrophil egression from bone marrow &neutrophils homeostasis*

Marine-Esteban V , Haematologica2022

DBF4 *defect in DNA trascription*

Willemsen J All Clin Immunol 2023

SRP19 and SRPRA *protein processing, intracellular trafficking and homeostasis*

Linder MI, Blood 2023

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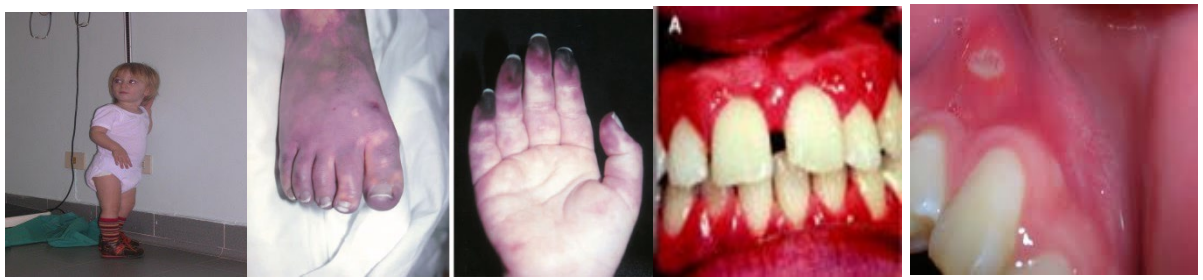
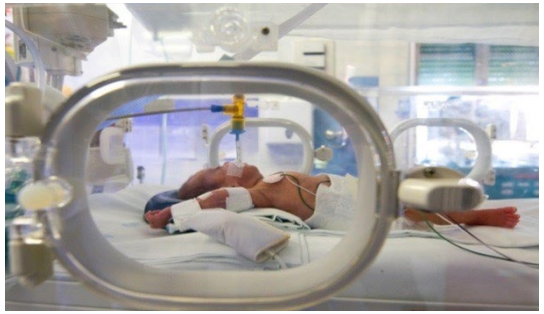
SCN NATURAL HISTORY

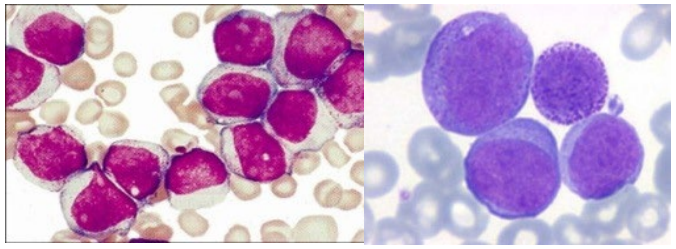
- ✓ Recurrent infections
- ✓ Not always easy eradication



Infections even lethal



Trasformation to MDS/ AL



SCN treatment

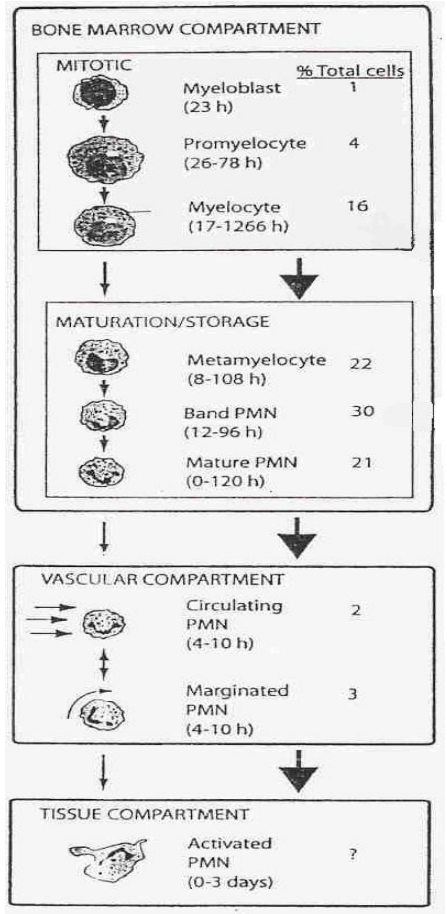
G-CSF

Tailored therapy: minimal dose for the best effect
standard 5 gamma/kg/die)

Goal: absolute neutrophil count (ANC)
1.0 - 5.0 $X10^9$/L

G-CSF responders 90% of pts

Responders till 15 µg/Kg/d
Scarse responders 15-20 µg/Kg/d
No responders > 20 µg/Kg/d



Donadieu J, Haematologica 2005, Welte K Sem Hematol 2006, Fioredda F , Am J Hematol 201

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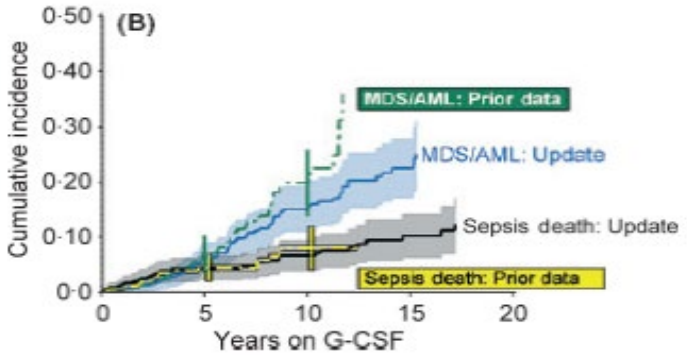
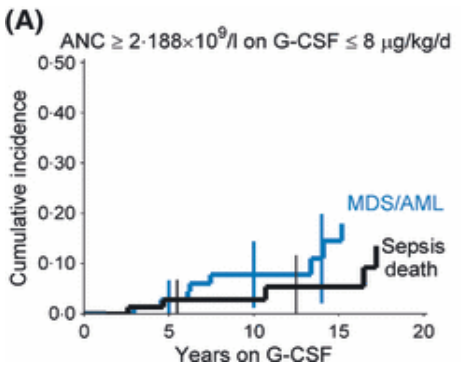
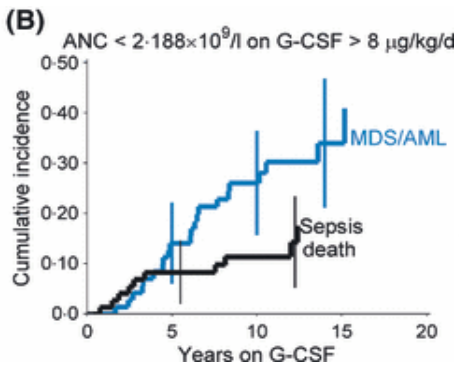
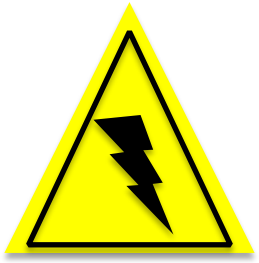
G-CSF
Reduction of infections lethality









Rosenberg PS , BJH2010

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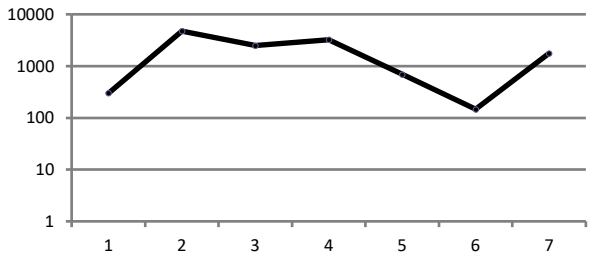
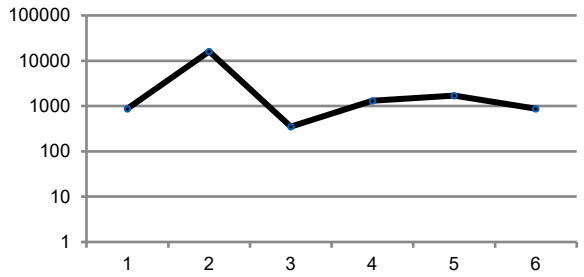
PEGFILGRASTIM in SCN

PT1



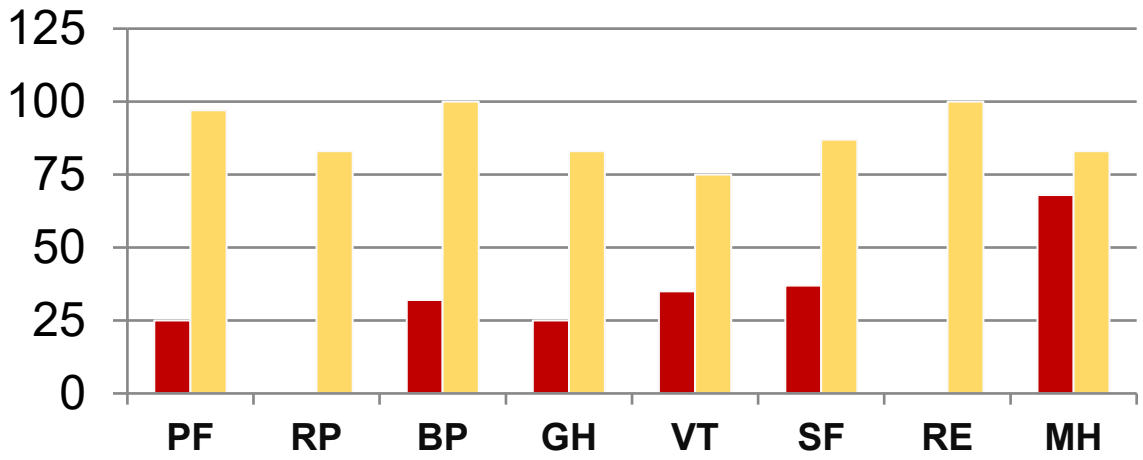
PT2



50-60 mcg/kg/week
Medium ANC 1.280/mmc/L

Increase of ANC
Reduced incidence of infections
Similar drug exposure

SF36



Physical function role physical, bodily pain , general health, vitality, social function, role emotional, mental health

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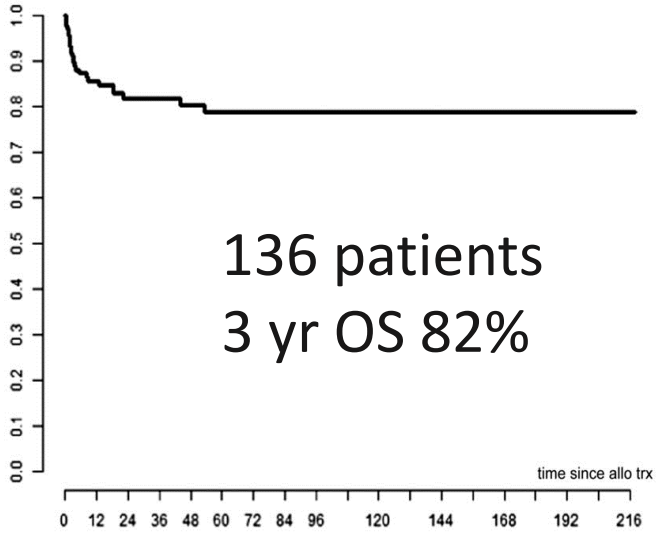
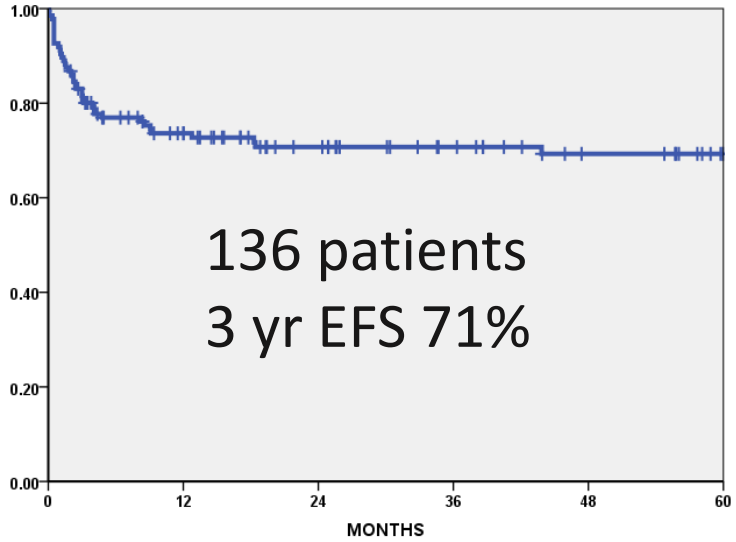
HAEMATOPOIETIC STEM CELL TRANSPLANTATION



136 patients
3 yr OS 82%



136 patients
3 yr EFS 71%

TRM 17 %
infections, GvHD, organ damage, relapse

cGVDH 28%

>> bone marrow *vs* peripheral cells *vs* cord

Fioredda F , Blood 2015

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INDICATION TO HSCT

Strong Indication to HSCT

MDS/AML or BM dysplastic features (monosomy 7, trisomy 8, trisomy 21)

CN due to mutations carrying an intrinsic high risk of leukemic transformation per se

No response to G-CSF (doses >20mcg/kg/day), poor response to G-CSF(10 -20 mcg/kg/day)

or poor control of infection irrespective of the G-CSF dose

Potential indication to HSCT Adequate management of infections with G-CSF at “intermediate doses” (10 mcg-15 mcg /kg/day) with availability of a healthy HLA-identical sibling or HLA identical matched donor

Weak indication to HSCT G-CSF response at doses up to 10 mcg/kg/day, good tolerability and compliance to daily subcutaneous injections, infections control and unavailability of HLA-matched donors

Fioredda F, in preparation

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ALTERNATIVE TREATMENT

Antioxidants (mut Ak2)

RissoneA J Exp Med 2015

Wnt3a + <<GCSF (ELANE-C223X.iPS)

Hiramoto T Proc Natl Acad Sci U S A 2013

NICOTINAMIDE +<< G-CSF

Deoardieva E , BJH 2021

Sivelestat (ELANE- Q97P el118N)

Nayak RC j Clin Invets 2015

Mavorixaflor phase 2 st (WHIM)

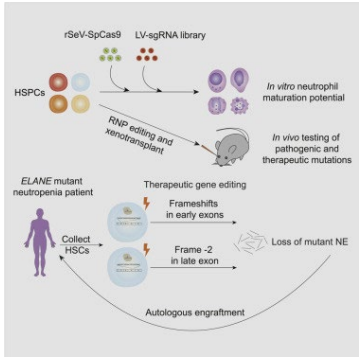
Dale D Blood 2020

Empaglifozin (G6PC3 and Glic 1b)

GENE Therapy

Gene mutation correction

Autologous Infusion



Tran NT Mol Ther 2020

Wortmann Sb , Blood 2020,
Boulangier C, J Inherit Metab Dis 2022

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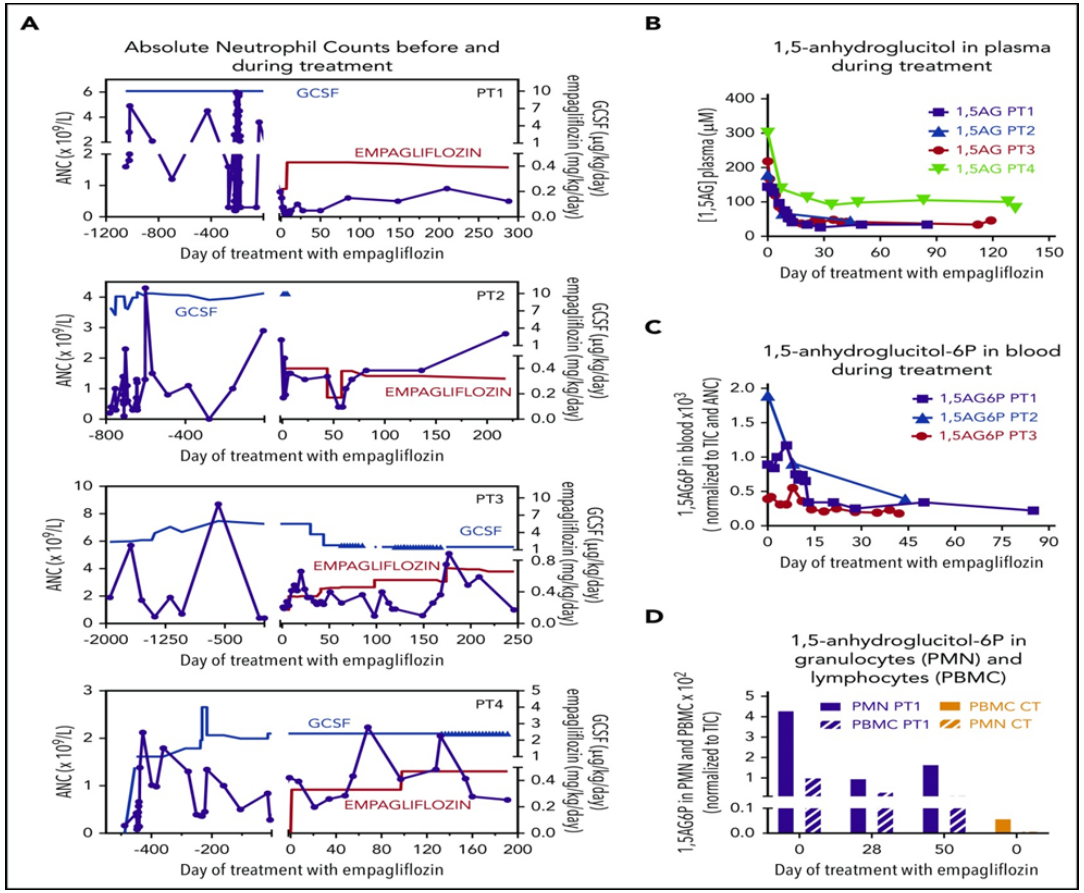
EMPAGLIFOZIN

G6PC3 and G6PT/SLC37A4 deficiency

Missing defosforilation of 1,5-anydroglucitol-6-posphate (1,5 –AG6P)

Accumulation inside neutrophil → inihibition of glucose utilization by the neutrophil-> disfunction



Empaglifozin counter acts the renal riabsoption of 1,5-AG6P

Wortmann SB Blood 2000, Boulanger C J Inherit Metab Dis 2022

European Reference Network

Empagliflozin or dapaglifozin

French Registry

0.2mg/kg/day or 0.4mg/kg/day

21 patients (GSD1b 14 , G6PC3 7)
Median fUP 0.8 yrs
Median age at start th 18.8 yrs(0.4 37.7)

- Lower value of 1,5-AG in plasma
- Increase value of neutrophils
- Reduced dose of G-CSF (from 2,5 ug7kg/d to 0.31 ug/kg/d)
- Reduced IBD
- Less damage ro ER in the neutrophild (electronic image)
- Side effects Neutrophilia in G6PC3, transient vomit

AbASH2022

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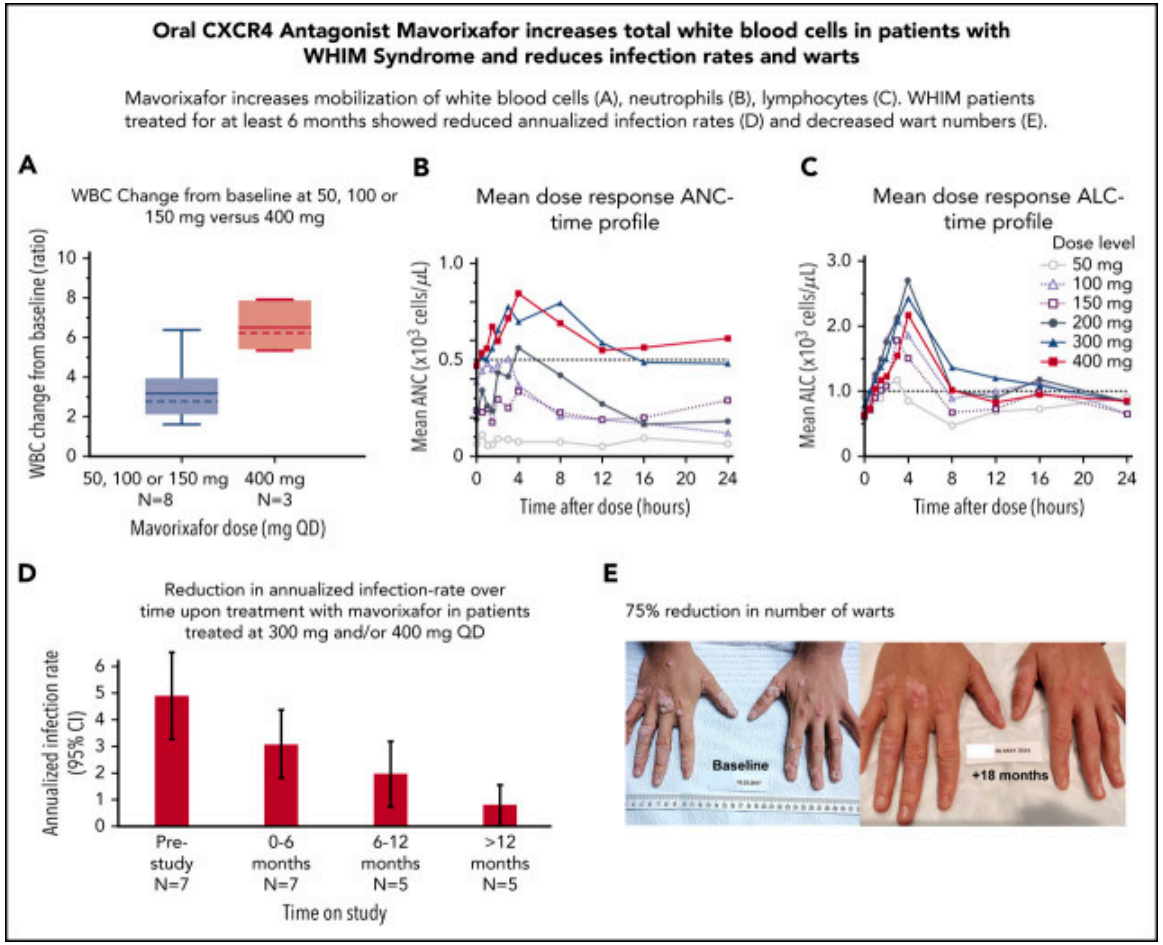
MAVORIXAFLOR in CXCR4 NP

Mavorixafor is an oral small molecule selective antagonist of the CXCR4 receptor that increases mobilization and trafficking of white blood cells from the bone marrow.



Dale DC , Blood 2020

European Reference Network

SEVERE CONGENITAL NEUTROPENIA

rationale for follow up

To monitor neutropenia associated clinical manifestation (gingivitis, periodontitis) and G-CSF chronic side effects (splenomegaly, osteoporosis etc)

To adjust G-CSF doses according to individual infective burden

To monitor the risk of MDS/AML risk transformation

Fioredda F, Haemasphere 2023

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NEED FOR FOLLOW UP AND FREQUENCIES

Annual BM or more often if count drops

- morphology
- cytogenetics
- NGS for somatic mutations in malignant myeloid genes to intercept CLONAL EMOPOIESIS and early MDS/Leukemia

(CSF3-R, RUNX1,TP53 biallelic mutations in SDS)

CSF3-R mutations may stay as such for years w/out development of leukemia

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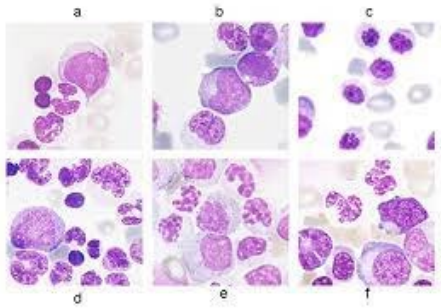
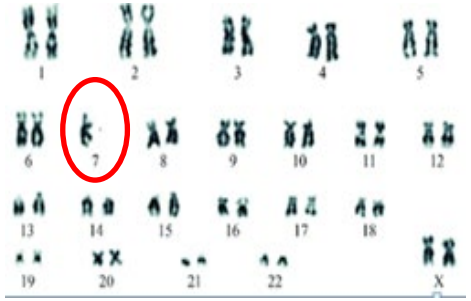
Fioredda F, Haemasphere 2023

Predictors of transformation to MDS/AML

- Marrow dysplastic changes



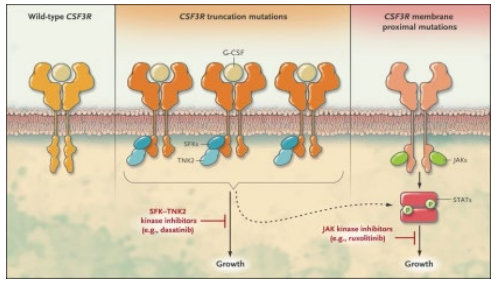
- Cytogenetic abnormalities: trisomy 21, monosomy 7, del q7

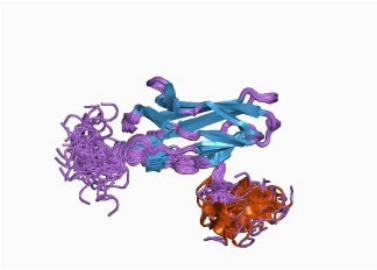


- Somatic leukemia-associated mutations

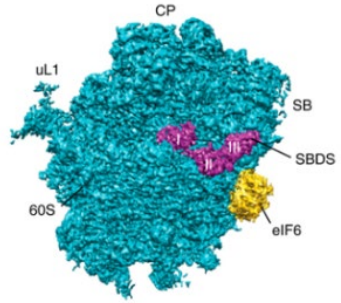
  CSF3R, RUNX1, ASXL1.

  Also PTPN11, TP53,SETBP1 in combination with CSF3R





- In SDS biallelic TP53 mutations



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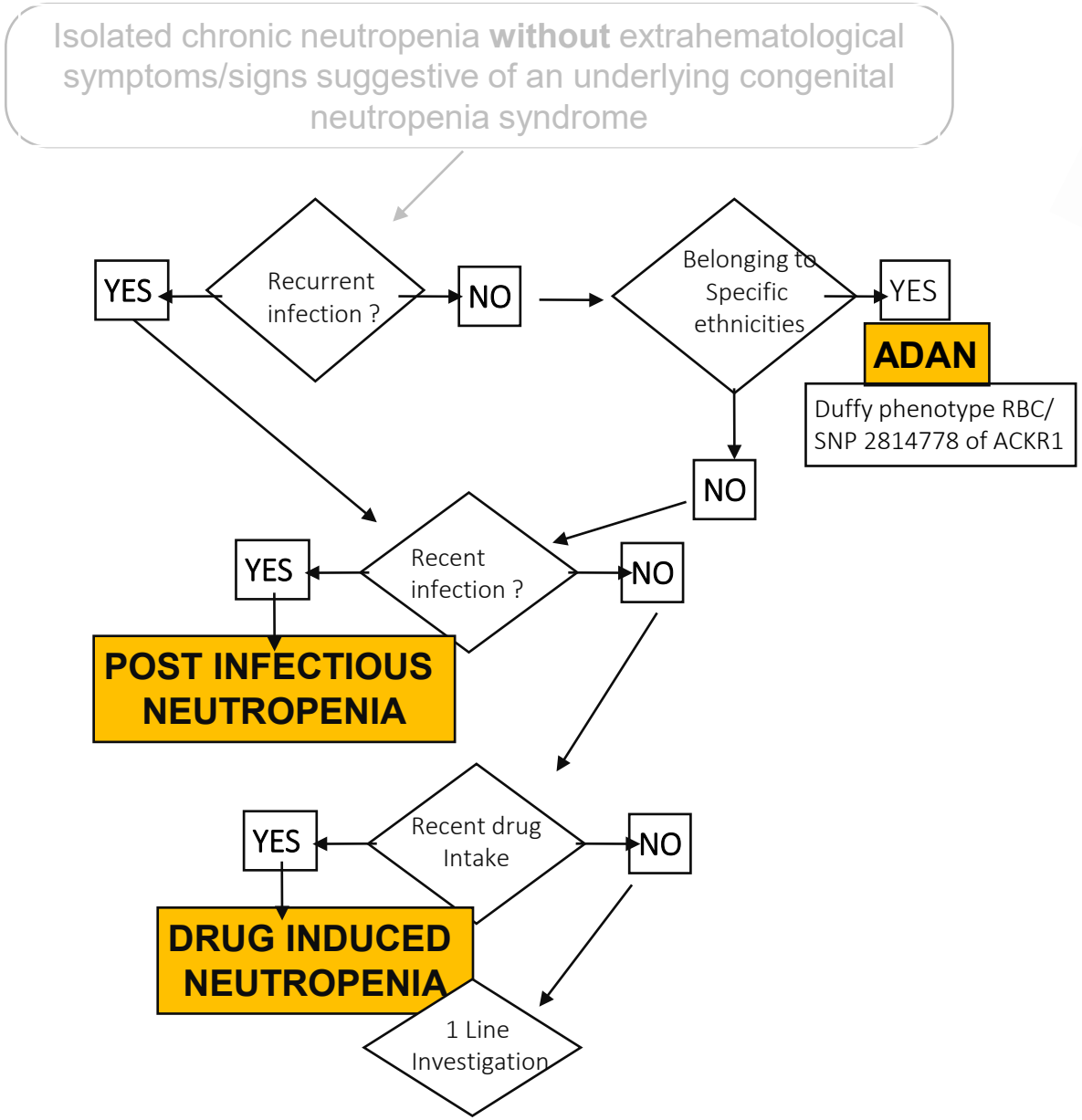
DIAGNOSTIC ALGORYTHM 2



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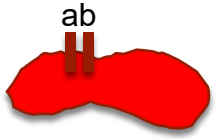
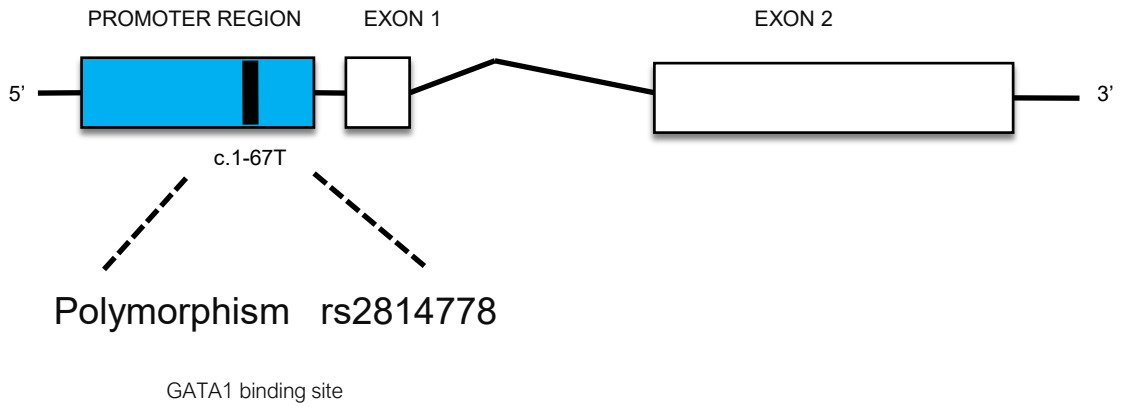
DUFFY null phenotype -/-



Red Blood Cells
Endothelial cell

(DARC) Duffy Antigen Receptor for Chemokines
or
(ACKR1) Atypical Chemokine Receptor 1

Rs2814778 polymorphism DARC/ACKR1 gene



Rappoport N BJH 2018, Palmblad JPBC 2018

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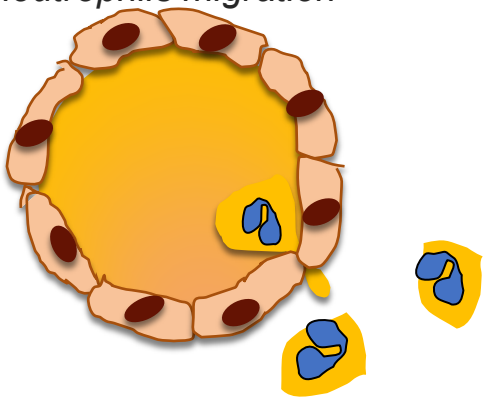
ADAN mechanism

DARC/ACKR1
Atypical chemokine receptor

CCL2, CCL5,CCL7.CCL11,CCL13.CCL14,CXCL6, IL8/CXCL8, GRO, RANTES, MCP-1

Chemokine Receptor
neutrophils migration



Fcy receptors expression (CD16/CD32 e CD45) on leukocytes
Neutrophils migration in the spleen

Duchene J, Nature Immunology 2'017. Rappoport N BJH 2018, Palmblad JPBC 2018, Mintz U Blood 1973, Dancey JY Am J medicine
Shoenfeld *Y Biomedicine & Pharmacotherapy*1985, *Phillips D Journal of Clinical Pathology 2000,*
Hsieh MM *Journal of Clinical Oncology 2010*

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First-line investigations

CBCs, PB smear, biochemistry tests including liver and kidney function, immunoglobulin levels, CRP, vitamin B12 and folate, flow cytometric analysis of PB lymphocyte subsets, virology antibody screening (i.e., HepB, HepC, HIV, EBV, CMV, and Parvovirus), **indirect antineutrophil antibodies (GIFT, GAT, and other);** thyroid hormones (FT3, FT4, TSH), antithyroid antibodies (anti-TG and anti-TPO).

Additional investigation in children: flow cytometric analysis of TCR-α/β-positive double-negative (CD4- and CD8-) CD3 PB lymphocytes.

Additional investigations in adults: antiphospholipid and anticardiolipin antibodies, flow cytometric analysis of LGL/TCR clonality in PB lymphocytes, serum ferritin, RF, ANA, ENA, ds-DNA, and ESR

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CLASSIFICATION of chronic neutropenias

CONGENITAL

- Isolated
- Associated with various extrahematological manifestations
- Associated with immunodeficiency/immune dysregulation
- Associated with metabolic disorders and nutritional deficiency
- Associated with bone marrow failure

ACQUIRED

- Primary or Idiopathic
  - ✓Antibody-mediated
  - ✓Non-antibody mediated
- Secondary due to
  - ✓Hypersplenism
  - ✓Infections
  - ✓Autoimmune diseases
  - ✓Nutritional deficiencies
  - ✓Hematologic diseases
  - ✓Drug-induced

LIKELY ACQUIRED

In children/adolescents, young adults

Late-onset/Long lasting

Fioredda *F, Haemasphere 2023*

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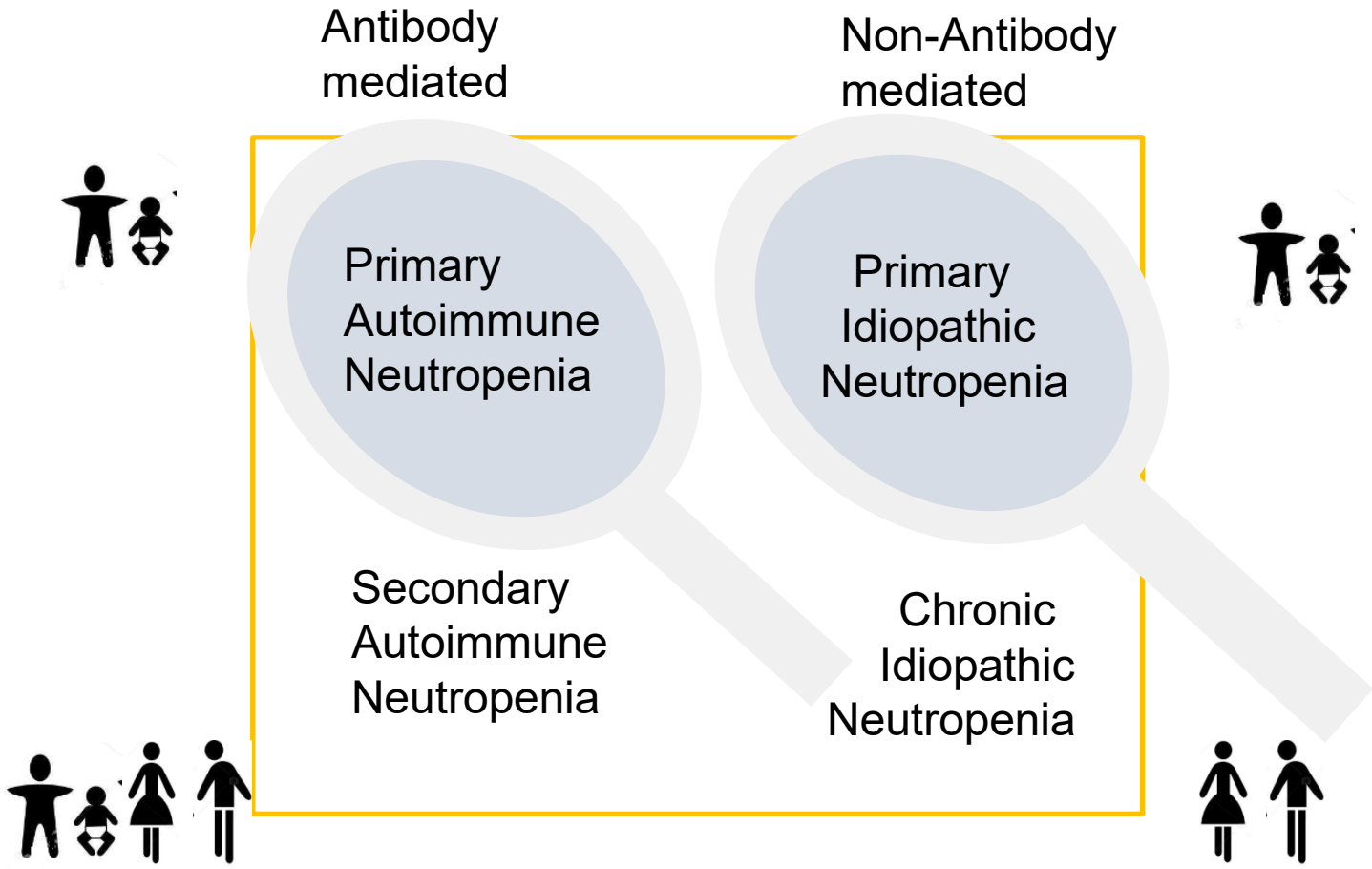
ACQUIRED NEUTROPENIA 1



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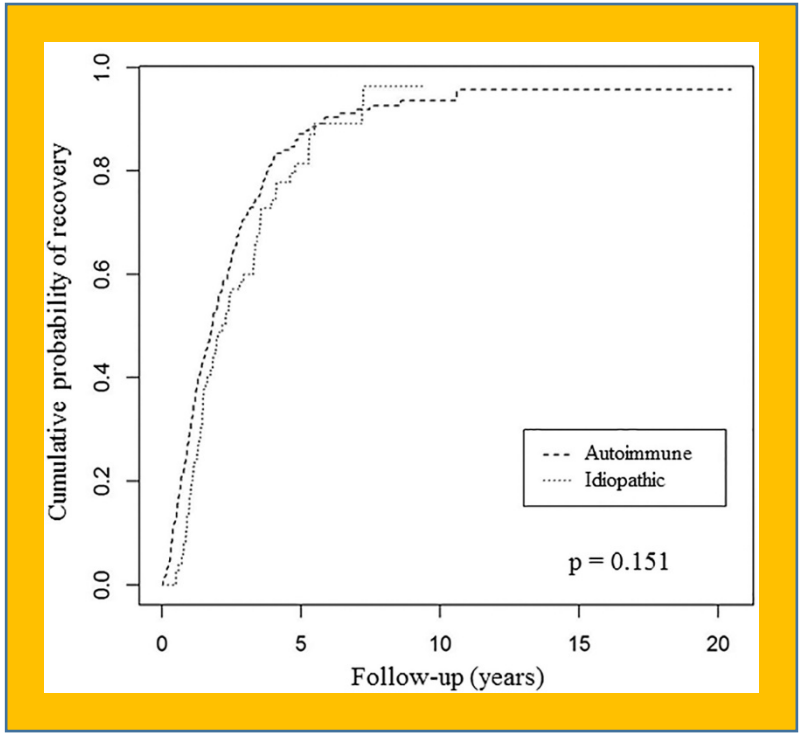
PRIMARY AUTOIMMUNE/IDIOPATHIC NEUTROPENIA of infancy

- Early infancy
- Usually detection by chance
- Rather low rate of severe infections (10%)
- Self limiting course within 24 -36 mo



Presence/absence of AbantiN !!

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Farruggia P, Am J Hematol 2015, Farruggia P et al Am J Hematol 2019

Management of primary AIN/IN

Counselling and contact

- Avoid overtreatment (blood count 3-4 times/y, repeat
- Repeat Ab against neutrophils if negative
- No need for basal bone marrow examination

- In case of recurrent of deep/severe infections G-CSF
- G-CSF schedule: preferably on demand use of the least dose for the best effect (1-3 ug/kg)

Fioredda F , Ped Blood and Cancer 2022

European Reference Network

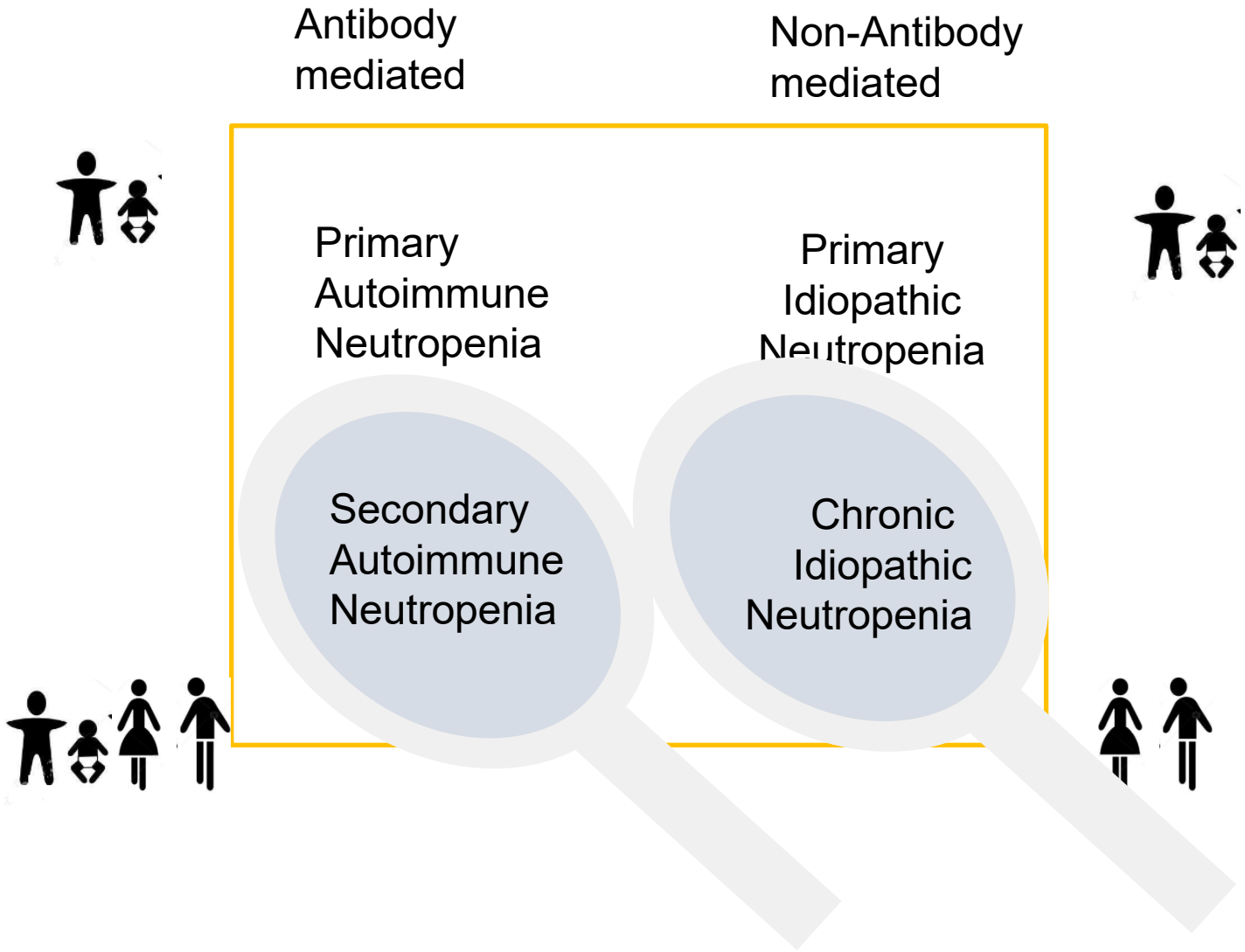
Why FUP?

- Family reassurance (time of resolution not always short…)
- Verify the remission of pAIN/pIN

SUDDEN resolution 70 % of cases TRANSIENT/ INTERMITTENT oscillation in 30% of cases

Farruggia et al, Am J Hematol 2015

ACQUIRED NEUTROPENIA 2



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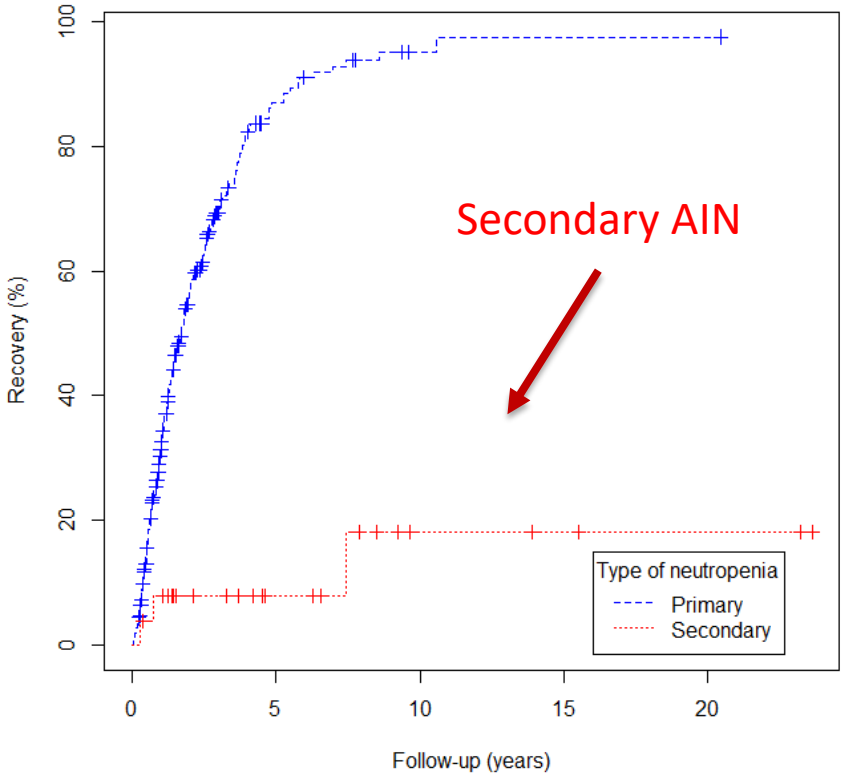
SECONDARY AUTOIMMUNE NEUTROPENIA

Children

Recovery: primary vs secondary AIN of infancy



Adults

- Evans
- Autoimmune Thyroiditis
- SLE
- Sjogren syndrome
- Rheumatoid arthritis
- Felty's syndrome
- Crohn disease
- Autoimmune hepatitis
- Multiple sclerosis
- Drug
- Neoplasm/BMT

Farruggia et al, Am J Hematol 2017

European Reference Network

CHRONIC IDIOPATHIC NEUTROPENIA

ADULTS

Mild clinical phenotype/ mild NP

Pro-apoptotic mediators in the bone marrow

Leuco/lymphopenia

Occasionaly altered immunoglobulin levels
(<IgG,<IgA and > IgM)

> naïve B IgD^{+} $CD27^{-}$ cells

< class-switched memory B IgD^{-} $CD27^{+}$ cells

AntiN Ab negative

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Maouvrodi I Cli Immunol 2017, Tsaknakis G, Blood 2021

Management of CIN/sAIN

In case of recurrent of deep/severe infections G-CSF (the least dose for the best protection against infections)

Which type of FUP?

Blood Cell Count (morphological evaluation) every 3-4 months

BONE MARROW in patients with decreasing ANC or additional changes in other blood cell count (i.e.macrocytosis or morphological abnormalities) or in patients treated continuously with G-CSF

NGS panel/ Flow cytometry to exclude somatic variants

Somatic clones with VAF>10% closer follow-up (>4 times/year)

Consider Genetic investigations for constitutional variants

Fioredda F, Haemasphere 2023

……**What about** neutropenic Children with /without Ab
Whose **NEUTROPENIA** does not remit??? …not associated with Other AI disorders?

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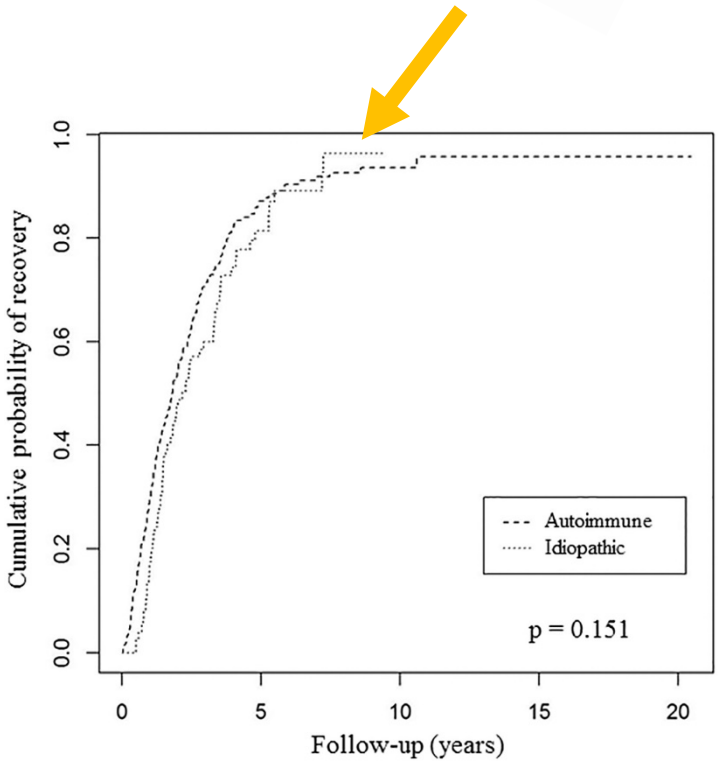
Long lasting/late onset AUTOIMMUNE & IDIOPATHIC Np

- **Persistent neutropenia (>36 months if onset <3 years, >12 months if onset >3 years)**
- Antineutrophil Antibodies **POSITIVE and NEGATIVE**
- **No other cytopenias and related autoimmune disease at onset**



Fioredda F, AJH2024

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Characteristic of the Cohort

	Total, n = 63
Female, n (%)	31 (49)
Type of neutropenia, n (%)	
Positive anti-neutrophil Abs (AIN)	32 (49)
Negative anti-neutrophil Abs (IN)	25 (40)
LO-Np	45 (71)
LL-Np	18 (29)
Median age at onset (yrs) (IQR) (min-max)	**9.2 (0-23.9)**
Median age at diagnosis (yrs) (IQR) min-max	**12.9 (0.3-50.9)**
Median follow-up time (yrs) (IQR) min-max	**5.2 (1.3-30.7)**

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Fioredda F, AJH 24

Infections

Frequency 71.4% (45/63)		N (%) patients with RECURRENCE
Upper respiratory infections	27 (60)	**18/27 (66.7)**
Aphthae, gingivitis, periodontitis	22 (48.9)	**19/22 (86.4)**
Skin infections	13(28.9)	8/13 (61.5)
Fever of unknown origin (FUO)	16 (35.6)	**11/16 (68.7)**
Otitis	11 (24.4)	**7/11 (63.6)**
Pneumonia	8 (17.8)	2/8 (25)
Urinary tract infections	6 (13.3)	1/6 (16.7)
Severe infections	**6 (13.3)**	
"Opportunistic" infections	3* (6.7)	
**** 2 recurrent Herpes Zoster, 1 Campylobacter Jejuni***		

SEPSIS, MENINGITIS, PNEUMONIA (>1), PERICARDITIS

Recurrence in 25/45 (**55.6%**) *oral infections + upper airway + otitis*

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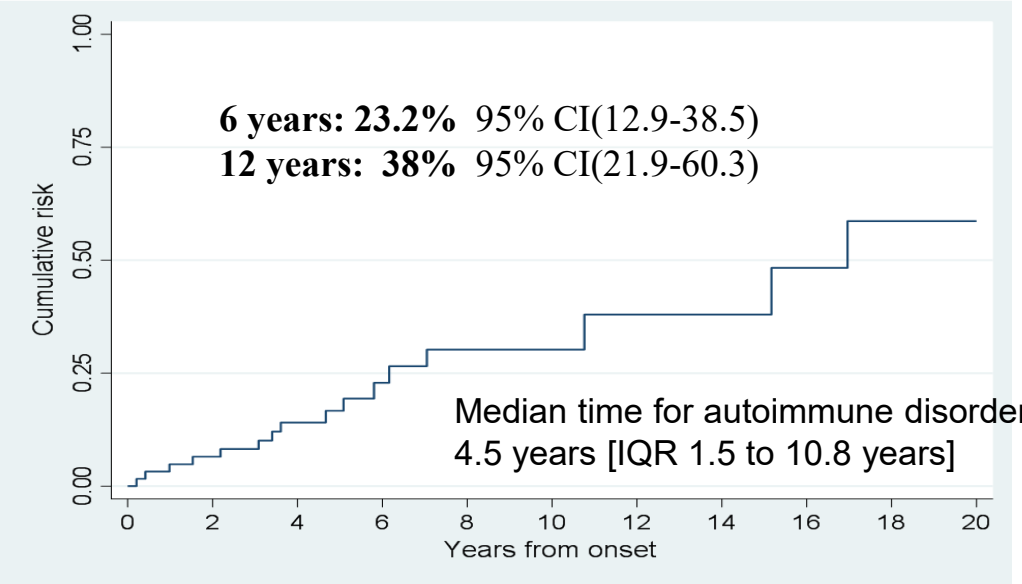
Autoimmunity



Positive ANA, ENA,

Thyroiditis, coeliac disease,

ALPS, arthritis, bone pain,

chronic fatigue

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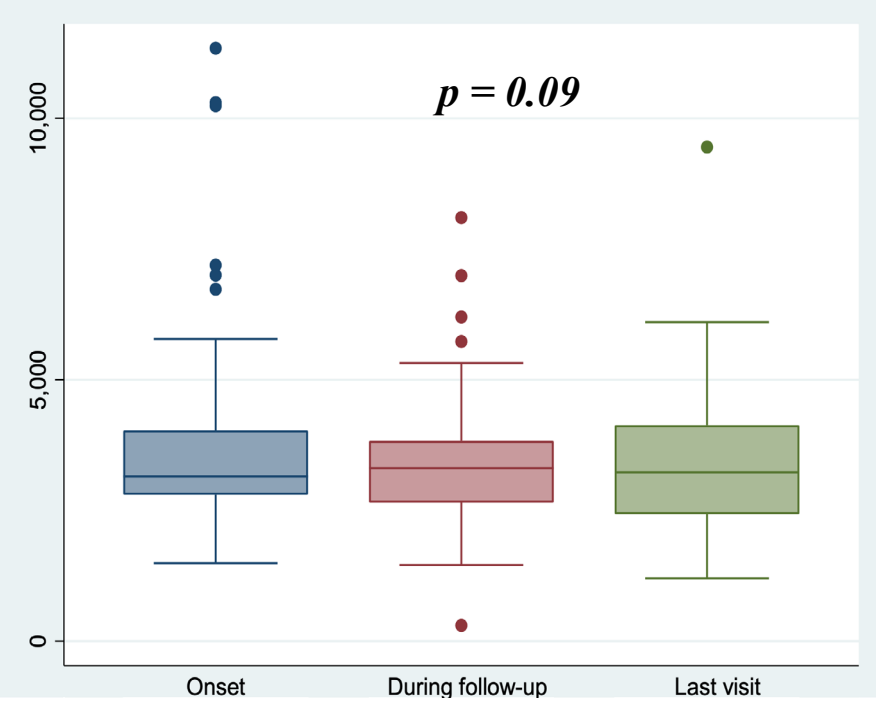
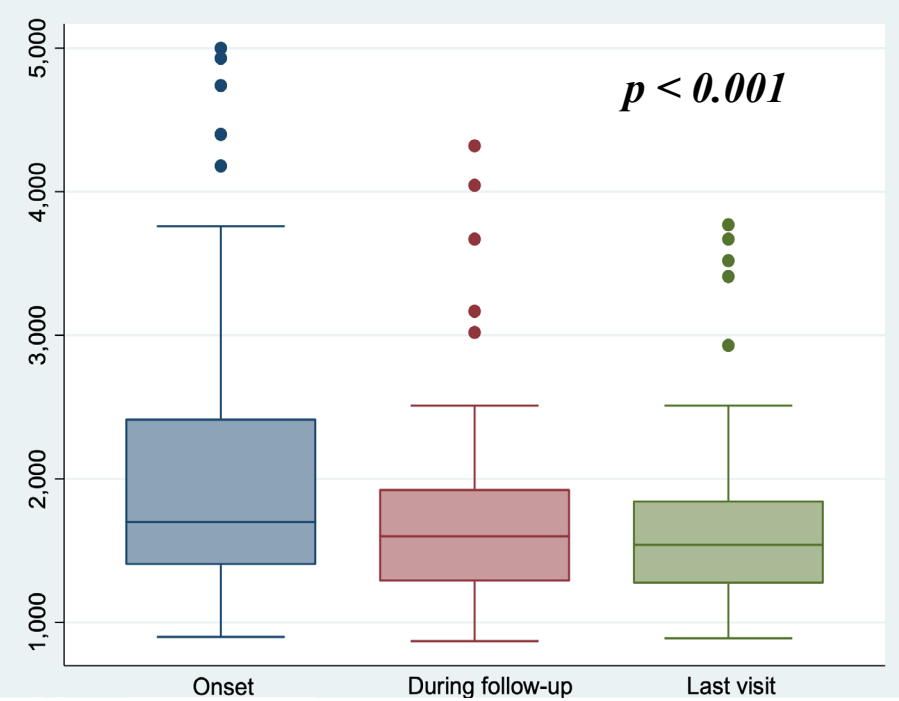
Blood count overtime

LEUCOCYTES



LYMPHOCYTES



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Immune profile

IgG/IgA/IgM

normal values in 85-94%

Hyper IgM 11.5% patients

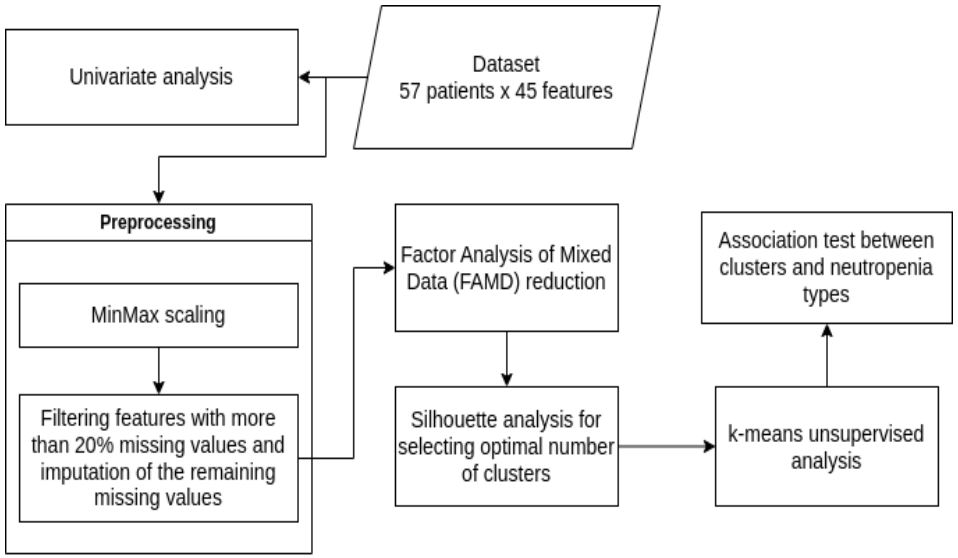
Low CD8/B/NK cella, Tregulatory, B memory
High γ/δ, HLADR+ T cells
Low B switched memory
Increased marginal zone B lymphocyte
Increased Double Negative B cells(total and DN2) and CD21 (DN1)
Shift T : naive >>memory effector

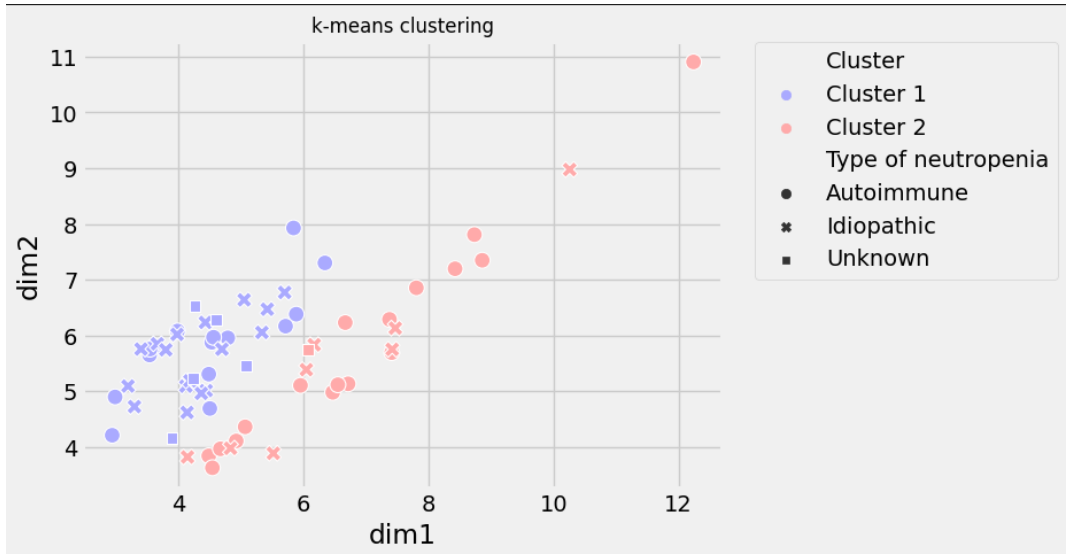
Found in several autoimmune diseases/CVID!!

Schiavo E, 2012, Mavroudi I 2008, Walter J, 2019, Mormile I, 2021

**Ranges according to the age*

Machine Learning Analysis
AUTOIMMUNE vs IDIOPATHIC





p-value = 1.0

=> **NO DIFFERENCE !!!**

Fioredda F, AJH 24

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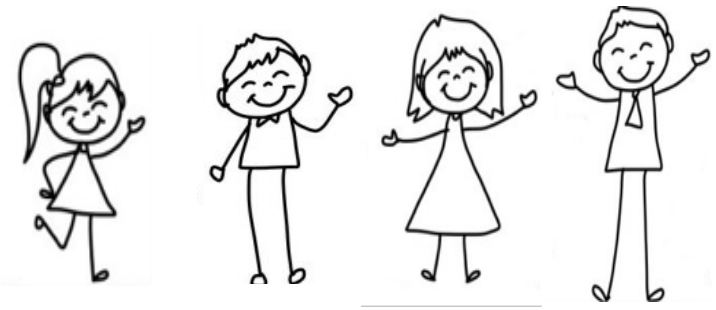
«NEW PHENOTYPE»

- Mild/silent phenotype at all ages
- Leukopenia& signs of immune-dysregulation
- Possible appearance of autoimmunity
- Antibodies against neutrophils +/-



WHAT ‘S UNDERNEATH?

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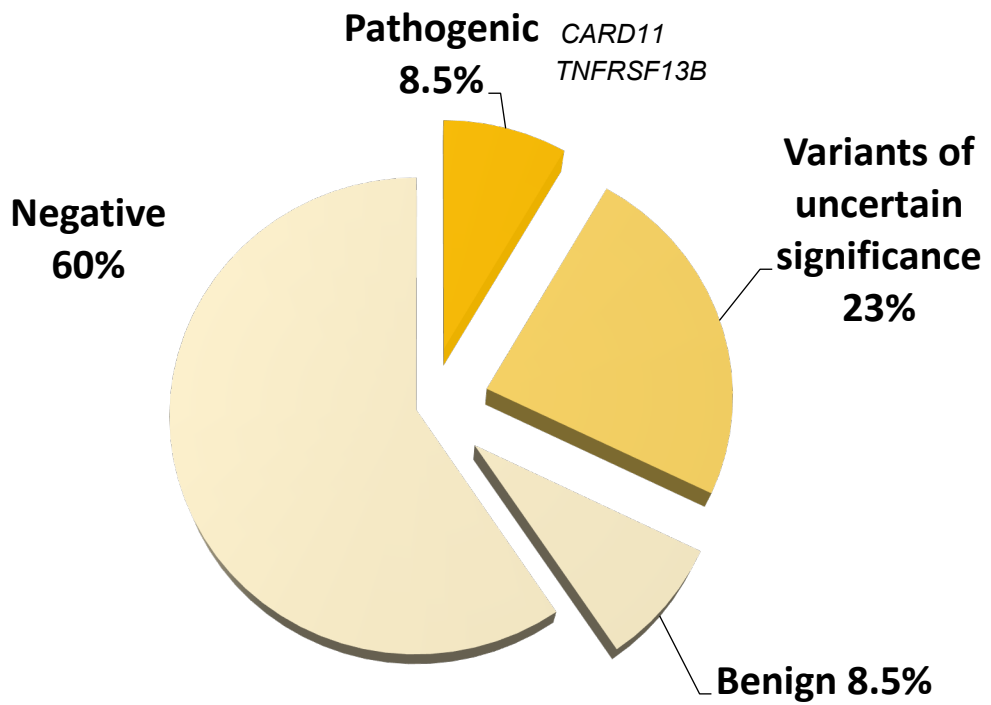
Genetic profile

NGS panel 160 variants of bone marrow failure/immunedyregulations

Analyzed 27/58 available samples

At least 1 variant in 23/58 (40%)



FASL
LYST
DDX41
PIK3CD
TSR2
RUNX1
DNM2
TINF2
RTEL1
TERT
SAMD9L

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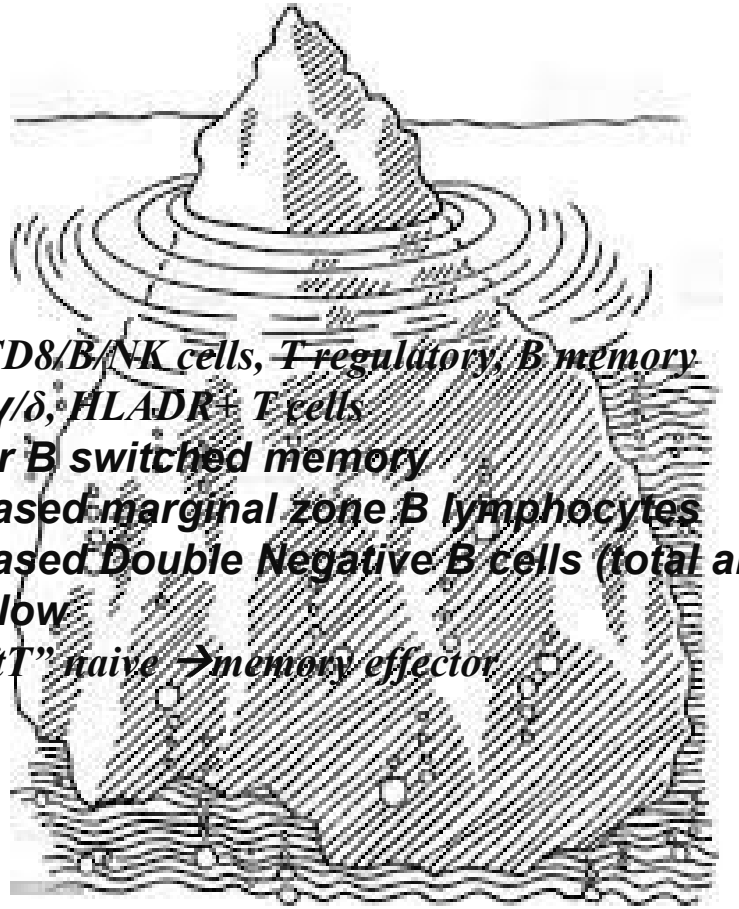
Fioredda F, AJH2024

NEUTROPENIA & PIRD/PID

Hypotesis:
Autoimmune/Idiopathic Neutropenia
“ tip of the iceberg”



Low CD8/B/NK cells, T regulatory, B memory
High γ/δ, HLADR+ T cells
Lower B switched memory
Increased marginal zone B lymphocytes
Increased Double Negative B cells (total and DN2) and CD21low
“ShiftT” naive →memory effector

PIRD/PID genes

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Hadjadj J Blood 2019, Fioredda F Blood Advance 2020, Fioredda F AJH 2024

CLASSIFICATION

of chronic neutropenias

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  - ✓ Antibody mediated
  - ✓ Non-Antibody mediated
- Secondary to
  - ✓ Hypersplenism
  - ✓ Infections
  - ✓ Auotimmune diseases
  - ✓ Nutritional deficiencies
  - ✓ Hematologic diseases
  - ✓ Drug induced

LIKELY ACQUIRED

In children/adolescents
young adults
Late-onset/Long lasting

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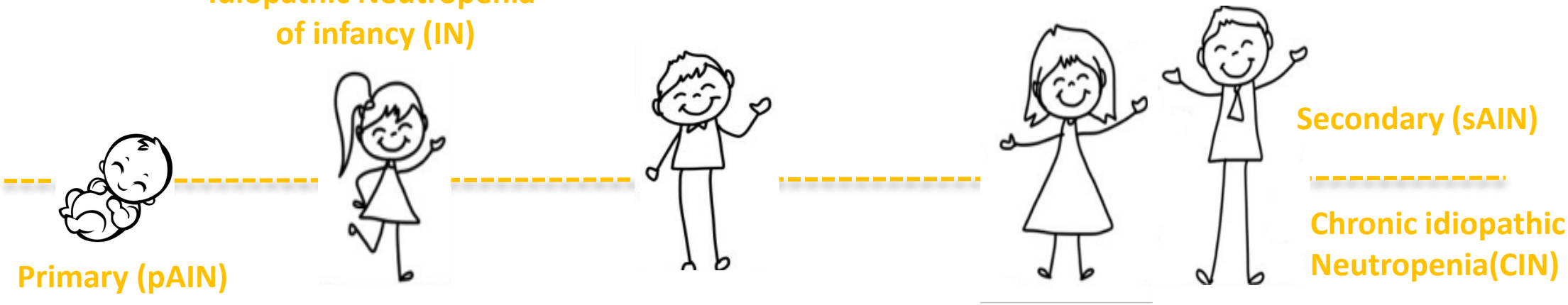
.....POSSIBLE CONTINUITY..... !

Idiopathic Neutropenia of infancy (IN)



Primary (pAIN)

Secondary (sAIN)

Chronic idiopathic Neutropenia(CIN)

THE “LIKELY ACQUIRED” PHENOTYPE

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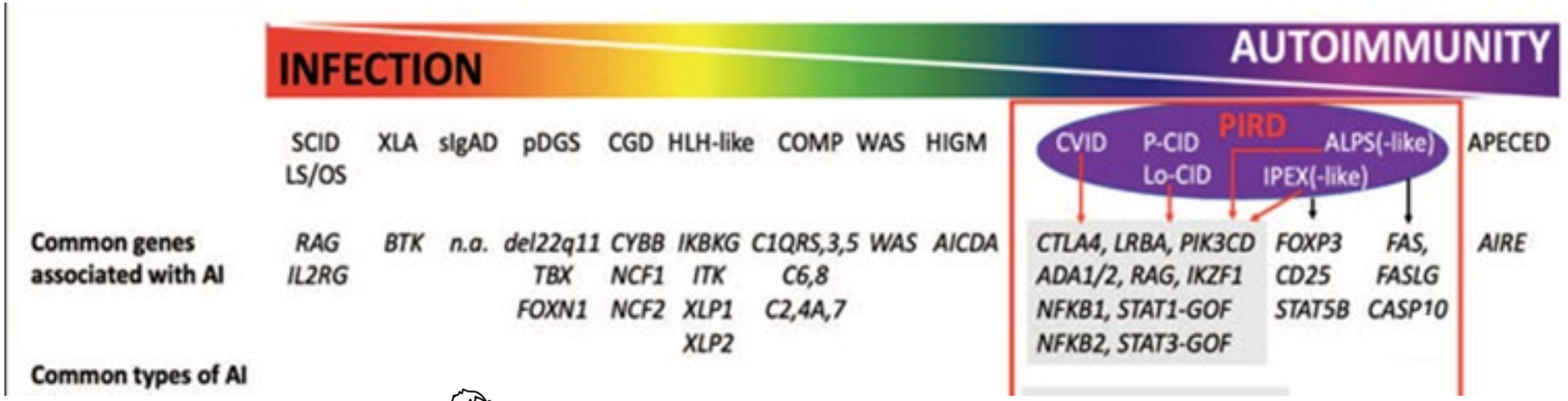
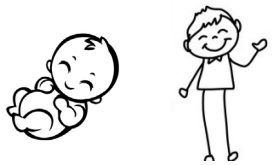
CYTOPENIA as SIGN OF PRIMARY IMMUNODISREGULATION DISORDER (PIRD)





Walter JE, Frontiers Immunol 2019

European Reference Network

WES in CIN

CHRONIC IDIOPATHIC NEUTROPENIA
in 16 adults
Median age 59 yrs (30-72 yrs)

Bone MarrowFailure

G6PC3
FANCM
CTC1

PIRD
Primary Immune Dysregulation Disorders

DCLRE1C
ORAI 1
SPINK5
PEPD

Autoinflammatory disorders

MEFV
IRF7
PSMG2

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Tsanakis G , ASH 2023

Which type of FUP?

- Monitoring the patients for the appearance of systemic autoimmune symptoms and disease or surveilling any change in lymphocyte subset and immunoglobulin pattern
- Management of symptoms (i.e. aphate, atrhalgia, thyroiditis etc) with rheumatologists/endocrinologist if needed
- Enlarge the genetic analysis with more wide and/or modern technique

THANKS !!

EuNet INNOCHRON